Global Health & Medicine. 2024; 6(6):363-374.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2024.01053

Adverse reactions to mRNA COVID-19 vaccine in people with allergies in Japan

Naoko Shoji[1], Suminobu Ito[2,3], Shuko Nojiri[1,2,3], Wataru Urasaki[3,4], Tamaki Nara[1,2,3], Atsushi Okuzawa[1,2,3], Morikuni Tobita[1,2,3,*]

[1] Department of Healthcare Innovation, Juntendo University Graduate School of Medicine, Tokyo, Japan;
[2] Medical Technology Innovation Center, Juntendo University, Tokyo, Japan;
[3] Clinical Research and Trial Center, Juntendo University Hospital, Tokyo, Japan;
[4] Graduate School of Science and Technology, Tokyo University of Science, Tokyo, Japan.

Abstract: mRNA vaccines emerged as a new therapeutic modality during the COVID-19 pandemic. Individuals with allergies often experience anxiety about potential adverse reactions to these vaccines. This study aims to elucidate the relationship between adverse reactions and various allergies, asthma, or atopic disorders. Data from approximately 20,000 Japanese healthcare workers participating in a prospective cohort study were analyzed. The number of vaccinated individuals was 19,792 (first dose), with systemic reactions occurring in 35.8% after the first dose and 75.3% after the second dose. Participants with allergies were categorized into groups: food and/or drug allergies (n = 806), asthma and/or atopic disorders (n = 2,370), asthma (both past medical history [PMH] and present illness [PI]) (n = 1,983), and atopic disorders (PI) (n = 567). Most systemic reactions in those with food and/or drug allergies occurred within the first three days of vaccination. Logistic regression analysis showed that food and/or drug allergies, asthma (PMH and PI), and asthma and/or atopic disorders were significantly associated with systemic reactions (odds ratios [95% confidence interval]: 1.65 [1.43-1.91], 1.36 [1.23-1.49], and 1.32 [1.21-1.45], respectively, for the first dose). These findings suggest the risk of systemic reactions after COVID-19 vaccination in individuals with the specified allergies, potentially contributing to vaccine hesitancy. Medical professionals should clearly communicate the risks and benefits of vaccination to those with allergies to alleviate their concerns. Additionally, our study's data may be useful for making decisions whether or not to get vaccinated in those with allergies and inform the development of future mRNA vaccines.

***Keywords*:** vaccine safety, vaccine hesitancy, asthma, atopy, food allergy, drug allergy

Introduction

The COVID-19 pandemic accelerated the development of vaccines, leading to the rise of mRNA vaccines as a promising new modality distinct from traditional vaccines such as recombinant protein vaccines, inactivated vaccines, live attenuated vaccines, and toxoid vaccines. mRNA COVID-19 vaccines have been effective in reducing transmission globally and have shown promise against other viruses, such as respiratory syncytial virus (*1*), and are being evaluated for influenza (*2*). Moreover, multiple mRNA cancer vaccines are under clinical trials for various cancers (*3*).

Initially, concerns about the safety and efficacy of the newly developed COVID-19 vaccines were prevalent, especially among individuals with a history of allergies or comorbidities. As vaccination campaigns progressed and more safety data were gathered (*4*), large-scale international studies confirmed the good safety profile of COVID-19 vaccines (*5,6*). However, there is a lack of comprehensive data on the safety of mRNA vaccines for individuals with allergic diseases in Japan, despite several small-scale studies. According to the Rheumatology and Allergy Control Committee Report, about one in two Japanese individuals has some form of allergy (*7*). Anaphylaxis, a severe allergic reaction, is one of the most clinically significant adverse reactions following COVID-19 vaccination. Studies (*8,9*) showed that most individuals who experienced anaphylaxis after vaccination had a history of allergies to foods, medical products, or insect stings. Additionally, higher incidences of certain adverse reactions (*e.g.*, vomiting, local swelling, redness, and pain) (*10*) or prolonged reactions (*e.g.*, fatigue, malaise, headache, and chills) (*11*) have been observed in allergic individuals compared to those without allergies. These reports could contribute

to vaccine hesitancy among those with a history of allergies.

Given these concerns, we investigated the incidence of local and systemic reactions to COVID-19 mRNA vaccination in individuals with various allergies (food and/or drug allergies, asthma [past medical history (PMH) and present illness (PI)], asthma and/or atopic disorders, and atopic disorders) using data from a large-scale cohort study of hospital-based healthcare workers in Japan from February 17, 2021 to January 30, 2022.

This report focuses on adverse reactions following BNT162b2 vaccination in individuals with food and/or drug allergies, asthma (PMH and PI), atopic disorders (PI), and asthma and/or atopic disorders.

Materials and Methods

Original prospective cohort study and population

An original prospective cohort study, titled "Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan" (For details, see UMIN000073345 (*12*)), aimed to evaluate the safety of the BNT162b2 mRNA COVID-19 Vaccine (Pfizer-BioNTech) in healthcare workers. Participants included doctors, nurses, pharmacists, medical technologists, radiological technologists, physical therapists, care workers, clerks, and other staff from the National Hospital Organization (52 sites), Japan Community Health Care Organization (27 sites), and Japan Organization of Occupational Health and Safety (21 sites) member hospitals. The study was part of the "Emerging/Re-emerging Infectious Diseases and Vaccination Policy Promotion Research Project" of the Ministry of Health, Labor and Welfare (MHLW) of Japan, conducted between February 17, 2021 and January 30, 2022 (preparation ongoing as of June 10, 2024). Approximately 20,000 participants completed their primary vaccination series, consisting of two doses at least three weeks apart.

Data collection from study participants

In the prospective cohort study (*12*), participants who received either the first dose only or both doses completed daily symptom diaries for eight days (Day 1 to Day 8) after each dose and continued for up to 28 days after the last dose. Diaries were collected from 19,792 participants after the first dose and 19,592 participants after the second dose. Post-vaccination adverse reactions recorded included injection-site reactions (redness, swelling, induration, pain, warmth, and pruritus), systemic reactions (headache, malaise, and rhinorrhea), and body temperature. If symptoms persisted beyond Day 8, participants continued recording until resolution. Each participant's history of food allergy, drug allergy, asthma, and atopic disorders was obtained before vaccination.

