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## Original article

# Association between a low response to rubella vaccination and reduced anti-severe acute respiratory syndrome coronavirus 2 immune response after vaccination with BNT162b2: a cross-sectional study

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## ABSTRACT

**Objectives:** Some vaccinated individuals fail to acquire an adequate immune response against infection. We aimed to determine whether mRNA severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination could induce a sufficient immune response against SARS-CoV-2 in low responders to other vaccinations.

**Methods:** Using data from health-care workers who received two doses of the BNT162b2 vaccine (BioNTech/Pfizer), we conducted a single-centre, cross-sectional study to determine whether low responders to measles, rubella, and hepatitis B virus (HBV) vaccinations could acquire sufficient antibodies after SARS-CoV-2 vaccination. From May 2021 to June 2021, participants were tested for anti-SARS-CoV-2 spike (anti-S) IgG antibodies at least 2 weeks after the second dose of BNT162b2. The association between a low response to measles, rubella, and HBV vaccinations and the post-vaccination anti-S IgG titre was evaluated using the multivariable linear regression analysis.

**Results:** All 714 participants were positive for the anti-S IgG titre ( $\geq 50.0$  AU/mL) after two doses of BNT162b2 (median, 7126.8 AU/mL; interquartile range, 4496.2–11 296.8). There were 323 (45.2%), 131 (18.3%), and 43 (6.0%) low responders to measles, rubella, and HBV vaccinations, respectively. In the multivariable linear regression analysis, low responders to rubella vaccination had significantly low acquisition of the anti-S IgG titre after two doses of the BNT162b2 vaccine (standardized coefficient  $\beta$ ,  $-0.110$ ; 95% CI,  $-0.175$  to  $-0.044$ ).

**Conclusions:** A low response to rubella vaccination is a potential predictor of a reduced response to SARS-CoV-2 vaccination. Further studies are needed to determine whether a low response to rubella vaccination is associated with the durability of SARS-CoV-2 vaccination-induced immune response.

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## Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has severely

affected all countries worldwide. Vaccination is essential to contain the COVID-19 pandemic. In Japan, as a part of a nationwide vaccination programme against SARS-CoV-2, mRNA SARS-CoV-2 vaccines, such as BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), have been mainly used. These mRNA vaccines have shown promising efficacy in clinical trials and effectiveness in observational studies in real-world settings [1–3].

Health-care workers (HCWs) are at the risk of exposure to serious infections other than COVID-19 and should receive appropriate

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vaccines to reduce the chances of contracting and spreading vaccine-preventable diseases (VPDs). HCWs are recommended to receive vaccination against VPDs such as measles, rubella, and hepatitis B virus (HBV) [4,5]. Vaccination against these diseases is administered worldwide and has been reported to be highly effective in preventing these; however, some vaccinated persons do not develop sufficient immune responses after vaccination. It is also known that even individuals who have acquired sufficient antibody titres after vaccinations may experience a decline in their immune response over time [6,7]. Data on whether individuals with inadequate immune responses to vaccination against these VPDs can develop an adequate anti-SARS-CoV-2 immune response after SARS-CoV-2 vaccination are still lacking.

Information on factors associated with the immune response following SARS-CoV-2 vaccination is essential for developing future vaccination strategies. In the present study, using data from HCWs who received two doses of BNT162b2, we examined whether SARS-CoV-2 vaccination could induce a sufficient immune response against SARS-CoV-2 in low responders to measles, rubella, and HBV vaccinations.

## Methods

This single-centre, cross-sectional study was conducted at Jikei University Hospital, a 1075-bed academic medical centre in Tokyo, Japan. In the present study, we examined whether HCWs with a low response to measles, rubella, and HBV vaccinations could acquire sufficient antibodies against SARS-CoV-2 after SARS-CoV-2 vaccination. This study was approved by the institutional review board of Jikei University School of Medicine. Informed consent was obtained from all participants.

