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Acute Adverse Events at a Mass Vaccination Site after the Third and Fourth COVID-19 Vaccinations in Japan

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The third and fourth doses of the vaccine against coronavirus disease 2019 (COVID-19) were widely administered in Japan since December 2021. Currently, however, data are scarce regarding acute adverse events with the third and fourth doses. The present study reports the profiles of acute adverse events after the third and fourth COVID-19 vaccine doses, seen at the site of a mass vaccination center in Japan. Between December 2021 and July 2022, 267,515 individuals received the third, and 32,934 received the fourth COVID-19 vaccine dose at the mass vaccination center, of whom 442 recipients of the third (0.19%), and 22 recipients of the fourth (0.07%) dose reported acute adverse events and were examined by doctors on site. The most common diagnosis was vasovagal syncope/presyncope (incidence: 0.01-0.10%), followed by other miscellaneous complaints, acute allergic reactions (0.05-0.005%), and anaphylaxis (< 0.005%). Vasovagal syncope/presyncope occurred most frequently in recipients in those in their 20s, whereas acute allergic reactions were most frequent in those in their 40s. Both reactions were more frequent in women than men. The peak occurrence of vasovagal syncope/presyncope was earlier than 15 min after the injection, whereas that of acute allergic reaction was later than 15 min after the injection. The incidence of acute allergic reactions appeared to differ between various vaccine manufacturers, whereas that of vasovagal syncope/presyncope did not. These real-world data may benefit the safe and efficient implementation of mass vaccination campaigns for citizens who want to receive COVID-19 vaccines now and in the future.

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Introduction

As of the end of 2022, the world is still struggling with the ongoing coronavirus disease 2019 (COVID-19) pandemic, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (World Health Organization 2022). Mass vaccination campaigns against COVID-19 have been implemented across nations worldwide, and most of the real-world reports have indicated a vaccine effectiveness > 50% at suppressing transmission of the disease (Lopez Bernal et al. 2021; Akaishi et al. 2022b; Mahumud et al. 2022; Wilder-Smith 2022), even with the newer Omicron subvariants (Vitiello et al. 2022), and effectiveness is expected to be maintained up to 6 months after the full series of injections (Tartof et al. 2021; Akaishi et al. 2022a). The third dose of the COVID-19 vaccine has been offered in Japan since December 2021. As of December 2022, > 65% of people in Japan have completed three doses of the COVID-19 vaccine (Prime Minister of Japan and His Cabinet 2022). Local governments across the country have established and managed mass vaccination centers in order to conduct efficient mass vaccination campaigns for residents. The safety of those receiving vaccines at mass vaccination centers is of the utmost importance.

In Miyagi Prefecture, a mass vaccination center was collaboratively established and managed by the Miyagi prefectural government and Tohoku University Hospital between May 2021 and July 2022. During this time, a total

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of > 600,000 COVID-19 vaccine doses have been administered at this center, and electronic medical records from recipients who became ill and required examinations by on-site doctors were continuously gathered. The profiles of acute adverse events after the first and second vaccine doses were previously reported, based on data from individuals who had acute adverse events after the first and second vaccines at the same vaccination center (Akaishi et al. 2022c). In that report, a significantly higher rate of vasovagal syncope/presyncope was reported after the first, compared to the second dose, especially in younger recipients. Moreover, that report showed that the incidence of acute allergic reactions at the vaccination center was < 0.1%, and that of anaphylaxis was < 0.01% in all recipients.

The profiles of acute adverse events after the third or fourth COVID-19 vaccine, however, currently remain largely unevaluated. Therefore, the present study reported the detailed profiles of the acute adverse events observed at the vaccination center after the third and fourth doses of the COVID-19 vaccine, with an aim to further support and facilitate safe and efficient mass vaccinations for recipients who want to receive the vaccine now and in the future.

Methods

Study design

All individuals who received the third and/or fourth COVID-19 vaccine doses at a mass vaccination center in Sendai City, Japan, between December 20, 2021 and July 31, 2022, were enrolled in the present study. This mass vaccination center was first established in May 2021, and was collaboratively managed by Tohoku University Hospital (Sendai, Japan) and the Miyagi Prefecture government. Individuals who had previously experienced a severe allergic reaction within 30 min of receiving COVID-19 vaccines were recommended to forgo the subsequent vaccines. All recipients were asked to stay in the observation area for at least 15 min after the injection, although they were allowed to stay in the observation area until they felt well enough to go home. Recipients who had previously experienced some vaccine-related allergic reactions were asked to stay in the observation area for at least 30 min after the injection.

