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Original Article

Adverse reactions to the BNT162b2 and mRNA-1273 mRNA COVID-19 vaccines in Japan

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ABSTRACT

Introduction: The BNT162b2 and mRNA-1273 COVID-19 vaccines are the main vaccines that have been used for mass vaccination in Japan. Information on adverse reactions to COVID-19 vaccines in the Japanese population is limited.

Methods: We conducted an online survey on self-reported adverse reactions in individuals who had received two doses of the BNT162b2 or mRNA-1273 vaccine. The incidence of adverse events after each dose of vaccine was investigated. Propensity score matching was used to compare the incidence of adverse reactions after the second dose of the BNT162b2 and mRNA-1273 vaccines.

Results: After the first and second doses of the BNT162b2 vaccine, and the first and second doses of the mRNA-1273 vaccine, 890, 853, 6401, and 3965 individuals, respectively, provided complete responses. Systemic reactions, including fever, fatigue, headache, muscle/joint pain, and nausea were significantly more common in females, individuals aged <50 years, and after the second dose. The incidence of injection site pain did not differ significantly according to the dose. The incidence of delayed injection site reactions after the first dose of mRNA-1273 vaccine was 3.9% and 0.8% among females and males, respectively, and 10.6% among females aged 40–69 years. Local and systemic reactions after the second dose, including fever, fatigue, headache, muscle/joint pain, nausea, and skin rash were more common in individuals who had received the mRNA-1273 vaccine.

Conclusions: Adverse reactions were more frequently reported in females, younger individuals, and after the mRNA-1273 vaccine.

1. Introduction

Coronavirus disease (COVID-19) was first reported in Wuhan, China, on December 31, 2019, and rapidly expanded globally and became a pandemic [1]. The World Health Organization encourages vaccination against COVID-19 to stop the COVID-19 pandemic [2].

To date, three COVID-19 vaccines have been approved in Japan: the BNT162b2 (Pfizer-BioNTech) messenger RNA (mRNA)-based vaccine was approved on February 14, 2021; the mRNA-1273 (Moderna), mRNA-based vaccine was approved on May 21, 2021; and the ChAdOx1 nCoV-19 (Oxford-AstraZeneca), viral vector-based vaccine was approved on May 21, 2021. In mid-February 2021, a nationwide immunization program was launched, which initially focused primarily on healthcare workers and the older population. The program was subsequently expanded to other populations and is currently ongoing. Mass vaccination has mainly been carried out using the BNT162b2 and mRNA-1273 vaccines.

Participants reported local and systemic adverse reactions in clinical trials of mRNA-based vaccines [3,4]. The incidence of adverse reactions was significantly higher in younger participants than in older

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participants, in females than in males, and after the second dose than after the first dose [3,4]. A previous survey conducted in Japan showed that COVID-19 vaccine hesitancy was more common among younger individuals, and that many respondents were concerned about the side effects and safety of the vaccine as a major reason for hesitancy to be vaccinated [5]. Therefore, continued monitoring of adverse reactions to COVID-19 vaccines under programmatic conditions, especially in young age groups, may provide relevant information to the public and contribute to people's acceptance of COVID-19 vaccines. However, programmatic evidence on the reactogenicity of COVID-19 vaccines in the Japanese population is limited [6,7]. In addition, there is a lack of evidence on the comparative side effects of different COVID-19 vaccines.

Therefore, we conducted an online-based survey on self-reported adverse reactions in people who received either the BNT162b2 or the mRNA-1273 vaccine.

2. Material and methods

2.1. Study design

An online questionnaire survey was conducted at Hiroshima University and Hiroshima University Hospital from July 15 to 19 for the first dose of vaccine and from August 19 to 22, 2021 for the second dose of vaccine. The survey was conducted in conjunction with mass vaccination conducted at Hiroshima University and Hiroshima University Hospital. The 6059 staff and 15,347 students at Hiroshima University and Hiroshima University Hospital were asked to take part in a self-reported online questionnaire survey (created using Microsoft Forms) to report any adverse reactions regardless of the number of doses that they had received at the time of completing the questionnaire. Participation in this study was voluntary, and the participants received no financial compensation to minimize the risks of response bias and performance bias.

