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Antibody responses induced by the BNT162b2 mRNA COVID-19 vaccine in healthcare workers in a single community hospital in Japan

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ABSTRACT

Introduction: The effectiveness of several vaccines against coronavirus disease (COVID-19) has been reported in the real-world setting. However, it is still unknown how long antibodies persist following vaccination and whether or not the persistence of antibodies has a protective effect against COVID-19.

Methods: Healthcare workers who had received two doses of the BNT162b2 mRNA COVID-19 vaccine were enrolled, and a single-center study was conducted at the National Hospital Organization Hakodate National Hospital. Serum samples from all participants were collected 13–21 weeks (median: 20 weeks) after the second dose of vaccination. The antibody titers were measured using an electrochemiluminescence immunoassay (Elecsys® Anti-SARS-CoV-2 S). Data on characteristics of the participants were gathered from patient records and interview sheets.

Results: A total of 401 participants, among whom 70.1% were women and the median age was 42 years, were evaluated in this study. None of the participants had a definite COVID-19 history, and all participants who received complete vaccination showed positive antibody titers. The antibody titer was observed to be higher in participants with younger age (p < 0.001) and those who were females (p = 0.028). Despite the higher risk of infection than that of the general public, no vaccinated staff developed breakthrough infections.

Conclusions: This study demonstrates the significant contribution of the BNT162b2 vaccine in the acquisition of anti-SARS-CoV-2S antibodies; therefore, the general population should benefit from these two vaccine doses, which are expected to be protective for at least five months.

1. Text

Owing to the rapid development of vaccines against coronavirus disease (COVID-19) based on a large number of studies conducted, several vaccines are currently being approved worldwide [1–6]. Among the vaccines available for clinical use, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines are most widely used. They play a key role in managing the COVID-19 pandemic in major countries. In Japan, the BNT162b2 mRNA COVID-19 vaccine (Comirnaty®; BioNTech and Pfizer) was the first to be approved by regulatory affairs, where its inoculation started on February 17, 2021. This was followed by the approval of the mRNA-1273 SARS-CoV-2 vaccine (Moderna) and
the ChAdOx1 AZD1222 vaccine (AstraZeneca) on May 21, 2021 [1–3]. Healthcare workers were given priority for inoculation due to the extremely high risk of exposure to SARS-CoV-2 and the need to secure the country’s healthcare system; thus, almost all of the said workers are already vaccinated with the BNT162b2 mRNA COVID-19 vaccine in Japan.

The promising effectiveness of the BNT162b2 mRNA vaccine has already been reported in previous research [7]. In a clinical study conducted in Israel with a nationwide mass vaccination setting, the estimated effectiveness of the BNT162b2 vaccine after full vaccination was 92% for documented infection and 87% for hospitalization rates [8]. Further, the real-world efficacy announced by the United States Center for Disease Prevention has shown that globally approved mRNA vaccines (Pfizer-BioNTech and Moderna) reduce the risk of symptomatic illness by 94% among healthcare providers after the second vaccine dose [9]. However, antibody titers reportedly decreased gradually over time post-vaccination [10]. It is still unknown how long antibodies persist following vaccination, and whether or not the persistence of antibodies confers protective immunity against COVID-19.

In this study, the researchers analyzed the antibody titers against SARS-CoV-2 spike (S) protein receptor binding domain (RBD) at least 13 weeks after the second dose of BNT162b2 vaccination in a real-world setting in healthcare workers at a single national community hospital in Japan.

The vaccination program using the BNT162b2 mRNA COVID-19 vaccine (Pfizer, NY, USA, and BioNTech, Mainz, Germany) started on March 12, 2021, and all healthcare workers were given priority for vaccination at the National Hospital Organization (NHO) Hakodate Hospital, Japan. This is one of the first institutions in Japan in which COVID-19 vaccination was started for staff. The workers’ characteristics, including age, sex, weight, height, occupation, exposure to patient with COVID-19, previous COVID-19 infection, current smoker, comorbidities, and medications received were gathered from medical records and interview sheets. Serum samples of all participants were also collected from August 3–18, 2021; that is, 13–21 weeks after the second dose of vaccination during regular staff checkup.

The study protocol was approved by the NHO Hakodate National Hospital Ethics Committee on Clinical Research (#R3-0728001) and was conducted in compliance with all applicable national and institutional regulations. All participants provided oral consent to participate in the study.

