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Review

Review of a Series of Surveys on Adverse Reactions to the COVID-19 mRNA-1273 Vaccine at Okayama University

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This paper presents the results of a series of surveys conducted from July 2021 to March 2023 to investigate the post-vaccination adverse reactions to the mRNA-1273 (Moderna) vaccine among faculty, staff, and students at Okayama University. These studies complement the official surveys conducted by the Ministry of Health, Labour and Welfare (MHLW) and provide a more representative picture of adverse reactions in the general population including large numbers of healthy young people. Pain, swelling, redness at the injection site, fever, headache, and malaise were the main adverse reactions reported. The proportion of adverse reactions was generally higher after the second vaccination and decreased with each additional vaccination. No statistically significant differences in the adverse reactions were found for males and females and those with/without a history of allergy, but a lower proportion of fever was observed in older participants and those with underlying medical conditions. We also evaluated the association between adverse reactions and antibody titers after the third vaccination and found no significant differences in antibody levels one month after vaccination. This series of studies highlights the importance of conducting surveys in diverse populations to provide a more representative picture of post-vaccination adverse reactions during a pandemic.

Key words: coronavirus disease 2019, adverse reactions, mRNA vaccine, antibody titers, young adults

As the coronavirus disease 2019 (COVID-19) pandemic continued to impact public health worldwide, vaccination efforts were a critical means of mitigating its effects [1]. The mRNA vaccine, first introduced in the United Kingdom in December 2020, markedly reduced the short-term risk of morbidity and severe disease caused by COVID-19 after two initial doses [2]. Subsequently, an additional third dose was administered to counteract the attenuation of vaccine effectiveness over time [3,4]. To further cope with the emergence of mutant strains, additional bivalent vaccines adapted to the Omicron strain were introduced in the fall of 2022 [5,6].

The mRNA vaccine for COVID-19 was clinically introduced at an unprecedented speed approximately one year after the emergence of COVID-19 [7]. However, because of the high prevalence of associated fever and other systemic adverse reactions, strong public concern about the vaccine's safety led to vaccine hesitancy [8]. Following the findings on adverse effects from overseas [9,10], the Ministry of Health, Labour and Welfare (MHLW) conducted adverse reaction surveys in Japan.

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<https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/vaccine_yuukousei_anzensei.html> (accessed May 22, 2023). However, they targeted mainly Self-Defense Forces personnel members, *i.e.*, predominantly middle-aged men, and the need remained for a survey report based on a sample that included more sectors of the general public, especially young people.

To address this gap, Okayama University conducted a post-vaccination adverse reaction survey of the mRNA-1273 (Moderna) vaccine among students and faculty members who received the university-based vaccination. The survey was distributed five times on four vaccination occasions (two primary vaccinations, the third vaccination, and the additional Omicron-strain-adapted bivalent vaccination); the additional survey was conducted one month after the primary vaccination. The relationship between adverse reactions and antibody titers after the third vaccination was also evaluated. Our survey subjects included a large number of young people and thus complemented the sample population in the official surveys.

This review summarizes the findings from these surveys and describes the contribution and content of the survey conducted at Okayama University.

Procedures

Study participants and ethics. In Japan, COVID-19 vaccination was initiated in February 2021 for healthcare workers and older adults to prevent COVID-19 infection and severe conditions. <https://www.kantei.go.jp/jp/headline/kansensho/vaccine_supply.html> (last accessed May 15, 2023). Following the expansion of the vaccination coverage age in July 2021, Okayama University launched a large-scale university-based vaccination project for its faculty, staff, and students. The only vaccine given at the university was mRNA-1273 (Moderna).

The Health Service Center at Okayama University sent multiple informational emails regarding the on-campus vaccination program to all university members. University faculty, staff, and students who were vaccinated through the on-campus program comprised 17,182 participants for the primary vaccination (8,622 and 8,560 for the first and second doses, respectively), 4,805 for the third vaccination, and 2,193 for the additional Omicron-strain-adapted bivalent vaccination. We surveyed university faculty, staff, and students who received these COVID-19 vaccines from July 2021 to March 2023 for post-vaccination adverse reactions to each vaccination session. The survey periods were from July 14 to September 27, 2021 for the primary vaccination, March 16 to July 18, 2022 for the third vaccination, and November 8, 2022 to January 8, 2023 for the additional Omicron-strain-adapted bivalent vaccination. Only those who had received the mRNA-1273 vaccine for all previous vaccinations were targeted in the surveys.