There was a doctor stationed inside a first-aid office within the vaccination center, and all vaccine recipients who felt unwell, became faint, or had other symptoms during the on-site observation period were examined and diagnosed by that doctor. Electronic medical records, including demographic data, clinical symptoms, time from the injection to the onset of symptoms, vaccine types used (mRNA-1273, BNT162b2, NVX-CoV2373), diagnosis, drugs administered (oral medications, intravenous treatments, intramuscular adrenaline injections), and outcomes (discharged home, transferred to the hospital) of those individuals who experienced adverse reactions were retrospectively evaluated. The diagnoses were categorized as vasovagal syncope/presyncope, acute allergic reaction, anaphylaxis, and other. Each diagnosis was made clinically, without performing blood tests. The incidence of acute adverse events after the third and/or fourth dose of the vaccination was compared with the incidence after the first two doses of the vaccination, and was also compared among the three vaccine types from different manufacturers.

Individuals who had previously experienced an acute adverse reaction at the vaccination center within 30 min of receiving the first, second, or third COVID-19 vaccine dose were recommended by doctors during their pre-vaccination interview to forgo the subsequent vaccines. Nevertheless, some of them wished to receive them. In these cases, doctors in charge of pre-vaccination interview recommended them to receive the vaccine in the first-aid office for closer symptom observation and quicker treatment interventions, when needed.

Vaccine types and dosages

The following COVID-19 vaccines, from three different manufacturers, were used as the third vaccine dose during the study period: Moderna mRNA-1273 [messenger RNA (mRNA) vaccine; intramuscular injection, 0.25 mL] (Baden et al. 2021); Pfizer BNT162b2 (mRNA vaccine; intramuscular injection, 0.30 mL) (Polack et al. 2020); and Novavax NVX-CoV2373 (protein-based, adjuvanted vaccine; intramuscular injection, 0.50 mL) (Heath et al. 2021). Moderna mRNA-1273 was used between January and July 2022. Pfizer BNT162b2 was used for a week each in December 2021 and May 2022. Novavax NVX-CoV2373 was used only in July 2022 (4 weeks). Only Moderna's mRNA-1273 vaccine was available for the fourth vaccine dose. All the vaccine recipients of Moderna mRNA-1273 and Novavax NVX-CoV2373 were aged ≥ 18 years, and those of Pfizer BNT162b2 were aged ≥ 12 years.

Statistical analysis

The age distribution in each group was described as mean and interquartile range (IQR; 25th-75th percentiles) due to the non-normal distribution of age. The age distributions between groups were compared using the Mann-Whitney U test. Comparisons of the incidence of acute adverse events between groups were performed using the chi-squared or Fisher's exact test, depending on the size of each subgroup. In the binary logistic regression analyses, age, sex, and vaccine manufacturer (Moderna, Pfizer, Novavax) were used as the explanatory variables, and the occurrence of each type of acute adverse events was used as the dependent variable. Adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated. Two-sided *P*-values < 0.05 were considered statistically significant in the present study. Adjustment for multiple comparisons was not performed, due to the exploratory nature of the present study (Bender and Lange 2001). Statistical analyses were performed using R statistical software version 4.0.5 (R Foundation, Vienna, Austria).

Ethical approval

The protocol for the present study was approved by the institutional review board at Tohoku University Graduate School of Medicine (approval number: 2021-1-566). All procedures in the present study were performed in accordance with the latest version of the Declaration of Helsinki, as revised in 2013. Written informed consent was waived by the review board, based on the retrospective nature of the present study and anonymity of the data, and informed consent was obtained in an opt-out manner.

