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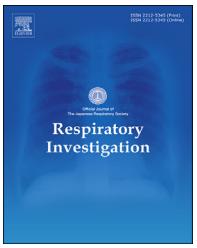

Original article

Adverse reactions to BNT162b2 mRNA COVID-19 vaccine in medical staff with a history of allergy

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ABSTRACT

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19) vaccination is progressing globally. Several adverse reactions have been reported with vaccination against COVID-19. It is unknown whether adverse reactions to COVID-19 vaccination are severe in individuals with allergies.

Methods: We administered the COVID-19 vaccine to the medical staff at Yamagata University Hospital from March to August 2021. Subsequently, we conducted an online questionnaire-based survey to investigate the presence of allergy and adverse reactions after vaccination and examine the association between allergy and adverse reactions after immunization.

Results: Responses were collected from 1586 to 1306 participants after the first and second administration of the BNT162b2 mRNA COVID-19 vaccine, respectively. Adverse reactions included injection site pain, injection site swelling, fever, fatigue or malaise, headache, chills, nausea, muscle pain outside the injection site, and arthralgia. The frequency of some adverse reactions and their severity were higher, and the duration of symptoms was longer in participants with allergies than in those without allergies. Although several participants visited the emergency room for treatment after the first and second vaccinations, no participant was diagnosed with anaphylaxis.

Conclusions: This study suggests that the frequency and severity of adverse reactions after injection of BNT162b2 mRNA COVID-19 vaccine were higher in individuals with allergy; however, no severe adverse reactions such as anaphylaxis or death were observed. These results indicate that individuals with allergic histories may tolerate the BNT162b2 mRNA COVID-19 vaccine.

Abbreviations: COVID-19, coronavirus disease 2019; JAK, Janus kinase; mRNA, messenger ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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1. Introduction

As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19) pandemic continues to spread worldwide, COVID-19 vaccination is one of the solutions to control it. BNT162b2 mRNA COVID-19 vaccine (Pfizer Inc. NY, USA, BioNTech SE, Mainz, Germany) was the first available mRNA vaccine in Japan since February 2021, and was initially administered to healthcare workers [1]. Currently, several types of COVID-19 vaccines are available, and many people are being vaccinated [1–3]. Although the efficacy of COVID-19 vaccination varies depending on the type of vaccine, the BNT162b2 has been reported to be 95% effective in preventing symptomatic COVID-19 infection in vaccinated individuals, indicating its high efficacy [1]. Effective medications against COVID-19 include dexamethasone [4,5], antiviral agent remdesivir [6], and Janus kinase (JAK) inhibitor baricitinib [7], all of which are currently available in Japan for COVID-19 treatment. Although various other drugs are therapeutic options for COVID-19 treatment, reports have described their inefficacy, including for those currently available; hence, no reliable treatment is available [8].

Therefore, suppression of the COVID-19 pandemic by vaccination is considered important. However, there is a risk for adverse reactions to vaccination, and various adverse reactions have been reported with the COVID-19 vaccine [9]. Adverse reactions, such as pain at the vaccination site or fever, are the most frequently reported. A particular problem with adverse reactions is allergic symptoms, and if anaphylaxis develops, there is a risk of life-threatening consequences [1–3]. Since most people are receiving the COVID-19 vaccine for the first time, it is unknown whether the vaccination will cause adverse reactions, such as allergy or severe anaphylaxis. Particularly, it is difficult to determine whether individuals with allergies can receive the COVID-19 vaccine. However, to verify the safety of COVID-19 vaccines, individuals with a history of allergy to vaccine components were excluded from clinical trials. As a result, very few studies have examined the safety of COVID-19 vaccination in people with allergies.

At Yamagata University Hospital, in Japan, BNT162b2 was administered to hospital staff and students. After vaccination, we conducted a questionnaire survey to investigate their allergic history and adverse reactions after immunization. By analyzing these data, we aimed to verify the safety of the COVID-19 vaccine in people with a history of allergy.