All studies were approved by the Okayama University Hospital Ethics Committee (approval nos. K 2110-025 and K 2112-044). Online informed consent was obtained from all participants following full disclosure and explanation of the study's purpose and procedures. We used Stata version 17/SE (StataCorp, College Station, TX, USA) for all statistical analyses.

Post-vaccination adverse reaction survey. A flyer with a link to the Post-Vaccination Adverse Reaction Online Survey was distributed to all target participants at the time of vaccination, encouraging them to respond to the survey one week after vaccination. To boost the response rate, a lottery system in which a 1,000-yen gift certificate was offered to 100 respondents was implemented. To further encourage response, a reminder e-mail with a link to the post-vaccination adverse reaction survey was sent to all participants 7 to 14 days after each vaccination.

The questionnaire consisted of three parts: basic attributes of the respondents, adverse reactions to the vaccine, and the respondents' thoughts on COVID-19 and vaccination. This was a repeated cross-sectional study with no individual linkage between surveys. Basic attributes included gender, age, nationality, position within the university, underlying medical conditions, history of allergies, and pregnancy status. The participants were asked about the date of vaccination, the number of vaccinations, the presence of an immediate adverse reaction within two hours of vaccination, the daily occurrence of local (pain, swelling, redness, pruritus, and swollen lymph nodes) and systemic (fever, headache, malaise, chills, nausea/vomiting, diarrhea, myalgia, joint pain, rash, and chest pain) reactions, as well as the participants' reactions to adverse events in the week following vaccination. Subjective impressions of adverse reactions were also requested for each vaccination session. Participants in the control group received the influenza vaccine for the primary vaccination, the

first dose for the third dose, and the third dose for the Omicron-strain-adapted bivalent dose.

The participants were also asked about their attitudes toward COVID-19 infection control and vaccination, their reasons for receiving the vaccine, and whether they were forced to be vaccinated.

There were no missing responses because the survey used Google Forms with a mandatory response setup. Respondents were further asked to provide their e-mail addresses, and in the event of duplicate responses, only the last response was taken. The results of each survey were summarized as a descriptive analysis [11].

Supplementary survey and research. Because the mRNA vaccine was introduced into clinical practice within a short period (*i.e.*, less than a year after the start of the pandemic), the degree of information literacy and people's concerns about the long-term possible consequences of vaccination of the target population appeared to influence vaccination behaviors [12]. Therefore, the Primary Vaccination Adverse Reaction Survey also queried respondents about situations in which they felt the need to wear masks, activities in which they were willing to engage, and their information literacy [13]. We conducted an additional survey one month after the primary vaccination to elicit residual post-vaccination symptoms [14]. These results are summarized as a descriptive analysis.

Furthermore, the high proportion of fever after mRNA-1273 vaccination led to research questions regarding the presence of fever as an adverse reaction and the increase in antibody titer. Results of several previous studies of BNT162b2 (Pfizer/BioNTech), the other mRNA vaccine, have been inconsistent regarding the association between adverse reactions and the increase in antibody titer [15, 16]. The inconsistency may be attributable to a lack of consideration of changes over time, given that most studies have focused on comparisons at only two time points, *i.e.*, the time point of vaccination and a follow-up [17, 18]. Furthermore, despite the reported higher prevalence of adverse reactions for the mRNA-1273 than for the BNT162b2 vaccine [19], few similar studies have been conducted on the mRNA-1273 vaccine. Therefore, we collected fingertip samples of whole blood at repeated time points after the third mRNA-1273 vaccination from 49 applicants who agreed to participate in the study and analyzed the association between post-vaccination fever and elevated SARS-CoV-2 spike receptor binding domain (S-RBD-IgG) antibodies using a mixed-effects model [20].

Adverse Reactions after Vaccination

Characteristics of respondents. The adverse reaction surveys conducted one week after vaccination were completed by a total of 7,506 people after the primary vaccination (3,919 for the first dose [45.5% response rate] and 3,587 for the second dose [41.9% response rate]), 1,733 for the third dose (36.1% response rate), and 955 for the additional Omicron-strain-adapted bivalent vaccination (43.5% response rate). An adverse reaction survey was also conducted one month after the primary vaccination, yielding 3,447 responses (40.2% response rate; Fig. 1). The gender ratio was similar throughout the surveys, with respondents in their 20s accounting for more than half of the total respondents. As the number of surveys progressed, the proportion of older respondents increased, and the proportion of student respondents decreased. The number of respondents with a history of COVID-19 infection also increased: from 2.7% in the third post-vaccination survey to 23.8% in the fourth post-vaccination survey