Results

Participants

During the study period, from December 2021 through July 2022, a total of 267,515 individuals received the third and/or fourth COVID-19 vaccine at the aforementioned mass vaccination center – 234,581 received the third, and 32,934 received the fourth vaccination. The demographic data of the participants are summarized in the top half of Table 1. Those receiving the third dose received either the Moderna mRNA-1273 (n = 221,716), Pfizer BNT162b2 (n = 10,912), or Novavax NVX-CoV2373 (n = 1,953) vaccine. All participants who received the fourth dose received the Moderna mRNA-1273 vaccine (n = 32,934). The age distribution of those who received the fourth dose was significantly higher than that of those who received the third dose ($P < 0.0001$, Mann-Whitney U test), primarily because from the onset of the nationwide vaccination campaign in early 2021, the Japanese government gave priority to older individuals (aged ≥ 65 years).

Incidence of acute adverse events by number of doses received

The incidence and type of acute adverse events after receiving the third and/or fourth COVID-19 vaccine at the mass vaccination center are summarized in the bottom half of Table 1. The occurrence of vasovagal syncope/presyncope (129 women, 73 men) and acute allergic reaction (58 women, 11 men) with the third vaccine dose was significantly higher in women than in men ($P < 0.0001$ for both events). Compared to the incidence of overall acute adverse events after the first (n = 1,426/131,544; 1.08%) or second mRNA-1273 dose (n = 476/126,419; 0.38%), which were previously reported (Akaishi et al. 2022c), the incidence rates after the third ($P < 0.0001$, both against the first and second doses) and/or fourth mRNA-1273 dose ($P < 0.0001$, both against the first and second doses) were significantly lower. The incidence rates of vasovagal syncope/presyncope after the third ($P < 0.0001$, both against the first and second doses) and/or fourth mRNA-1273 dose ($P < 0.0001$, both against the first and second dose) were also significantly lower than that after the first (n = 952/131,544; 0.72%) or second dose (n = 197/126,419; 0.16%). The incidence rates of acute allergic reactions, not including anaphylaxis, after the third ($P < 0.0001$, both against the first and second doses) and/or fourth mRNA-1273 dose ($P < 0.0001$, both against the first and second doses) were also significantly lower than the incidence after the first (n = 97/131,544; 0.07%) or second dose (n = 78/126,419; 0.06%). The incidence rates of anaphylaxis after the third ($P = 0.0868$ against the first dose and $P = 0.1490$ against the second dose) and/or fourth mRNA-1273 dose ($P > 0.99$, both against the first and second doses) were not significantly different from the incidence after the first (n = 6/131,544; 0.005%) or second dose (n = 5/126,419; 0.004%). It should be noted that individuals who had previously experienced a severe allergic reaction after the first or second COVID-19 vaccine were advised to forgo the third or fourth vaccine; therefore, many of those individuals did not receive the subsequent vaccination.

Symptom profiles

The overall number of individuals with each type of common acute adverse event occurring at the mass vaccination center, irrespective of the vaccine manufacturer, is shown in Table 2. After both the third and fourth vaccine doses, the common symptoms observed at the mass vaccination center included the following: dizziness; vertigo; palpitations; paresthesia of the limbs; pruritus; headache; pharyngeal discomfort; dyspnea; chest pain; and chest discomfort. None of the types of symptoms noted among those with acute adverse events at the mass vaccination center differed significantly between the third and fourth vaccinations.

Among the 208 patients with vasovagal syncope/presyncope, the symptoms included: dizziness/vertigo (n = 128; 61.54%); cold sweats (n = 59; 28.37%); nausea (n = 44; 21.15%); palpitations (n = 34; 16.35%); headache (n = 16; 7.69%); and paresthesia of the limbs (n = 12; 5.77%). Among the 71 patients with acute allergic reactions, the symptoms included: pruritus (n = 39; 54.93%); pharyngeal discomfort (n = 10; 14.08%); dyspnea or chest discomfort (n = 9; 12.68%); headache (n = 8; 11.27%); nausea (n = 7; 9.86%); dizziness/vertigo (n = 7; 9.86%); and skin reddening (n = 5; 7.04%). Among the four patients who experienced anaphylaxis, three experienced itching sensation in the face or throat accompanied by dyspnea, and the other patient experienced nausea and vertigo. None of the four patients were hypotensive or lost consciousness.