### Participant selection and data collection

Physicians or nurses working at our hospital who had received two doses of the BNT162b2 vaccine as of 30 May 2021 were recruited as study participants. Data on age, sex, SARS-CoV-2 vaccination records, and history of diagnosis of COVID-19 before receiving the first dose of BNT162b2 were obtained using a questionnaire survey. Data on vaccination history and antibody titres related to measles, rubella, and HBV were obtained from the hospital database. The database contains information on the vaccination history and antibody titres of HCWs in our hospital. All HCWs who engaged in patient care or handled patient-derived specimens were tested for antibody titres against these diseases when hired. HCWs who did not have sufficient antibody titres received additional booster doses and were tested the following year. Those who still failed to acquire sufficient antibodies were listed as low responders and followed up periodically for antibody titres. Participants who received the second dose of BNT162b2 <2 weeks prior to the study; those without information on vaccination history and antibody titres related to measles, rubella, and HBV vaccinations; and those who had been diagnosed with COVID-19 after the first dose of BNT162b2 were excluded.

In our hospital, HCWs are required to receive vaccination against mumps and varicella-zoster virus (VZV) as well as measles, rubella, and HBV; however, our database had more missing information on antibody titres for mumps and VZV than on antibody titres for measles, rubella, and HBV. Because we judged that the insufficient quality of information on antibody titres for mumps and VZV would lead to a bias in the analysis and interpretation of the results, mumps and VZV were not included in the analysis of the present study.

### Assessment of the presence of SARS-CoV-2 antibodies

Blood samples were obtained from each participant to assess the presence of SARS-CoV-2 antibodies during the period from 25 May 2021 to 25 June 2021. The level of anti-SARS-CoV-2 spike (anti-S) IgG antibodies (SARS-CoV-2 IgG II Quant assay of Abbott Laboratories; positive threshold,  $\geq 50.0$  AU/mL) and anti-SARS-CoV-2 nucleocapsid protein (anti-N) IgG antibodies (SARS-CoV-2 IgG of Abbott Laboratories; positive threshold,  $\geq 1.4$  signal/cut-off index) were measured in each participant. The anti-S IgG titres measured using this assay correlated well with the levels of neutralizing antibody titres in vaccine recipients [8]. In the present study, we used the anti-S IgG titre as an indicator of the humoral immune response induced by SARS-CoV-2 vaccination. Because antibodies against the SARS-CoV-2 nucleocapsid protein are not elicited by SARS-CoV-2 vaccination, which targets the spike protein, an anti-N IgG titre above the cut-off value indicates that the participant may have been infected with SARS-CoV-2 within the past few months [9,10]. Therefore, in the present study, participants who reported a previous diagnosis of COVID-19 in the questionnaire survey or those who had an anti-N IgG titre above the cut-off value were considered to have a history of COVID-19.

### Definition of low responders to measles, rubella, and HBV vaccinations

The response to measles, rubella, and HBV vaccinations was assessed based on guidelines published by the Japanese Society for Infection Prevention and Control. The 'Vaccine Guidelines for Health Care Professionals version 3.0' (in Japanese) provides information on different types of vaccines recommended for HCWs and the reference values for antibody titres which are considered to indicate adequate protection against each infectious disease [11]. For measles, an IgG antibody titre of  $\geq 16$  enzyme immunoassay (EIA) units, determined using EIA, was regarded as an infection-protective level. For rubella, a hemagglutination inhibition antibody titre of  $\geq 1:32$  or an IgG antibody titre of  $\geq 8$  EIA units, determined using EIA, was regarded as an infection-protective level. For HBV, an anti-hepatitis B surface antigen-antibody titre of  $\geq 10$  mIU/mL was regarded as an infection-protective level. At our hospital, HCWs whose antibody titres for each VPD do not meet the abovementioned criteria when hired receive additional booster doses. One dose of measles-containing vaccine is given to low responders to measles vaccination. One dose of rubella-containing vaccine is given to low responders to rubella vaccination. Three doses of HBV vaccine are given to low responders to HBV vaccination. HCWs who receive these booster doses are then periodically tested for the corresponding antibody titres. For HCWs who still do not meet the criteria after these booster doses, the booster doses are to be repeated. Although the timing of VPD antibody titre assessment is not standardized among HCWs in our hospital, we determined that individuals with VPD antibody titres below the positive threshold at multiple measurements could be considered low responders to the corresponding vaccination. Therefore, in the present study, we defined participants who had never met the criteria by the time of the first dose of BNT162b2 as low responders to each infectious disease vaccination.