2. Materials and methods

2.1. Study design

The questionnaire survey was administered to the medical staff of Yamagata University Hospital and the staff and medical students of Yamagata University Faculty of Medicine who received the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) from March 3, 2021 to August 27, 2021. After the first and second vaccinations, a paper containing an internet link to the questionnaire was distributed. The questionnaire was designed using the free web-based Google Forms software. The following data regarding the participants were collected; gender, age, occupation, history of allergy to food and/or medicine, history of allergic diseases, history of anaphylaxis, and history of adverse reactions to vaccination. Concerning adverse reactions after the immunization, the participants were asked regarding injection site pain, injection site swelling, fever, fatigue or malaise, headache, chills, nausea, muscle pain outside the injection site, and arthralgia, as well as the timing of adverse reactions appearance and duration and degree of symptoms. In this study, severe adverse reactions after vaccination, other than fever, were defined as those that interfered with daily life and required medical treatment. Severe fever was defined as a body temperature of 38 °C or higher. The Institutional Ethics Committee of the Yamagata University Faculty of Medicine approved this study (approval number; 2021-130, approval date: June 29, 2021). The opt-out method was used to obtain informed consent, which is available on our website. Patients who refused to participate were excluded from the study. The individuals participated anonymously.

2.2. Statistical analysis

All classified variables were presented as numbers and percentages. The differences between groups were evaluated using the chi-squared test. Significance was inferred for p values of <0.05. Statistical analyses were performed using JMP version 11.0 software (SAS Institute, Cary, NC, USA).

3. Results

There were 1586 questionnaires returned from individuals who had received the first vaccination of BNT162b2, and 1306 questionnaires from individuals who had received the second vaccination after approximately 3 weeks. Table 1 shows the profiles and allergy histories of these individuals. The first vaccination was received by 522 (32.9%) male and 1064 (67.1%) female individuals. On stratification by age, 546 participants (34.4%) were in their 20s, 402 (25.3%) were in their 30s, 336 (21.2%) were in their 40s, 220 (13.9%) were in their 50s, and 82 (5.2%) were in their 60s or older. Of the participants, 193 (12.2%) had a history of allergy to food and/or medicine. There were 698 (44.0%) participants with allergic diseases, such as rhinitis and bronchial asthma, 27 (1.7%) had a history of anaphylaxis, and 90 (5.7%) had a history of adverse reactions after vaccination. The profiles were similar to those after the second vaccination. The frequencies of allergic histories by gender and age are summarized in Table 2. In the first and second vaccinations, the frequencies of history of allergies to food and/or medicine, and history of adverse reactions after vaccination were significantly higher in female than in male individuals. In the first vaccination, the frequency of history of allergies to food and/or medicine was significantly higher in older than in younger individuals. In the second vaccination, the frequency of history of anaphylaxis was significantly higher in older than in younger individuals.

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Table 1 – Profile of participants vaccinated with BNT162b2 mRNA COVID-19 vaccine.

	First vaccination (1586)	Second vaccination (1306)
Male/Female	522/1064	388/918
Type of Job		
Doctor	320 (20.3%)	216 (16.6%)
Nurse	558 (35.3%)	509 (39.0%)
Technician	152 (9.6%)	123 (9.4%)
Clerk	371 (23.4%)	299 (22.9%)
Student	179 (11.3%)	157 (12.0%)
Unknown (no answer)	6 (3.8%)	2 (0.2%)
Age, years		
20–29	546 (34.4%)	427 (32.7%)
30–39	402 (25.3%)	321 (24.6%)
40–49	336 (21.2%)	288 (22.1%)
50–59	220 (13.9%)	197 (15.1%)
60-	82 (5.2%)	73 (5.6%)
History of allergy (food and/or medicine)	193 (12.2%)	160 (12.3%)
History of allergic diseases	698 (44.0%)	564 (43.2%)
History of anaphylaxis	27 (1.7%)	13 (1.0%)
History of adverse response to vaccination	90 (5.7%)	91 (7.0%)

COVID-19, coronavirus disease 2019; mRNA, messenger ribonucleic acid.

The frequency of adverse reactions after the first and second vaccinations is shown in Fig. 1. Adverse reactions other than pain at the injection site occurred more frequently after the second vaccination.