Although the ChAdOx1 nCoV-19 (AstraZeneca-Oxford) was approved in May 2021, it had not yet been deployed on a large scale in Japan at the time of the study. Therefore, the data of all individuals who had received two doses of either the BNT162b2 vaccine or the mRNA-1273 vaccine were selected for analysis. Information was collected from each participant on their sex, age, type of vaccine received, and local and systemic adverse reactions, including the date of onset, duration, and severity of the adverse reactions. Local adverse events included injection site pain and systemic adverse events included fever, fatigue, headache, muscle and joint pain, nausea, diarrhea, and skin rash outside the injection site. The severity of adverse reactions was reported in three categories: mild (not requiring medicine or interfering with daily routine activities), moderate (requiring medicine and causing some difficulty with daily activities), and severe (requiring absence from attending university classes or taking at least one day off from work). The timing of the onset and the duration of the adverse reactions were also assessed. Delayed injection site reaction was defined as a skin reaction such as erythema or pruritus around the injection site, with an onset at least 2 days after vaccination [8]. Information about delayed injection site reaction was extracted from the responses to an open-ended question about other symptoms.

2.2. Ethics

This study was approved by the Ethical Committee for Epidemiology of Hiroshima University (approval number: E−2123-2). Informed consent was waived by the Institutional Review Board because of the observational nature of the study and because participant identifiers were completely encrypted before analysis.

2.3. Statistical analysis

Categorical variables were reported as numbers (percentages) and chi-square tests were used to assess the statistical significance of differences between groups. The Cochran-Armitage test was performed to assess the linear trend of adverse reactions across age groups. A 1:1 propensity-score matching with caliper score of 0.05 was used to reduce selection bias due to differences in the baseline characteristics of the participants who received a second dose of the mRNA-1273 vaccine and a second dose of the BNT162b2 vaccine. Propensity scores were calculated using logistic regression analysis of age and sex. Categorical variables according to the vaccine type were compared after propensity-score matching using chi-square tests. All P values were two-sided, and P values < 0.05 were considered statistically significant. Data analysis was performed using JMP Pro 16.0 software (SAS Institute Inc., Cary, NC, USA).

3. Results

For the first and second doses of COVID-19 vaccination, 7360 and 4854 individuals, respectively, participated in this survey. For the first and second doses of the BNT162b2 vaccine, and the first and second doses of the mRNA-1273 vaccine, 890, 853, 6,401, and 3965 individuals, respectively, provided complete responses. In total, 105 participants were excluded from the analysis because they did not receive any type of COVID-19 vaccine, received a COVID-19 vaccine other than the BNT162b2 or mRNA-1273 vaccine, or provided inconsistent or incomplete responses to key items (such as age and vaccine type).

The demographic characteristics and adverse reactions reported by the participants following the first and second doses of the BNT162b2 and mRNA-1273 vaccines are shown in Table 1 and Supplementary Figs. 1 and 2. The local and systemic reactions after the second dose of the BNT162b2 and mRNA-1273 vaccines according to sex and age are shown in Tables 2a and 2b, respectively.

Comparing the first and second doses of the BNT162b2 vaccine, all systemic reactions except skin rash were reported significantly more frequently after the second dose than after the first dose (Table 1). However, there was no significant difference in the incidence of injection site pain between the first and second doses. Injection site pain was the most commonly reported adverse effect after both the first and second doses of the vaccine. After the second dose of the vaccine, the most commonly reported systemic side effect was fatigue (75.4%), followed by muscle/joint pain (49.8%). Both systemic and local reactions tended to occur on the day or day after vaccination and lasted 1–2 days after the vaccination (Supplemental Table 1). After the second dose of the BNT162b2 vaccine, injection site pain and systemic adverse events, except for diarrhea and skin rash, were reported more frequently in females than in males (Table 2a). In addition, systemic reactions other than diarrhea and skin rash were reported less frequently in the older age group ($\geq$50 years) than in the younger age group ($<$50 years). The incidence of injection site pain did not differ significantly according to age.