Subgroup analysis

Participant characteristics were analyzed, and the incidence rate of each reaction after each dose was calculated by sex and age group. Adverse reactions occurring between Day 1 and Day 8 post-vaccination were used for subgroup analysis to examine differences in the time-to-onset and duration of each reaction based on the presence or absence of food and/or drug allergies or allergic diseases (asthma and/or atopic disorders). Bar charts were created for each reaction to illustrate any significant differences between individuals with food and/or drug allergies or asthma and/or atopic disorders and those without.

Odds ratios from logistic regression model

To assess the associations of food and/or drug allergies, asthma, atopic disorders, or asthma and/or atopic disorders with local and systemic reactions after BNT162b2 vaccination, the odds ratio (OR) with a 95% confidence interval (CI) for each reaction was calculated using a logistic regression model.

Statistical analysis

Categorical variables are presented as numbers and percentages. Reaction duration is defined as the time between symptom onset and resolution. Pearson's chi-squared test or Fisher's exact test was used to determine statistically significant differences in reactions between individuals with and without food and/or drug allergies or asthma and/or atopic disorders. A p-value less than 0.05 was considered statistically significant. Logistic regression analysis, adjusted for age and sex, was used to calculate the OR with a corresponding 95% CI to describe the association of food and/or drug allergies, asthma, atopic disorders, or asthma and/or atopic disorders with each reaction. All statistical analyses were performed using R statistical software (version 4.0.3).

Ethical statement

The study was approved by the Tokushukai Group Ethics Committee (TGE01643-701) prior to initiation and conducted in accordance with the principles of the Declaration of Helsinki (trial registration number: UMIN000043377). Informed consent was obtained from all participants in the original prospective cohort study.

Results

Participant characteristics

The study included 19,792 participants who received the first dose and 19,592 who received the second dose of the vaccine. Among those receiving the first dose, 13,108

(66.2%) were female. Over 90% of participants who received both doses fell into the age groups 20-29, 30-39, 40-49, and 50-59 years. Participants with allergies were categorized into four groups: food and/or drug allergies (806 for the first dose and 791 for the second dose), asthma and/or atopic disorders (2,370 and 2,335), asthma (PMH and PI) (1,983 and 1,955), and atopic disorders (567 and 556). Among the 13,108 vaccinated females, 4.7% had a history of food and/or drug allergies (compared to 2.8% of the 6,684 vaccinated males). A slightly higher percentage (5.3%) of individuals with food and/or drug allergies was observed in the 50-59 years group (Table 1).

Local and systemic reactions to COVID-19 vaccine primary series

Incidence of adverse reactions following vaccination

Local reactions, including redness, swelling, induration, pain (92.0%), warmth, and pruritus, occurred in 92.5% of participants after the first dose. Systemic reactions, including headache, malaise, and rhinorrhea, were observed in 35.8% of participants after the first dose. For the second dose, local reactions, including pain (89.5%), occurred in 90.7% of participants, while systemic reactions occurred in 75.3% of participants. The incidence of specific systemic reactions increased significantly after the second dose compared to the first: headache (21.3% to 53.1%), malaise (23.2% to 68.8%), fever ≥ 37.5°C (3.3% to 38.1%), and fever ≥ 38.0°C (0.9% to 21.3%) (Table 2).

Subgroup analysis of adverse reactions by age and sex

Adverse reactions were more common in females than males after each dose. Participants aged 70 years and older experienced fewer adverse reactions compared to younger participants. In the 20-29 years age group, fever ≥ 37.5°C was reported more frequently after the second dose than the first dose (49.7% *vs.* 5.8%), with incidence decreasing with age. Systemic reactions (headache, malaise, and rhinorrhea) after the second dose were more prevalent in the 20-29 and 30-39 years age groups (approximately 80%) compared to other age groups (Table 3).

Subgroup analysis of food and/or drug allergies

Among vaccinated participants, 806 and 791 individuals had a history of food and/or drug allergies for the first and second doses, respectively. Local reactions were similar between participants with and without food and/or drug allergies. However, systemic reactions (headache, malaise, and rhinorrhea) were more frequent in individuals with these allergies, particularly after the second dose. The incidence of fever ≥ 37.5°C after the second dose was relatively high at 42.7% (Supplemental Table S1a, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=95*).

Table 1. History of food and/or drug allergies, asthma (PMH and PI), asthma and/or atopic disorders, and atopic disorders by sex and age group

	Sex		Age group				
First dose (n = 19,792)	Male n = 6,684 n (%)	Female n = 13,108 n (%)	20-29 n = 4,152 n (%)	30-39 n = 4,753 n (%)	40-49 n = 4,934 n (%)	50-59 n = 4,236 n (%)	60-69 n = 1,559 n (%)	≥ 70 n = 158 n (%)
History of food and/or drug allergies* (n = 806)	189 (2.8)	617 (4.7)	135 (3.3)	152 (3.2)	223 (4.5)	226 (5.3)	65 (4.2)	5 (3.2)
History of asthma and/or atopic disorders** (n = 2,370)	765 (11.4)	1605 (12.2)	542 (13.1)	636 (13.4)	616 (12.5)	430 (10.2)	131 (8.4)	15 (9.5)
Asthma (PMH and PI) (n = 1,983)	633 (9.5)	1350 (10.3)	418 (10.1)	510 (10.7)	521 (10.6)	393 (9.3)	126 (8.1)	15 (9.5)
Atopic disorders (PI) (n = 567)	195 (2.9)	372 (2.8)	175 (4.2)	185 (3.9)	134 (2.7)	64 (1.5)	9 (0.6)	0
Second dose (n = 19,592)	Male n = 6,630 n (%)	Female n = 12,962 n (%)	20–29 n = 4,075 n (%)	30–39 n = 4,702 n (%)	40–49 n = 4,887 n (%)	50–59 n = 4,218 n (%)	60–69 n = 1,553 n (%)	≥70 n = 157 n (%)
History of food and/or drug allergies* (n = 791)	188 (2.8)	603 (4.7)	130 (3.2)	149 (3.2)	219 (4.5)	223 (5.3)	65 (4.2)	5 (3.2)
History of Asthma and/or atopic disorders** (n = 2,335)	757 (11.4)	1578 (12.2)	527 (12.9)	629 (13.4)	606 (12.4)	428 (10.1)	131 (8.4)	14 (8.9)
Asthma (PMH and PI) (n = 1,955)	626 (9.4)	1329 (10.3)	406 (10.0)	504 (10.7)	513 (10.5)	392 (9.3)	126 (8.1)	14 (8.9)
Atopic disorders (PI) (n = 556)	193 (2.9)	363 (2.8)	170 (4.2)	183 (3.9)	131 (2.7)	63 (1.5)	9 (0.6)	0

*: 1) food allergy to wheat, egg, shrimp, and crab, among others, and 2) drug allergy to penicillin, contrast media, fluoroquinolones, *etc.* **: Multiple choices allowed. PMH: past medical history, PI: present illness.

