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Original Article

Incidence and Risk Factors of Immediate Hypersensitivity Reactions and Immunization Stress-Related Responses With COVID-19 mRNA Vaccine

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What is already known about this topic? Although studies have estimated a low incidence rate of anaphylaxis to mRNA vaccines and identified several potential risk factors, there exists a knowledge gap regarding the incidence and risk factors for nonserious immediate hypersensitivity reactions (IHSR) and immunization stress-related responses (ISRR).

What does this article add to our knowledge? Adverse events were more commonly classified as ISRR, instead of IHSR, and the incidence rates of IHSR were very low. We found that the several risk factors were associated with the increased risk of IHSR and ISRR.

How does this study impact current management guidelines? Although recipients with risk factors are associated with increased risks of IHSR and ISRR, their incidence rates were low. Hence, these risk factors are not of sufficient magnitude to warrant special measures regarding their vaccination.

BACKGROUND: With the implementation of mass vaccination campaigns against COVID-19, the safety of vaccine needs to be evaluated.

OBJECTIVE: We aimed to assess the incidence and risk factors for immediate hypersensitivity reactions (IHSR) and immunization stress–related responses (ISRR) with the Moderna COVID-19 vaccine.

METHODS: This nested case-control study included recipients who received the Moderna vaccine at a mass vaccination center, Japan. Recipients with IHSR and ISRR were designated as cases 1 and 2, respectively. Controls 1 and 2 were selected from recipients without IHSR or ISRR and matched (1 case: 4 controls) with cases 1 and cases 2, respectively. Conditional logistic regression analysis was used to identify risk factors associated with IHSR and ISRR.

RESULTS: Of the 614,151 vaccine recipients who received 1,201,688 vaccine doses, 306 recipients (cases 1) and 2478 recipients (cases 2) showed 318 events of IHSR and 2558 events of ISRR, respectively. The incidence rates per million doses were estimated as IHSR: 266 cases, ISRR: 2129 cases, anaphylaxis: 2 cases, and vasovagal syncope: 72 cases. Risk factors associated with IHSR included female, asthma, atopic dermatitis, thyroid diseases, and a history of allergy; for ISRR, the risk factors were younger age, female, asthma, thyroid diseases, mental disorders, and a history of allergy and vasovagal reflex.

CONCLUSION: In the mass vaccination settings, the Moderna vaccine can be used safely owing to the low incidence rates of IHSR and anaphylaxis. However, providers should be aware of the occurrence of ISRR. Although recipients with risk factors are associated with slightly increased risks of IHSR and ISRR, this is not of sufficient magnitude to warrant special measures regarding their vaccination. **(J Allergy Clin Immunol Pract 2022;10:2667-76)**

Key words: *mRNA vaccine; COVID-19; SARS-CoV-2; Moderna; Immediate hypersensitivity reactions; Immunization stress-related responses; Adverse events; Risk factors*

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Abbreviations used
AEFI- Adverse events following immunization
CARPA- Complement activation-related pseudoallergy
CI- Confidence interval
FND- Functional neurological disorder
GVIF- Generalized variance inflation factor
IHSR- Immediate hypersensitivity reactions
ISRR- Immunization stress-related responses
OR- Odds ratio
PEG- Polyethylene glycol

Mass vaccination campaigns for COVID-19 are being implemented worldwide to overcome the ongoing global pandemic caused by SARS-CoV-2. A standardized 2-dose regimen of the Pfizer-BioNTech[1] and Moderna[2] mRNA vaccines provided a high level of protection against COVID-19 and are widely used. To evaluate the safety of the mRNA vaccine, the acute and long-term adverse events following immunization (AEFI) are being actively investigated by government agencies and the scientific community.

AEFI is grouped into 5 categories: vaccine product−related reaction containing immediate hypersensitivity reactions (IHSR; eg, skin, cardiac, gastrointestinal, and respiratory symptoms), vaccine quality defect−related reaction, immunization error−related reaction, immunization stress−related responses (ISRR; eg, symptoms and signs due to vasovagal reflex, panic attack, and functional neurological disorders [FNDs]), and coincidental event.[3] Investigations into AEFI that occur immediately after the injection, especially IHSR and ISRR, are particularly important to evaluate the safety of mass vaccine administration. Hitherto, the rate of anaphylaxis, which is an acute life-threatening and serious IHSR, to the Pfizer-BioNTech and Moderna mRNA vaccines has been reported to be extremely low (2.5-11.1 cases per million doses);[4,5] female gender and a history of allergy were reported as prominent risk factors.[5,6] In terms of ISRR, a high incidence rate of vasovagal syncope after receiving the COVID-19 vaccine (8.2 per 100,000 doses) has been reported, especially in females, adolescents, people with a mental disorder, or a history of vasovagal syncope.[7]

However, the majority of existing reports[4-7] analyzed a database of passive surveillance systems, such as the Vaccine Adverse Event Report System[8] in the United States, which have well-documented limitations of passive surveillance systems, such as high inconsistencies in the report quality, and underreporting or biased reporting.[9] Previous studies mainly focused on the incidence rate and risk factors for anaphylaxis[4-6] or vasovagal syncope[7] as indicators of vaccine safety. However, there exists a knowledge gap regarding the incidence and risk factors for nonserious IHSR and ISRR. Information regarding such reactions is crucial for clinicians who work in mass vaccination centers. Therefore, it is necessary to understand the detailed clinical characteristics of recipients with nonserious IHSR and ISRR to establish a safe mass vaccination system, and to identify the people who are at high risk for developing IHSR and ISRR.

At the Self-Defence Forces Tokyo Large-scale Vaccination Centre, Japan, a total of 1,201,688 Moderna COVID-19 vaccines have been administered between May 24 and September 24, 2021, to civilian residents, and active surveillance of AEFI was conducted. We also performed a detailed analysis of the clinical profile of all recipients both with and without IHSR and ISRR who received the Moderna COVID-19 vaccine to identify the incidence and risk factors of IHSR and ISRR.

MATERIALS AND METHODS

Study design and participants

We conducted a nested case-control study at the Self-Defence Forces Tokyo Large-scale Vaccination Centre in Japan. An overview of the vaccination center organization and standard operating procedures of vaccine administration is shown in Text 1, available in this article's Online Repository at www.jaci-inpractice.org. The adult vaccine recipients (≥18 years old) who received the Moderna COVID-19 vaccine between May 24 and September 24, 2021, were enrolled in this study. AEFI, which occurred during the stay of the recipient at the center, was collected. Recipients who showed IHSR were designated as case 1 and those who developed ISRR were designated as case 2 (Figure 1). In case the recipients showed the same type of AEFI at both first and second doses, data for only the first dose were collected. If the recipient experienced 2 different types of AEFI at both first and second doses, each dose was selected. Vaccine recipients without AEFI were designated to controls.

Baseline clinical characteristics (age, sex, comorbidities of hypertension, dyslipidemia, diabetes, cardiovascular diseases, asthma, atopic dermatitis, thyroid diseases, malignancy and mental disorders, and history of allergic episodes for drugs and foods, and vasovagal episode) were collected using a pre-vaccination screening questionnaire for the COVID-19 vaccine distributed by the Ministry of Health, Labour and Welfare, Japan,[10] which was filled by the recipients before the injection and collected at each dose. Data for the date of vaccination and the number of doses received were collected using the in-house COVID-19 vaccine reservation and reception system (MRSO Inc, Tokyo, Japan). Next, all relevant clinical findings (symptoms, signs, the timing of onset of symptoms after the injection, medication received, if any, and the clinical outcome of requiring transportation to the hospitals and death) of the vaccine recipients with an AEFI were collected via medical records maintained in the first-aid rooms. During the study period, 2 trained physicians (KI and KE) and an emergency physician (FT) reviewed medical records to classify an AEFI daily.

This study was reviewed and approved by the Institutional Review Board of the Self-Defence Forces Central Hospital, Tokyo, Japan (Approval number: 03-006). Informed consent was obtained from all participants in the form of opt-out.

Definitions

As defined by the World Health Organization, "AEFI" was described as "any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of the vaccine. The adverse event may be any unfavourable or unintended sign, an abnormal laboratory finding, a symptom, or a disease."[3] Acute AEFI were classified according to the following standard criteria: (1) coincidental events, traumatic injuries, or symptoms/signs that have occurred before the recipient received the vaccine; (2) localized pain by vaccine product-related reactions, localized pain at the injection site without other symptoms/signs; (3) IHSR—1 or more of following symptoms/signs were exhibited: urticarial or any type of rash, angioedema, local or generalized pruritus, wheezing, stridor, persistent cough, hoarseness, and anaphylaxis; (4) ISRR—symptoms/signs that were not accompanied by coincidental events, localized pain by vaccine product-related reactions or IHSR; discomfort in the mouth and throat, palpitations, cold sweat, shortness of breath, chest pain, abdominal pain, nausea, vomiting, diarrhea, vertigo, syncope, general weakness, numbness or loss of sensation, headache, malaise, hyperventilation/panic attack, photophobia, feeling of a hot flush, and vital signs abnormalities indicative of a vasovagal reflex (hypotension and/or bradycardia). Confirmatory anaphylaxis was diagnosed based on the Brighton Collaboration