### Statistical analyses

Descriptive statistics were expressed as frequencies and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. In a multivariable linear regression analysis adjusted for age (continuous), sex, days after the second dose of BNT162b2 (continuous), and history of COVID-19,

we tested the association between a low response to measles, rubella, and HBV vaccinations and the anti-S IgG titre after the receipt of the second dose of the BNT162b2 vaccine. Log<sub>10</sub>-transformed anti-S IgG titres were used in this model. The multicollinearity was assessed using the variance inflation factor. A variance inflation factor of >5–10 was considered to indicate existing multi-collinearity [12]. Statistical analyses were performed using R (version 4.1.3) and RStudio (version 2022.02.1). Statistical significance was defined as a two-sided p value of <0.05.

## Results

In total, 714 participants were included in the analysis. Their median age was 28.0 years (IQR, 24.3–36.0), and 85.6% of the participants were women (Table 1). The median interval between the second dose of the BNT162b2 vaccine and blood sampling was 50.0 days (IQR, 46.0–53.0). Approximately 1.8% of the total participants had a history of COVID-19 (defined above), of whom six were positive for the anti-N IgG titre. All the participants were positive for the anti-S IgG titre (median, 7126.8 AU/mL; IQR, 4496.2–11 296.8).

A total of 323 (45.2%), 131 (18.3%), and 43 (6.0%) participants were low responders to measles, rubella, and HBV vaccinations, respectively. The distributions of the anti-S IgG titres in low responders and responders to measles, rubella, and HBV vaccinations are shown in Fig. 1. In the multivariable linear model adjusted for age, sex, days after the second dose of BNT162b2, and history of COVID-19 (adjusted  $R^2 = 0.260$ ), a low response to rubella vaccination was significantly associated with reduced acquisition of the anti-S IgG titre after the second dose of BNT162b2 (Table 2). The back-transformed value of the estimated regression coefficient 'β' for a low response to rubella vaccination was 0.818 (95% CI, 0.725–0.923). In the model, age, sex, days after the second dose of BNT162b2, and history of COVID-19 were also associated with low immunity acquisition. The standardized coefficient β of the model along with the 95% CI for the variables are shown in Fig. 2. A low response to rubella vaccination was inversely associated with the anti-S IgG titre after two doses of BNT162b2 (β = -0.110; 95% CI, -0.175 to -0.044). Multi-collinearity was not present because the variance inflation factors for the independent variables in the model were <2.0.

## Discussion

We evaluated the association between a low response to measles, rubella, and HBV vaccinations and the anti-SARS-CoV-2

immune response induced by SARS-CoV-2 vaccination using data from HCWs who received two doses of the BNT162b2 vaccine. In the present study, we found that all participants who received two doses of BNT162b2 tested positive for the anti-S IgG titre (≥50.0 AU/mL). In addition, a low response to rubella vaccination was associated with reduced acquisition of the anti-S IgG titre after two doses of BNT162b2.

A low or no response to vaccination affects approximately 2% to 10% of vaccinated healthy individuals [13]. A low response to HBV vaccination is particularly well known to occur and has been reported to have an association with several genetic factors [14–16]. In a study examining the association between the immune response to HBV vaccination and vaccine-induced anti-SARS-CoV-2 immune response, a low response to HBV vaccination (anti-hepatitis B surface antigen-antibody < 10 mIU/mL) was associated with a weak response to SARS-CoV-2 vaccination after the first dose, although a good response was almost always achieved after the second dose, even among low responders to HBV vaccination [17]. Although the anti-S IgG titres were only assessed after the second dose of the BNT162b2 vaccine, the results in our study were consistent with those of the study [17].

