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# Antibody titers among healthcare workers for coronavirus disease 2019 at 6 months after BNT162b2 vaccination



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## ABSTRACT

**Background:** Antibody levels decrease substantially at 6 months after the BNT162b2 vaccine. The factors influencing titer of antibodies against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) among healthcare workers for coronavirus disease 2019 (COVID-19) is unclear.

**Methods:** We conducted a 6-month longitudinal prospective study in Japanese healthcare workers in a tertiary care hospital for COVID-19. Participants in the study were tested for the presence of anti-spike protein (SP) IgG antibodies before and at 1 and 6 months after the last vaccination dose.

**Results:** Among 1076 healthcare workers, 794 received the vaccine, and 469 entered the study. Five were infected with SARS-CoV-2 (none among COVID-19 section workers) by the end of the study and 451 participants were finally analyzed (mean age, 42.5 years; 27.3 % male; 18.8 % COVID-19 section workers). Median SP IgG index values were 0.0, 44.4, and 5.5 before and at 1 and 6 months after the last dose, respectively. Regression analysis revealed a negative correlation of SP IgG antibody levels with age ( $P < 0.0001$ ), and higher levels in COVID-19 section workers ( $P = 0.0185$ ) and in females ( $P = 0.0201$ ).

**Conclusion:** In healthcare workers at a COVID-19 hospital, IgG antibody titer was substantially lower at 6 months after receipt of the last dose of the BNT162b2 vaccine compared with that 1 month after the last dose, but was better preserved among younger participants, COVID-19 section workers and females.

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## 1. Introduction

Coronavirus disease 2019 (COVID-19) is a newly emerged disease that has affected many countries [1,2]. In Japan, vaccination against COVID-19 began in March 2021, using the BNT162b2 (Pfizer-BioNTech) messenger RNA (mRNA) vaccine [3,4]. First priority was given to healthcare workers and persons aged  $\geq 65$  years. Approximately 77 % of the Japanese population had received at least one vaccine dose by the end of this study, 30 November 2021 [5].

**Abbreviations:** COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SP, spike protein; NP, nucleocapsid.

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Despite the high effectiveness of the vaccine, antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induced by the BNT162b2 vaccine decrease substantially over 6 months, particularly among men, those aged  $>65$  years, and persons with immunosuppression [6]. Despite the rapid decline in humoral response, protection against hospitalization and death is reported to persist for 6 months after the second dose [7]. However, the potential factors that influence levels of antibodies to SARS-CoV-2 virus in healthcare workers is not fully understood. We prospectively examined antibody levels in healthcare workers at a tertiary care hospital for COVID-19 at six months after receiving the last dose of the BNT162b2 vaccine.

## 2. Subjects and methods

### 2.1. Participants

Participants were recruited in March 2021 from among 1076 healthcare workers at the Saitama Cardiovascular and Respiratory

Center. Of the 794 workers (73.8 %) who had received at least one dose of BNT162b2 vaccine between March 2021 and May 2021, 469 gave informed consent to participate in the study, and a final total of 451 were eligible for inclusion in analysis at 6 months after the last dose (Fig. 1). The booster vaccination had not been started by the end of this study in our hospital. Between 11 February 2020 and 30 November 2021, 851 patients with COVID-19 were admitted to our 342-bed hospital, which includes 76 beds for COVID-19 patients.

### 2.2. Methods

The study was approved by the ethics committee of Saitama Cardiovascular and Respiratory Center (IRB No. 2020053) and carried out in accordance with the principles of the Declaration of Helsinki. We conducted a prospective longitudinal cohort study. Study recruitment including its purpose and design was announced on hospital notice boards and participants visited a study room and provided informed consent prior to blood sampling. Blood samples were collected before receipt of the first vaccine dose and at one month ( $\pm 3$  days) and 6 months ( $\pm 14$  days) after the last dose. The entry criterion for antibody analysis was no SARS-CoV-2 infection before or during the observation period, which was defined as negative anti-spike protein IgG (SP IgG) before vaccination and negative anti-nucleocapsid IgG (NP IgG) at the time of blood sampling 6 months after the last dose. Individuals who tested positive to SARS-CoV-2 by polymerase chain reaction (PCR) during the follow up period were also excluded from the analysis. All participants completed a check sheet (age, sex, comorbidities, and allergic history) at the time of the first blood sampling and were asked to record any side effects (temperature, local pain, high blood pressure, redness, fatigue, arthralgia, or any symptoms) in a follow-up sheet for two weeks after each dose.