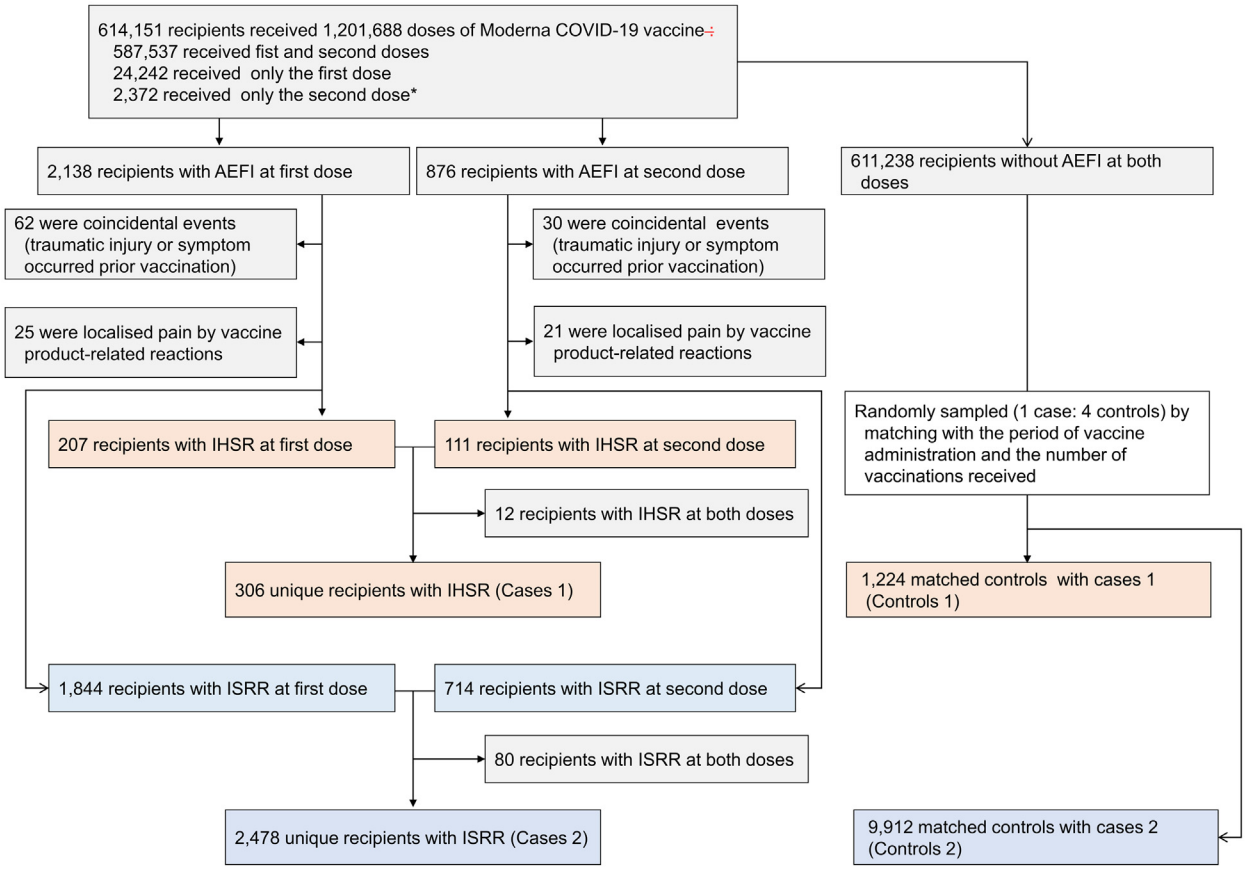

FIGURE 1. Flow diagram of vaccine recipients at the mass vaccination center.*A total of 2372 recipients received first dose of the Moderna vaccine in other medical facilities and received its second dose in our center. *AEFI*, Adverse events following immunization; *IHSR*, immediate hypersensitivity reactions; *ISRR*, immunization stress-related responses.

definition.[11] Grade 3 hypertension was defined as systolic blood pressure >180 mm Hg and/or diastolic blood pressure >110 mm Hg.[12]

Statistical analysis

We calculated the incidence rates and 95% confidence interval (CI) for AEFI using the number of vaccine doses administered at a center as the denominator. Categorical variables are presented as frequency and percentage (%) and were compared using a χ^2 test or the Fisher exact test, as appropriate.

As reported by the existing literature, age, sex, multiple comorbidities, and a history of allergy or vasovagal reflex after vaccination increased the risk of IHSR to other drugs.[5,6,13-15] Also, age, sex, mental disorders, and history of vasovagal reflex increased the risk of ISRR to other vaccines.[7,16] Therefore, we also selected comparable characteristics—age, sex, the presence of comorbidities (hypertension, diabetes, dyslipidemia, cardiovascular diseases, asthma, atopic dermatitis, thyroid diseases, malignancy, and mental disorders), and a history of allergy to drugs and foods or a vasovagal reflex as variables of interest. The period of vaccine administration and the number of vaccinations received were considered as potential confounders. Thus, controls 1 and controls 2 were matched with cases 1 and 2, respectively, based on the period of vaccine administration (May 24-June 23, June 24-July 23, July 24-August 23, and August 24-September 24) and the number of vaccinations received (first dose and second dose) (Figure 1). We selected controls randomly sampled from recipients without AEFI at both doses (1 case: 4 controls) matched with the period of vaccine administration and the number of vaccinations received.

All variables that may be potentially associated with an increased risk of IHSR or ISRR as observed by univariate analysis ($P < .10$) were further processed through multivariable models. The final model was selected using backward stepwise conditional logistic regression to minimalize the Akaike information criterion. All models included age and sex and were adjusted by the period of the vaccine administration and the number of vaccination doses. A 2-sided P value of $<.05$ was considered statistically significant. Missing values were imputed with the use of multiple imputations by fully conditional specification using multivariate imputation by the chained equation (mice) package in R.[17] The generalized variance inflation factor (GVIF)1/(2*degree of freedom) was used for diagnosing the collinearity in the multivariate logistic regression. GVIF1/(2*degree of freedom) < 2 determined that there was no multicollinearity.

Two types of sensitivity analyses were performed to test the robustness of the results: (1) excluding recipients with missing data (complete case analysis) with the initial case definition, (2) complete case analysis with changing the definitions of IHSR and ISRR within the case. The case definition was gradually narrowed down to eliminate possible misclassifications between IHSR and ISRR (case definition of IHSR-2 and -3 or ISRR-2 and -3). Matched

TABLE I. Baseline characteristics

	Immediate hypersensitivity reactions			Immunization stress-related responses		
Demographic characteristic	**Cases 1 (N = 306)**	**Controls 1 (N = 1224)**	***P* value***	**Cases 2 (N = 2478)**	**Controls 2 (N = 9912)**	***P* value†**
Age (y)						
>65	108 (35)	467 (38)	.817	430 (20)	2344 (26)	<.001
51-65	69 (23)	258 (21)		361 (13)	1913 (18)	
36-50	68 (22)	264 (22)		620 (26)	2815 (29)	
≤35	61 (20)	235 (19)		1067 (41)	2840 (27)	
Sex						
Male	63 (21)	692 (57)	<.001	827 (33)	5475 (55)	<.001
Female	243 (79)	532 (44)		1651 (67)	4437 (45)	
Comorbidities						
Hypertension	40 (13)	156 (13)	.848	163 (7)	899 (9)	<.001
Dyslipidemia	17 (6)	58 (5)	.552	89 (4)	406 (4)	.303
Diabetes	12 (4)	59 (5)	.647	55 (2)	351 (4)	.002
Cardiovascular diseases	5 (2)	40 (3)	.182	57 (2)	197 (2)	.284
Asthma	24 (8)	17 (1)	<.001	96 (4)	123 (1)	<.001
Atopic dermatitis	5 (2)	3 (0)	.010	21 (1)	36 (0)	.002
Thyroid diseases	15 (5)	13 (1)	<.001	50 (2)	89 (1)	<.001
Malignancy	6 (2)	21 (2)	.807	26 (1)	90 (1)	.476
Mental disorders	7 (2)	20 (2)	.463	113 (5)	127 (1)	<.001
Missing data of comorbidities	4 (1)	0		33 (1)	0	
History						
Allergic episodes for drugs	86 (28)	41 (3)	<.001	320 (13)	303 (3)	<.001
Allergic episodes for foods	80 (26)	33 (3)	<.001	308 (12)	327 (3)	<.001
Vasovagal episode	9 (3)	10 (1)	.006	246 (10)	136 (1)	<.001
Missing data of histories	6 (2)	0		45 (2)	10 (0)	
No. of vaccine received						
First	207 (68)	828 (68)	1.000	1844 (74)	7376 (74)	1.000
Second	99 (32)	396 (32)		634 (26)	2536 (26)	
Period						
May 24-June 23	98 (32)	392 (32)	1.000	486 (20)	1944 (20)	1.000
June 24-July 23	58 (19)	232 (19)		323 (13)	1292 (13)	
July 24-August 23	89 (29)	356 (29)		1071 (43)	4284 (43)	
August 24-September 24	61 (19)	244 (20)		598 (24)	2392 (24)	

Data are presented as n (%).
**P* value showed a comparison between cases 1 and control 1.
†*P* value showed a comparison between cases 2 and control 2.

controls for each case of the IHSR and ISRR groups were extracted from controls 1 or controls 2, respectively (Figures E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org). Case definitions in each sensitivity analysis are shown in Tables E1 and E2 (available in this article's Online Repository at www.jaci-inpractice.org). Final models selected in the initial analysis were evaluated by new cases and their controls. Sample size consideration is shown in this article's Online Repository Text 2 at www.jaci-inpractice.org. All statistical analyses were performed using R software (v 4.0.2; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

RESULTS

Baseline characteristics of participants

Between May 24 and September 24, 2021, 614,151 people received the Moderna vaccine at the study center (587,537 received both first and second doses, 24,242 received only the first dose and 2372 received the second dose). A total of 1,201,688 vaccine doses (611,779 and 589,909 for the first dose and second dose, respectively) were administered at the study center. During the study period, 3014 instances of AEFI were observed in 2913 recipients—a total of 101 recipients showed AEFI twice, both at the first and second doses. Based on the clinical symptoms and signs, 318 events of IHSR were observed in 306 recipients (11%, cases 1) and 2558 events of ISRR in 2478 recipients (85%, cases 2) (Figure 1). Among the 611,237 recipients without AEFI, 1208 recipients were selected as matched controls 1 for cases 1 and 9940 recipients as control 2 for cases 2 (Figure 1). Each control was matched (1 case: 4 controls) with each case based on the period of vaccine administration and the number of vaccinations received. The summary of available data among 611,238 recipients without AEFI and selected controls is shown in Table E3 (available in this article's Online Repository at www.jaci-inpractice.org). The baseline characteristics of cases and selected controls are shown in Table I.