Table 2. Incidence of local and systemic reactions after each dose

Local and systemic reactions	First dose *n* = 19,792 *n* (%)	Second dose *n* = 19,592 *n* (%)
Local reactions	18,316 (92.5)	17,765 (90.7)
Redness	2,742 (13.9)	3,123 (15.9)
Swelling	2,470 (12.5)	2,758 (14.1)
Induration	2,106 (10.6)	1,972 (10.1)
Pain	18,203 (92.0)	17,534 (89.5)
Warmth	2,544 (12.9)	3,722 (19.0)
Pruritus	1,585 (8.0)	2,335 (11.9)
Systemic reactions	7,078 (35.8)	14,759 (75.3)
Headache	4,225 (21.3)	10,411 (53.1)
Malaise	4,584 (23.2)	13,478 (68.8)
Rhinorrhea	2,020 (10.2)	2,829 (14.4)
Fever ≥ 37.5 ℃	654 (3.3)	7,470 (38.1)
Fever ≥ 38.0 ℃	174 (0.9)	4,179 (21.3)

Local reactions include redness, swelling, induration, pain, warmth, and pruritus. Systemic reactions include headache, malaise, and rhinorrhea. Japan's criteria for evaluating some adverse reactions are different from those prescribed by the Food and Drug Administration. See Supplemental Tables S2a and S2b.

We investigated the relationship between food and/or drug allergies and the onset and duration of adverse reactions. Most systemic reactions occurred within the first three days after vaccination, with some lasting more than four days. Significant differences in the onset and duration of malaise and headache, as well as the duration of rhinorrhea, were observed between those with and without food and/or drug allergies. Fevers (both ≥ 37.5°C and ≥ 38.0°C) generally occurred within 1-3 days post-vaccination, with a small percentage lasting beyond four days (Figures 1A, 1B, 1C and Figure 2A, 2B, and 2C).

Subgroup analysis of asthma and/or atopic disorders

Among vaccinated participants, 2,370 and 2,335 individuals had a history of asthma and/or atopic disorders for the first and second doses, respectively. Systemic reactions were more frequent in individuals with these conditions compared to those without (Supplemental Table S1b, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=95*). Most local and systemic reactions occurred within the first three days post-vaccination, with some reactions persisting beyond four days. Significant differences in the onset and duration of malaise and headache were observed after the second dose between individuals with and without asthma and/or atopic disorders. Most fevers (≥ 37.5°C) occurred within 1-3 days post-vaccination, with a small percentage lasting beyond four days for both doses (Figures 3A, 3B, 3C and Figures 4A, 4B, and 4C).

Subgroup analysis using logistic regression models for food and/or drug allergies, asthma, atopic disorders, and asthma and/or atopic disorders

Food and/or drug allergies were associated with systemic reactions (ORs [95% CI]: 1.65 [1.43-1.91] for the first dose and 1.53 [1.26-1.85] for the second dose). Asthma and/or atopic disorders were associated with systemic reactions (ORs: 1.32 [1.21-1.45] for the first dose and 1.25 [1.12-1.40] for the second dose). Asthma (PMH and PI) was associated with systemic reactions (ORs: 1.36 [1.23-1.49] for the first dose and 1.30 [1.15-1.46] for the second dose). Atopic disorders (PI) were not associated with nearly all local and systemic reactions. Food and/or drug allergies, asthma and/or atopic disorders, and asthma (PMH and PI) were associated with fever ≥ 37.5°C (Table 4).

Discussion

The original prospective cohort study, "Cohort Survey at the Beginning of SARS-CoV-2 Vaccination in Japan", was based on Japan's criteria for reporting adverse reactions following COVID-19 vaccination. These criteria were developed by doctors involved in a 2006 clinical trial for a new influenza vaccine and have since been used to evaluate vaccine reactions in Japan. In contrast, the FDA has its own independent criteria, leading to differences in grading the severity of pain, redness, swelling, induration, and fever between Japan and the FDA (Supplemental Tables S2a and S2b for further details, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=95*).

As a preventive measure against COVID-19, vaccination efforts accelerated globally until Spring 2023. Despite the demonstrated safety and effectiveness of COVID-19 vaccines, high incidences of adverse reactions, such as injection site pain, headache, and malaise, are well-documented (*13,14*). Severe allergic reactions to COVID-19 vaccines are rare but can occur (*15*). Safety concerns about vaccination are a significant factor in vaccine hesitancy.

