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Antibody response after COVID-19 vaccine BNT162b2 on health care workers in Japan

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ABSTRACT
Background: Vaccination is one of the most important tools to control the COVID-19 pandemic. However, there is little information on the antibody response in humans after the COVID-19 vaccination.

Methods: This single-center, prospective study was conducted in Yokohama, Japan. We included health care workers who had received two doses of COVID-19 vaccination (BNT162b2) 21 days apart. We measured serum immunoglobulin G (IgG) to nucleoprotein and spike protein of SARS-CoV-2 with commercially available kits before and 7, 14, and 35 days after the first dose of vaccination.

Results: A total of 104 workers participated in this study. Of these, 7 participants were seropositive with anti-bodies to spike protein at baseline and 4 of the 7 seropositive participants had COVID-19 history. The mean level of IgG to spike protein (QT) was 45.2, 1219, 2845, and 23489 AU/mL at baseline, on days 7, 14, and 35, respectively, although the values for nucleoprotein (NG) were 0.2, 0.21, 0.22, and 0.19 S/C, respectively. On day 7, QT in seropositive participants at baseline was elevated, whereas it was not elevated in seronegative participants at baseline until day 14.

Conclusions: QT was elevated over the cutoff in all the participants at day 35, but NG did not change between baseline and day 35.

1. Introduction
The novel coronavirus disease (COVID-19) was first reported from Wuhan, China, on December 31, 2019, and has been expanding globally with over 153 million confirmed cases [1]. According to the World Health Organization, vaccines are a critical new tool in the battle against COVID-19, and most people 18 years and older should get vaccinated [2]. BNT162b2 is a vaccine against COVID-19 that was approved in the United States, Japan, and many other countries. A phase 1/2 study revealed that two doses of BNT162b1 caused an increase of the receptor binding domain-binding (RBD) immunoglobulin G (IgG) concentrations and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-neutralizing titer [3]. Many commercial kits are available to measure the antibodies’ level to SARS-CoV-2; however, there have been only a few studies on antibodies’ level using commercially available kits after BNT162b2 injection to humans globally, and no study has been reported in Japan so far.

2. Methods
We conducted a prospective study in Yokohama Municipal Citizen’s Hospital. Eligibility criteria were as follows: 1) the health care worker should be from our hospital, 2) should have received two doses of BNT162b2 injection, and 3) should provide a sign informed consent form. We measured serum IgG levels for SARS-CoV-2 at baseline (0–28 days before the first dose of BNT162b2), day 7 (6–8 days after the first injection), day 14 (13–15 days after the first injection), and day 35 (34–36 days after the first injection). Participants received 0.3 mL of BNT162b2 intramuscularly at days 0 and 21 in March and April 2021. We measured the serum SARS-CoV-2 IgG level with ARCHITECT SARS-CoV-2 IgG and ARCHITECT SARS-CoV-2 IgG II Quant (Abbott, Illinois, U.S.A.), with cutoff points of 1.4 sample result divided by the calibrator result (S/C) and 50 Arbitrary Units (AU)/mL, respectively, which was recommended by the manufacturer [4,5]. The former kit identifies IgG to nucleoprotein (NG), and the latter kit identifies IgG to spike protein (QT). We examined age, sex, preexisting diseases, and history of COVID-19 with questionnaire forms at day 0. This study was approved.
by the Yokohama Municipal Citizen’s Hospital ethical committee. We used the softwares Excel 2016, JMP 16.0, and R 3.5.3 for statistical analysis, and defined a p value of <0.05 as significant.

3. Results

A total of 104 workers were eligible for the study (Table 1). Their mean age was 39 years; there were 24 men and 80 women, and all were Asian. Of them, 4, 3, and 2 participants had a history of COVID-19 infection, hypertension, and asthma, respectively. All participants except for one engaged in direct care for COVID-19 patients on the job. All participants received two doses of the vaccination at days 0 and 21, but 2 participants did not receive the second dose and 2 participants received the second dose on days other than day 21 (days 20 and 24). Therefore, we excluded the data at day 35 of the 2 participants who did not receive the second dose of vaccination.

The SARS-CoV-2 IgG level with ARCHITECT SARS-CoV-2 IgG and that with ARCHITECT SARS-CoV-2 IgG II Quant at baseline were higher than the cutoff in 2 and 7 participants, respectively. Of the 7 seropositive participants with high QT, 4 persons had a history of COVID-19 and 3 did not. Of the 4 participants with a history COVID-19, only one had higher NG than the cutoff at baseline.

The average NG was 0.2, 0.21, 0.22, and 0.19 S/C, and average QT was 45.2, 1219, 2845, and 23489 AU/mL at baseline, days 7, 14, and 35, respectively (Fig. 1). The average QT values at days 7, 14, and 35 were significantly higher than those at baseline although the average NG values at day 35 were almost same at each point.