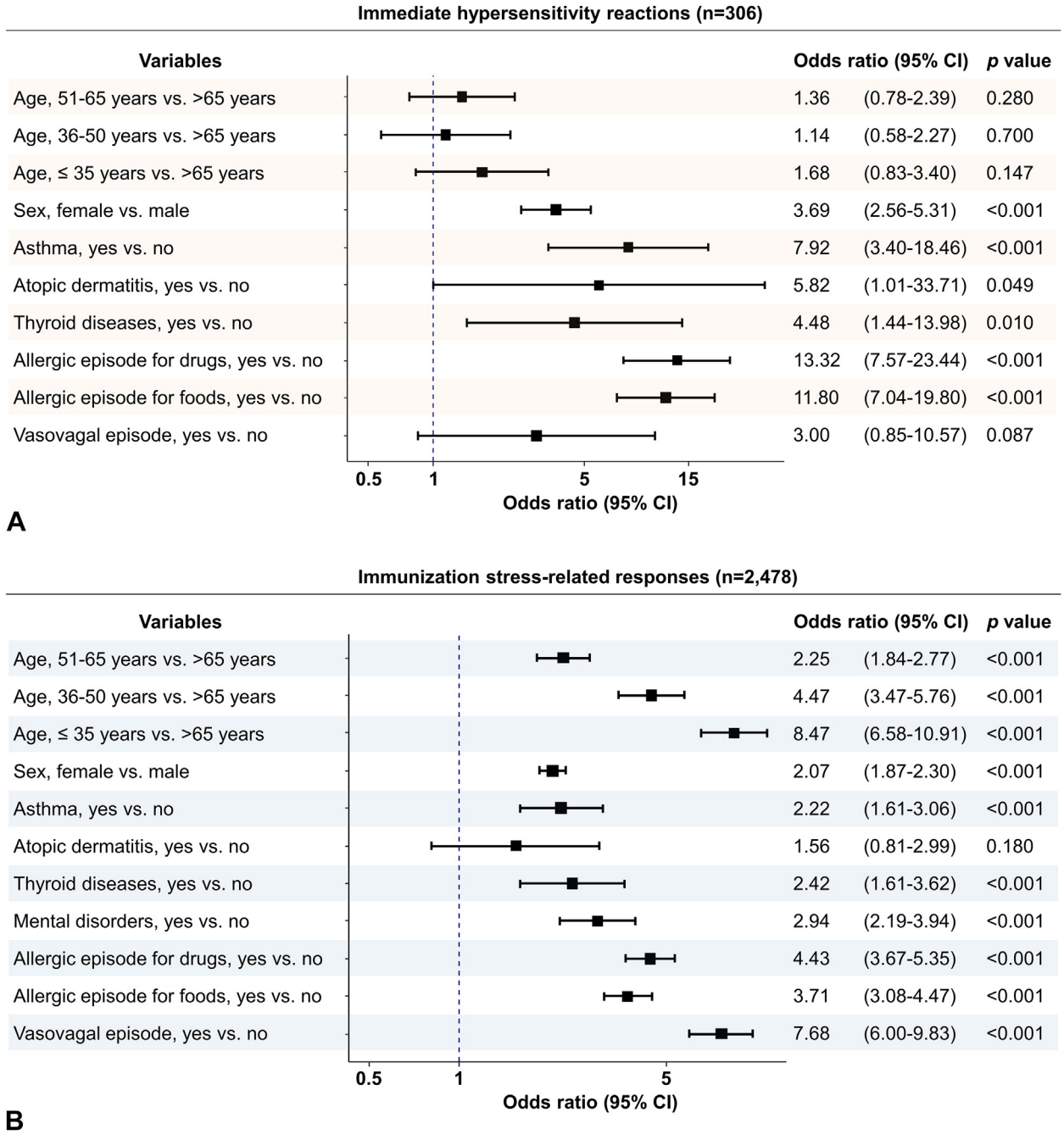

FIGURE 2. Risk factors associated with immediate hypersensitivity reactions and immunization stress-related responses to the Moderna COVID-19 vaccine. (**A**) Forest plot showing the odds ratio for an increased risk of immediate hypersensitivity reactions and (**B**) immunization stress-related responses using multivariable analysis of conditional logistic regression analysis. Plots and horizontal lines indicate estimated odds ratio and 95% confidence intervals (CI), respectively.

Risk factor analysis

In the univariable analysis, we observed that recipients with ISRR were significantly younger ($P < .001$) than their controls (cases 2 vs controls 2), but no significant difference was found in the IHSR group (cases 1 vs controls 1). The proportion of females were significantly higher ($P < .001$) in recipients with both IHSR and ISRR than in their respective controls. The variables potentially associated with the IHSR group included asthma, atopic dermatitis, thyroid diseases, history of allergy to drugs and foods, and history of vasovagal reflex; those potentially associated with the ISRR group included hypertension, diabetes, asthma, atopic dermatitis, thyroid diseases, mental disorders, history of allergy to drugs and foods, and history of vasovagal reflex ($P < .100$) (Table I).

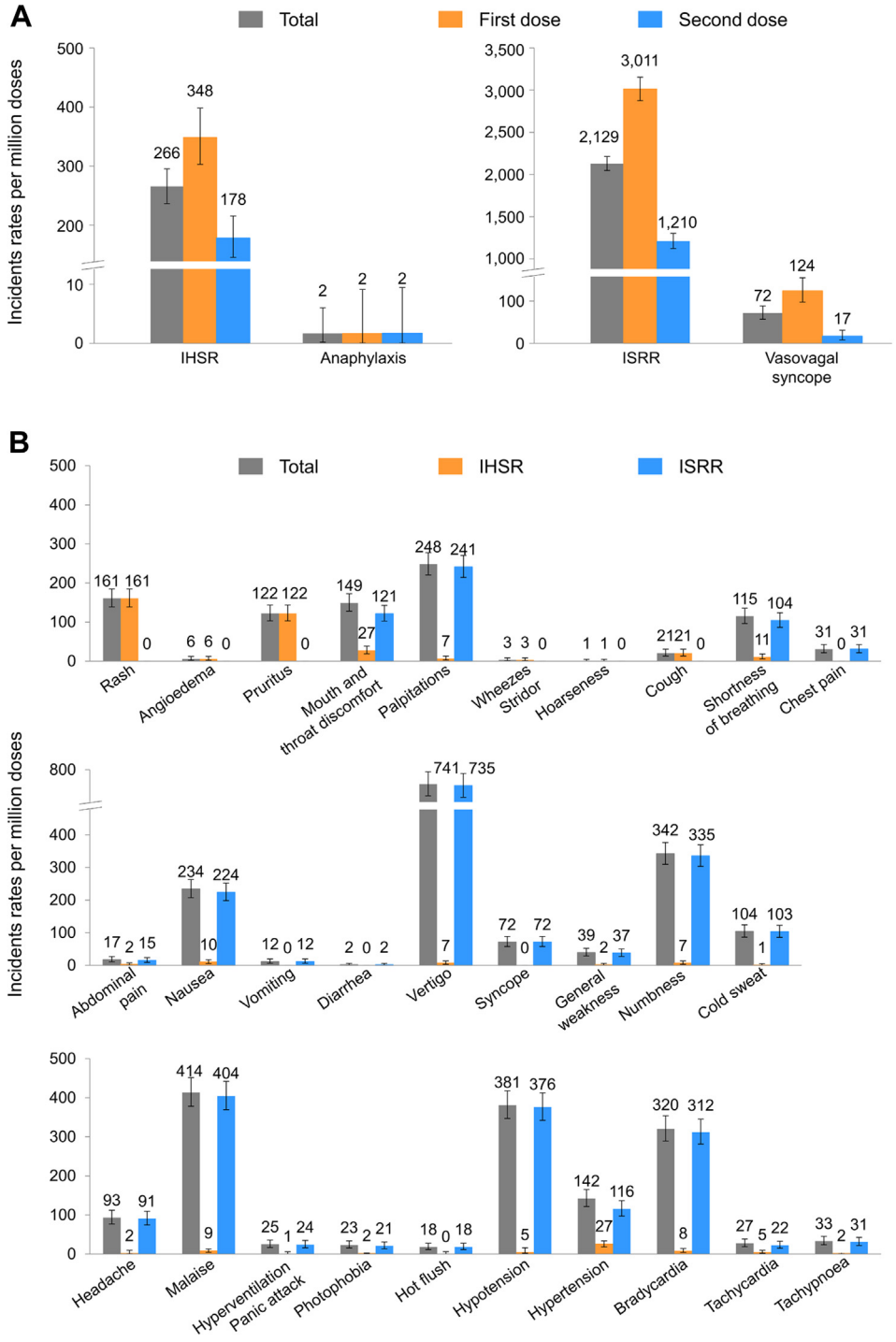

FIGURE 3. Incidence rates of adverse events following immunization to the Moderna COVID-19 vaccine. (**A**) Bar plot showing the incidence rates of immediate hypersensitivity reactions (IHSR) and immunization stress-related responses (ISRR) and of (**B**) clinical symptoms and signs. The incidence rates were estimated using vaccine doses administered as the denominator. The error bars indicate 95% confidence intervals.