This study examined the safety of the BNT162b2 vaccine in the Japanese population. Most reactions to the BNT162b2 vaccine reported in our study were mild and transient, consistent with the known safety profile of the vaccine (*14,16*). Fever was more common after the second dose and among younger age groups compared to older participants (60-69 and ≥ 70 years). A notable finding from our data, compared to a US online cohort study with 19,586 participants (*17*), was the incidence of fatigue. The US study reported higher fatigue rates after the second dose in both males and females (female: ~35% for the first dose and 60% for the second dose; male: ~22% and 45%). Our study showed a similar trend, with fatigue after the second dose occurring almost three times more often than after the first dose in Japan (female: 26.2% and 73.5%; male: 17.1% and 59.6%). Additionally, this study explored the relationships between food and/or drug allergies, asthma, and atopic disorders with local and systemic reactions. Consistent with other studies (*18,19*), food and/or drug allergies and asthma and/or atopic disorders were more common in

Table 3. Local and systemic reactions after each dose by sex and age group

	Sex		Age group					
First dose (n = 19,792)	Male n = 6,684 n (%)	Female n = 13,108 n (%)	20-29 n = 4,152 n (%)	30-39 n = 4,753 n (%)	40-49 n = 4,934 n (%)	50-59 n = 4,236 n (%)	60-69 n = 1,559 n (%)	≥ 70 n = 158 n (%)
Local reactions (n = 18,316)	5,955 (89.1)	12,361 (94.3)	3,863 (93.0)	4,429 (93.2)	4,649 (94.2)	3,883 (91.7)	1,368 (87.7)	124 (78.5)
Redness (n = 2,742)	523 (7.8)	2,219 (16.9)	572 (13.8)	655 (13.8)	731 (14.8)	565 (13.3)	200 (12.8)	19 (12.0)
Swelling (n = 2,470)	532 (8.0)	1,938 (14.8)	574 (13.8)	595 (12.5)	627 (12.7)	499 (11.8)	160 (10.3)	15 (9.5)
Induration (n = 2,106)	460 (6.9)	1,646 (12.6)	401 (9.7)	538 (11.3)	549 (11.1)	456 (10.8)	142 (9.1)	20 (12.7)
Pain (n = 18,203)	5,933 (88.8)	12,270 (93.6)	3,843 (92.6)	4,429 (93.2)	4,610 (93.4)	3,839 (90.6)	1,361 (87.3)	121 (76.1)
Warmth (n = 2,544)	425 (6.4)	2,119 (16.2)	748 (18.0)	629 (13.2)	585 (11.9)	454 (10.7)	119 (7.6)	9 (5.7)
Pruritus (n = 1,585)	174 (2.6)	1,411 (10.8)	383 (9.2)	376 (7.9)	387 (7.8)	326 (7.7)	106 (6.8)	7 (4.4)
Systemic reactions (n = 7,078)	1,689 (25.3)	5,389 (41.1)	1,523 (36.7)	1,853 (39.0)	1,886 (38.2)	1,394 (32.9)	394 (25.3)	28 (17.6)
Headache (n = 4,225)	768 (11.5)	3,457 (26.4)	968 (23.3)	1,106 (23.3)	1,135 (23.0)	806 (19.0)	196 (12.6)	14 (8.9)
Malaise (n = 4,584)	1,146 (17.1)	3,438 (26.2)	1,042 (25.1)	1,177 (24.8)	1,205 (24.4)	902 (21.3)	247 (15.8)	11 (7.0)
Rhinorrhea (n = 2,020)	492 (7.4)	1,528 (11.7)	372 (9.0)	529 (11.1)	543 (11.0)	427 (10.1)	141 (9.0)	8 (5.1)
Fever > 37.5°C (n = 654)	127 (1.9)	527 (4.0)	239 (5.8)	199 (4.2)	144 (2.9)	56 (1.3)	16 (1.0)	0
Fever > 38.0°C (n = 174)	40 (0.6)	134 (1.0)	71 (1.7)	43 (0.9)	41 (0.8)	14 (0.3)	5 (0.3)	0
Second dose (n = 19,592)	Male n = 6,630 n (%)	Female n = 12,962 n (%)	20–29 n = 4,075 n (%)	30–39 n = 4,702 n (%)	40–49 n = 4,887 n (%)	50–59 n = 4,218 n (%)	60–69 n = 1,553 n (%)	≥70 n = 157 n (%)
Local reactions (n =17,765)	5,703 (86.0)	12,062 (93.1)	3,691 (90.6)	4,280 (91.0)	4,509 (92.3)	3,830 (90.8)	1,342 (86.4)	113 (72.0)
Redness (n = 3,123)	566 (8.5)	2,557 (19.7)	567 (13.9)	758 (16.1)	840 (17.2)	706 (16.7)	236 (15.2)	16 (10.2)
Swelling (n = 2,758)	607 (9.2)	2,151 (16.6)	575 (14.1)	658 (14.0)	720 (14.7)	581 (13.8)	204 (13.1)	20 (12.7)
Induration (n = 1,972)	441 (6.7)	1,531 (11.8)	323 (7.9)	478 (10.2)	529 (10.8)	475 (11.3)	152 (9.8)	15 (9.6)
Pain (n = 17,534)	5,644 (85.1)	11,890 (91.7)	3,645 (89.4)	4,227 (89.9)	4,446 (91.0)	3,789 (89.8)	1,317 (84.8)	111 (70.7)
Warmth (n = 3,722)	722 (10.9)	3,000 (23.1)	967 (23.7)	893 (19.0)	861 (17.6)	762 (18.1)	216 (13.9)	23 (14.6)
Pruritus (n = 2,335)	247 (3.7)	2,088 (16.1)	424 (10.4)	533 (11.3)	585 (12.0)	596 (14.1)	183 (11.8)	14 (8.9)
Systemic reactions (n = 14,759)	4,256 (64.2)	10,503 (81.0)	3,287 (80.7)	3,826 (81.4)	3,795 (77.7)	2,969 (70.4)	831 (53.5)	51 (32.5)
Headache (n = 10,411)	2,444 (36.9)	7,967 (61.5)	2,499 (61.3)	2,769 (58.9)	2,667 (54.6)	1,985 (47.1)	467 (30.1)	24 (15.3)
Malaise (n = 13,478)	3,950 (59.6)	9,528 (73.5)	3,063 (75.2)	3,505 (74.5)	3,485 (71.3)	2,658 (63.0)	724 (46.6)	43 (27.4)
Rhinorrhea (n = 2,829)	671 (10.1)	2,158 (16.6)	644 (15.8)	723 (15.4)	709 (14.5)	583 (13.8)	162 (10.4)	8 (5.1)
Fever ≥37.5°C (n = 7,470)	1,976 (29.8)	5,494 (42.4)	2,026 (49.7)	2,116 (45.0)	1,833 (37.5)	1,227 (29.1)	256 (16.5)	11 (7.0)
Fever ≥38.0°C (n = 4,179)	1,074 (16.2)	3,105 (24.0)	1,216 (29.8)	1,209 (25.7)	1,000 (20.5)	643 (15.2)	106 (6.8)	5 (3.2)

Local reactions include redness, swelling, induration, pain, warmth, and pruritus. Systemic reactions include headache, malaise, and rhinorrhea. Japan's criteria for evaluating some adverse reactions are different from those prescribed by the Food and Drug Administration. See Supplemental S2a and S2b.