Comparing the first and second doses of the mRNA-1273 vaccine, all systemic reactions were reported more frequently after the second dose than after the first dose, whereas there was no significant difference in the frequency of injection site pain between the first and second doses (Table 1). After the second dose of the mRNA-1273 vaccine, adverse reactions, except for diarrhea and skin rash, were reported more frequently in females than in males (Table 2b). In addition, local and systemic reactions other than diarrhea and skin rash were reported less frequently in the older age group ($\geq$50 years old) than in the younger age group ($<$50 years). Both local and systemic reactions often occurred on the day of injection or the next day and lasted 1–2 days after the vaccination (Supplemental Table 1).

Delayed injection site reaction was reported by 2.2% and 0.5% of participants after the first and second doses of the mRNA-1273 vaccine, respectively (Tables 1 and 3). The incidence of delayed injection site reaction after the first dose of mRNA-1273 vaccine was 3.9% and 0.8% among females and males, respectively, and 10.6% among females aged

Table 1
Demographic characteristics and adverse reactions reported by the participants according to the vaccine type.

	BNT162b2 vaccine			mRNA-1273 vaccine		
	First dose (N = 890) n (%)	Second dose (N = 853) n (%)	p value	First dose (N = 6401) n (%)	Second dose (N = 3965) n (%)	p value
Sex			0.43			0.17
Female	566 (63.6)	527 (61.8)		2941 (45.9)	1877 (47.3)	
Male	324 (36.4)	326 (38.2)		3460 (54.1)	2088 (52.7)	
Age group (years)			<0.001			<0.001
<20	12 (1.3)	5 (0.6)		1309 (20.5)	605 (15.3)	
20–29	265 (29.8)	178 (20.9)		3221 (50.3)	1849 (46.6)	
30–39	195 (21.9)	203 (23.8)		564 (8.8)	404 (10.2)	
40–49	233 (26.2)	246 (28.8)		576 (9.0)	462 (11.7)	
50–59	125 (14.4)	149 (17.5)		523 (8.2)	449 (11.3)	
60–69	54 (6.1)	71 (8.3)		207 (3.2)	193 (4.9)	
70–79	6 (0.7)	1 (0.1)		1 (0.0)	3 (0.0)	
Local adverse reaction						
Injection site pain	816 (91.7)	760 (89.1)	0.067	5947 (92.9)	3686 (93.0)	0.91
Delayed injection site reaction	3 (0.3)	3 (0.4)	0.96	144 (2.2)	19 (0.5)	<0.001
Systemic adverse reactions						
Fever (≥38.0 °C)	14 (1.6)	263 (30.8)	<0.001	584 (9.1)	2719 (68.6)	<0.001
Fatigue	298 (33.5)	643 (75.4)	<0.001	3057 (47.8)	3221 (81.2)	<0.001
Headache	112 (12.6)	324 (38.0)	<0.001	1421 (22.2)	2228 (56.2)	<0.001
Muscle/joint pain	355 (39.9)	425 (49.8)	<0.001	3347 (52.3)	2369 (59.7)	<0.001
Nausea	22 (2.5)	45 (5.3)	0.002	261 (4.1)	418 (10.5)	<0.001
Diarrhea	27 (3.0)	49 (5.7)	0.006	172 (2.7)	201 (5.1)	<0.001
Skin rash	21 (2.4)	29 (3.4)	0.19	339 (5.3)	259 (6.5)	0.009

Data are presented as number (%).

40–69 years. The incidence of delayed injection site reactions after the first dose of the mRNA-1273 vaccine was significantly higher than that after the second dose ($p < 0.001$). In addition, the incidence of delayed injection site reaction after the first dose of the mRNA-1273 vaccine was significantly higher than that after both the first and second doses of the BNT162b2 vaccine (first dose 2.2% vs. 0.4%, $p < 0.001$; second dose 2.2% vs. 0.5%, $p < 0.001$). The median time from vaccination to onset was 7 days (range, 4–15 days).

Compared with participants who received a second dose of BNT162b2 vaccine, participants who received a second dose of mRNA-1273 vaccine were significantly younger and a higher proportion were male. After adjusting for age and sex by propensity-score matching (c-statistics = 0.76), individuals vaccinated with a second dose of mRNA-1273 vaccine were more likely to experience local and systemic reactions, other than diarrhea, than those vaccinated with a second dose of BNT162b2 vaccine (Table 4). Fatigue was the most frequent adverse reaction among participants who received either vaccine.