### 2.3. IgG antibodies for SARS-CoV-2 with AIA-CL1200

Index values of SARS-CoV-2 SP and NP IgG were measured using commercial CLEIA reagents (CL AIA-PACK anti-SARS-COV-2-SP-IgG and CL AIA-PACK anti-SARS-COV-2-NP-IgG, TOSOH Corp., Tokyo, Japan). Previous validations of these reagents have shown to have high sensitivity and specificity [8]. The cut off values for SP IgG and NP IgG were both 1.0, according to the manufacturer’s instructions. SP IgG index values have been reported to correlate with 50 % neutralizing titer (NT50) values [9].

### 2.4. Statistical analysis

Data are expressed as the median (range) or mean (standard deviation, SD). The values of different groups were compared by the Mann-Whitney *U* test for two groups or the Kruskal-Wallis test followed by Dunn’s test for three or more groups. Paired data before and after vaccination were compared by Friedman test. Categorical data were compared using Fisher’s exact test. A multivariable regression model was used to examine the association between the variables and SP IgG index values.  $P < 0.05$  was considered statistically significant. JMP Ver. 13, (SAS Institute Japan Ltd., Tokyo, Japan) and Prism 9.3 (GraphPad Software, San Diego, CA, USA) were used for statistical analyses.

### 3. Results

The characteristics of the participants are shown in Fig. 1 and Table 1. Thirteen participants dropped out of the study by 6 months, and five were excluded from analysis due to evidence of SARS-CoV-2 infection before or during the study period, all of whom were non-COVID-19 section workers that were asymptomatic or had only mild symptoms. Among the 451 participants