Table 3 summarizes the frequency of adverse reactions by gender and age. The frequency of fatigue or malaise, headache, chills, nausea, and muscle pain outside the injection site after the first vaccination was significantly higher in female than in male individuals. After the second vaccination, the frequency of fever, fatigue or malaise, headache, chills, nausea, muscle pain outside the injection site, and arthralgia was significantly higher in female than in male individuals. No adverse reactions had a significantly higher incidence in male individuals. In the analysis by age, the frequency of injection site pain, injection site swelling, fever, and nausea after the first vaccination was significantly higher in younger people. The frequency of injection site pain, fever, fatigue or malaise, headache, chills, nausea, and muscle pain outside the injection site after the second vaccination was significantly higher in the younger age group.

Table 4 summarizes the frequency of adverse reactions by allergic status. Those who had a history of allergy to food and/or medicine had a significantly higher incidence of fatigue or malaise, headache, chills, nausea, and arthralgia after the first vaccination and a higher incidence of headache, nausea, muscle pain outside the injection site, and arthralgia after the second vaccination than those without a history of allergy to food and/or medicine. Those who had a history of allergic diseases, such as bronchial asthma and allergic rhinitis, had a significantly higher incidence of injection site pain, injection site swelling, fever, fatigue or malaise, headache, nausea, and arthralgia after the first vaccination, and a higher incidence of injection site swelling and nausea after the second vaccination than those without a history of allergic diseases. Those who had a history of anaphylaxis had a significantly higher incidence of fatigue or malaise after the first vaccination and a lower incidence of headache after the second vaccination than those without a history of anaphylaxis. Those who had a history of adverse reactions after vaccination had a significantly higher incidence of injection site swelling, fever, fatigue or malaise, headache, and chills after the first vaccination and a higher incidence of injection site pain and injection site swelling, nausea, and arthralgia after the second vaccination than those without a history of adverse reactions after vaccination.

Table 5 shows whether individuals with allergies continued to have adverse reactions after vaccination for a long period. The frequency of fatigue or malaise after the first and second vaccinations and headache and chills after the second vaccination, lasting more than 2 days, was significantly higher among participants with a history of allergy to food and/or medicine than in those without. The frequency of fever after the first vaccination and injection site pain after the second vaccination, lasting more than 2 days, was significantly higher among participants with a history of allergy

Table 2 – Frequency of allergic histories by gender and age.

	Gender		p value	Age					p value
	Male	Female		20–29	30–39	40–49	50–59	60-	
First vaccination Number	522 (%)	1064 (%)		546 (%)	402 (%)	336 (%)	220 (%)	82 (%)	
History of allergies to food and/or medicine	8.4	14.0	0.0014[a]	9.7	11.4	16.1	11.8	17.1	0.0412[a]
History of allergic diseases	45.4	43.3	0.4513	45.8	47.0	41.4	40.9	36.6	0.2132
History of anaphylaxis	1.2	2.0	0.3029	1.5	1.5	2.1	1.8	2.4	0.9296
History of adverse reactions after vaccination	3.3	6.9	0.0036[a]	5.9	5.5	6.3	6.8	0.0	0.2191
Second vaccination Number	388 (%)	918 (%)		427 (%)	321 (%)	288 (%)	197 (%)	73 (%)	
History of allergies to food and/or medicine	9.3	13.5	0.0338[a]	9.4	12.5	14.2	12.2	20.6	0.0599
History of allergic diseases	45.1	42.4	0.3922	45.9	41.4	42.0	43.7	38.4	0.6342
History of anaphylaxis	0.8	1.1	0.7655	0.2	0.6	1.4	1.5	4.1	0.0249[a]
History of adverse reactions after vaccination	3.9	8.3	0.0041[a]	7.7	6.2	7.6	8.1	0.0	0.1513

[a] Significantly different between the groups.