Time from injection to onset

The mean and IQR of the elapsed time from the vaccine injection to the onset of acute adverse events at the mass vaccination center were 14 (9-18) min in those with vasovagal syncope/presyncope and 18 (11-25) min in those with acute allergic reactions. The elapsed time from injection to the onset of acute adverse events was significantly shorter in patients with vasovagal syncope/presyncope than in those with acute allergic reactions ($P = 0.0043$; Mann-Whitney U test).

Table 1. Participant demographics and acute adverse event profiles after the third and/or fourth COVID-19 vaccine dose.

	Third vaccine dose	Fourth vaccine dose	*P*-values
Overall recipients (n)	234,581	32,934	n.a.
(Moderna mRNA-1273)	221,716 (94.52%)	32,934 (100.0%)	n.a.
(Pfizer BNT162b2)	10,912 (4.65%)	0	n.a.
(Novavax NVX-CoV2373)	1,953 (0.83%)	0	n.a.
Male [n (%)]	121,695 (51.88%)	17,868 (54.25%)	< 0.0001
(Moderna mRNA-1273)	114,950 (51.85%)	17,868 (54.25%)	< 0.0001
(Pfizer BNT162b2)	5,758 (52.77%)	0	n.a.
(Novavax NVX-CoV2373)	987 (50.54%)	0	n.a.
Age*	48 (33-60) years	69 (64-74) years	< 0.0001
(Moderna mRNA-1273)	48 (33-60) years	69 (64-74) years	< 0.0001
(Pfizer BNT162b2)	38 (18-49) years	-	n.a.
(Novavax NVX-CoV2373)	42 (33-50) years	-	n.a.
Overall acute adverse events at the vaccination center [n (%)]	442/234,581 (0.19%)	22/32,934 (0.07%)	< 0.0001
(Moderna mRNA-1273)	400/221,716 (0.18%)	22/32,934 (0.07%)	< 0.0001
(Pfizer BNT162b2)	34/10,912 (0.31%)	-	n.a.
(Novavax NVX-CoV2373)	8/1,953 (0.41%)	-	n.a.
Acute adverse events requiring drug administration [n (%)]†	65/234,581 (0.03%)	3/ 2,934 (0.01%)	0.0426
(Moderna mRNA-1273)	62/221,716 (0.03%)	3/32,934 (0.01%)	0.0418
(Pfizer BNT162b2)	1/10,912 (0.01%)	-	n.a.
(Novavax NVX-CoV2373)	2/1,953 (0.10%)	-	n.a.
Acute adverse events requiring transfers to the hospital [n (%)]	4/234,581 (0.002%)	1/32,934 (0.003%)	0.4815
(Moderna mRNA-1273)	4/221,716 (0.002%)	1/32,934 (0.003%)	0.4997
(Pfizer BNT162b2)	0/10,912 (0.00%)	-	n.a.
(Novavax NVX-CoV2373)	0/1,953 (0.00%)	-	n.a.
Diagnosis with vasovagal syncope/presyncope [n (%)]	202/234,581 (0.09%)	6/32,934 (0.02%)	< 0.0001
(Moderna mRNA-1273)	182/221,716 (0.08%)	6/32,934 (0.02%)	< 0.0001
(Pfizer BNT162b2)	17/10,912 (0.16%)	-	n.a.
(Novavax NVX-CoV2373)	3/1,953 (0.15%)	-	n.a.
Male with vasovagal syncope/presyncope [n (%)]	73 (36.14%)	2 (33.33%)	> 0.99
Diagnosis with acute allergic reaction [n (%)]	69/234,581 (0.03%)	2/32,934 (0.006%)	0.0103
(Moderna mRNA-1273)	61/221,716 (0.03%)	2/32,934 (0.006%)	0.0142
(Pfizer BNT162b2)	5/10,912 (0.05%)	-	n.a.
(Novavax NVX-CoV2373)	3/1,953 (0.15%)	-	n.a.
Male with acute allergic reaction [n (%)]	11 (15.94%)	0 (0.0%)	> 0.99
Diagnosis with anaphylaxis (n [%])	3/234,581 (0.001%)	1/32,934 (0.003%)	0.4087
(Moderna mRNA-1273)	3/221,716 (0.001%)‡	1/32,934 (0.003%)§	0.4253
(Pfizer BNT162b2)	0/10,912 (0.00%)	-	n.a.
(Novavax NVX-CoV2373)	0/1,953 (0.00%)	-	n.a.
Male with anaphylaxis [n (%)]	1 (33.33%)	0 (0.0%)	> 0.99

*Median (IQR).