Table 2a
Adverse reactions after the second dose of the BNT162b2 vaccine according to sex and age.

		Sex		p value	Age group							Age group		
Adverse reactions	Total (n = 853)	Female (n = 527)	Male (n = 326)		10s (n = 5)	20s (n = 178)	30s (n = 203)	40s (n = 246)	50s (n = 149)	60s (n = 71)	70s (n = 1)	p for trend	<50 years (n = 632)	≥50 years (n = 221)	p value
Local reaction															
Injection site pain	760 (89.1)	478 (90.7)	282 (86.5)	0.032	5 (100.0)	164 (92.1)	176 (86.7)	224 (91.1)	129 (86.6)	62 (87.3)	0 (0.0)	<0.001	569 (90.0)	191 (86.4)	0.14
Systemic reaction															
Fever (≥38.0 °C)	263 (30.8)	192 (36.4)	71 (21.8)	<0.001	2 (40)	79 (44.4)	71 (35.0)	70 (28.5)	31 (20.8)	10 (14.1)	0 (0.0)	<0.001	222 (35.1)	41 (18.6)	<0.001
Fatigue	643 (75.4)	425 (80.6)	218 (66.9)	<0.001	4 (80.0)	152 (85.4)	161 (79.3)	191 (77.6)	103 (69.1)	31 (43.7)	1 (100.0)	<0.001	508 (80.4)	135 (61.1)	<0.001
Headache	324 (38.0)	245 (46.5)	79 (24.2)	<0.001	3 (60.0)	90 (50.6)	77 (37.9)	94 (38.2)	46 (30.9)	14 (19.7)	0 (0.0)	<0.001	264 (41.8)	60 (27.1)	<0.001
Muscle/joint pain	425 (49.8)	286 (54.3)	139 (42.6)	0.001	4 (80.0)	107 (60.1)	114 (56.2)	123 (50.0)	55 (36.9)	22 (31.0)	0 (0.0)	<0.001	348 (55.1)	77 (34.8)	<0.001
Nausea	45 (5.3)	37 (7.0)	8 (2.5)	0.004	0 (0.0)	16 (9.0)	12 (5.9)	12 (4.9)	5 (3.4)	0 (0.0)	0 (0.0)	<0.001	40 (6.3)	5 (2.3)	0.020
Diarrhea	49 (5.7)	34 (6.5)	15 (4.6)	0.26	0 (0.0)	13 (7.3)	5 (2.5)	21 (8.5)	8 (5.4)	2 (2.8)	0 (0.0)	0.24	39 (6.2)	10 (4.5)	0.37
Skin rash	29 (3.4)	18 (3.4)	11 (3.4)	0.97	0 (0.0)	10 (5.6)	5 (2.5)	8 (3.3)	5 (3.4)	1 (1.4)	0 (0.0)	0.44	23 (3.6)	6 (2.7)	0.51

Data are presented as number (%).

Table 2b
Adverse reactions after the second dose of the mRNA-1273 vaccine according to sex and age.