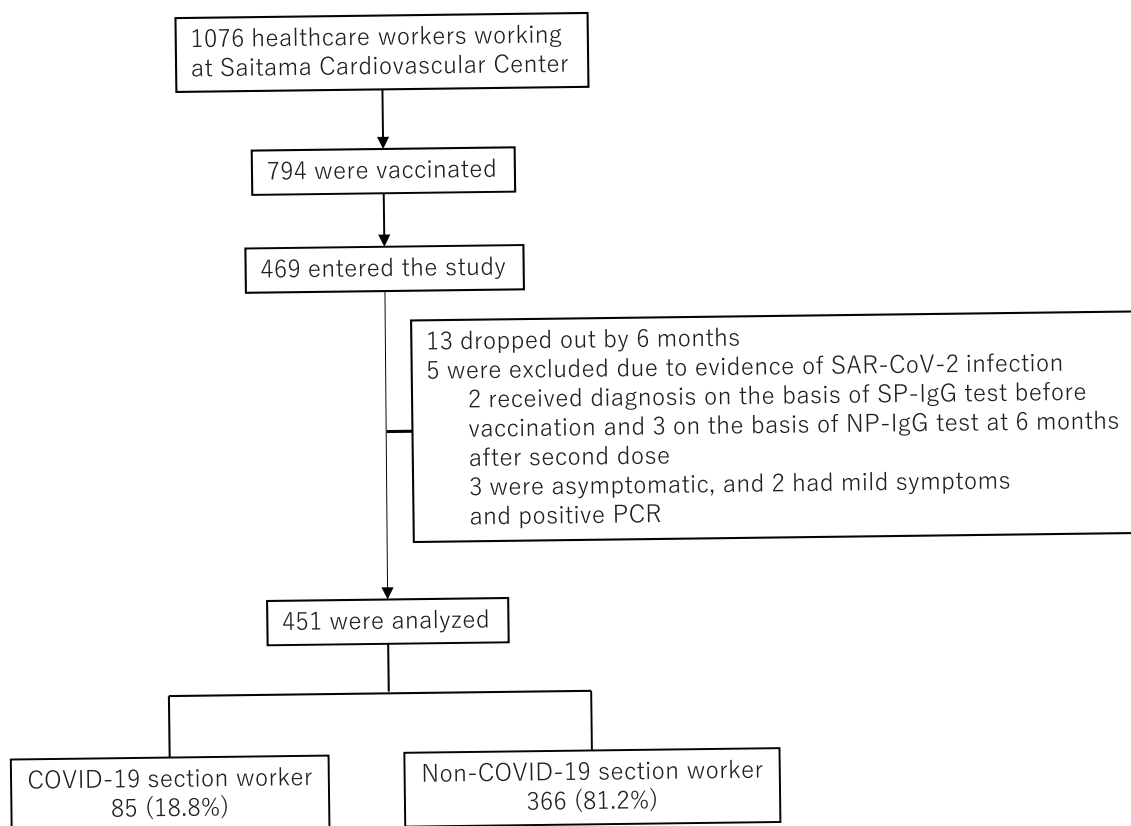


Fig. 1. Flow chart of recruitment of participants and classification. Abbreviations: PCR, polymerase chain reaction; SP, spike protein; NP, nucleocapsid protein; IgG, immunoglobulin; COVID-19, coronavirus disease 19.

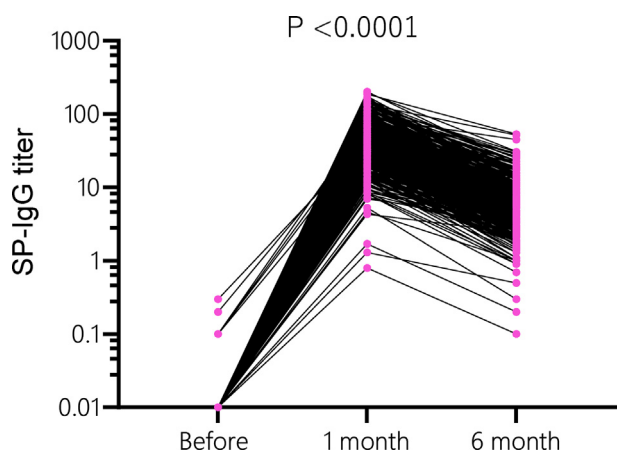
analyzed, 85 (18.8 %) were COVID-19 section workers. The COVID-19 areas were separated from non-COVID-19 areas by different wards and different rest areas. The stuffs of the original wards that had changed to COVID-19 wards were assigned to COVID-19 section workers with regular rotation. All stuffs who had worked in COVID-19 area were designated as COVID-19 section workers. During the period from the admission of the first COVID-19 patient to our hospital until the end of the study, no COVID-19 section worker was infected with COVID-19.

The median SP IgG index values (range) were 0.0 (0.0–0.3) before vaccination, 44.4 (0.8–202.2) one month after the last dose, and 5.5 (0.1–53.2) 6 months after the last dose (Fig. 2).

**Table 1**  
Participant characteristics.

Participants, (n)	451
Sex, male, n (%)	123 (27.3 %)
Age, mean, SD	42.5, 12.0
COVID-19 section worker, n (%)	85 (18.8 %)
Received second dose, n (%)	448 (99.3 %)
Comorbidities, n (%)	71 (15.7 %)
Allergic history, n (%)	65 (14.4 %)

Abbreviations: SD, standard deviation; COVID-19, coronavirus disease 2019.