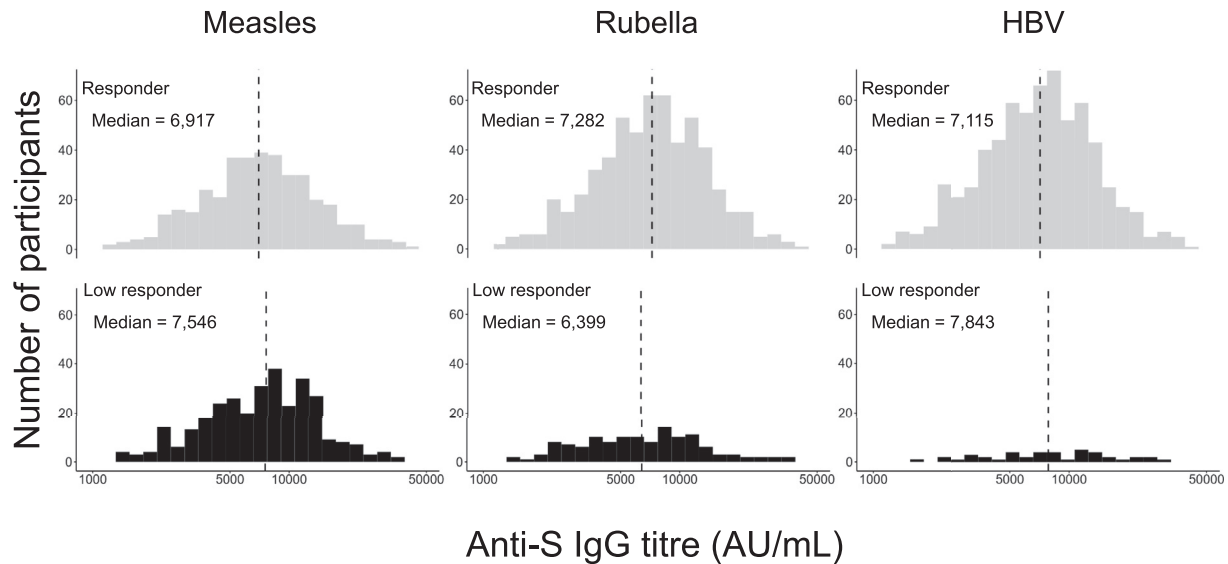
However, no study has evaluated the association between a low response to measles and rubella vaccinations and the response to SARS-CoV-2 vaccination. The lack of a simple method to measure the level of neutralizing antibodies in clinical settings may have contributed to the difficulty in assessing the proportion of low responders to measles and rubella vaccinations. Although IgG antibodies, detected using EIA and hemagglutination inhibition, which were used as indicators of protection against measles and rubella in the present study, do not act as neutralizing antibodies, these antibodies were well correlated with neutralizing antibodies [18–20]. Because the criteria according to the guidelines published by the Japanese Society for Infection Prevention and Control are used in many Japanese clinical settings to evaluate the ability of vaccines to protect against measles and rubella, the same criteria were used in the present study to define a low response to measles and rubella vaccinations. To our knowledge, this was the first study to show an association between a low response to rubella vaccination and low acquisition of the anti-S IgG titre after the receipt of SARS-CoV-2 vaccination. Rubella vaccination, as well as vaccination against other VPDs, is administered worldwide. The finding that the response to popularly practised vaccination may predict the immune response after SARS-CoV-2 vaccination may provide helpful information for the development of future vaccination strategies.

The findings identified several issues which should be investigated in the future. In the present study, we only evaluated the anti-

**Table 1**  
Characteristics of study participants

Variable	Overall (n = 714)
Age (y), median (interquartile range)	28 (24.3–36.0)
Age category (y), n (%)	
21–30	433 (60.6)
31–40	160 (22.4)
41–50	87 (12.2)
≥50	34 (4.8)
Sex	
Female	611 (85.6)
Male	103 (14.4)
Days after the second dose of BNT162b2 (d), median (interquartile range)	50 (46.0–53.0)
History of COVID-19, n (%)	13 (1.8)
Positive for anti-N IgG titre, n (%)	6 (0.8)
Low response, n (%)	
Measles vaccination	323 (45.2)
Rubella vaccination	131 (18.3)
Hepatitis B vaccination	43 (6.0)

Anti-N, anti-severe acute respiratory syndrome coronavirus 2 nucleocapsid protein; COVID-19, coronavirus disease 2019.