Adverse reactions	Total (n = 3965)	Sex			Age group							Age group		
		Female (n = 1877)	Male (n = 2088)	p value	10s (n = 605)	20s (n = 1849)	30s (n = 404)	40s (n = 462)	50s (n = 449)	60s (n = 193)	70s (n = 3)	p for trend	<50 years (n = 3320)	≥50 years (n = 645)	p value
Local reaction															
Injection site pain	3687 (93.0)	1767 (94.1)	1924 (92.1)	0.003	569 (94.1)	1751 (94.7)	373 (92.3)	425 (92.0)	401 (89.3)	165 (85.5)	3 (100.0)	<0.001	3118 (93.9)	569 (88.2)	<0.001
Systemic reaction															
Fever (≥38.0 °C)	2719 (68.6)	1389 (74.0)	1330 (63.7)	<0.001	450 (74.4)	1386 (75.0)	269 (66.6)	288 (62.3)	253 (56.3)	73 (37.8)	0 (0.0)	<0.001	2393 (72.1)	326 (50.5)	<0.001
Fatigue	3221 (81.2)	1602 (85.3)	1623 (77.7)	<0.001	486 (80.3)	1541 (83.3)	335 (82.9)	397 (85.9)	329 (73.3)	131 (67.9)	2 (66.7)	<0.001	2759 (83.1)	462 (71.6)	<0.001
Headache	2228 (56.2)	1186 (63.2)	1045 (50.0)	<0.001	358 (59.2)	1154 (62.4)	234 (87.9)	244 (52.8)	182 (40.5)	55 (28.5)	1 (33.3)	<0.001	1990 (59.9)	238 (36.9)	<0.001
Muscle/joint pain	2369 (59.7)	1240 (66.1)	1129 (54.1)	<0.001	343 (56.7)	1151 (62.3)	257 (63.6)	307 (66.5)	229 (51.0)	81 (42.0)	1 (33.3)	<0.001	2058 (62.0)	311 (48.2)	<0.001
Nausea	418 (10.5)	263 (14.0)	156 (7.5)	<0.001	71 (11.7)	220 (11.9)	44 (10.9)	43 (9.3)	30 (6.7)	10 (5.2)	0 (0.0)	<0.001	378 (11.4)	40 (6.2)	<0.001
Diarrhea	201 (5.1)	106 (5.6)	96 (4.6)	0.047	22 (3.6)	88 (4.8)	32 (7.9)	29 (6.3)	19 (4.2)	11 (5.7)	0 (0.0)	0.24	171 (5.2)	30 (4.7)	0.60
Skin rash	259 (6.5)	163 (8.7)	96 (4.6)	<0.001	29 (4.8)	107 (5.8)	40 (9.9)	40 (8.7)	34 (7.6)	8 (4.1)	1 (33.3)	0.50	216 (6.5)	43 (6.7)	0.88

Data are presented as number (%).

4. Discussion

This study showed that the incidence of adverse reactions to the first and second doses of the BNT162b2 and mRNA-1273 vaccines in the Japanese population, based on self-report. For both the BNT162b2 and mRNA-1273 vaccines, almost all systemic reactions were significantly more frequent in females than in males, in the younger age group (<50 years) than in the older age group (≥50 years), and after the second dose. These results are generally consistent with the results of previous studies [3,4,7,9,10]. In contrast, there were no significant difference in the incidence of injection site pain with either vaccine between first and second dose. Local and systemic adverse reactions were generally transient, starting within 2 days of vaccination and resolving within 2 days. The incidence of serious adverse reactions was limited. The most severe and most frequent systemic adverse reaction was fatigue, with both the BNT162b2 and the mRNA-1273 vaccines. The incidence of absenteeism following the BNT162b2 vaccine is consistent with that of a previous study from Japan [7]. The frequency of reported reactions is generally consistent with the results observed in previous studies [3,4,7,9,10]. In this study, injection site pain was the most common adverse reaction after both the first and second doses of both vaccines. The incidence of injection site pain in this study was higher than that reported in previous large studies conducted in the US and UK [9,10], but similar to that of a previous study conducted in Japan [7]. The differences in the reported incidence of injection site pain between studies may be because the participants in this study were younger than those of previous studies conducted in the US and UK [3,4,9]. The demographic of participants in this study were similar to those of a previous study of Japanese healthcare workers [7]. Previous studies have shown that local side effects are more frequent with the mRNA-based vaccines than with viral vector-based vaccines, while systemic side effects are more frequent with the viral vector-based vaccines [9,11].

In this study, the incidence of fever after the second dose of the mRNA-1273 vaccine was higher than in previous reports [4,10]. This may also be because participants were younger than in previous studies [4,10].