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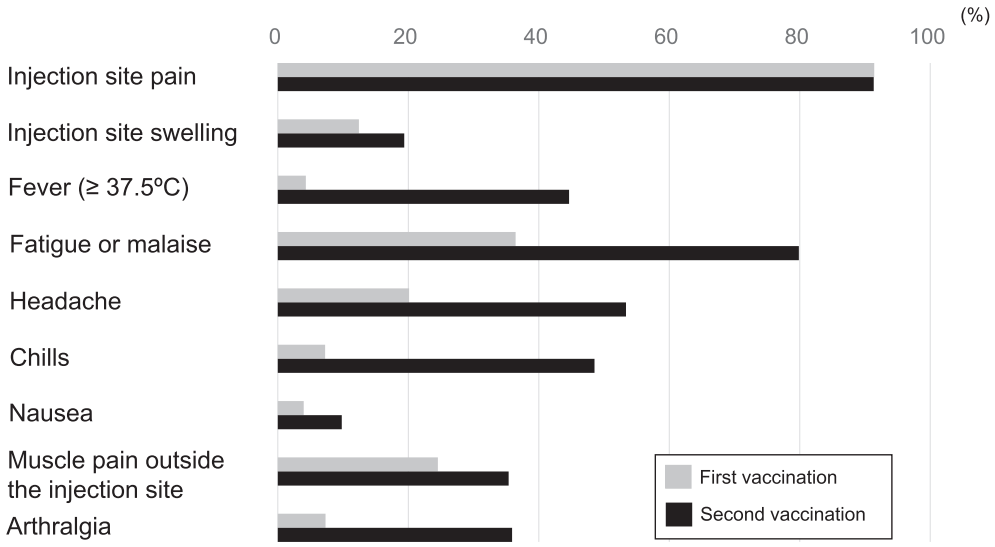

Fig. 1 – Frequency of adverse reactions after the first and second vaccinations. Adverse reactions other than pain at the injection site occur more frequently after the second vaccination than after the first.

Table 3 – Frequency of adverse reactions by gender and age.

	Gender		p value	Age					p value
	Male	Female		20–29	30–39	40–49	50–59	60-	
First vaccination Number	522 (%)	1064 (%)		546 (%)	402 (%)	336 (%)	220 (%)	82 (%)	
Injection site pain	91.0	91.6	0.7028	92.1	96.0	90.8	85.0	84.2	<0.0001[a]
Injection site swelling	10.7	13.3	0.1685	15.8	9.5	10.4	11.8	14.6	0.0327[a]
Fever (≥37.5°C)	4.4	4.2	0.8953	7.1	5.0	1.2	1.8	1.2	<0.0001[a]
Fatigue or malaise	30.1	39.6	0.0002[a]	38.3	37.3	33.9	37.7	26.8	0.2606
Headache	14.0	23.1	<0.0001[a]	22.2	23.1	16.7	16.8	14.6	0.0560
Chills	4.6	8.6	0.0038[a]	8.2	8.0	7.4	5.0	2.4	0.2314
Nausea	1.3	5.3	<0.0001[a]	6.0	3.5	2.4	2.7	2.4	0.0400[a]
Muscle pain outside the injection site	15.3	29.0	<0.0001[a]	24.9	21.9	23.5	30.0	24.4	0.2579
Arthralgia	5.8	8.1	0.1009	8.4	6.0	6.6	8.6	6.1	0.5408
Second vaccination Number	388 (%)	918 (%)		427 (%)	321 (%)	288 (%)	197 (%)	73 (%)	
Injection site pain	89.7	92.1	0.1958	93.9	94.4	91.0	83.8	84.9	<0.0001[a]
Injection site swelling	17.5	20.2	0.2844	21.6	17.8	17.4	19.8	20.6	0.6161
Fever (≥37.5°C)	36.6	48.0	0.0002[a]	54.1	46.1	42.4	34.5	19.2	<0.0001[a]
Fatigue or malaise	71.4	83.4	<0.0001[a]	82.0	81.9	80.9	75.6	65.8	0.0093[a]
Headache	41.5	58.4	<0.0001[a]	60.2	56.7	48.6	45.7	38.4	0.0001[a]
Chills	37.6	53.2	<0.0001[a]	50.1	54.8	50.4	39.6	28.8	<0.0001[a]
Nausea	4.6	12.0	<0.0001[a]	12.7	8.1	8.7	10.7	2.7	0.0467[a]
Muscle pain outside the injection site	25.7	39.7	<0.0001[a]	37.7	33.0	32.6	42.1	24.7	0.0351[a]
Arthralgia	25.5	40.3	<0.0001[a]	37.0	38.6	34.4	37.1	20.6	0.0576

[a] Significantly different between the groups.

than in those without. The frequency of adverse reactions lasting more than 2 days after vaccination did not differ with the presence or absence of a history of anaphylaxis. The frequency of fatigue or malaise and headache after the second vaccination, lasting more than 2 days, was significantly higher among participants with a history of adverse reactions after vaccination than in those without.