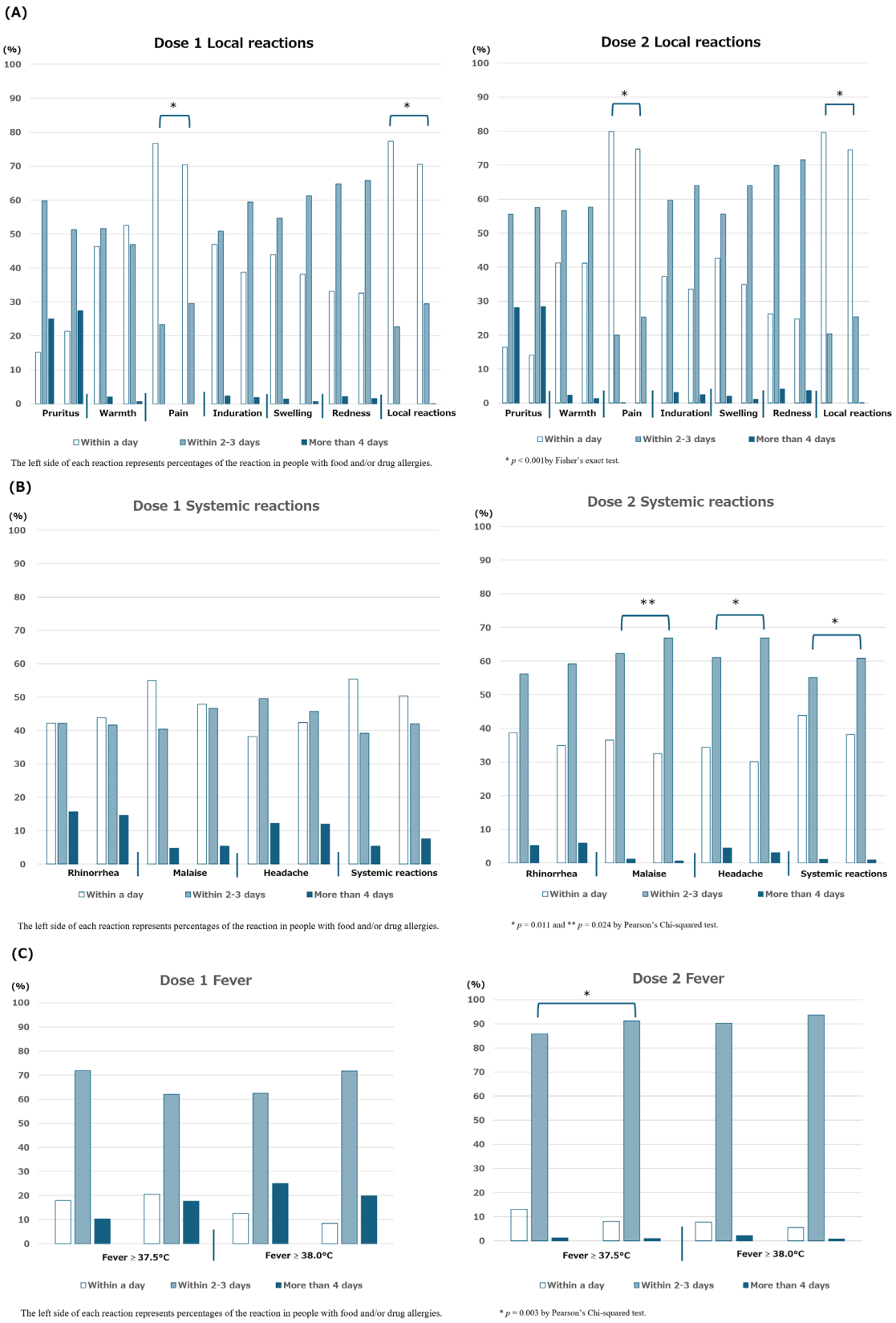

Figure 1. Time-to-onset of adverse reactions in participants with a history of food and/or drug allergies. (A) Local reactions include redness, swelling, induration, pain, warmth, and pruritus. **(B)** Systemic reactions include headache, malaise, and rhinorrhea. **(C)** Fever. Allergies include 1) food allergy to wheat, egg, shrimp, and crab, *etc.*, and 2) drug allergy to penicillin, contrast media, and fluoroquinolones, *etc*. Pearson's chi-squared test or Fisher's exact test is used, as appropriate. Japan's criteria for evaluating some adverse reactions are different from those prescribed by the Food and Drug Administration. See Supplemental Tables S2a and S2b.

Figure 2. Duration of adverse reactions in participants with a history of food and/or drug allergies. (A) Local reactions include redness, swelling, induration, pain, warmth, and pruritus. **(B)** Systemic reactions include headache, malaise, and rhinorrhea. **(C)** Fever. Allergies include 1) food allergy to wheat, egg, shrimp, and crab, among others, and 2) drug allergy to penicillin, contrast media, and fluoroquinolones, among others. Pearson's chi-squared test or Fisher's exact test is used, as appropriate. Japan's criteria for evaluating some adverse reactions are different from those prescribed by the Food and Drug Administration. See Supplemental Tables S2a and S2b.