†Oral and/or intravenous medications.

‡One female in her 40s, one male in his 40s, and one female in her 60s. The female in her 40s was not hypotensive but had nausea and dizziness. She received an intramuscular adrenaline injection and was transferred to the hospital. The other two did not receive intramuscular adrenaline.

§A female patient in her 40s was not hypotensive, although she complained of systemic pruritus and throat discomfort. The patient received an intramuscular adrenaline injection and was transferred to the hospital.

n.a., not available.

Table 2. Symptom profiles of acute adverse events after the third and/or fourth vaccinations.

	Third vaccine dose	Fourth vaccine dose	*P*-values*
Nausea	76/442 (17.19%)	1/22 (4.55%)	0.1486
Dizziness, vertigo	166/442 (37.56%)	8/22 (36.36%)	> 0.99
Tinnitus, hearing problems	7/442 (1.58%)	0/22 (0.00%)	> 0.99
Pharyngeal discomfort	27/442 (6.11%)	1/22 (4.55%)	> 0.99
Palpitations	68/442 (15.38%)	4/22 (18.18%)	0.7616
Headache	44/442 (9.95%)	2/22 (9.09%)	> 0.99
Paresthesia of the limbs	58/442 (13.12%)	3/22 (13.64%)	> 0.99
Weakness of limbs	5/442 (1.13%)	1/22 (4.55%)	0.2540
Dyspnea, chest pain/discomfort	35/442 (7.92%)	1/22 (4.55%)	> 0.99
Abdominal pain/discomfort	6/442 (1.36%)	0/22 (0.00%)	> 0.99
Problems of the injection site	5/442 (1.13%)	0/22 (0.00%)	> 0.99
Pruritus	41/442 (9.28%)	3/22 (13.64%)	0.4534

*Two-tailed *P*-values based on Fisher's exact test.

Incidence of acute adverse events by age groups

Next, the incidence of vasovagal syncope/presyncope or acute allergic reactions (not including anaphylaxis) was compared between the third and fourth vaccinations, after stratification by age group. The incidence rate for each age group is shown in Table 3. In all age groups, the incidence rate of vasovagal syncope/presyncope or acute allergic reactions was not significantly different between the third and fourth vaccinations. The incidence of vasovagal syncope/presyncope after the third vaccination was highest in the ≤ 19 and 20-29 year-old groups, which was the same as the results of the first and second vaccinations, as previously reported (Akaishi et al. 2022c). When compared to the same data after the second vaccination, the incidence rate of vasovagal syncope/presyncope was not significantly different both in ≤ 19 years (second vs. third: 0.24% vs. 0.13%; $P = 0.0648$, chi-square test) and 20-29 year-old group (second vs. third: 0.23% vs. 0.20%; $P = 0.2984$). The incidence of acute allergic reactions after the third vaccination was highest in 30-39 and 40-49 year-old groups, which was also the same as the results after the second vaccination, as previously reported. When compared to the same data after the second vaccination, the incidence rate of acute allergic reactions after the third vaccination was slightly lower in the 30-39 year-old group (second vs. third: 0.08% vs. 0.03%; $P = 0.0237$), while it was not significantly different in the 40-49 year-old group (second vs. third: 0.07% vs. 0.04%; $P = 0.1303$).

Incidence of acute adverse events based on vaccine manufacturer

To compare the incidence of acute adverse events of vaccines between the three manufacturers (Moderna, Pfizer, and Novavax) utilized for the third COVID-19 vaccine, binary logistic regression analyses were performed by adjusting for age and sex, including the 234,581 individuals who received the third vaccine dose. The results are summarized in Table 4. The age- and sex-adjusted incidence rates of vasovagal syncope/presyncope were not significantly different among the three manufacturers, whereas that of acute allergic reactions was significantly higher for the Novavax NVX-CoV2373 than the Moderna mRNA-1273 vaccine (adjusted OR, 5.33; 95% CI, 1.67-17.04; $P = 0.0047$). Comparing the Pfizer BNT162b2 and Novavax NVX-CoV2373 vaccine, there was no significant difference (adjusted OR, 0.29; 95% CI, 0.07-1.20; $P = 0.0870$).