**Fig. 2.** SP IgG index titers before and at 1 and 6 months after the last dose of BNT162b2 vaccine. Before vaccination, SP IgG titers of all subjects were below the threshold (index 1.0). The index titers below detection limit are designated as 0.01 in the figure. Abbreviations: SP, spike protein; IgG, immunoglobulin.

**Table 2**  
Index SP-IgG titer values according to participant background and side effects of vaccination.

	Yes	n	no	n	P value
COVID-19 section worker	7.5 (0.7–53.2)	85	5.3 (0.1–45)	366	0.0003
Arthralgia, myalgia	6 (0.1–53.2)	210	5.1 (0.2–30.7)	202	0.0014
Local pain	5.8 (0.1–53.2)	361	4.5 (0.2–23.2)	57	0.0014
Sex, male	4.6 (0.2–28.3)	123	5.8 (0.1–53.2)	328	0.0015
Received second dose	5.5 (0.2–53.2)	448	0.5 (0.1–2)	3	0.0048
Fever	7 (1.4–52)	80	5.3 (0.1–53.2)	337	0.0054
Induration	6.35 (1.9–30.7)	84	5.35 (0.1–53.2)	334	0.0116
Comorbidities	4.9 (0.2–28.1)	71	5.8 (0.1–53.2)	379	0.0307
General malaise	5.8 (0.1–53.2)	253	5.1 (0.2–45)	161	0.0344
Redness	6.6 (0.1–26.4)	63	5.4 (0.2–53.2)	350	0.277
Headache	5.9 (1–30.9)	110	5.4 (0.1–53.2)	305	0.4908
Diarrhea, nausea	6.05 (1.5–14.6)	48	5.4 (0.1–52)	365	0.5281
Allergic history	5.6 (0.5–30.9)	65	5.5 (0.1–53.2)	386	0.5605
Numbness	5.3 (1.3–22.9)	29	5.5 (0.1–53.2)	385	0.7041

Abbreviations: SP, spike protein; IgG, immunoglobulin; COVID-19, coronavirus disease 2019.

The relationships between SP IgG index values and background conditions and side effects of vaccination are shown in Table 2. Simple analyses showed that COVID-19 section worker, arthralgia/myalgia, female sex, fever, induration, comorbidities, and general malaise were associated with higher SP IgG antibody titer at 6 months after vaccination. Levels of SP IgG antibody differed according to age group and sex (Fig. 3). Male participants in their 50 s and 60 s had lower SP IgG antibody levels than males in their 20 s. There was no significant difference in IgG antibody levels among the female age groups. SP IgG antibody level differed according to area of work in the hospital (Fig. 4), with the median index value 1.42 times higher in workers in the COVID-19 section compared with workers in the non-COVID-19 section (7.5 vs 5.3, P = 0.0003).

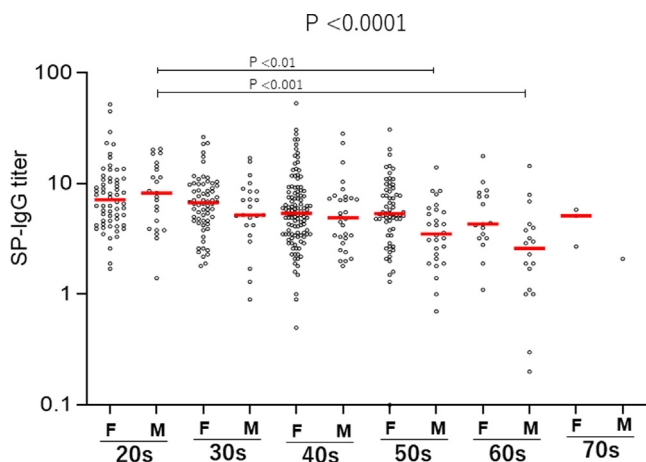
There was a difference between the COVID-19 section workers and non-COVID-19 section workers in male percentages (16.5 % vs 29.7 %, respectively, P = 0.0146), but not in ages (mean 41.1 years vs 42.8 years, respectively, NS).