Figure 3. Time-to-onset of adverse reactions in participants with a history of asthma and/or atopic disorders. (A) Local reactions include redness, swelling, induration, pain, warmth, and pruritus. **(B)** Systemic reactions include headache, malaise, and rhinorrhea. **(C)** Fever. Pearson's chi-squared test or Fisher's exact test is used, as appropriate. Japan's criteria for evaluating some adverse reactions are different from those prescribed by the Food and Drug Administration. See Supplemental Tables S2a and S2b.

females than males. As previously reported (*13,17,20,21*), injection site pain was the most common local reaction (92.0% for the first dose and 89.5% for the second dose). Logistic regression model results indicated that food and/or drug allergies (ORs: 1.65 for the first dose and 1.53 for the second dose), asthma and/or atopic disorders (ORs: 1.32 for the first dose and 1.25 for the second dose), and asthma (PMH and PI) (ORs: 1.36 for the first

Figure 4. Duration of adverse reactions in participants with a history of asthma and/or atopic disorders. (A) Local reactions include redness, swelling, induration, pain, warmth, and pruritus. **(B)** Systemic reactions include headache, malaise, and rhinorrhea. **(C)** Fever. Pearson's chi-squared test or Fisher's exact test is used, as appropriate. Japan's criteria for evaluating some adverse reactions are different from those prescribed by the Food and Drug Administration. See Supplemental Tables S2a and S2b.

dose and 1.30 for the second dose) were associated with systemic reactions (headache, malaise, and rhinorrhea). These systemic reactions can significantly impact daily activities, leading people to instinctively avoid vaccines due to fear of unpleasant side effects. An internet survey on COVID-19 vaccine hesitancy in Japan (*22*)

Table 4. Associations between some types of allergies and adverse reactions

History of food and/or drug allergies	First dose OR (95% CI)	Second dose OR (95% CI)
Local reactions	1.20 (0.89-1.62)	1.05 (0.81-1.37)
Redness	1.26 (1.04-1.51)	1.34 (1.13-1.60)
Swelling	1.51 (1.25-1.82)	1.39 (1.16-1.67)
Induration	1.52 (1.25-1.85)	1.64 (1.35-2.00)
Pain	1.03 (0.79-1.36)	0.95 (0.75-1.20)
Warmth	1.54 (1.28-1.85)	1.62 (1.38-1.90)
Pruritus	1.37 (1.09-1.71)	1.50 (1.24-1.81)
Systemic reactions	1.65 (1.43-1.91)	1.53 (1.26-1.85)
Headache	1.56 (1.34-1.83)	1.37 (1.18-1.59)
Malaise	1.71 (1.47-1.99)	1.52 (1.28-1.81)
Rhinorrhea	1.62 (1.33-1.97)	1.42 (1.18-1.70)
Fever ≥ 37.5 ℃	1.60 (1.14-2.23)	1.26 (1.09-1.46)
Fever ≥ 38.0 ℃	1.20 (0.59-2.46)	1.24 (1.05-1.47)
History of asthma and/or atopic disorders	First dose OR (95% CI)	Second dose OR (95% CI)
Local reactions	1.37 (1.14-1.65)	1.19 (1.01-1.39)
Redness	1.16 (1.03-1.32)	1.21 (1.08-1.36)
Swelling	1.26 (1.11-1.42)	1.26 (1.12-1.41)
Induration	1.34 (1.18-1.52)	1.37 (1.20-1.57)
Pain	1.33 (1.11-1.59)	1.14 (0.98-1.33)
Warmth	1.16 (1.02-1.31)	1.23 (1.10-1.36)
Pruritus	1.20 (1.03-1.39)	1.13 (0.99-1.29)
Systemic reactions	1.32 (1.21-1.45)	1.25 (1.12-1.40)
Headache	1.22 (1.10-1.35)	1.24 (1.13-1.35)
Malaise	1.31 (1.18-1.44)	1.15 (1.04-1.26)
Rhinorrhea	1.37 (1.20-1.56)	1.38 (1.24-1.55)
Fever ≥ 37.5 ℃	1.28 (1.03-1.59)	1.13 (1.03-1.23)
Fever ≥ 38.0 ℃	0.75 (0.45-1.23)	1.09 (0.98-1.21)
Asthma (PMH and PI)	First dose OR (95% CI)	Second dose OR (95% CI)
Local reactions	1.41 (1.15-1.73)	1.17 (0.99-1.40)
Redness	1.20 (1.06-1.36)	1.30 (1.15-1.47)
Swelling	1.30 (1.14-1.48)	1.30 (1.14-1.47)
Induration	1.39 (1.22-1.60)	1.47 (1.28-1.69)
Pain	1.34 (1.11-1.62)	1.14 (0.97-1.34)
Warmth	1.21 (1.06-1.38)	1.26 (1.12-1.41)
Pruritus	1.28 (1.09-1.50)	1.20 (1.04-1.38)
Systemic reactions	1.36 (1.23-1.49)	1.30 (1.15-1.46)
Headache	1.28 (1.14-1.42)	1.25 (1.13-1.38)
Malaise	1.34 (1.20-1.48)	1.18 (1.06-1.32)
Rhinorrhea	1.44 (1.25-1.65)	1.41 (1.25-1.59)
Fever ≥ 37.5 ℃	1.32 (1.05-1.67)	1.16 (1.05-1.27)
Fever ≥ 38.0 ℃	0.83 (0.48-1.41)	1.13 (1.01-1.27)
Atopic disorders (PI)	First dose OR (95% CI)	Second dose OR (95% CI)
Local reactions	1.14 (0.81-1.63)	1.51 (1.07-2.14)
Redness	1.04 (0.81-1.32)	0.93 (0.73-1.19)
Swelling	1.19 (0.94-1.51)	1.19 (0.94-1.50)
Induration	1.23 (0.95-1.59)	1.04 (0.78-1.38)
Pain	1.19 (0.84-1.68)	1.41 (1.03-1.95)
Warmth	0.86 (0.66-1.12)	1.13 (0.91-1.39)
Pruritus	1.06 (0.78-1.44)	0.90 (0.68-1.20)
Systemic reactions	1.22 (1.03-1.45)	1.11 (0.90-1.38)
Headache	1.15 (0.94-1.40)	1.07 (0.89-1.27)
Malaise	1.29 (1.07-1.56)	1.15 (0.94-1.40)
Rhinorrhea	1.11 (0.85-1.45)	1.16 (0.92-1.46)
Fever ≥ 37.5 ℃	1.08 (0.71-1.64)	0.99 (0.83-1.18)
Fever ≥ 38.0 ℃	1.00 (0.44-2.28)	0.98 (0.80-1.20)

PMH: past medical history, PI: present illness, OR: odds ratio, 95% CI: 95% confidence interval. Local reactions include redness, swelling, induration, pain, warmth, and pruritus. Systemic reactions include headache, malaise, and rhinorrhea. Allergies include 1) food allergy to wheat, egg, shrimp, and crab, *etc.* and 2) drug allergy to penicillin, contrast media, and fluoroquinolones, *etc*. Japan's criteria for evaluating some adverse reactions are different from those prescribed by the Food and Drug Administration. See Supplemental Tables S2a and S2b.

analyzed 23,142 responses and found that over 70% of respondents cited concerns about adverse reactions as the primary reason for not getting vaccinated. However, our results showed that most participants, including those with allergies, completed their primary vaccination series (two doses).