Regarding the 7 seropositive participants with high QT at baseline (HQ), their QT values increased from baseline to day 14, and decreased from day 14–35 in 4 of 7 participants (Fig. 2). In contrast, QT values in the seronegative participants at baseline (LQ) were not elevated over the cutoff at day 7, but they were elevated at day 14 in 88 of the 89 seronegative participants. The mean QT in LQ/HQ was 3.7 ± 4.5/620 ± 824, 5.2 ± 7.3/1.6 × 10^4 ± 1.3 × 10^4, 776 ± 812/2.9 × 10^4 ± 1.8 × 10^4, and 2.2 × 10^1 ± 1.2 × 10^3/3.6 × 10^3 ± 2.4 × 10^4 AU/mL at baseline, days 7, 14, 35, respectively. The mean QT in HQ was higher than that in LQ at day 7 and day 14 significantly (p = 0.018, 0.0069) but not significantly at day 35 (p = 0.17).

4. Discussion

To the best of our knowledge, this is the first report of antibody response after COVID-19 vaccination in humans in Japan. Using a commercially available kit, our study revealed that anti-spike protein antibodies increased after vaccination. In contrast, antibodies to nucleoprotein did not increase after the vaccination. This is reasonable because BNT162b2 contains nucleoside-modified ribonucleic acid encoding the SARS-CoV-2 full-length spike protein [6].

A prior phase 1/2 study revealed that the RBD IgG was not elevated 7 days after the first BNT162b2 administration but it was elevated after 21 days. Our study revealed that QT in HQ was elevated above the cutoff in none of the 88 participants at day 7, but it was elevated in 88 of the 89 participants at day 14. This suggests that antibodies are induced and elevated to significant levels around day 14 after the first dose of vaccination. Moreover, these data are compatible with a prior phase 3 study that showed that early protection by the vaccine start as soon as 12 days after the first dose [6]. The NG did not change significantly during the follow-up period in our study. Therefore, antibodies to nucleoprotein seem not to be influenced by the BNT162b2 administration.

Charlotte et al. reported that among previously uninfected, seronegative individuals, anti-spike protein titers after one dose of BNT162b2 were comparable to peak anti-spike protein titers in individuals with a previous natural infection who had not yet been vaccinated [7]. Moreover, it has also been reported that among those with a previous SARS-CoV-2 infection, vaccination increased anti-spike protein titers more than 140-fold from peak pre-vaccine levels. These results are compatible with those of the present study, but QT in HQ increased 76-fold on average from baseline to day 14. The difference of fold numbers between the present study and that of Charlotte et al. might be caused by participants’ characteristics and timing of the blood tests (19–29 days after the vaccination in the report).

After the second dose, QT increased in LQ at day 35 compared with that at day 14. Interestingly, in 4 of 7 participants in HQ, QT at day 35 was lower than that at day 14. Joseph et al. also reported that spike-specific IgG antibody levels and ACE2 antibody binding inhibition responses elicited by a single dose of BNT162b2 in individuals with prior SARS-CoV-2 infection were similar to those seen after two doses of vaccine in individuals without prior infection [8]. SARS-CoV-2-specific neutralizing antibody titers were reported to be correlated with spike-protein antibodies [9]. These data suggest that a single dose of BNT162b2 might be enough for seropositive participants and a second dose might not be necessary or could be postponed. Actually, one dose of the vaccine is recommended for people who have previously contracted COVID-19 in France [10]. A previous study revealed that vaccine recipients with preexisting immunity had systemic side effects at higher frequencies than those without preexisting immunity [11]. This also supports the fact that seropositive individuals might skip the second dose of BNT162b2 as primary vaccination.

The present study has limitations. First, all participants were health care workers in a Japanese hospital. Therefore, we did not get data about non-Asian, younger, older, or immunocompromised individuals. Second, the follow-up period was 7 weeks, and antibody response for a longer period was unclear. Third, we used readily available commercial kits. Several kits are available, and the antibody levels measured using these might vary in response to the same vaccination.

In conclusion, anti-spike protein antibodies are significantly induced not at day 7 but around day 14 after one dose of BNT162b2. However, antibodies to nucleoprotein were not induced by the two doses of vaccination.

Table 1

| Participant characteristics                      | 104 |
|------------------------------------------------|-----|
| number of participants                          | 104 |
| mean age ± SD [years]                           | 39 ± 10 |
| male: female                                    | 24 : 80 |
| Asian                                           | 104 |
| history of COVID-19                             | 4   |
| risk of exposure to COVID-19 patients on the job| 103 |
| Hypertension                                    | 3   |
| Asthma                                          | 2   |
| chronic kidney disease                          | 1   |
| autoimmune hepatitis                            | 1   |
| ulcerative colitis                              | 1   |
| myocardial infarction                           | 1   |

Declarations of interest

None.

Authorship

All authors meet the ICMJE authorship criteria.

Authorship statement

NT and YY designed the study, and YY wrote the manuscript. HS, KM and NM commented on the manuscript and approved the final version.

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