For quantitative detection of antibodies to the SARS-CoV-2 spike (S) protein RBD in human serum samples, Elecsys® Anti-SARS-CoV-2 S was used on the Cobas 8000 e601 Analyzer (Roche Diagnostics Rotkreuz, Switzerland). This system is an electrochemiluminescence immunoassay that uses a double-antigen sandwich assay which predominantly captures anti-SARS-CoV-2 IgG as well as anti-SARS-CoV-2 IgA and IgM. The measuring range of this assay is 0.4–2500 U/mL (for 10-fold diluted samples). Antibody titers ≥0.8 U/mL were considered positive and converted to a logarithmic scale for statistical analysis.

Data were analyzed using Mann–Whitney U test, and two-sided p-values less than 0.05 were considered statistically significant. Spearman’s correlations between clinical variables and antibody titers were calculated. All statistical analyses were performed using JMP Pro version 14.0 software (SAS Institute Inc., Cary, NC, USA).

A total of 464 employees in the NHO Hakodate National Hospital were fully vaccinated (defined as receipt of the second dose of the BNT162b2 vaccine) from March 12, 2021, to April 30, 2021. Four hundred sixty-six healthcare workers had received the first dose of vaccination, although two of them (0.43%) did not receive the second dose for non-medical reasons. Among the 464 fully vaccinated employees, 401 (86.4%) participated in this study. The median age was 42 years, with an interquartile range (IQR) of 31–51. Among the participants, 281 (70.1%) were women, and 120 (29.9%) were men. The participants with occupations that are at high risk of exposure to patients were 73.8% (n = 296) of the study population, including nurses (65.8%, n = 264) and physicians (8.0%, n = 32). Thirty-five participants (8.7%) had a close contact, which was defined as being within 6 feet from an infected person for a cumulative total of 15 min or more over a 24-h period. None of the participants had a history of COVID-19 infection confirmed by polymerase chain reaction testing, or had an illness with clinically compatible symptoms. Detailed demographic characteristics of the participants are shown in Table 1.

Serum samples were collected at least 13 weeks after the BNT162b2 final vaccination, and antibody titers against SARS-CoV-2 spike protein RBD were quantified. All participants who received full vaccinations showed positive antibody titers, and none of them developed COVID-19 after vaccinations. Twenty-four serum samples of employees who did not have the BNT162b2 vaccination were also tested for antibody titers, and all samples showed negative results (<0.4 U/mL). The median value of measured antibody titers was 761.6 U/mL (range: 13.7–>2500; IQR: 490–1183). The antibody titers were higher in younger (p < 0.001) and female (p = 0.028) participants, as shown in Figs. 1 and 2. Significant correlations were not observed in participants who are current smokers (p = 0.054) or who had contact with COVID-19-positive patients (p = 0.160). For comorbidities, hypertension was associated with lower antibody titers (p = 0.0004). Atopic dermatitis (p = 0.80), dyslipidemia (p = 0.34), asthma (p = 0.28), diabetes mellitus (p = 0.21), malignancies (p = 0.42), thyroid disease (p = 0.99), autoimmune disease (p = 0.065), ischemic heart disease (p = 0.26), and cerebral infarction (p = 0.37) had no correlations with antibody titers. Additionally, inhaled corticosteroids (p = 0.35), antibiotics (p = 0.77), immunosuppressants (p = 0.20), and medications for allergies (p = 0.75); dyslipidemia (p = 0.43); diabetes mellitus (p = 0.21); thyroid disease (p = 0.77); malignant disease (p = 0.24); and hormonal therapy (p = 0.12) also had no correlations with antibody titers. Blood samples were collected with a median interval of 142 days (range: 95–159 days; IQR: 139–145) after receipt of the final vaccination. There was no significant association observed between the elapsed time from the final vaccination to the blood collection and antibody titers.

One serious adverse event (0.2%; 1/401) was reported as intestinal obstruction, which resulted in a laparoscopic surgery three weeks after vaccination.

Table 1

| Characteristics                      | N   | %    |
|--------------------------------------|-----|------|
| **Sex**                              |     |      |
| Female                               | 281 | 70.1 |
| Male                                 | 120 | 29.9 |
| **Age (years)**                      |     |      |
| Mean (IQR)                           | 42.2 (51–31) |
| Median (range)                       | 42 (19–68) |
| Weight (kg)                          |     |      |
| Mean (IQR)                           | 58.5 (65–50) |
| Median (range)                       | 56 (35–118) |
| BMI (kg/m²)                          |     |      |
| Mean (IQR)                           | 22.4 (24.1–19.9) |
| Median (range)                       | 21.9 (13.3–39.5) |
| **Jobs**                             |     |      |
| Physician                            | 32  | 8.0  |
| Nurse                                | 264 | 65.8 |
| Others                               | 105 | 26.2 |
| **Current smoker**                   |     |      |
| Flu-like symptoms within a year      | 55  | 13.7 |
| Fever, cough, sore throat, headache  | 35  | 8.7  |
| **Exposure/close contact**           |     |      |
| Exposure                             | 35  | 8.7  |
| Close contact                        | 0   | 0.0  |
| **Previous COVID-19 infection**      |     |      |
| Time from second vaccination (days)  |     |      |
| Mean (IQR)                           | 140.3 (145–139) |
| Median (range)                       | 142 (95–159) |
| **Use of antipyretic after vaccination** |     |      |
| %                                     | 237 | 59.1 |
the first vaccination. Occurrences of other severe adverse reactions, including cardiovascular and anaphylaxis-related events, have not been reported. One evident lymphadenopathy, which occurred in the axilla and neck region, was reported. This was not defined as a severe adverse event, but it may be possibly related to the vaccination.