While there are several large-scale studies on the BNT162b2 vaccine involving populations outside Japan, this study is significant as it focuses on a regional, large-scale cohort of approximately 20,000 Japanese healthcare workers. It examines the incidence of local and systemic reactions after the BNT162b2 vaccination in subgroups with allergies (food and/or drug allergies, asthma and/or atopic disorders, asthma [PMH and PI], and atopic disorders (PI)), highlighting the patterns of adverse reactions in Japan. However, the sample size for those aged ≥ 70 years was relatively small (158 for the first dose and 157 for the second dose), which may not provide sufficient data to fully assess adverse reaction incidence in this age group.

In our study, individuals with food and/or drug allergies, asthma, and asthma and/or atopic disorders were more likely to develop systemic adverse reactions following vaccination, though these reactions were generally not severe, such as anaphylaxis. Previous reports indicate that most anaphylaxis cases after receiving the BNT162b2 vaccine occurred in individuals with a history of food allergy, drug allergy, or insect stings (*8*). Among 25,929 individuals who received the first dose of the BNT162b2 vaccine, seven cases of anaphylaxis were reported, all of whom had a history of allergies or anaphylaxis and recovered after treatment (*9*). Although a study on a naturally hypersensitive porcine model suggested that complement activation might contribute to rare (pseudo) allergic reactions induced by COVID-19 mRNA vaccines (*23*), the mechanisms underlying these allergic reactions remain unclear.

Some highly allergic patients have successfully received COVID-19 mRNA vaccines under medical supervision (*24*). Several reports (*25,26*) indicate that individuals who experienced anaphylaxis after the first dose of the BNT162b2 vaccine were able to safely receive the second dose in a supervised setting.

The WHO Global Advisory Committee on Vaccine Safety defines immunization stress-related response (ISRR) as vaccination-induced stress and anxiety that may present as adverse events (*27*). Healthcare workers should be aware of ISRR, which can cause anxiety-induced reactions in some individuals following vaccination. To mitigate stress and anxiety related to COVID-19 vaccination, healthcare workers should clearly communicate the risks and benefits of the vaccines to those experiencing vaccine-related anxiety. In our study, all participants received the BNT162b2 vaccine shortly after its approval in Japan. As previously reported (*28*), some participants may have experienced ISRR, leading to more frequent reporting of adverse reactions during the study compared to subsequent doses.

Our study has several limitations. Firstly, a large cohort of approximately 20,000 healthcare workers is not a representative sample of the general population. Compared to the general population, healthcare workers would have the ability to find, understand, and use health-related information, and inform health-related decisions and take actions for themselves and others. This leads to a positive attitude toward vaccines in healthcare workers. On the other hand, in the general population, inadequate health literacy would lead to less interest in vaccination, having difficulty expressing what they have the symptoms or concerns, or having difficulty in symptom perception. This population bias may limit the external validity of our findings. The dataset shows more females and younger individuals, and few older adults and no children included. This selection bias may impact the study results. However, we believe this regional large-scale cohort study provides valuable insights into adverse reactions following vaccination in the Japanese population. Secondly, the self-reported nature of adverse reactions may introduce response biases. Participants might underreport or overreport symptoms, but we assume healthcare workers are more likely to report symptoms accurately and consistently. Despite the limitations of self-reporting, we believe this study achieves high reporting reliability.

mRNA technology has been used in developing vaccines for various infectious diseases (*e.g.*, CMV infection, influenza A & B, RSV infection, herpes zoster, HIV infection) and various cancers (*29*). Vaccine hesitancy, often driven by concerns about adverse reactions to new mRNA vaccines, could significantly impact the acceptance of such vaccines. The findings of this study could serve as a reference for evaluating new mRNA vaccines and aid in their acceptance by the public.

Systemic reactions were more common in individuals with food and/or drug allergies, asthma (PMH and PI), and asthma and/or atopic disorders. These reactions could significantly impact daily activities, potentially leading to vaccine hesitancy. As a way to manage and reduce stress and anxiety during vaccination consultations, healthcare workers and allergy specialists provide allergic patients with information that systemic reactions may be more common than in nonallergic patients, but most symptoms are generally mild and transient. The WHO (*30*) recommends that healthcare workers use a structured approach in motivational interviewing during vaccination consultations. To promote vaccine confidence, healthcare workers provide patients with consistent and accurate information about vaccine safety and benefits in a respectful and positive manner.

This study provides valuable data for medical and allergy specialists to explain vaccine-related adverse reactions to individuals with allergies, thereby reducing stress and anxiety. Additionally, as mRNA technology continues to be used in developing vaccines for various infectious diseases and various cancers, the results of this study could help enhance the acceptance of new mRNA vaccines. Real-world vaccination data for children and older adults need to be collected and analyzed to further the development of new mRNA vaccines in the future.