In the multivariable conditional logistic regression analysis, the variables significantly associated with an increased risk of IHSR included female gender, asthma, atopic dermatitis, thyroid diseases, and history of allergy to drugs and foods (Figure 2, *A*), of which a history of allergy to drugs (odds ratio [OR]: 13.32 [95% CI: 7.57-23.44]) and foods (OR: 11.80 [95% CI: 7.04-19.80]) had the strongest association for an increased risk of IHSR (Figure 2, *A*). Similarly, in recipients who developed

TABLE II. Descriptive characteristics of vaccine recipients with acute adverse events following immunization

Clinical characteristic and outcome	No. of total events (N = 2876)	No. of events of immediate hypersensitivity reactions (N = 318)	No. of events of immunization stress-related responses (N = 2558)
Onset of initial symptoms/signs			
≤15 min	2107 (73)	179 (56)	1928 (75)
≤30 min	2744 (95)	294 (93)	2450 (96)
>30 min	71 (3)	17 (5)	54 (2)
Missing	61	7	54
Medications at a center			
Epinephrine	9 (0)	7 (2)	2 (0)
Antihistamine	3 (0)	3 (1)	0
Corticosteroid	1 (0)	1 (0)	0
Outcome			
Transported to the hospitals	75 (3)	27 (9)	48 (2)
Recovered at a center	2801 (97)	291 (92)	2510 (98)
Recovered with medication	6 (0)	4 (1)	2 (0)
Recovered without medication	2795 (97)	287 (90)	2508 (98)
Death	0	0	0

Data are presented as n (%).

ISRR, younger age (≤65 years), female gender, asthma, mental disorders, history of allergy to drugs and foods, and history of vasovagal reflex were significantly associated with an increased risk (Figure 2, *B*). Younger the recipient's age, the greater the risk of developing ISRR. Multicollinearity was not detected among the variables.

Sensitivity analysis

The complete case analysis with the initial case definition did not change the study findings. According to the new case definition, 284 cases (IHSR-2) and 188 cases (IHSR-3) were selected from the case 1 group and were compared with 1136 and 752 matched controls, respectively. Likewise, 2304 cases (ISRR-2) and 2129 cases (ISRR-3) were selected from cases 2 to compare with 9208 and 8516 matched controls selected from controls 2, respectively (Tables E4 and E5, and Figures E3 and E4, available in this article's Online Repository at www.jaci-inpractice.org). We observed that changing the case definitions of IHSR and ISRR did not change the study findings, although the association of atopic dermatitis for an increased risk of IHSR did not reach statistical significance as per the new case definition. Multicollinearity was not detected among the variables in sensitivity analysis.

Incidence rates of IHSR and ISRR

Of the 318 IHSR events, 2 events were classified as anaphylaxis according to the Brighton Criteria (one event at the first dose—level 2-2, and another at the second dose—level 3). Of the 2558 IHSR events, 86 events of vasovagal syncope were observed. Overall, the incidence rate per million doses of AEFI in the 1,201,688 vaccine doses administered was estimated as follows: IHSR: 266 cases (95% CI: 236-295 cases), ISRR: 2129 cases (95% CI: 2047-2212 cases), anaphylaxis: 2 cases (95% CI: 0.2-6 cases), and vasovagal syncope: 72 cases (95% CI: 57-88 cases) (Figure 3, *A*; Table E6, available in this article's Online Repository at www.jaci-inpractice.org). The incidence rate of AEFI at the first dose, except for anaphylaxis, was significantly higher than at the second dose ($P < .001$) (Table E6).

Symptoms and signs of vaccine recipients with IHSR and ISRR

In the ISRR events, vertigo, malaise, and numbness or loss of sensation in part of the body were the most common clinical symptoms (Figure 3, *B*; Table E7, available in this article's Online Repository at www.jaci-inpractice.org). In the IHSR events, any types of rash and pruritus were the most common symptoms. Syncope (included in the standard criteria for ISRR) was observed in the ISRR events only, and all of these cases were diagnosed with vasovagal syncope. Hypotension and bradycardia due to vasovagal reflex were the most common vital sign abnormalities in the ISRR events, whereas grade 3 hypertension (not included in the standard criteria for either IHSR or ISRR) was the most common vital sign abnormality in the IHSR events.

Symptom onset within 15 minutes of the vaccination was recorded in 179 of 318 (56%) events of IHSR and 1928 of 2558 (75%) events of ISRR, whereas in 294 of the 318 (93%) events of IHSR and 2450 of the 2558 (96%) events of ISRR, the symptoms appeared within 30 minutes of vaccination (Table II). Epinephrine was used for 7 events with a clinical diagnosis of severe IHSR at the first-aid rooms. Erroneous administration of epinephrine for hypotension due to vasovagal reflex was reported for 2 events in the ISRR events. A total of 75 events (3%) required additional treatment in neighboring hospitals. Twenty-seven events (9%) required additional treatment at neighboring hospitals in the IHSR event, whereas 48 events (2%) required additional examination at neighboring hospitals in the ISRR events including 14 events of persistent grade 3 hypertension and 17 events of neurological disorders (1 or more symptoms of general weakness, numbness, loss of sensation, and movement disorders). In the IHSR events, 287 events (90%) were self-limiting requiring no medication or treatment.

Recurrence rates of IHSR and ISRR

Of 207 recipients who showed IHSR at the first dose, 174 (84%) recipients received the second dose in the center. No premedication before the second dose was prescribed. Of 174

TABLE III. Immediate reactions at second dose among recipients showed IHSR and ISRR at first dose

Immediate reactions at second dose	IHSR at first dose (N = 174)	ISRR at first dose (N = 1561)
None	159 (91)	1480 (95)
IHSR	12 (7)	1 (0)
ISRR	3 (2)	80 (5)
Anaphylaxis	0	0
Vasovagal syncope	0	1 (0)
Outcome		
Medications at a center	0	0
Transported to the hospitals	1 (1)	2 (0)
Death	0	0

Data are presented as n (%).
IHSR, Immediate hypersensitivity reactions; *ISRR*, immunization stress-related responses.

recipients, 12 (7%) recipients showed recurrent IHSR at the second dose, and no recipient was diagnosed with anaphylaxis. Of 1844 recipients who showed ISRR at the first dose, 1561 (85%) recipients received the second dose in the center. Of 1561 recipients, 80 (5%) recipients showed the recurrent ISRR at the second dose. Therefore, the recurrent rates of IHSR and ISRR were calculated as 6.9% (95% CI: 3.6%-11.7%) and 5.1% (95% CI: 4.1%-6.4%), respectively. At the second dose, 3 recipients (1 was IHSR and 2 were ISRR) needed additional examination and treatment at a center or neighborhood hospitals. The remaining recipients were self-limited without medication (Table III).

DISCUSSION

This single-center nested case-control study provides an outline of the incidence rates and risk factors for developing IHSR and ISRR among recipients of the Moderna COVID-19 vaccine in Japan. We conducted active surveillance at our center to document the clinical findings of all recipients who developed an AEFI regardless of the severity. Notably, more than 80% of all instances AEFI were classified as ISRR, instead of IHSR, and the incidence rates of both IHSR and ISRR were significantly higher after the first dose compared with the second one; however, the overall incidence of AEFI was very low at both first and second doses. By comparing clinical characteristics between recipients with and without AEFI, we identified several risk factors associated with the development of IHSR and ISRR.

We observed that the incidence rate of IHSR was very low, approximately 266 cases per million doses (0.03%) of all recipients, at both first and second doses, which is significantly different from the estimated incidence reported previously. Blumenthal et al[18] conducted a questionnaire-based study and described that the incidence rate of IHSR within 3 days after the injection was 2.1% of 64,900 health care employees who received their first dose of the Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines. Contrarily, Myles et al[19] conducted real-time surveillance by an allergist at a mass vaccination center and reported an incidence rate of 0.12% of IHSR among the 14,655 vaccine recipients. Our results are in line with those reported by Myles et al.[19] Likewise, the anaphylaxis rate was also extremely low in our study (2 cases per million doses), which is consistent with the existing data reports for the United States.[4,5]

The mechanisms of IHSR after the Moderna vaccine administration are not completely clarified; however, polyethylene glycol (PEG)-2000 is the identified candidate allergen.[20] Currently, only the female gender and history of allergy are known factors associated with an increased risk of anaphylaxis to mRNA vaccines. Shimabukuro et al[5] reported that anaphylaxis was more frequently observed in females than males. Similarly, Desai et al[6] documented that people with a history of allergy and anaphylaxis had a 2 to 7 times higher incidence of anaphylaxis after vaccination compared with people without any history of allergy. Our findings were comparable to these studies regarding the risk factors for IHSR. In addition, we identified comorbidities (asthma, atopic dermatitis, and thyroid diseases) that were associated with a greater risk of IHSR. Thyroid diseases were also identified as a risk factor for IHSR to contrast media[14] but not to other common drugs. Asthma and atopic dermatitis are established risk factors for IHSR to several drugs.[15] Thus, it seems that populations with atopic dermatitis and asthma are predisposed to develop IHSR to drugs, including mRNA vaccines, but the response may not be specific to mRNA vaccine components, such as PEG-2000. Taking the low incidence rate of IHSR into account, recipients with risk factors are at an increased risk of IHSR, but this is not of sufficient magnitude to warrant a contraindication to vaccinations or special measures regarding their vaccination (premedication or a change in the postvaccination observation period).