In the regression analysis, younger age (P < 0.0001), COVID-19 section worker (P = 0.0185) and female sex (P = 0.0201) were independently associated with higher SP IgG titer (Table 3).

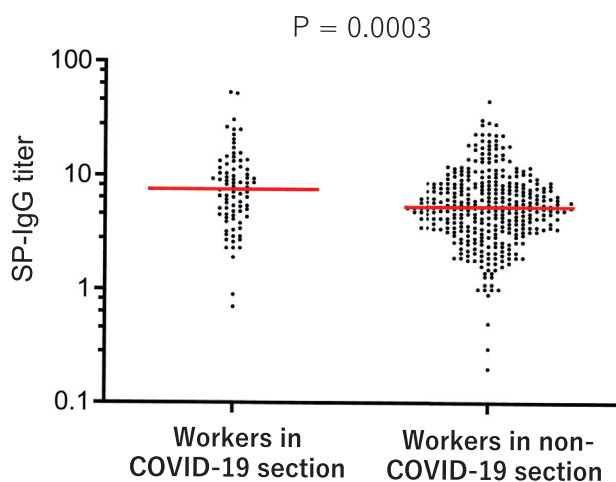
#### 4. Discussion

This prospective observational study of healthcare workers in a tertiary hospital for COVID-19 found a significant decrease in SP IgG antibody levels at 6 months after receipt of the last dose of BNT162b2 vaccine. Antibody titer was associated with age, sex, comorbidities, reactions after vaccination, and working in a COVID-19 area. In particular, COVID-19 section workers had significantly higher SP IgG antibody titers than non-COVID-19 section workers. Furthermore, COVID-19 section workers did not record a single event of SARS-CoV-2 infection during the study period. The results of this study indicate the factors influencing antibody levels 6 months after vaccination and are encouraging for healthcare workers that may be repeatedly exposed to COVID-19 positive patients.

Neutralizing antibodies are considered to correlate with protection [10,11]. The CL-AIA SP IgG index value used in this study has been reported to correlate with neutralizing activities for SARS-CoV-2 [9]. In a previous study, subjects with an SP IgG index value greater than 10 had high enough NT50 values [9]. In the present study, 19.1 % of participants had an index value of SP IgG greater than 10 at 6 months after the last dose. Of note, it has been reported that effectiveness against any SARS-CoV-2 infection was approximately 20 % in months 5–7 after the second dose of BNT162b2 [7].



**Fig. 3.** Distribution of SP IgG index titers at 6 months after the last dose of BNT162b2 vaccine. The horizontal lines indicate median values, shown according to sex and decade of age. The difference in medians as a whole was tested by the Kruskal-Wallis test, and the differences between groups were tested by Dunn's test. Abbreviations: SP, spike protein; IgG, immunoglobulin; F, female; M, male.



**Fig. 4.** SP IgG index titers in COVID-19 section workers and in non-COVID-19 section workers at 6 months after the last dose of BNT162b2 vaccine. The horizontal lines indicate median values. Abbreviations: SP, spike protein; IgG, immunoglobulin; COVID-19, coronavirus disease 2019.

**Table 3**  
Regression analysis for SP-IgG antibodies.

Variable	coefficient	SD	t value	P value
Received second dose	0.6654	0.1083	6.14	<0.0001
Age	-0.0069	0.0014	-5.17	<0.0001
COVID-19 section worker, no	-0.0452	0.0192	-2.37	0.0185
Sex, male	-0.0413	0.0177	-2.33	0.0201
Arthralgia, no	-0.0295	0.0165	-1.79	0.0747
Induration, no	-0.0346	0.0207	-1.67	0.0952
Fever, no	-0.0319	0.0198	-1.61	0.1075
Headache, no	0.0291	0.0181	1.61	0.1082
Pain, no	-0.0369	0.0235	-1.57	0.1169
General malaise, no	-0.0235	0.0175	-1.34	0.1798
Diarrhea, nausea, no	0.0233	0.0245	0.95	0.3441
Allergic history, no	-0.0133	0.0219	-0.61	0.5411
Numbness, no	0.0084	0.0302	0.28	0.7782
Redness, no	0.0015	0.0228	0.07	0.9482
Comorbidity, no	-0.0007	0.0217	-0.03	0.9728

Abbreviations: SP, spike protein; IgG, immunoglobulin; COVID-19, coronavirus disease 2019.