Table 6 demonstrates whether the frequency of moderate to severe adverse reactions after vaccination differs, according to the presence or absence of allergy. Individuals with a history of allergy to food and/or medicine had a significantly higher incidence of moderate to severe arthralgia after the first vaccination and muscle pain outside the injection site after the second vaccination than those without. The frequency of moderate to severe adverse reactions after vaccination did not differ with the presence or absence of a history of allergic diseases or anaphylaxis. Individuals with a history of adverse reactions after vaccination had a significantly higher incidence of moderate to severe fatigue or malaise after the first vaccination and injection site pain and chills after the

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Table 4 – Frequency of adverse reactions by allergic history.

	History of allergies to food and/or medicine		p value	History of allergic diseases		p value	History of anaphylaxis		p value	History of adverse reactions after vaccination		p value
	No	Yes		No	Yes		No	Yes		No	Yes	
First vaccination Number	1393 (%)	193 (%)		888 (%)	698 (%)		1559 (%)	27 (%)		1496 (%)	90 (%)	
Injection site pain	91.4	91.7	1.0000	89.4	94.0	0.0015[a]	91.3	96.3	0.7236	91.1	96.7	0.0788
Injection site swelling	12.1	15.0	0.2446	10.7	14.6	0.0213[a]	12.5	7.4	0.5664	11.7	24.4	0.0014[a]
Fever (≥37.5°C)	4.1	5.7	0.3401	3.4	5.4	0.0463[a]	4.2	11.1	0.1059	3.9	11.1	0.0039[a]
Fatigue or malaise	34.9	47.7	0.0008[a]	32.1	42.0	<0.0001[a]	36.1	55.6	0.0440[a]	35.7	48.9	0.0131[a]
Headache	18.8	29.5	0.0008[a]	17.3	23.6	0.0020[a]	20.2	14.8	0.6315	19.5	30.0	0.0209[a]
Chills	6.5	12.4	0.0069[a]	6.2	8.6	0.0788	7.1	14.8	0.1265	6.8	15.6	0.0050[a]
Nausea	3.4	8.3	0.0027[a]	2.7	5.6	0.0042[a]	4.0	3.7	1.0000	3.8	6.7	0.1659
Muscle pain outside the injection site	24.2	26.9	0.4219	24.4	24.6	0.9531	24.7	14.8	0.3652	24.7	21.1	0.5282
Arthralgia	6.7	11.9	0.0121[a]	5.7	9.3	0.0085[a]	7.4	3.7	0.7164	7.2	10.0	0.2972
Second vaccination Number	1146 (%)	160 (%)		742 (%)	564 (%)		1293 (%)	13 (%)		1215 (%)	91 (%)	
Injection site pain	90.9	94.4	0.1763	90.2	92.9	0.0911	91.3	100.0	0.6186	90.7	100.0	0.0003[a]
Injection site swelling	19.1	21.3	0.5224	17.1	22.3	0.0197[a]	19.5	7.7	0.4823	18.6	29.7	0.0131[a]
Fever (≥37.5°C)	44.1	48.8	0.2709	44.5	44.9	0.9106	44.6	46.2	1.0000	44.4	48.4	0.5122
Fatigue or malaise	79.5	82.5	0.4017	78.3	81.9	0.1097	79.7	92.3	0.4848	79.3	86.8	0.1031
Headache	51.9	63.8	0.0052[a]	51.5	55.9	0.1306	53.7	23.1	0.0464[a]	52.9	59.3	0.2760
Chills	47.8	53.8	0.1768	48.1	49.1	0.7375	48.3	69.2	0.1670	48.2	53.9	0.3281
Nausea	8.6	18.8	0.0002[a]	8.0	12.2	0.0111[a]	9.9	0.0	0.6291	9.1	19.8	0.0027[a]
Muscle pain outside the injection site	34.2	43.8	0.0216[a]	35.4	35.3	1.0000	35.4	30.8	1.0000	34.9	41.8	0.2111
Arthralgia	34.5	46.3	0.0048[a]	35.7	36.2	0.9073	35.7	61.5	0.0777	35.1	46.2	0.0411[a]

[a] Significantly different between the groups.