The 2 previous studies evaluated the recurrence rate of IHSR after the second dose in recipients with a previous history of IHSR at the first dose. The first study by Krantz et al,[21] which was based on a group of 159 recipients with a history of IHSR including 19 cases of anaphylaxis, investigated the second dose tolerance in the United States. The study found that the incidence rate of IHSR to the second dose was 20% among recipients who had a history of IHSR to the first dose, and their symptoms were self-limited, mild, and/or resolved with antihistamines alone. Recently, Macy et al[22] reported a population-based cohort study that enrolled 391,123 recipients in the United States. The study found that the 6.7% of incidence rate of IHSR at the second dose among recipients with a vhistory of IHSR included none of the anaphylaxis cases. In the present study, the recurrence rate of IHSR was low (7%), and dominantly recurrent IHSR were self-limited. No anaphylaxis cases were observed at the second dose in Japanese population, similar to those reported by previous studies.[21,22] Our findings reconfirmed that the Moderna vaccine may have good tolerance to the second dose among recipients with a history of IHSR to the first dose and that the IHSR events at the first dose may not be usually a contraindication to further vaccinations. IHSR can be attributed to IgE-mediated and non−IgE-mediated mechanisms, including complement activation-related pseudoallergy (CARPA). Warren et al[23] investigated patients with IHSR to mRNA COVID-19 vaccines and suggested that the IHSR are likely due to IgG anti−PEG-induced CARPA based on the results of the skin test and basophil activation test. The evidence that patients have gone on to receive second doses uneventfully may support that their initial reactions were not IgE-mediated mechanisms.

It is known that ISRR is caused by anxiety and fear about injection, needles, vaccine components, adverse events, or preexisting conditions.[16] The incidence rate of ISRR in our study was low but not enough to be ignored (2129 cases per million

doses: 0.21%). A notable finding was the significantly high incidence rate of vasovagal syncope (72 cases per million doses), although people who had a history of vasovagal reflex were screened and were administered the vaccine in a lying position. Hause et al[7] also reported a high incidence of vasovagal syncope after the J&J/Janssen COVID-19 vaccine, a viral vector vaccine, estimated at 8.2 per 100,000 doses in mass vaccination centers in the United States. Strikingly, the incidence rate of vasovagal syncope after COVID-19 vaccines was significantly higher than the influenza vaccine (0.05 per 100,000 doses),[7] and similar to that of the quadrivalent human papillomavirus vaccine (7.8 cases per 100,000 doses).[24] In addition, we found that several clinical symptoms and signs resulted from ISRR, especially, a type of neurological symptoms, known as the FNDs,[25] that were difficult to assess as caused by psychological or organic factors in the setting of mass vaccination. Indeed, 2% of recipients with ISRR were transported to hospitals, and one-third of these patients showed neurological symptoms most likely due to FNDs, although more careful evaluations are needed for the diagnosis. Further studies with active surveillance are needed for a better understanding of the incidence of FNDs and to take appropriate mitigating measures at mass vaccination centers.

For effective implementation of precautionary measures, it is important to first identify individuals with a high risk of ISRR.[16] In general, adolescence, female gender, mental disorders, and history of vasovagal reflex were considered as the risk factors for ISRR.[7,16] Our findings reaffirm that these risk factors increase the chances of developing an ISRR after mRNA vaccines. In addition, specific comorbidities (asthma and thyroid diseases) and a history of allergy were identified as additional risk factors of ISRR. There are several possibilities regarding these associations. The presence of comorbidities and a history of allergy may provoke strong anxiety and fear about the allergic adverse events and the effects of vaccination on comorbidities, especially during the first dose. The present scenario that this mRNA vaccine is a novel type of vaccine for infectious diseases may increase the associated fear and anxiety. Also, asthma[26] and thyroid diseases[27] increase the risk of mental disorders by 1.5 times and 2.3-3.5 times, respectively, and undiagnosed or under-reported mental disorders may increase the risk of ISRR. Therefore, at mass vaccination centers, providers should be aware that a greater proportion of recipients are predisposed to ISRR after vaccination compared with the known high-risk cases.

Several symptoms, especially respiratory and gastrointestinal, are overlapped between IHSR and ISRR. To check for potential misclassification between IHSR and ISRR, we performed sensitivity analyses by narrowing the case definitions to reduce the effect of misclassification. The risk factors for IHSR and ISRR were consistent in our sensitivity analysis even while using narrowed case definitions, except for atopic dermatitis for IHSR with low prevalence, suggesting that there is little effect of misclassification.

There are several limitations to this study. First, a selection bias may limit the generalizability of our findings. This study was conducted at a single center and a single country. ISRR can be affected by environmental factors of the vaccination center and can occur in clusters or group settings.[28] Therefore, the incidence rate of ISRR cannot be specified in a mass vaccination center. Second, the possibility of underestimation of the incidence rate of IHSR and ISRR cannot be denied. The observation period after the administration of the vaccine was limited (mean observation time was 20 minutes: see this article's Online Repository Text 1 at www.jaci-inpractice.org) due to the study design. Third, the sample size of the case with IHSR was smaller than planned due to the low incidence rate of IHSR in our study (see this article's Online Repository Text 2 at www.jaci-inpractice.org). Therefore, our sample size of IHSR may not have statistical power to detect the factors that slightly increased the risk of IHSR with a low prevalence rate, such as atopic dermatitis, in the sensitivity analysis. Fourth, the simple randomization method without bootstrapping algorithms was used for matching and may cause biases in the estimation of the effect on increased risk of IHSR and ISRR. Fifth, the data on comorbidities were collected based on the recipient's self-reported information. We did not evaluate the treatment states or etiology of comorbidities, such as thyroid diseases. We suggest that multicenter and multinational studies may complement the limitations of our study.

CONCLUSION

The incidence rate of IHSR and anaphylaxis in our single-center study was very low, suggesting that the Moderna COVID-19 vaccine can be used safely for mass vaccinations. However, health care providers need to take appropriate measures to prevent and respond adequately to the development of ISRR. Although recipients with risk factors are at an increased risk of IHSR and ISRR, this is not of sufficient magnitude to warrant a contraindication to vaccinations or special measures regarding their vaccination.

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ONLINE REPOSITORY

TEXT 1: THE OVERVIEW OF THE SELF-DEFENCE FORCES TOKYO LARGE-SCALE VACCINATION CENTRE IN JAPAN

Location

A center located in Otemachi, Chiyoda-ku, Tokyo, Japan.

Floor layout

1F: Entrance and a first-aid room
2F: Vaccination floor and a first-aid room.
4F: Vaccination floor and a first-aid room.
7F: Vaccination floor and a first-aid room.
10F: Vaccination floor and a first-aid room.

Each first-aid room located close to each observation room, except for 1F.

Dosing and schedule

The Moderna COVID-19 vaccine was used in the center. The vaccine was stored at −20°C before its use and then thawed to the required temperature. Within 6 hours after thawing, the vaccine was administered intramuscularly (0.5 mL each). The standard vaccination interval between a first and a second dose was 28 days, and the permissible interval was 21-42 days.

Target population

In Japan, vaccination voucher is required for COVID-19 vaccination. The local governments established in the cities have distributed the vaccination vouchers to the residents. In addition, each local government has prioritized the distribution of vaccination vouchers to the residents (eg, medical workers, elderly person, and people who have any comorbidities). Therefore, the distribution schedule of vaccination vouchers and the possible timing of receiving vaccination were different among the cities. The center initially targeted people who received a vaccination voucher, were aged over 65 years, and lived in Kanto area, Japan, from May 24 to June 16, 2021. Then the target was expanded to people aged over 18 years who lived in Japan from June 17 to September 24, 2021.

Exclusion criteria for vaccine administration

According to the national guidelines, the exclusion criteria for vaccine administration in the center were defined as follows: people who have a fever (body temperature >37.5°C), acute serious illness that is treatable, and anaphylaxis episode for polyethylene glycol.

Number of administration doses

The target number of administration doses in the center was 10,000 per day. During May 24 to September 24, a total of 1,201,688 vaccine doses (611,779 and 589,909 for a first dose and a second dose, respectively) were administrated in the center. The average of vaccination doses per day was 9770 doses.

Administration procedure

1. All recipients needed to fill all items in the pre-vaccination screening questionnaire for COVID-19 vaccine distributed by the Ministry of Health, Labour and Welfare, before the injection of each first and second dose.
2. A nurse checked all items in the pre-vaccination screening questionnaire. A nurse asked recipients detailed questions about their comorbidities, history of allergy, and history of vasovagal reflex after the injection or collecting blood. If a misstatement or omission was found, the recipient was requested to revise and fill all items.
3. A medical doctor conducted medical inquiries for recipients and checked all items in the pre-vaccination screening questionnaire. The medical doctor determined the observation period after the injection based on the history of allergy. The observation period was 30 minutes for the recipient who had a history of anaphylaxis for any causes and 15 minutes for all other recipients.
4. A trained nurse injected the vaccine intramuscularly for the recipients. Generally, a recipient was injected when sitting on a chair. If a recipient had a history of vasovagal reflex, then the recipient was injected lying on the bed.
5. Center staff collected the pre-vaccination screening questionnaire. Recipients who received a first dose of vaccination got a reservation for a second dose.
6. The recipient was observed for his or her condition in the observation room according to the observation period. The average time of staying from the injection to leaving the center was 20 minutes. If the recipient felt discomfort or any abnormalities, he or she was moved to a first-aid room and medically checked by a medical doctor. After the observation period, the recipient was allowed to leave the observation room. Center staff confirmed the appropriate completion of the observation period.

First-aid rooms in the center

The medical doctor medically checked each recipient, and the clinical findings were recorded. It was recommended that the recipients who showed severe immediate hypersensitivity reactions (IHSR) and anaphylaxis to the first dose should avoid a second dose of the Moderna vaccine. During May 24 to September 24, the average number of recipients who visited first-aid rooms per day was 24. If needed, the recipients were treated by medicine and transported to neighborhood hospitals. Information on the outcome of transported recipients in neighborhood hospitals was mailed to first-aid rooms and recorded.