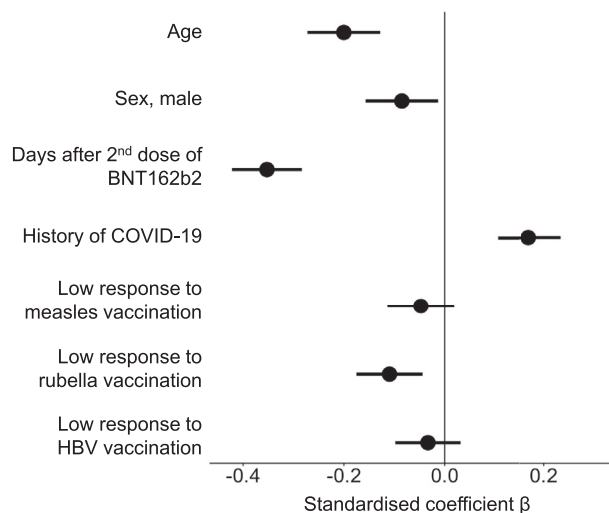
**Fig. 1.** Distributions of anti-severe acute respiratory syndrome coronavirus 2 spike IgG titres in low responders and responders to measles, rubella, and hepatitis B virus vaccinations. The anti-severe acute respiratory syndrome coronavirus 2 spike IgG titres on the x-axis are indicated using a logarithmic scale. HBV, hepatitis B virus.

**Table 2**  
Multivariable linear regression for anti-severe acute respiratory syndrome coronavirus 2 spike IgG titres after two doses of the BNT162b2 vaccine

Variables	Regression coefficients ( $\beta$ )	95% CI	p
Age	-0.007	-0.009 to -0.004	<0.001
Sex, male	-0.075	-0.138 to -0.011	0.021
Days after the second dose of the BNT162b2 vaccine	-0.010	-0.011 to -0.008	<0.001
History of COVID-19	0.392	0.245–0.540	<0.001
Low response			
Measles vaccination	-0.029	-0.071 to 0.012	0.162
Rubella vaccination	-0.087	-0.140 to -0.035	0.001
HBV vaccination	-0.043	-0.127 to 0.041	0.314

The increment units were 1 year for 'age' and 1 day for 'days after the second dose of the BNT162b2 vaccine'. COVID-19, coronavirus disease 2019; HBV, hepatitis B virus.

S IgG titres 2 weeks after the second dose of BNT162b2. For future vaccination strategies against SARS-CoV-2, it is necessary to determine the difference in the durability of the SARS-CoV-2



**Fig. 2.** Standardized coefficient  $\beta$  with 95% CI for the variables in the multivariable linear regression model. Low response to rubella vaccination was negatively associated with the anti-severe acute respiratory syndrome coronavirus 2 spike IgG titre after a two-dose BNT162b2 vaccination ( $\beta = -0.110$ ; 95% CI, -0.175 to -0.044). COVID-19, coronavirus disease 2019; HBV, hepatitis B virus.

antibody response between those who have an inadequate response to rubella vaccination and those who do not. It also remains unclear why different results were observed in low responders to rubella vaccination versus in low responders to measles or HBV vaccination. Genetic elements have been known to be important factors influencing inter-individual variation in the immune response to rubella-containing vaccines [21]. It is possible that any polymorphisms in the genetic elements which control the immune response to rubella virus may also be associated with the control of the immune response to SARS-CoV-2; however, there is no knowledge regarding this topic at this time. In addition, we think that this issue is very important and should be clarified in the future.

Several limitations of this study should be considered while interpreting its results. First, body mass index, alcohol consumption, and immuno-compromised status, which have been shown to be associated with the anti-SARS-CoV-2 antibody response after SARS-CoV-2 vaccination in several studies [22,23], were not assessed in the present study. Second, the anti-S IgG titre does not fully represent the humoral immune response induced by SARS-CoV-2 vaccination. It remains unclear to what extent reduction in the anti-S IgG titre associated with a low response to rubella vaccination demonstrated in this study affects the prevention of the onset and severe symptoms of COVID-19. Finally, this single-centre study only involved Japanese participants.

In conclusion, although a two-dose BNT162b2 vaccination induced a SARS-CoV-2 antibody response in all the participants, a



low response to rubella vaccination was associated with reduced acquisition of the anti-S IgG titre after the second dose of BNT162b2. These findings may provide useful information for the development of future vaccination strategies. Further investigations are warranted to determine whether a low response to rubella vaccination affects the durability of the anti-SARS-CoV-2 immune response.

### Author contributions

All authors conceived the study concept and design and performed data acquisition. KN and YN were responsible for performing the statistical analyses and created the initial draft of the manuscript. All authors participated in the interpretation of the results and approved the final version of the manuscript.

### Transparency declaration

MY serves as the president of the Japanese Society for Infection Prevention and Control. The remaining authors declare that they have no conflicts of interest. This study did not receive any funding.

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