We analyzed the association of SP IgG level with age, sex, comorbidities, side effects after vaccination, and history of working in the COVID-19 section. We found that antibody levels were higher in women than in men and decreased with age, as reported previously [6,12,13]. It would be important to note that young males showed similar antibody responses as females. It suggests that the men's lifestyle or sex hormones may affect antibody response later in their life. In addition, univariable analysis revealed that being a COVID-19 section worker, comorbidity, and side effects after vaccination (arthralgia/myalgia, fever, induration, or general malaise) were associated with high SP IgG antibody titer. After regression analysis, a factor of working in the COVID-19 section was more highly associated with high antibody titer than was sex. However, the effect of male percentages should partly influence the result of univariate analysis of COVID-19 section workers. The effect of reactions after vaccination has not been clarified. Significant symptoms after vaccination have been associated with high antibody titer [14]; however, another study showed no correlation between vaccine-associated symptoms and vaccine-induced antibody titers [15]. We previously reported that local pain was significantly related to antibody titer at 1 month after vaccination even after regression analysis [16]. However, there is limited evidence regarding the variables associated with antibody titer at 6 months after vaccination.

During the period of medical service for COVID-19, from February 2020 to the end of this study 30 November 2021, 5 (0.46 %) hospital staffs were infected with SARS-CoV-2 which was approximately one-third of the rate in the surrounding community (1.58 %; cumulative 115,839 COVID-19 patients per 7,342,262 population in Saitama prefecture) [17]. In the first vaccination campaign between March and May 2021, 794 (73.8 %) staff had been vaccinated and the final vaccination rate at our hospital by 30 November 2021 was ≥90 %. All infected staff either had mild disease or were asymptomatic. According to an American study, 15 % of healthcare workers were vaccine hesitant [18]. Previous studies from the UK reported that patient-facing healthcare workers had increased risk of admission with COVID-19 [19], and that healthcare workers were at high risk of COVID-19, 38 % of whom were asymptomatic [20]. Low infection rate with SARS-CoV-2 in our hospital could be attributed to a number of factors besides high vaccination rate, for example, improved access to personal protective equipment (PPE), higher awareness of potential COVID-19 exposure, and immunity from repeated subclinical exposure.

There are several limitations of this study that should be noted. First, the study size is relatively moderate so that it might not be enough to detect other meaningful covariables. Second, it was conducted in healthy workers and does not represent the general population. More data are required in the elderly and younger populations. Finally, we tested only IgG antibody against the spike protein, and other isotype antibodies or antigen-specific T cells were not evaluated. Therefore, the results of this study represent only a part of immune mechanisms induced by vaccines.

### 5. Conclusions

In healthcare workers at a COVID-19 hospital, IgG antibody titer at 6 months after receipt of the last dose of the BNT162b2 vaccine was substantially decreased compared with that at 1 month after vaccination, but was better preserved among younger staff, COVID-19 section workers, and females.

The results of this study provide additional insight into the immune response at 6 months after BNT162b2 vaccination. A sub-threshold exposure to SARS-CoV-2 might enhance antibody levels after BNT162b2 vaccination without symptomatic infection or antibody seroconversion in healthcare workers.



## Author contributions

All authors attest that they meet the ICMJE criteria for authorship. K Kurashima conducted the study and wrote the manuscript; Numano T, Yoshino A, Ohsawa A, Takaku Y, Kagiya N and Yanagisawa T collected data. All authors approved the final version of the manuscript for publication.

## Data availability

The authors do not have permission to share data.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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