TEXT 2: SAMPLE SIZE CONSIDERATION

In Japanese population, the prevalence rate of variable of interests was estimated from 1% (malignancy) to 30.6% (hypertension) according to the Ministry of Health, Labour and Welfare, Japan (https://www.mhlw.go.jp/toukei_hakusho/toukei/). In this matched controls study, we determined the minimum sample size as 408 cases and 1632 controls to detect the minimum odds ratio of 3.0 for increased risk factors with IHSR and immunization stress-related response (ISRR) with 1% prevalence rate, 80% power, and 0.05 two-sided type I error rate (α).

Before our study was started, Blumenthal et al[E1] reported that the incidence rate of IHSR to mRNA vaccine was 2.1% in vaccine recipients at the first dose. For other drugs such as penicillin and contrast media, the incidence rate of IHSR was approximately 0.1%. The incidence rate of ISRR was considered to be higher than that of IHSR. The target number of vaccination doses per day was set to 10,000 per day in the center. Thus, we assumed that approximately 1200-25,200 events of IHSR and more events of ISRR would be collected among 1,200,000 vaccine administration doses during the study period (May 24 to September 24).

However, the incidence rate of IHSR in this study was 0.03%, lower than a previous study and other drugs. Therefore, we collected only 318 events in 306 patients with IHSR in this study period. This sample size could detect the minimum odds ratios of 5.0, 4.0, 3.0, and 2.0 for 0.5%, 1%, 2%, and 5% prevalence rates of variable interests, respectively, with 80% power and 0.05 two-sided type I error rate (α; Table E8).

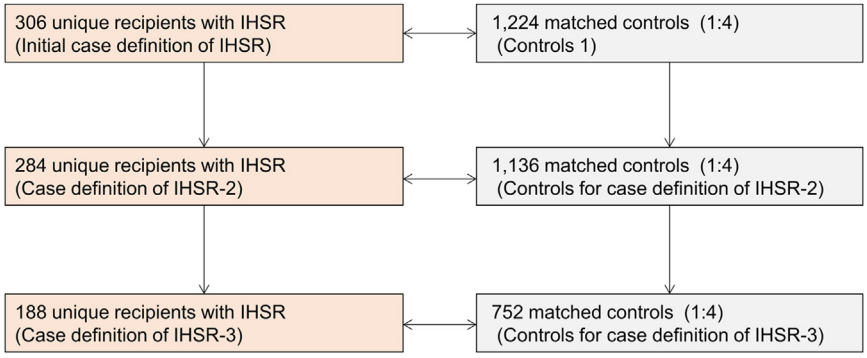

FIGURE E1. Flow diagram of immediate hypersensitivity reaction (IHSR) groups in sensitivity analysis. We excluded recipients with missing data in sensitivity analyses (complete case analysis). *IHSR-2*, Initial case definition without respiratory symptoms; *IHSR-3*, initial case definition included only clinical signs.

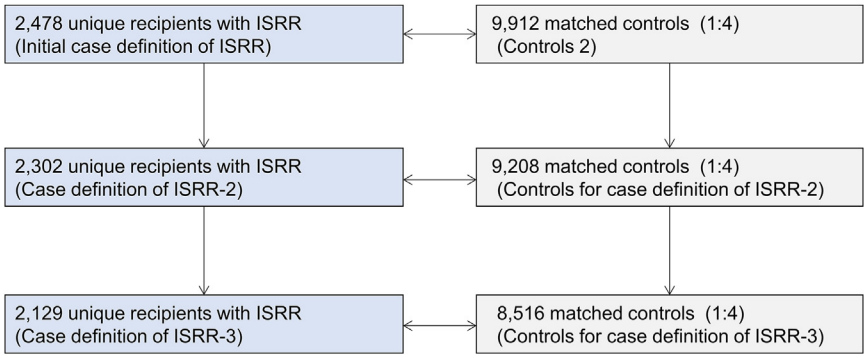

FIGURE E2. Flow diagram of immunization stress-related response (ISRR) groups in sensitivity analysis. We excluded recipients with missing data in sensitivity analyses (complete case analysis). *ISRR-2,* Initial case definition of ISRR without gastrointestinal symptoms; *ISRR-3,* initial case definition of ISRR without gastrointestinal and respiratory symptoms.

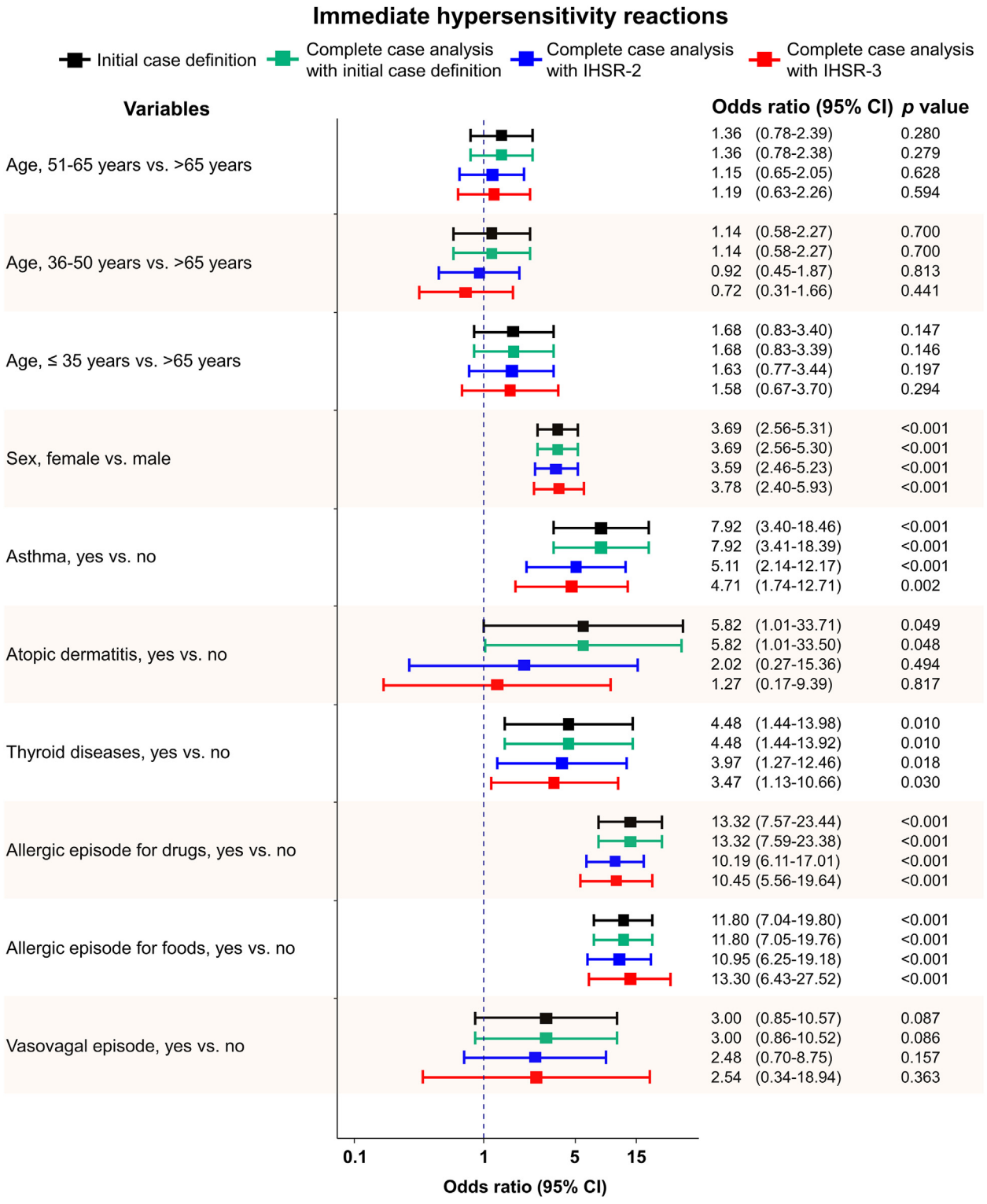

FIGURE E3. Multivariable conditional logistic regression for the immediate hypersensitivity reaction (IHSR) group in sensitivity analysis. Forest plot showing the odds ratio for increased risk of IHSR using multivariable analysis of conditional logistic regression analysis. The black, green, blue, and red plots indicate the estimated odds ratio by the initial case definition, complete case analysis with the initial case definition, the case definition of IHSR-2 and IHSR-3, respectively. The black, green, blue, and red horizontal lines indicate the estimated odds ratio and 95% confidence intervals by the initial case definition, and the case definition of IHSR-2, and IHSR-3, respectively. *CI*, Confidence interval; *IHSR-2*, initial case definition without respiratory symptoms; *IHSR-3*, initial case definition included only clinical signs.