Table 5 – Frequency of prolonged adverse reactions by allergic history.

	History of allergies to food and/or medicine		p value	History of allergic diseases		p value	History of anaphylaxis		p value	History of adverse reactions after vaccination		p value
	No	Yes		No	Yes		No	Yes		No	Yes	
First vaccination Number	1393 (%)	193 (%)		888 (%)	698 (%)		1559 (%)	27 (%)		1496 (%)	90 (%)	
Injection site pain	61.2	66.3	0.1209	59.3	65.0	0.3357	61.8	63.0	1.0000	61.2	72.2	0.1233
Injection site swelling	6.4	8.8	0.6888	6.1	7.4	0.4722	6.7	3.7	1.0000	6.3	13.3	1.0000
Fever (≥37.5°C)	0.9	1.6	0.7120	0.3	1.9	0.0233[a]	1.0	0.0	1.0000	0.9	2.2	1.0000
Fatigue or malaise	14.3	24.4	0.0469[a]	12.7	19.1	0.1071	15.5	14.8	0.2884	15.0	24.4	0.3379
Headache	6.2	10.4	0.7579	5.3	8.6	0.2841	6.9	0.0	0.5536	6.5	11.1	0.6671
Chills	1.7	3.6	0.6053	1.4	2.6	0.3949	1.8	7.4	0.1688	1.7	5.6	0.3221
Nausea	0.7	2.1	0.7337	0.6	1.3	1.0000	0.9	0.0	1.0000	0.8	2.2	0.6167
Muscle pain outside the injection site	16.0	20.2	0.2573	16.6	16.5	0.8222	16.6	11.1	1.0000	16.5	16.7	0.4493
Arthralgia	2.7	6.7	0.1525	2.6	3.9	1.0000	3.1	3.7	0.4425	3.0	5.6	0.5058
Second vaccination Number	1146 (%)	160 (%)		742 (%)	564 (%)		1293 (%)	13 (%)		1215 (%)	91 (%)	
Injection site pain	67.6	75.6	0.1536	64.7	73.8	0.0021[a]	68.4	84.6	0.7451	67.6	82.4	0.1282
Injection site swelling	13.3	15.0	1.0000	11.1	16.7	0.0979	13.5	7.7	1.0000	12.7	24.2	0.2647
Fever (≥37.5°C)	13.8	16.9	0.5152	12.8	16.0	0.1055	14.1	23.1	0.3900	13.8	18.7	0.3181
Fatigue or malaise	42.3	55.0	0.0049[a]	41.6	46.8	0.1664	43.7	61.5	0.5633	42.8	58.2	0.0336[a]
Headache	26.3	39.4	0.0403[a]	27.8	28.0	0.4439	27.9	23.1	0.2511	26.9	40.7	0.0159[a]
Chills	15.4	26.9	0.0021[a]	15.5	18.4	0.1533	16.6	30.8	0.5049	16.5	20.9	0.5342
Nausea	2.6	8.1	0.2699	2.7	4.1	1.0000	3.3	0.0	1.0000	3.1	5.5	0.7886
Muscle pain outside the injection site	20.0	30.6	0.0584	21.2	21.5	0.8456	21.3	23.1	1.0000	20.9	26.4	0.4702
Arthralgia	15.9	24.4	0.3757	15.8	18.4	0.1344	16.7	38.5	0.4876	16.4	24.2	0.4081

[a] Significantly different between the groups.

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Table 6 – Frequency of severe adverse reactions by allergic history (for fever, body temperature of 38 °C or higher, and for other adverse reactions, those that interfere with daily life or require medical treatment).

