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Adverse reactions and attitudes toward vaccines among young populations one month after receiving a second dose of mRNA-1273 in Japan

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Abstract: To investigate adverse reactions and attitudes toward the vaccine during the first month after mRNA-1273 vaccination in a larger sample including younger men and women in Japan, we distributed a 1-month post-vaccination questionnaire using a Google form to 8,566 people who received a second dose of mRNA-1273 at Okayama University. The response rate was about 40.2% (3,447 responses), the sex ratio was about the same, and 73.3 % (2,528 respondents) were students in their twenties or younger. Poisson regression with robust variance was performed to calculate the prevalence ratio of each symptom by different attributes. The most common adverse reactions after the second vaccine dose were local pain (80.4%), fever (85.1%), malaise (82.0%), headache (64.0%), and chills (57.4%). Approximately 99% of respondents reported that their adverse reactions resolved within 1 week. Over 80% of respondents were satisfied with their vaccination (87.2%), expressed interest in receiving the third vaccination (83.3%), and would recommend vaccination to their loved ones (80.2%). However, among them, 22.0% (757 respondents) would recommend and 28.4% (980 respondents) also stated that they would consider the type of vaccine in these decisions.

***Keywords*:** COVID-19, mRNA, adverse events, safety

An outbreak of a novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) began in Wuhan, China in 2019 and subsequently developed into a worldwide pandemic. To bring the pandemic under control, various efficacious vaccines have been developed and introduced, starting with the approval of BNT162b2 in December 2020 and now including mRNA-1273 and AZD1222. These vaccines have contributed significantly to reducing coronavirus disease 2019 (COVID-19) severity and mortality rates (*1,2*).

Although a sufficient proportion of the population needs to be vaccinated to fully benefit from the effects of vaccination (*3*), some individuals remain vaccine-hesitant (*4*). Vaccine hesitancy is partially attributed to concerns regarding medium- to long-term adverse events following administration of new types of vaccines such as mRNA vaccines. There have been reports of medium-term adverse reactions following vaccination in clinical trials conducted overseas (*5*). However, no reports of medium-term adverse reactions following COVID-19 vaccination in Japanese subjects are available. A post-vaccination health status survey conducted by the Ministry of Health, Labour, and Welfare of Japan made no mention of residual adverse reactions 1-month post-vaccination (*6*). In the mRNA-1273 post-vaccination survey, most of the respondents were Japan Self-Defense Forces personnel (more than 65% were aged 30-49 and 95% were male). Therefore, to provide information on actual adverse reactions to both men and women among young people who may hesitate to be vaccinated, it would be desirable to investigate early and medium-term adverse reactions to mRNA-1273 vaccination in a larger study population that includes younger individuals of both sexes.

We distributed a self-administered questionnaire survey to collect information on adverse reactions 1-month post-mRNA-1273 vaccination as well as respondents' thoughts regarding vaccination. Following informed consent, the questionnaire was distributed using a Google form in Japanese or English to 8,566 students and faculty members who received a second dose of mRNA-1273 between August 6 and September 15, 2021, at Okayama University. The questionnaire period was

Table 1. Adverse reactions after a second dose of mRNA-1273 vaccine (*n* = 3,447)

Adverse reactions	N/A (%)	Within 3 days (%)	Within 1 week (%)	Within 2 weeks (%)	Within 1 month (%)	Ongoing (%)
Local adverse reactions						
Pain	19.61	67.42	11.87	0.67	0.26	0.17
Swelling	46.82	42.30	9.81	0.93	0.12	0.03
Redness	60.40	29.39	8.67	1.25	0.26	0.03
Pruritus	70.09	18.86	8.70	1.83	0.46	0.06
Swollen lymph nodes	90.08	7.25	2.32	0.20	0.12	0.03
Systemic adverse reactions						
Fever ≥ 37.5°C	14.91	81.98	2.99	0.06	0.06	0.00
Headache	36.15	57.12	6.06	0.32	0.23	0.12
Malaise	18.02	72.99	7.63	0.75	0.41	0.20
Chills	42.65	55.90	1.39	0.03	0.03	0.00
Nausea and vomiting	89.61	9.49	0.58	0.23	0.09	0.00
Diarrhea	92.98	6.09	0.73	0.12	0.06	0.03
Myalgia	35.94	55.76	7.83	0.32	0.09	0.06
Joint pain	58.08	39.02	2.70	0.15	0.06	0.00
Rash	93.99	4.24	1.28	0.32	0.09	0.09
Chest pain	94.08	4.55	0.90	0.35	0.12	0.00

N/A, not applicable.

from September 27 to October 25, 2021. Descriptive analyses were conducted to assess adverse reactions during the first month after the second vaccine dose as well as respondents' thoughts concerning vaccination. We performed Poisson regression with robust variance to calculate the prevalence ratio of each symptom by different attributes. Stata version 17 (StataCorp LLC, College Station, TX, USA) was used for all analyses. The study was approved by the Institutional Review Board of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (No. 2110-025). Online informed consent was obtained from all participants following full disclosure and explanation of the study's purpose and procedures.

The response rate was about 40.2% (*n* = 3,447 responses). In the submitted surveys, there were no missing values because all questions were set as mandatory in Google forms. The proportions of male and female respondents were similar, and because this was a survey of university-based vaccination, about three-quarters of respondents were students in their twenties or younger. Most respondents were Japanese citizens. Only 6.1% of respondents (210 respondents) had underlying diseases while 44.2% (1,525 respondents) had a history of allergy, including pollen or food allergy (Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=46*). The most common adverse reactions after the second vaccine dose were local pain (80.4%), fever (85.1%), malaise (82.0%), headache (64.0%), and chills (57.4%). The majority of respondents (approximately 99%) reported that their adverse reactions resolved within 1 week (Table 1). However, a small number of patients complained of persisting discomfort 1-month post-vaccination. Fever was more common in those in their forties or younger than in those in their fifties or older and was slightly more common in those with a history of allergies (Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=46*). There was no difference in the frequency of fever by sex; the frequency of fever was slightly lower in those with underlying diseases. Even though 84.9% of respondents reported that the adverse reactions of mRNA-1273 vaccination were more severe than those of influenza vaccination and 43.3% of respondents reported that adverse events were more severe than they expected, over 80% of respondents were satisfied with their vaccination (87.2%), expressed interest in receiving a third vaccine dose (83.3%), and stated that they would recommend vaccination to their loved ones (80.2%) (Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=46*). However, among them, 22.0% (757 respondents) would recommend and 28.4% (980 respondents) also stated that they would consider the type of vaccine in these decisions.

A survey conducted by the Ministry of Health, Labour, and Welfare of Japan summarized adverse reactions after 10 days of vaccination (*6*). However, comparatively little is known regarding medium-to long-term adverse reactions in Japanese individuals over the first month after vaccination. While many respondents in our study indicated that their adverse reactions disappeared within 1-week post-vaccination and had positive opinions regarding vaccination, a small minority of individuals complained of medium-term discomfort. Although a causal relationship could not be established, the persisting symptoms of these individuals reminded us of the importance of longer-term follow-up. The intensity of adverse reactions to mRNA-1273 vaccination seemed to be widely known among respondents, and approximately one-quarter of respondents said that they would consider the type of vaccine for future vaccinations. The data from this

study may inform the direction of future vaccination strategies.

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