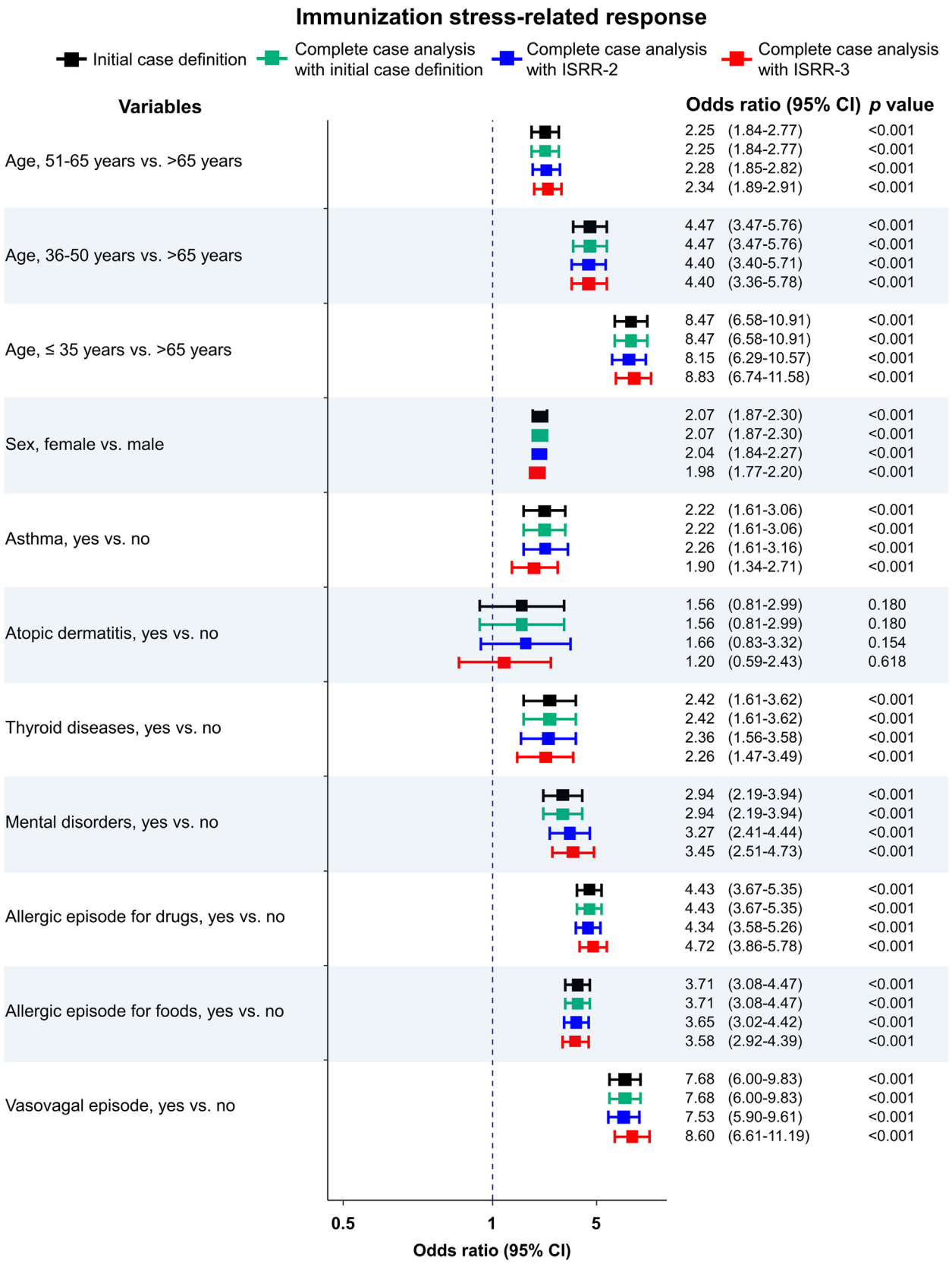

FIGURE E4. Multivariable conditional logistic regression for the immunization stress-related response (ISRR) group in sensitivity analysis. Forest plot showing the odds ratio for increased risk of ISRR using multivariable analysis of conditional logistic regression analysis. The black, green, blue, and red plots indicate the estimated odds ratio by the initial case definition, complete case analysis with the initial case

TABLE E1. Case definition of immediate hypersensitivity reaction (IHSR) in sensitivity analyses

Symptoms/signs	Initial	IHSR-2	IHSR-3
Any type of rash	Included	Included	Included
Angioedema	Included	Included	Included
Pruritus	Included	Included	
Wheezing	Included	Included	Included
Stridor	Included	Included	Included
Persistent cough	Included		
Hoarseness	Included		
Anaphylaxis	Included	Included	Included

IHSR-2, Initial case definition without respiratory symptoms; *IHSR-3*, initial case definition included only clinical signs.

TABLE E2. Case definition of immunization stress-related response (ISRR) in sensitivity analyses

Symptoms/signs	Initial	ISRR-2	ISRR-3
Mouth and throat discomfort	Included	Included	
Palpitations	Included	Included	Included
Cold sweat	Included	Included	Included
Shortness of breathing	Included	Included	
Chest pain	Included	Included	
Abdominal pain	Included		
Nausea	Included		
Vomiting	Included		
Diarrhea	Included		
Vertigo	Included	Included	Included
Syncope	Included	Included	Included
General weakness	Included	Included	Included
Numbness or loss of sensation	Included	Included	Included
Headache	Included	Included	Included
Malaise	Included	Included	Included
Hyperventilation/panic attack	Included	Included	Included
Photophobia	Included	Included	Included
Feeling of hot flush	Included	Included	Included
Vasovagal reflex	Included	Included	Included

Vasovagal reflex included hypotension and/or bradycardia.
ISRR-2, Initial case definition of ISRR without gastrointestinal symptoms;
ISRR-3, initial case definition of ISRR without gastrointestinal and respiratory symptoms.

definition, case definition of ISRR-2 and ISRR-3, respectively. The black, green, blue, and red horizontal lines indicate the estimated odds ratio and 95% confidence intervals by the initial case definition, and the case definition of ISRR-2 and ISRR-3, respectively. *CI*, Confidence interval; *ISRR-2*, initial case definition of ISRR without gastrointestinal symptoms; *ISRR-3*, initial case definition of ISRR without gastrointestinal and respiratory symptoms.

TABLE E3. Characteristics of all recipients without adverse events following immunization (AEFI) and matched controls

Demographic characteristic	Recipients without AEFI (N = 611,238)	Controls 1 (N = 1224)	Controls 2 (N = 9912)
Age (y)			
>65	196,168 (32)	467 (38)	2344 (26)
51-65	130,158 (21)	258 (21)	1913 (18)
36-50	140,193 (23)	264 (22)	2815 (29)
≤35	144,718 (24)	235 (19)	2840 (27)
Period at first dose			
May 24-June 23	235,749 (39)	591 (48)	3047 (31)
June 24-July 23	91,500 (15)	167 (14)	551 (6)
July 24-August 23	229,085 (37)	415 (34)	5334 (54)
August 24-September 24	55,106 (9)	48 (4)	957 (10)
Period at second dose			
May 24-June 23	782 (0)	0 (0)	2 (0)
June 24-July 23	254,220 (42)	532 (44)	2603 (27)
July 24-August 23	73,884 (12)	128 (11)	891 (9)
August 24-September 24	260,948 (43)	533 (45)	6282 (64)

Data are presented as n (%).

TABLE E4. Participant of immediate hypersensitivity reaction (IHSR) groups in sensitivity analysis

	IHSR-2			IHSR-3		
Demographic characteristic	Cases (N = 284)	Controls (N = 1136)	*P* value	Cases (N = 188)	Controls (N = 752)	*P* value
Age (y)						
>65	103 (36.3)	441 (38.8)	.853	74 (39.4)	324 (43.1)	.610
51-65	63 (22.2)	237 (20.9)		42 (22.3)	147 (19.5)	
36-50	62 (21.8)	249 (21.9)		36 (19.1)	156 (20.7)	
≤35	56 (19.7)	209 (18.4)		36 (19.1)	125 (16.6)	
Sex						
Male	61 (21.5)	651 (57.3)	<.001	44 (23.4)	446 (59.3)	<.001
Female	223 (78.5)	485 (42.7)		144 (76.6)	306 (40.7)	
Comorbidities						
Hypertension	40 (14.1)	148 (13.0)	.626	33 (17.6)	120 (16)	.582
Diabetes	12 (4.2)	58 (5.1)	.646	8 (11.7)	42 (5.9)	.587
Dyslipidemia	16 (5.6)	54 (4.8)	.541	15 (4.3)	44 (5.6)	.312
Cardiovascular diseases	4 (1.4)	39 (3.4)	.082	3 (1.6)	30 (4.0)	.125
Asthma	20 (7.0)	16 (1.4)	<.001	14 (7.4)	13 (1.7)	<.001
Atopic dermatitis	4 (1.4)	3 (0.3)	.033	4 (2.1)	3 (0.4)	.033
Thyroid diseases	14 (4.9)	11 (1.0)	<.001	11 (5.9)	9 (1.2)	<.001
Malignancy	5 (1.8)	19 (1.7)	1.000	3 (1.6)	16 (2.1)	.780
Mental disorders	6 (2.1)	19 (1.7)	.615	4 (2.1)	18 (2.4)	1.000
History						
Allergic episodes for drugs	81 (28.5)	36 (3.2)	<.001	54 (28.7)	28 (3.7)	<.001
Allergic episodes for foods	76 (26.8)	29 (2.6)	<.001	49 (26.1)	20 (2.7)	<.001
Vasovagal episode	8 (2.8)	10 (0.9)	.016	3 (1.6)	5 (0.7)	.202
No. of vaccine doses received						
First	189 (66.5)	756 (66.5)	1.000	128 (68.1)	512 (68.1)	1.000
Second	95 (33.5)	380 (33.5)		60 (31.9)	240 (31.9)	
Period						
May 24-June 23	90 (31.7)	360 (31.7)	1.000	72 (38.3)	288 (38.3)	1.000
June 24-July 23	57 (20.1)	228 (20.1)		30 (16.0)	120 (16.0)	
July 24-August 23	80 (28.2)	320 (28.2)		50 (26.6)	200 (26.6)	
August 24-September 24	57 (20.1)	228 (20.1)		36 (19.1)	144 (19.1)	

Data are presented as n (%).
IHSR-2, Initial case definition without respiratory symptoms; *IHSR-3*, initial case definition included only clinical signs.