	History of allergies to food and/or medicine		p value	History of allergic diseases		p value	History of anaphylaxis		p value	History of adverse reactions after vaccination		p value
	No	Yes		No	Yes		No	Yes		No	Yes	
First vaccination Number	1393 (%)	193 (%)		888 (%)	698 (%)		1559 (%)	27 (%)		1496 (%)	90 (%)	
Injection site pain	9.8	14.0	0.0989	10.7	9.9	0.4050	10.3	11.1	1.0000	10.0	15.6	0.1618
Injection site swelling	0.6	0.0	0.6093	0.7	0.3	0.1528	0.5	0.0	1.0000	0.4	2.2	0.2295
Fever	1.5	1.0	0.3101	1.4	1.6	0.4402	1.4	3.7	1.0000	1.3	4.4	0.7236
Fatigue or malaise	3.7	8.3	0.0794	3.8	4.9	1.0000	4.2	7.4	0.6984	3.7	13.3	0.0031[a]
Headache	7.2	11.9	1.0000	6.4	9.5	0.5648	7.9	0.0	0.0854	7.2	16.7	0.0659
Chills	1.7	2.6	0.7921	1.2	2.4	0.3852	1.7	7.4	0.2487	1.6	4.4	0.7423
Nausea	0.4	2.1	0.4358	0.5	0.9	1.0000	0.6	0.0	1.0000	0.6	1.1	1.0000
Muscle pain outside the injection site	3.2	5.7	0.2035	4.1	2.9	0.2413	3.5	3.7	0.4900	3.6	2.2	1.0000
Arthralgia	0.6	3.6	0.0165[a]	0.7	1.4	0.5994	1.0	3.7	0.1441	0.9	2.2	0.6151
Second vaccination Number	1146 (%)	160 (%)		742 (%)	564 (%)		1293 (%)	13 (%)		1215 (%)	91 (%)	
Injection site pain	33.1	36.3	0.6509	31.5	36.0	0.1825	33.3	53.8	0.2491	32.3	48.4	0.0232[a]
Injection site swelling	3.1	3.8	0.8091	2.6	4.1	0.6125	3.2	7.7	0.1673	3.4	1.1	0.0579
Fever	24.6	25.0	0.4630	25.2	23.9	0.3996	24.7	15.4	0.4144	24.4	27.5	0.8762
Fatigue or malaise	42.8	43.8	0.9251	42.7	43.3	0.5714	42.9	46.2	0.7788	42.2	52.7	0.2425
Headache	36.6	46.3	0.4723	36.5	39.4	1.0000	38.0	15.4	1.0000	36.9	49.5	0.0583
Chills	28.3	31.9	0.9051	29.2	28.0	0.4133	28.6	38.5	1.0000	27.7	41.8	0.0094[a]
Nausea	2.3	5.6	0.8174	1.8	3.9	0.1699	2.7	0.0	1.0000	2.5	5.5	1.0000
Muscle pain outside the injection site	14.0	23.8	0.0449[a]	14.6	16.0	0.3345	15.1	23.1	0.3303	14.7	20.9	0.2102
Arthralgia	19.6	24.4	0.3701	20.9	19.3	0.2948	20.0	38.5	1.0000	19.8	25.3	0.7353

[a] Significantly different between the groups.

second vaccination than those without. After the first and second vaccinations, a total of four (one male and three female) participants in their 20s–40s visited the emergency room for treatment, but none were diagnosed with anaphylaxis. One of them had a food allergy and allergic rhinitis while the other three had no allergy. No other life-threatening adverse reactions or deaths were reported.

4. Discussion

We administered the BNT162b2 mRNA COVID-19 vaccine to medical staff and investigated post-vaccination adverse reactions. Particularly, we examined adverse reactions after COVID-19 vaccination in participants with allergies. The results of our study revealed that female and older individuals were more likely to have a history of allergy, and this was similar to previous reports [10,11]. Although the frequency of allergies is known to be more in females, the detailed mechanisms underlying this are unknown; however, several factors, including hormonal influences, gender-specific behaviors, recognition of risk, and medications, may be involved [12]. It is not clear why older individuals are more likely to have a history of allergy; however, they may have been exposed to more foods and medications that could cause allergies during their long lifetime. In this study, after the vaccination of BNT162b2, the rate of adverse reactions was higher in female and younger individuals than in male and older individuals, respectively. These results were consistent with previous reports [13].