Acknowledgements

We thank Michie Yamano of the Center for Clinical Research and Clinical Trials for her guidance in drafting this article. We also thank Yuki Nagai from the Cohort Study Secretariat.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Wilson E, Goswami J, Baqui AH, *et al.* Efficacy and safety of an mRNA-Based RSV PreF vaccine in older adults. N Engl J Med. 2023; 389:2233-2244.
2. Russell CA, Fouchier RAM, Ghaswalla P, Park Y, Vicic N, Ananworanich J, Nachbagauer R, Rudin D. Seasonal influenza vaccine performance and the potential benefits of mRNA vaccines. Hum Vaccin Immunother. 2024; 20:2336357.
3. Wang B, Pei J, Xu S, Liu J, Yu J. Recent advances in mRNA cancer vaccines: Meeting challenges and embracing opportunities. Front Immunol. 2023; 14:1246682.
4. U.S. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19) vaccine safety *https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html* (accessed June 16, 2024).
5. Copland E, Patone M, Saatci D, Handunnetthi L, Hirst J, Hunt DPJ, Mills NL, Moss P, Sheikh A, Coupland

CAC, Harnden A, Robertson C, Hippisley-Cox J. Safety outcomes following COVID-19 vaccination and infection in 5.1 million children in England. Nat Commun. 2024; 15: 3822.
6. Faksova K, Walsh D, Jiang Y, *et al.* COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals. Vaccine. 2024; 42:2200-2211.
7. Health Sciences Council, Disease Control Subcommittee, Rheumatology and Allergy Control Committee. Rheumatology and Allergy Control Committee Report (August 2011). *https://www.mhlw.go.jp/stf/shingi/2r9852000001nes4-att/2r9852000001newa.pdf* (accessed June 16, 2024). (in Japanese)
8. Shimabukuro T, Nair N. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine. JAMA. 2021; 325:780-781.
9. Blumenthal KG, Robinson LB, Camargo CA Jr, Shenoy ES, Banerji A, Landman AB, Wickner P. Acute allergic reactions to mRNA COVID-19 vaccines. JAMA. 2021; 325:1562-1565.
10. Nittner-Marszalska M, Rosiek-Biegus M, Kopeć A, Pawłowicz R, Kosińska M, Łata A, Szenborn L. Pfizer-BioNTech COVID-19 vaccine tolerance in allergic versus non-allergic individuals. Vaccines (Basel). 2021; 9:553.
11. Inoue S, Igarashi A, Morikane K, Hachiya O, Watanabe M, Kakehata S, Sato S, Ueno Y. Adverse reactions to BNT162b2 mRNA COVID-19 vaccine in medical staff with a history of allergy. Respir Investig. 2022; 60:248-255.
12. National Institute of Public Health. JPRN (Japan Primary Registries Network) Search Portal Site. *https://rctportal.niph.go.jp/en/detail?trial_id=UMIN000043377* (accessed June 16, 2024).
13. Polack FP, Thomas SJ, Kitchin N, *et al.* Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020; 383:2603-2615.
14. Baden LR, El Sahly HM, Essink B, *et al.* Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021; 384:403-416.
15. Klein NP, Lewis N, Goddard K, *et al.* Surveillance for adverse events after COVID-19 mRNA vaccination. JAMA. 2021; 326:1390-1399.
16. Voysey M, Clemens SAC, Madhi SA, *et al.* Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS- CoV-2: An interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021; 397:99-111.
17. Beatty AL, Peyser ND, Butcher XE, Cocohoba JM, Lin F, Olgin JE, Pletcher MJ, Marcus GM. Analysis of COVID-19 vaccine type and adverse effects following vaccination. JAMA Netw Open. 2021; 4:e2140364.
18. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. Allergy. 2008; 63:1418-1427.
19. Leynaert B, Sunyer J, Garcia-Esteban R, *et al.* Gender differences in prevalence, diagnosis and incidence of allergic and non-allergic asthma: A population-based cohort. Thorax. 2012; 67:625-631.
20. Chapin-Bardales J, Gee J, Myers T. Reactogenicity following receipt of mRNA-based COVID-19 vaccines. JAMA. 2021; 325:2201-2202.
21. Menni C, Klaser K, May A, *et al.* Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: A prospective observational study. Lancet Infect Dis. 2021; 21:939-949.
22. Okubo R, Yoshioka T, Ohfuji S, Matsuo T, Tabuchi T. COVID-19 vaccine hesitancy and its associated factors in Japan. Vaccines (Basel). 2021; 9:662.
23. Dézsi L, Mészáros T, Kozma G, H-Velkei M, Oláh CZ, Szabó M, Patkó Z, Fülöp T, Hennies M, Szebeni M, Barta BA, Merkely B, Radovits T, Szebeni J. A naturally hypersensitive porcine model may help understand the mechanism of COVID-19 mRNA vaccine-induced rare (pseudo) allergic reactions: complement activation as a possible contributing factor. Geroscience. 2022; 44:597-618.
24. Shavit R, Maoz-Segal R, Iancovici-Kidon M, *et al.* Prevalence of allergic reactions after Pfizer-BioNTech COVID-19 vaccination among adults with high allergy risk. JAMA Netw Open. 2021; 4:e2122255.
25. Krantz MS, Bruusgaard-Mouritsen MA, Koo G, Phillips EJ, Stone CA Jr, Garvey LH. Anaphylaxis to the first dose of mRNA SARS-CoV-2 vaccines: Don't give up on the second dose! Allergy. 2021; 76:2916-2920.
26. Chu DK, Abrams EM, Golden DBK, Blumenthal KG, Wolfson AR, Stone CA Jr, Krantz MS, Shaker M, Greenhawt M. Risk of second allergic reaction to SARS-CoV-2 vaccines: a systematic review and meta-analysis. JAMA Intern Med. 2022; 182:376-385.
27. World Health Organization. Immunization stress-related responses: A manual for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization. *https://www.who.int/publications/i/item/9789241515948* (accessed June 16, 2024).
28. Khalid M, Utoh J, Zektser E, Guerrerio P. COVID-19 mRNA vaccine-induced immunization stress-related response (ISRR) and anaphylaxis: An early look at COVAAR clinical outcomes. J Allergy Clin Immunol. 2023; 151:AB221.
29. World Health Organization. Potential benefits and limitations of mRNA technology for vaccine research and development for infectious diseases and virus-induced cancers. Available at: *https://www.who.int/publications/i/item/9789240084551* (accessed June 16, 2024).
30. World Health Organization. Communicating with patients about COVID-19 vaccination. *https://iris.who.int/bitstream/handle/10665/340751/WHO-EURO-2021-2281-42036-57837-eng.pdf?sequence=1* (accessed October 05, 2024)

Received July 5, 2024; Revised October 7, 2024; Accepted October 23, 2024.

Released online in J-STAGE as advance publication November 29, 2024.

**Address correspondence to*:
Morikuni Tobita, Department of Healthcare Innovation, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo, Tokyo 1138421, Japan.
E-mail: mtobita@juntendo.ac.jp