TABLE E5. Participant of immunization stress-related response (ISRR) groups in sensitivity analysis

	ISRR-2			ISRR-3		
Demographic characteristic	Cases (N = 2302)	Controls (N = 9208)	*P* value	Cases (N = 2129)	Controls (N = 8516)	*P* value
Age (y)						
>65	400 (17.4)	2200 (23.9)	<.001	364 (17.1)	1987 (23.3)	<.001
51-65	342 (14.9)	1784 (19.4)		312 (14.7)	1657 (19.5)	
36-50	576 (25.0)	2596 (28.2)		516 (24.2)	2424 (28.5)	
≤35	984 (42.7)	2628 (28.5)		937 (44.0)	2448 (28.7)	
Sex						
Male	767 (33.3)	5081 (55.2)	<.001	727 (34.1)	4699 (55.2)	<.001
Female	1535 (66.7)	4127 (44.8)		1402 (65.9)	3817 (44.8)	
Comorbidities						
Hypertension	149 (6.5)	850 (9.2)	<.001	135 (6.3)	753 (8.8)	<.001
Diabetes	50 (2.2)	326 (3.5)	.001	44 (2.1)	294 (3.5)	.001
Dyslipidemia	85 (3.7)	383 (4.2)	.311	74 (3.5)	348 (4.1)	.560
Cardiovascular diseases	51 (2.2)	184 (2.0)	.510	45 (2.1)	172 (2.0)	.784
Asthma	85 (3.7)	112 (1.2)	<.001	75 (3.5)	106 (1.2)	<.001
Atopic dermatitis	18 (0.8)	33 (0.4)	.008	17 (0.8)	30 (0.4)	.007
Thyroid diseases	49 (2.1)	84 (0.9)	<.001	43 (2.0)	79 (0.9)	<.001
Malignancy	25 (1.1)	85 (0.9)	.473	21 (1.0)	68 (0.8)	.395
Mental disorders	104 (4.5)	119 (1.3)	<.001	96 (4.5)	107 (1.3)	<.001
History						
Allergic episodes for drugs	302 (13.1)	285 (3.1)	<.001	275 (12.9)	260 (3.1)	<.001
Allergic episodes for foods	286 (12.4)	304 (3.3)	<.001	254 (11.9)	283 (3.3)	<.001
Vasovagal episode	242 (10.5)	129 (1.4)	<.001	232 (10.9)	121 (1.4)	<.001
No. of vaccine doses received						
First	1708 (74.2)	6832 (74.2)	1.000	1591 (74.7)	6364 (74.7)	1.000
Second	594 (25.8)	2376 (25.8)		538 (25.3)	2152 (25.3)	
Period						
May 24-June 23	449 (19.5)	1796 (19.5)	1.000	405 (19.0)	1620 (19.0)	1.000
June 24-July 23	305 (13.2)	1220 (13.2)		275 (12.9)	1100 (12.9)	
July 24-August 23	998 (43.4)	3992 (43.4)		941 (44.2)	3764 (44.2)	
August 24-September 24	550 (23.9)	2200 (23.9)		508 (23.9)	2032 (23.9)	

Data are presented as n (%).
ISRR-2, Initial case definition of ISRR without gastrointestinal symptoms; *ISRR-3*, initial case definition of ISRR without gastrointestinal and respiratory symptoms.

TABLE E6. Estimated incidence rates of adverse events following immunization

	Total dose (N = 1,201,688)		First doses (N = 611,779)		Second doses (N = 589,909)		
Events	Total no. of events	Incidence rate (95% CI)	Total no. of events	Incidence rate (95% CI)	Total no. of events	Incidence rate (95% CI)	*P* value
IHSR	318	265.6 (236.3-295.3)	213	348.2 (303.0-398.2)	105	178.0 (145.6-215.5)	<.001
ISRR	2558	2128.7 (2047.1-2212.7)	1842	3010.9 (2875.1-3151.4)	714	1210.4 (1123.2-1302.4)	<.001
Anaphylaxis	2	1.7 (0.2-6.0)	1	1.6 (0-9.1)	1	1.7 (0-9.4)	1.000
Vasovagal syncope	86	71.6 (57.2-88.4)	76	123 (97.9-155.5)	10	17.0 (8.1-31.1)	<.001

Incidence rates of acute adverse events were calculated by using vaccine administration of doses in a center as the denominator. Incidence rates were shown as per million doses.
CI, Confidence interval; *IHSR*, immediate hypersensitivity reactions; *ISRR*, immunization stress-related responses.

TABLE E7. Number of events of clinical symptoms and signs

Symptoms/signs	Total events, N (rates per million doses [95% CI])	Immediate hypersensitivity reactions, N (rates per million doses [95% CI])	Immunization stress-related responses, N (rates per million doses [95% CI])
Skin, facial, and oral symptoms/signs			
Any type of rash*	193 (160.6 [138.8-184.9])	193 (160.6 [138.8-184.9])	0 (0)
Angioedema*	7 (5.8 [2.3-12.0])	7 (5.8 [2.3-12.0])	0 (0)
Pruritus*	147 (122.3 [103.4-143.8])	147 (122.3 [103.4-143.8])	0 (0)
Mouth and throat discomfort	179 (149.0 [127.9-172.4])	33 (27.5 [18.9-38.6])	146 (121.5 [102.6-142.9])
Cardiovascular symptoms/signs			
Palpitations	298 (248.0 [220.6-277.8])	8 (6.7 [2.9-13.1])	290 (241.3 [214.4-270.8])
Cold sweat	125 (104.0 [86.6-123.9])	1 (0.8 [0-4.6])	124 (103.2 [85.8-123.0])
Respiratory symptoms/signs			
Wheezes or stridor*	4 (3.3 [0.9-8.5])	4 (3.3 [0.9-8.5])	0 (0)
Hoarseness*	1 (0.8 [0-4.6])	1 (0.8 [0-4.6])	0 (0)
Persistent cough*	25 (20.8 [13.5-30.7])	25 (20.8 [13.5-30.7])	0 (0)
Shortness of breathing	138 (114.8 [96.5-135.7])	13 (10.8 [5.8-18.5])	125 (104.0 [86.6-123.9])
Chest pain	37 (30.8 [21.7-42.4])	0 (0)	37 (30.8 [21.7-42.4])
Gastrointestinal symptoms/signs			
Abdominal pain	21 (17.5 [10.8-26.7])	3 (2.5 [0.5-7.3])	18 (15.0 [8.9-23.7])
Nausea	281 (233.8 [207.3-262.8])	12 (10.0 [5.2-17.4])	269 (223.9 [197.9-252.3])
Vomiting	14 (11.7 [6.4-19.5])	0 (0)	14 (11.7 [6.4-19.5])
Diarrhea	2 (1.7 [0.2-6.0])	0 (0)	2 (1.7 [0.2-6])
Neurological symptoms/signs			
Vertigo	891 (741.5 [693.6-791.8])	8 (6.7 [2.9-13.1])	883 (734.8 [687.2-784.9])
Syncope	86 (71.6 [57.2-88.4])	0 (0)	86 (71.6 [57.2-88.4])
General weakness	47 (39.1 [28.7-52.0])	2 (1.7 [0.2-6])	45 (37.4 [27.3-50.1])
Numbness or loss of sensation	411 (342.0 [309.8-376.7])	8 (6.7 [2.9-13.1])	403 (335.4 [303.4-369.8])
Other symptoms/signs			
Headache	112 (93.2 [76.7-112.1])	3 (2.5 [0.5-7.3])	109 (90.7 [74.5-109.4])
Malaise	497 (413.6 [378-451.6])	11 (9.2 [4.6-16.4])	486 (404.4 [369.3-442])
Hyperventilation/panic attack	30 (25.0 [16.8-35.6])	1 (0.8 [0-4.6])	29 (24.1 [16.2-34.7])
Photophobia	28 (23.3 [15.5-33.7])	3 (2.5 [0.5-7.3])	25 (20.8 [13.5-30.7])
Feeling of hot flush	22 (18.3 [11.5-27.7])	0 (0)	22 (18.3 [11.5-27.7])
Abnormalities of vital signs			
Hypotension	458 (381.1 [347-417.7])	6 (5.0 [1.8-10.9])	452 (376.1 [342.3-412.5])
Hypertension	171 (142.3 [121.8-165.3])	32 (26.6 [18.2-37.6])	139 (115.7 [97.2-136.6])
Bradycardia	385 (320.4 [289.2-354.0])	10 (8.3 [4.0-15.3])	375 (312.1 [281.3-345.3])
Tachycardia	33 (27.5 [18.9-38.6])	6 (5.0 [1.8-10.9])	27 (22.5 [14.8-32.7])
Tachypnoea	40 (33.3 [23.8-45.3])	3 (2.5 [0.5-7.3])	37 (30.8 [21.7-42.4])

Data are presented as n (incidence rates per million doses [95% CI]).
CI, Confidence interval.
*Specific events for immediate hypersensitivity reactions. Hypotension: systolic blood pressure <90 mm Hg and/or diastolic blood pressure <60 mm Hg, hypertension: systolic blood pressure >180 mm Hg and/or diastolic blood pressure >110 mm Hg, bradycardia: heart rate <60 beats per minute, tachycardia: heart rate >120 beats per minute and tachypnoea: respiratory rate >24 per min.

TABLE E8. Sample size calculation

Prevalence rate (%)	Minimum odds ratio of detection	Power	Two-sided type I error rate (α)	Cases	Controls (1:4)
0.5	5.0	0.8	0.05	262	1048
0.5	4.0	0.8	0.05	413	1652
0.5	3.0	0.8	0.05	802	3208
0.5	2.0	0.8	0.05	2643	10,572
1	4.0	0.8	0.05	211	844
1	3.0	0.8	0.05	408	1632
1	2.0	0.8	0.05	1136	5344
2	4.0	0.8	0.05	110	440
2	3.0	0.8	0.05	211	844
2	2.0	0.8	0.05	683	2732
5	4.0	0.8	0.05	50	200
5	3.0	0.8	0.05	93	372
5	2.0	0.8	0.05	292	1168

REFERENCE

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