In this study, the incidence of delayed injection site reaction after the first dose of mRNA-1273 vaccine was significantly higher than that after the first and second doses of the BNT162b2 vaccine, and the second dose of the mRNA-1273 vaccine. Especially, 10.6% of females aged 40–69 years reported experiencing delayed injection site reaction after the first dose of mRNA-1273 vaccine. This result is consistent with the results of a previous study which found that 94% of delayed injection site reactions were associated with the mRNA-1273 vaccine [12]. In a survey of healthcare workers in the United States, 1.1% of females and no males reported experiencing delayed injection site reaction after receiving the first dose of mRNA-1273 vaccine [8]. In contrast, a survey of older Japanese individuals (median age, 68 years in females and 70 years in males), the incidence of delayed injection site reaction after the first dose of mRNA-1273 vaccine was 12.5% in females and 1.5% in males [13]. In the Japanese study, all participants were interviewed by a physician about their symptoms, rather than self-reported by the participants. Although this study was self-reporting survey, the incidence of delayed injection site reaction after first dose of mRNA-1273 vaccine was higher than that reported in the US study [8] and the incidence of delayed injection site reaction among females aged 40–69 years was similar to that reported in the Japanese study [13]. As the majority of participants of this study were Japanese, our results suggest that delayed local reaction may be relatively common among middle-aged Japanese females who receive the mRNA-1273 vaccine. In this study, delayed local reaction to the mRNA-1273 vaccine were reported less frequently after second dose than after the first dose, which is consistent with the results of previous studies [8,12,13]. Previous reports also found that delayed local reaction to the mRNA-1273 vaccine occurred earlier and were of shorter duration after the second dose of vaccine than after the first dose [8,12,13].

Table 3
Demographic characteristics of participants with delayed injection site reaction according to the vaccine type.

	BNT162b vaccine				mRNA-1273 vaccine			
	First dose		Second dose		First dose		Second dose	
	Total	Cases (%)	Total	Case (%)	Total	Case (%)	Total	Cases (%)
Total	890	3 (0.3)	853	3 (0.4)	6401	144 (2.2)	3965	19 (0.5)
Female	566	3 (0.5)	527	1 (0.2)	2941	115 (3.9)	1877	14 (0.7)
Age group (years)								
<20	3	0 (0.0)	4	0 (0.0)	700	6 (0.9)	345	1 (0.3)
20–29	194	0 (0.0)	133	0 (0.0)	1471	40 (2.7)	904	7 (0.8)
30–39	121	1 (0.8)	116	0 (0.0)	233	12 (5.2)	189	3 (1.6)
40–49	154	2 (1.3)	162	1 (0.6)	279	28 (10.0)	206	2 (1.0)
50–59	73	0 (0.0)	91	0 (0.0)	205	23 (11.2)	181	0 (0.0)
60–69	19	0 (0.0)	21	0 (0.0)	53	6 (11.3)	51	1 (2.0)
70–79	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	0 (0.0)
Male	324	0 (0.0)	326	2 (0.6)	3460	29 (0.8)	2088	5 (0.2)
Age group (years)								
<20	9	0 (0.0)	1	0 (0.0)	609	1 (0.2)	260	0 (0.0)
20–29	71	0 (0.0)	45	0 (0.0)	1750	14 (0.8)	945	2 (0.2)
30–39	74	0 (0.0)	87	0 (0.0)	331	3 (0.9)	215	0 (0.0)
40–49	79	0 (0.0)	84	1 (1.2)	297	5 (1.7)	256	1 (0.4)
50–59	52	0 (0.0)	58	1 (1.7)	318	4 (1.3)	268	2 (0.7)
60–69	35	0 (0.0)	50	0 (0.0)	154	2 (1.3)	142	0 (0.0)
70–79	4	0 (0.0)	1	0 (0.0)	1	0 (0.0)	2	0 (0.0)

Data are presented as number (%).

Table 4
Comparison of demographic characteristics and adverse reactions after the second dose of vaccine after propensity-score matching according to the vaccine type.