Significance of previous acute adverse events

Finally, to estimate the incidence of acute adverse events after receiving the third and/or fourth COVID-19 vaccine in individuals who experienced acute adverse events after receiving the first and/or second dose, we evaluated the incidence of acute adverse events after the third and/or fourth vaccine of those who received the vaccination at the first-aid office due to having had a previous acute adverse event. During the study period, 1,277 individuals received the third and/or fourth COVID-19 vaccine dose at the first-aid office, among whom 21 (1.64%) had an acute adverse event; 3 (0.23%) had vasovagal syncope/presyncope, 11 (0.86%) had an acute allergic reaction, and 7 (0.55%) had other miscellaneous symptoms. None of the patients had anaphylaxis. Compared with the 266,238 recipients who received vaccines in a standard injection booth, the incidence of overall acute adverse events was significantly higher in these 1,277 recipients (OR, 10.03; 95% CI, 6.45-15.60; $P < 0.0001$). While the incidence of vasovagal syncope/presyncope among the 1,277 recipients did not significantly differ from the remaining recipients (OR, 3.06; 95% CI, 0.98-9.57; $P = 0.0785$), the incidence of acute allergic reactions was significantly higher (OR, 38.55; 95% CI, 20.22-73.48; $P < 0.0001$). These findings indicate that the incidence rate of acute allergic reactions is significantly higher among those who had previously experienced acute adverse events after previous COVID-19 vaccinations than among those who did not.

Table 3. Incidence rates of vasovagal syncope/presyncope and acute allergic reactions by age groups.

	Third vaccine dose	Fourth vaccine dose	*P*-values*
Vasovagal syncope/presyncope [n (%)]			
-19 years old	13/9,966 (0.13%)	0/9 (0.00%)	> 0.99
20-29 years old	76/38,842 (0.20%)	0/147 (0.00%)	> 0.99
30-39 years old	38/32,442 (0.12%)	1/323 (0.31%)	0.3206
40-49 years old	24/45,092 (0.05%)	0/681 (0.00%)	> 0.99
50-59 years old	33/49,001 (0.07%)	0/1,797 (0.00%)	0.6312
60-69 years old	8/33,216 (0.02%)	2/13,574 (0.01%)	0.7338
70-79 years old	7/20,475 (0.03%)	2/12,756 (0.02%)	0.4971
80-89 years old	3/5,043 (0.06%)	1/3,317 (0.06%)	> 0.99
90- years old	0/5,04 (0.00%)	0/330 (0.00%)	> 0.99
Acute allergic reactions [n (%)]			
-19 years old	2/9,966 (0.02%)	0/9 (0.00%)	> 0.99
20-29 years old	14/38,842 (0.04%)	0/147 (0.00%)	> 0.99
30-39 years old	11/32,442 (0.03%)	0/323 (0.00%)	> 0.99
40-49 years old	20/45,092 (0.04%)	1/681 (0.15%)	0.2701
50-59 years old	13/49,001 (0.03%)	0/1,797 (0.00%)	> 0.99
60-69 years old	5/33,216 (0.02%)	0/13,574 (0.00%)	0.3305
70-79 years old	4/20,475 (0.02%)	1/12,756 (0.01%)	0.6553
80-89 years old	0/5,043 (0.00%)	0/3,317 (0.00%)	> 0.99
90- years old	0/504 (0.00%)	0/330 (0.00%)	> 0.99

The numbers of patients with acute allergic reactions did not include those with anaphylaxis.
*Two-tailed *P*-values based on Fisher's exact test.