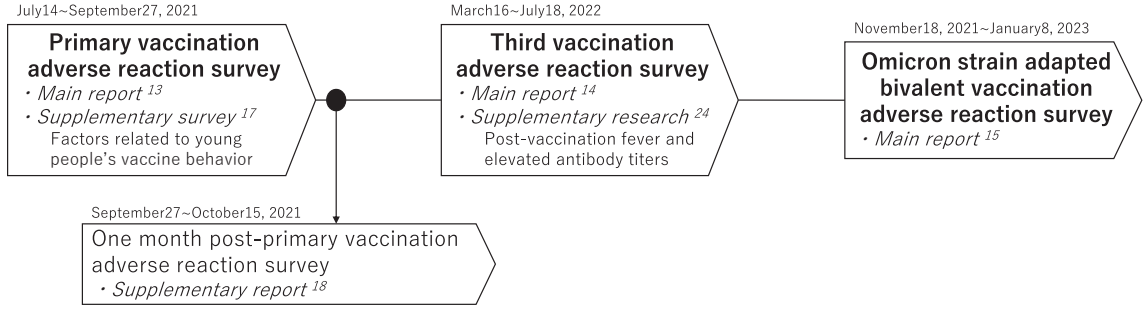

Fig. 1 Flowchart of a series of surveys on adverse reactions to the COVID-19 mRNA vaccine at Okayama University.

(Table 1). We describe below the results of the adverse reaction survey at each administration session and the results of the supplementary research.

Adverse reactions after primary vaccination. The Primary Post-Vaccination Adverse Reaction Survey focused on the occurrence of major adverse reactions after vaccination and how these effects differed by gender, age, and characteristics such as underlying medical conditions or history of allergies [12]. The most common adverse reactions were injection site pain, fever greater than 37.5°C, fatigue, and headache — all of which mostly resolved within three days. These adverse reactions appeared more frequently after the second dose than after the first (Table 2), with fever after the second dose occurring in about 90% of respondents in their 40s and younger and decreasing with increasing age in respondents in their 50s and older (80.7% in their 50s and 75.4% in their 60s and older). No statistically significant differences were observed in the proportion of fever by gender, presence of underlying disease, or history of allergy after the second vaccination. Local swelling and redness at the vaccination site (COVID arm) was observed at approximately the seventh day post-vaccination in ~2-3% of respondents, and in even fewer respondents after the second vaccination.

The proportion of systemic adverse reactions among our population was higher than that for healthcare workers in Okayama Prefecture who received the BNT162b2 vaccine (the proportion of fever was 88.6% for mRNA-1273 vs 48.1% for BNT162b2 after the second dose in a comparison limited to those in their 20s or younger; Table 3). In addition, 74.4% of patients receiving the second dose reported more severe adverse reactions than with the influenza vaccine. Serious adverse reactions reported to the MHLW included one anaphylactic reaction (after the second vaccination), one case of myocarditis (after the second vaccination), and one case of generalized skin rash (after the first vaccination). None of the patients required hospitalization, and the myocarditis resolved spontaneously within two weeks of vaccination.

Table 1 Descriptive characteristics of the respondents

		First dose n = 3,919 (%)	Second dose n = 3,587 (%)	Third dose n = 1,733 (%)	Fourth dose (Omicron) n = 922 (%)
Gender	Male	51.0	51.5	50.1	49.3
	Female	49.0	48.5	49.7	50.3
	Other	0.0	0.0	0.2	0.3
Pregnant		0.26	0.22	0.40	0.33
Age (years)	Under 20	23.5	23.0	12.4	5.1
	20s	52.7	52.2	58.3	53.3
	30s	6.9	6.0	6.9	11.0
	40s	8.1	9.4	10.5	13.7
	50s	7.3	7.4	9.1	13.7
	Over 60	1.5	2.0	2.8	3.4
Attributes	Student	77.3	76.1	71.1	58.9
	Faculty	10.9	11.5	14.7	18.2
	Administrative staff	11.1	11.5	13.6	22.9
	Other	0.8	0.9	0.5	0.0
History of COVID-19	Yes	N.A.	N.A.	2.7	23.8
Underlying diseases†	Yes	6.4	6.1	6.7	8.4
Allergy history‡	Yes	40.7	40.5	43.6	42.2

†Underlying disease includes obesity (BMI ≥ 30), chronic respiratory disease, chronic heart disease and hypertension, chronic kidney disease, chronic liver disease (except fatty liver and chronic hepatitis), neurologic and neuromuscular disorders, hematologic disorders (except iron deficiency anemia), diabetes, immunosuppression associated with disease or treatment, sleep apnea syndrome, and other.