Participants who had a history of allergy to food and/or medicine, allergic diseases such as bronchial asthma or allergic rhinitis, a history of anaphylaxis, or adverse reactions after vaccination had a significantly higher frequency of some adverse reactions compared to those without. Some adverse reactions showed a higher frequency of longer symptom duration after vaccination and a higher frequency of moderate or severe adverse reactions, but the differences were not remarkably large. Additionally, no severe life-threatening allergic events were experienced after the BNT162b2 vaccination at our hospital.

In a previous report, the COVID-19 vaccination of hospital staff was performed, and the frequency of adverse reactions was examined according to the presence or absence of allergy [14]. They found that participants with a history of allergy had a significantly higher incidence of adverse reactions after vaccination than those without. They concluded that the BNT162b2 is less tolerated in individuals with allergy than in those without allergy, but the adverse reactions that occurred were mild and did not interfere with the successful completion of vaccination. Our results and conclusions are comparable, although our study is valuable since we did not only investigate the presence or absence of allergy but also a detailed history of anaphylaxis and previous histories of adverse reactions to vaccination. Furthermore, our data are from the Japanese population. Therefore, we believe that our findings will be useful information for Japanese people who have a history of allergy to food and/or medicine, history of allergic diseases, history of anaphylaxis, and history of adverse reactions to vaccination.

There were several limitations to our study. First, the survey was an internet-based questionnaire, and symptoms and allergy history were self-reported. Particularly, it is unclear

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whether the diagnosis of allergic diseases was correct. Second, few participants had a history of anaphylaxis or adverse reactions to vaccinations; thus, the statistical reliability of the study may not be high. Anaphylaxis was reported at a rate of 11.1 per million doses of BNT162b2 vaccination [15]. We need to consider that with the number of individuals who participated in this study, we may not be able to detect severe adverse reactions such as anaphylaxis or death. Third, it is possible that some of the staff did not receive the vaccine because of a history of allergy; thus, reducing the number of people who could have participated in the study. It is expected that large-scale and detailed data on adverse reactions to COVID-19 vaccination will be accumulated in the future, and the advantages and disadvantages of vaccination, especially for people with a history of allergy, will be verified. Fourth, BNT162b2 vaccination is not recommended in cases of allergy to polyethylene glycol (PEG), which is a component of the vaccine. We did not investigate the history of allergy to PEG or information on the daily use of cosmetics containing PEG in this study. This will be a subject for further studies. However, it is worthwhile to observe how the frequency of adverse reactions after BNT162b2 vaccination differs depending on the presence or absence of various allergic histories, such as food and/or drug allergy, allergic disease, anaphylaxis, or history of adverse reactions after other vaccinations.

In conclusion, although the tolerance of BNT162b2 was worse in individuals with allergies than those without, no severe adverse reactions such as anaphylaxis or death were observed in our study population. For those who are hesitant regarding COVID-19 vaccination because of allergy, data from a large adverse reaction study can be expected to be very helpful. We hope that the results of this study will be used to successfully complete the vaccination.

Authors' contributions

Conception: SK, SS, YU; Study design: SI, MW, KM, OH; Making database: OH, KM; Data collection: KM, OH, SK; Data analysis: SI, AI; Data interpretation, all authors; Writing and reviewing the manuscript: all authors. Final approval of the manuscript: all authors.

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work. SI has received lecture fees from AstraZeneca K.K., and Novartis Pharma K.K. MW has received lecture fees from Otsuka Pharmaceutical Co., Ltd., and Nippon Boehringer Ingelheim Co., Ltd. OH has received donations from Taiho Pharmaceutical Co., Ltd., and Chugai Pharmaceutical Co., Ltd. SS has received donation course for medical science and education from NISSIN PHARMACEUTICAL CO., LTD. no other relationships or activities that could appear to have influenced the submitted work.

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