Discussion

The incidence rates and types of acute adverse events after the third and/or fourth COVID-19 vaccine doses observed at the mass vaccination center have been described above in the present report. The most common diagnosis was vasovagal syncope/presyncope, comprising nearly half of the observed acute adverse events, followed by acute allergic reactions. The incidence of anaphylaxis was much lower, estimated to be < 0.005% (i.e., < 5 of every 100,000 injections) among all individuals who received the third and/or fourth COVID-19 vaccines. The peak age of those who experienced vasovagal syncope/presyncope was < 29 years of age, whereas the peak age of those who had an acute allergic reaction was between 20 and 49 years of age. The incidence of vasovagal syncope/presyncope and acute allergic reactions with the third vaccine dose were both significantly higher in female than in male recipients, particularly acute allergic reaction. The findings reported herein were almost the same as those observed after the first and/or second vaccine doses, with the minor exception of the abnormally high incidence of vasovagal syncope/presyncope with the first vaccine dose (> 1% of all vaccine recipients).

One of the notable new findings of the present study was the possible difference in the incidence of acute allergic reactions at the vaccination center among the three vaccine manufacturers utilized for the third dose. Moderna's mRNA-1273 and Pfizer's BNT162b2 vaccines are lipid nanoparticle (LNP)-formulated nucleotide-modified mRNA vaccines (Muramatsu et al. 2022), while Novavax's NVX-CoV2373 vaccine is an adjuvanted recombinant spike protein nanoparticle vaccine comprising a full-length spike SARS-CoV-2 spike trimer protein (Rydyznski Moderbacher et al. 2022). During NVX-CoV2373 production, nucleoside-modified spike proteins were expressed in insect cells and extracted from the membrane (Tian et al. 2021). Although all vaccines prompt the creation of neutralizing antibodies against the SARS-CoV-2 spike protein, these vaccines may elicit a different spectrum of immune responses in vaccine recipients. The largest difference between the vaccines is that both mRNA-1273 and BNT162b2 are RNA-based vaccines containing mRNA constructs, whereas NVX-CoV2373 is a protein subunit vaccine containing purified recombinant SARS-CoV-2 spike proteins (Shang and Cao 2022). Additionally, the mRNA-1273 and BNT162b2 vaccines use LNPs, utilizing ionizable lipids to stabilize the mRNA. LNPs may also have some adjuvant properties (Chung et al. 2020), and may cause allergic reactions in vaccine recipients (Selvaraj et al. 2021). The NVX-CoV2373 vaccine uses saponin-based adjuvant Matrix-M1, which would mediate a different spectrum of immune responses from LNPs in vaccine recipients (Pulendran et al. 2021; Shinde et al. 2021).

Table 4. Binary logistic regression analyses to compare three manufacturers after adjusting for age and sex.

	aOR	95% CI	*P*-values
Overall acute adverse events (Yes: 442 / No: 234,139)			
Age	0.985*	0.979-0.990*	< 0.0001
Male	0.373	0.303-0.460	< 0.0001
Moderna, Inc.	1.000	-	-
Pfizer, Inc.	1.386	0.962-1.999	0.0800
Novavax, Inc.	2.111	1.046-4.258	0.0370
Vasovagal syncope/presyncope (Yes: 202 / No: 234,379)			
Age	0.965*	0.957-0.974*	< 0.0001
Male	0.560	0.420-0.747	< 0.0001
Moderna, Inc.	1.000	-	-
Pfizer, Inc.	1.224	0.728-2.059	0.4451
Novavax, Inc.	1.653	0.528-5.179	0.3885
Acute allergic reaction† (Yes: 69 / No: 234,512)			
Age	0.989*	0.975-1.003*	0.1337
Male	0.182	0.095-0.347	< 0.0001
Moderna, Inc.	1.000	-	-
Pfizer, Inc.	1.521	0.603-3.838	0.3744
Novavax, Inc.	5.333	1.669-17.044	0.0047

aOR, adjusted odds ratio; CI, confidence interval.
*Unit OR for an increment of one year.
†Not including anaphylaxis.

Although a higher incidence of acute allergic reactions was seen in the recipients of the NVX-CoV2373 vaccine compared to those of the mRNA-1273 vaccine, caution is needed when interpreting these results, because individuals who experienced severe acute allergic events with the first and/or second dose of mRNA-1273 were advised to forgo the third vaccination. Consequently, individuals who were at higher risks of experiencing an allergic reaction to Moderna's LNPs may have been excluded in advance from the present study, which could partially explain the significantly lower incidence of acute allergic reactions after the third vaccine dose among the recipients of Moderna's mRNA-1273 vaccine. A recent meta-analysis suggested, however, that the incidence rate of acute allergic reactions after the second dose of the COVID-19 vaccine was not remarkably high among individuals who had previously experienced an acute allergic reaction to the first dose (Chu et al. 2022). To determine the incidence rates of and differences in acute adverse events between the various COVID-19 vaccines, more real-world data from a larger number of recipients is needed.