In this study, antibody titer and the factors that affected antibody reaction after two doses of the BNT162b2 mRNA COVID-19 vaccine in healthcare workers were evaluated. The levels of serum anti-SARS-CoV-2S antibodies were detectable and defined as positive in all participants. Although the antibody titer was not measured before the first vaccination, it can be said that all participants acquired a meaningful antibody response against SARS-CoV-2 by BNT162b2 vaccination as none of the subjects had a history of COVID-19 infection. These results suggest that full vaccination has a significant contribution to the efficient acquisition of anti-SARS-CoV-2 antibodies. On the other hand, it is still unclear whether or not the measured antibody titers reflect the actual protective effect against the virus. In the present study, despite the higher risk of infection than that of the general public in Japan (overall infection rate of 1.4%), no vaccinated staff at our institution had a breakthrough infection. Given this result, we believe that vaccination might be effective in this real-world setting.

Antibody titers were significantly higher in women and in younger participants even more than three months after the second dose of the vaccine. Several studies have indicated that sex and age are associated with antibody responses [11–13], and the findings of this study are consistent with these reports. Kageyama et al. reported that the use of medications for allergies had a correlation with lower antibody titers [13], although the results from this study showed no association. Instead, it suggested hypertension as a factor for lower antibody titers.

This study was conducted on healthy hospital staff. Only two participants were under immunosuppressive therapy, where one received treatment with methotrexate and prednisolone, and the other with 6-mercaptopurine. Their antibody titers were 739.7 and 58.8 U/mL, respectively. In addition, two other participants received antibody drugs (Adalimumab and Dupilumab), and their antibody titers were 315.5 and 243.7 U/mL, respectively. Several studies have reported that administration of immunosuppressive drugs is associated with decreased antibody reactions following COVID-19 vaccination [11,12]. However, it was difficult to perform further statistical analysis to show the association between immunosuppressive therapy and antibody titer due to the small number of subjects in this cohort. The researchers hope that the relationship between past medical history and medications and antibody titers will be more clearly understood in the future through larger studies involving non-healthcare workers with more comorbidities.

This study has several limitations. First, the results of this study may not be applicable to other populations since this is a single-center study for Japanese healthcare workers only, and the dominant variant of the virus may possibly differ with the region. Second, the antibody titers before and after the first vaccination were not measured, and the degree of increase in antibody titer caused by the first and second vaccinations is unclear. Third, the accuracy of the data could not be verified. The proponents collected most of the clinical information, such as medical history and medications, using a self-reported questionnaire. Fourth, in this study, the decrease in antibody titers could not be examined since the differences of the elapsed period from final inoculation to blood collection were relatively small. Further follow-up is required. Finally, we used an electrochemiluminescence immunoassay for measuring antibody titers. Several studies have tested the concordance of this assay with the standard neutralization assay, and such RBD-based immunoassays are suitable for monitoring the humoral immune response of post-vaccination patients [14,15]. However, it should be noted that this assay does not detect neutralizing antibodies accurately.

In spite of these limitations, this study demonstrated the contribution of the BNT162b2 mRNA vaccine for health care workers in a community hospital in Japan. The general population should also benefit from two doses of vaccine, which are expected to be protective for at least five months.

Authorship statement

All authors meet the ICMJE authorship criteria.

Kazuya Yonezawa was responsible for the study. Kei Hiraoka, Masato Suzuoki, and Shinya Otsuka designed the study and collected the data. Kei Hiraoka and Shinya Otsuka wrote the manuscript. Shinya Otsuka performed data analysis. Hideki Ujiie, Tatsuya Kato, Isao Yokota, Nozomu Iwashiro, Kazuya Yonezawa, Motosugu Kato, Keiji Oguma, and Masanori Ohara commented on the manuscript and approved the final version.
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Declaration of competing interest

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