	BNT162b2 (n = 853)	mRNA-1273 (n = 853)	p value
Demographics			
Sex			
Female	527 (61.8)	527 (61.8)	1.0
Male	326 (38.2)	326 (38.2)	1.0
Age group			
10s	5 (0.6)	5 (0.6)	1.0
20s	178 (20.9)	178 (20.9)	1.0
30s	203 (23.8)	203 (23.8)	1.0
40s	246 (28.8)	246 (28.8)	1.0
50s	149 (17.5)	149 (17.5)	1.0
60s	71 (8.3)	71 (8.3)	1.0
70s	1 (0.1)	1 (0.1)	1.0
Adverse reactions			
Local reaction			
Injection site pain	760 (89.1)	790 (92.6)	0.01
Systemic reaction			
Fever (≥38.0 °C)	263 (30.8)	542 (63.5)	<0.001
Fatigue	643 (75.4)	710 (83.2)	<0.001
Headache	324 (38.0)	477 (55.9)	<0.001
Muscle/joint pain	425 (49.8)	525 (61.5)	<0.001
Nausea	45 (5.3)	82 (9.6)	<0.001
Diarrhea	49 (5.7)	51 (6.0)	0.84
Skin rash	29 (3.4)	74 (8.7)	<0.001

Data are presented as number (%).

There is a lack of evidence on the comparative side effects of different COVID-19 vaccines [9]. In this study, after adjusting for age and sex, individuals vaccinated with a second dose of the mRNA-1273 vaccine were more likely to experience local and systemic side effects other than diarrhea, than those vaccinated with a second dose of the BNT162b2 vaccine. This result is consistent with the results observed in a previous study conducted in the US [10]. These findings may have an impact on the vaccine choice. The cause of the observed difference in the safety profiles of the two mRNA-based vaccines is unclear and should be further evaluated in future studies. Clinicians should counsel vaccine recipients that these local and systemic reactions are most commonly reported on the first day following the second dose and that the symptoms are generally mild and transient.

This study has several limitations. First, given the nature of the self-reporting survey, the frequency of reported adverse reactions may have been over- or underestimated. Second, the reported adverse reactions were not medically verified. Third, we did not ask the participants when they received the vaccine, so there may have been some recall bias. Fourth, we evaluated only short-term adverse effects, and long-term surveillance in the general population is required to investigate possible long-term effects. Fifth, we did not investigate the participants' past history of COVID-19, comorbidities, or allergy history. Previous studies have shown that a history of prior COVID-19 infection increases the incidence of vaccination side effects [11,14]. Sixth, as vaccination of healthcare workers was initiated using the BNT162b2 vaccine, it is possible that many of those who received the BNT162b2 vaccine were healthcare workers. However, in this study, we did not distinguish between healthcare workers and non-healthcare workers in the questionnaire. Additionally, vaccination of healthcare workers preceded that of university staff and students who mainly received the mRNA-1273 vaccine. Therefore, the reporting of adverse reactions to the BNT162b2 vaccine may have been more affected by recall bias than the reporting of adverse reactions to the mRNA-1273 vaccine. In addition, there were fewer participants who responded about the second dose of the mRNA-1273 vaccine was lower than those who responded about the first dose. This may be because university students mainly received the mRNA-1273 vaccine, and the survey period of the second dose was during their summer vacation. We did not include a specific question about delayed injection site reactions in the questionnaire and extracted the data from the responses to the open-ended questions about other symptoms. This may have led to the incidence of delayed injection site reaction being underestimated, and we were unable to analyze the symptom severity or duration. In addition, we did not include specific questions about anaphylaxis or myocarditis in the questionnaire. However, this study is relatively large compared to previous studies conducted in Japan [6,7] and is the first study in Japan to compare the adverse reactions to the two mRNA-based vaccines.

In conclusion, after adjusting for age and sex, individuals vaccinated with the mRNA-1273 vaccine were more likely to experience systemic reactions than those vaccinated with the BNT162b2 vaccine. Delayed injection site reaction was reported most frequently in middle-aged females after receiving the first dose of the mRNA-1273 vaccine. Our study results provide detailed information about adverse events, especially in younger individuals. This information will be useful in promoting

COVID-19 vaccination in Japan. Larger nationwide studies focusing on mRNA-based vaccines as well as viral vector-based vaccines are warranted to verify these findings.

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Author contributions

HK, AS, SN, AK, and JT designed the study. AS, SN, AK, and JT participated in the acquisition of data. HK, YK, AS, SN, AK, TA and JT participated in the analysis and interpretation of the data. HK drafted the manuscript. TN, KO, NS, TA, JT, and HO revised the manuscript. All authors approved the final version of the manuscript.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2021.12.034.

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