Although the results of the present study suggested a low incidence of serious acute adverse events at the mass vaccination center after the third and/or fourth COVID-19 vaccinations, an increasing number of case reports regarding possible serious adverse events observed several days to weeks after receiving COVID-19 vaccines have been recently published. Representative case reports have indicated associations with type 1 diabetes mellitus (DM), which was observed three days to six weeks after receiving the first and/or second COVID-19 vaccine dose (Ohuchi et al. 2022; Sakurai et al. 2022; Sasaki et al. 2022a,b; Sato et al. 2022; Tang et al. 2022; Yano et al. 2022). Most of these reported cases of type 1 DM showed decreased serum C-peptide immunoreactivity levels and negative results for anti-glutamic acid decarboxylase autoantibodies. Human leukocyte antigen (HLA) genotype analysis revealed HLA-DRB1*04:05-DQB1*04:01 alleles in three of the seven aforementioned cases (Sakurai et al. 2022; Sasaki et al. 2022a,b), which are considered to be associated with type 1 DM (Jiang et al. 2021). Notably, two patients with type 1 DM were treated with nivolumab, an immune checkpoint inhibitor, for malignant melanoma (Ohuchi et al. 2022; Sato et al. 2022). In addition to type 1 DM, cerebral venous thrombosis is another rare but serious adverse events, possibly induced by COVID-19 vaccines (Perry et al. 2021). There was a case report of a 25-year-old female with an inherited antithrombin deficiency in her sixth week of pregnancy, who died from a severe cerebral venous thrombosis with an onset approximately four weeks after receiving the second mRNA COVID-19 vaccine (Takikawa et al. 2022). Other possible long-term adverse effects that could last weeks to months include prolonged gastrointestinal symptoms, such as vomiting, diarrhea, and abdominal pain (Akaishi et al. 2022d; Chey et al. 2022). To be noted, as the exact causal relationships between COVID-19 vaccines and these serious medical events have yet to be determined, some of the reported symptoms might have been falsely

attributed to COVID-19 vaccines. More time and case reports are needed to determine whether COVID-19 vaccines may truly increase the incidence of such acute-to-subacute serious adverse events, which may sometimes result in a fatal outcome.

The present study had several limitations. First, the majority of the vaccine recipients went home after staying in the observation area for only 15 min after receiving the injection and could have left the center within 30 min of receiving the injection. Therefore, the present study may have missed acute adverse events which occurred within the first 30 min after receiving the injection in those who only stayed in the observation area for 15 min. Another possible limitation was that an unknown number of individuals opted not to receive the third and/or fourth vaccine dose because they had experienced a serious adverse reaction to previous COVID-19 vaccines. Therefore, the incidence of acute adverse events reported in the present study was for those who had not experienced a serious adverse reaction to the first and second vaccine doses. Another limitation is that the present report only evaluated the acute adverse events seen at the vaccination center, which were mostly observed within 30 min after receiving the vaccine. The present study did not evaluate the adverse events that occurred after the recipients left the vaccination center. Finally, almost all vaccine recipients at the mass vaccination center included in the present study were of East Asian ancestry; therefore, the generalizability of the findings to other populations of different races and ethnicities is uncertain.

In conclusion, the acute adverse events frequently observed after the third and/or fourth vaccine dose at the mass vaccination center evaluated in the present study included vasovagal syncope/presyncope and acute allergic reactions, both of which occurred more frequently in female recipients. The incidence of vasovagal syncope/presyncope did not differ significantly among the various vaccine manufacturers, while the incidence of acute allergic reactions did appear to differ among the manufacturers. Additional real-world data are needed to determine the difference in the incidence of adverse events among vaccines from different manufacturers.

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Author Contributions

T.A. analyzed and drafted the manuscript. T.O. played a primary role in the management of the mass vaccination center. T.T., H.H., and T.I. supervised all processes of this study. All authors contributed to the data collection and critically reviewed and revised the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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