‡Allergy history includes bronchial asthma, atopic dermatitis, allergic rhinitis (including hay fever), food allergy, drug allergy, insect allergy (*e.g.* allergy to bees), anaphylaxis, and other.

N.A., not applicable.

Table 2 Adverse reactions after the mRNA-1273 vaccine for each vaccination round

	First dose n = 3,919 (%)	Second dose n = 3,587 (%)	Third dose n = 1,733 (%)	Fourth dose (Omicron) n = 922 (%)
Local adverse reactions				
Pain	91.5	90.1	89.6	88.8
Swelling	19.8	40.8	53.9	50.4
Redness	40.1	54.8	30.6	27.3
Pruritus	17.5	31.9	22.8	21.4
Swollen lymph nodes	N.A.	N.A.	24.8	14.4
Systemic adverse reactions				
Fever ≥ 37.5°C	23.1	88.2	67.5	44.9
Headache	29.6	74.6	62.0	48.9
Malaise	48.3	84.2	78.8	68.8
Chills	12.5	63.1	52.8	38.7
Nausea and vomiting	5.0	13.1	54.4	46.3
Diarrhea	4.4	8.5	40.2	29.2
Myalgia	59.2	64.0	8.0	5.8
Joint pain	15.9	50.0	5.1	3.8
Rash	2.4	5.7	3.9	2.3
Chest pain	N.A.	N.A.	5.7	3.9
Reaction to adverse reactions				
Use of antipyretics	20.2	73.1	55.4	40.1
Absence	15.7	35.7	11.8	10.5
Lateness or withdrawal	6.4	11.7	32.8	23.5

N.A., not applicable.

Adverse reactions after third vaccination. The Third Vaccination Adverse Reaction Survey focused on comparing adverse reactions after the third dose to those following the second dose and queried the respondents about the presence of local lymphadenopathy and chest pain based on previous findings on adverse reactions. The proportion of systemic adverse reactions decreased. For example, a fever of 37.5°C or higher was reported by 88.2% of respondents after the second dose and 67.5% after the third dose. Answers to an additional question about maximum body temperature indicated that approximately 90% had a fever of less than 39°C. Although 60.3% of the respondents reported that their adverse reactions were milder than those after the second vaccination, 21.1% reported more intense reactions, indicating individual differences in immune processes.

Adverse reactions after Omicron-adapted-bivalent vaccination. The Omicron-Adapted Bivalent Vaccination Study focused on comparing the proportion of adverse reactions of the Omicron bivalent vaccine with those reported after the third vaccination. Although the increased opportunity for infection resulted in a much greater incidence of prior COVID-19 infection (23.8%) in respondents, the proportion of systemic adverse reactions was lower than that after the third dose. For example, fever over 37.5°C was reported by 67.5% of respondents after the third dose and 44.9% after the dose of the Omicron-adapted-bivalent vaccine. Moreover, fever over 39°C was observed in less than 4% of all cases. In total, 54.9% of the respondents reported milder adverse reactions and only 20.2% reported more severe reactions than after the third vaccination.

Factors related to young people's vaccine behaviors. Because vaccine avoidance among young people became a social problem, the Primary Post-Vaccination Adverse Reaction Survey further focused on factors related to behavioral decisions and information literacy among those receiving vaccines [13]. Although more than half of the respondents indicated that it was difficult to obtain accurate information, the most common reasons for vaccination were based on official information provided by University and Public Health Centers. Seventy-four respondents reported being forced to be vaccinated, most often because of strong recommendations from family members. Notably, despite the high

Table 3 Comparison of the proportion of BNT162b and mRNA-1273 vaccine adverse reactions (limited to respondents in their 20s and younger)

	First dose (%)		Second dose (%)	
	BNT162b2† n=1,304	mRNA-1273 n=2,984	BNT162b2† n=1,020	mRNA-1273 n=2,698
Local adverse reactions				
Pain	88.3	92.2	85.5	90.0
Swelling	12.1	19.7	18.2	39.0
Redness	20.6	41.8	34.1	54.6
Pruritus	9.2	16.6	14.9	29.7
Systemic adverse reactions				
Fever≥37.5°C	3.7	26.0	48.1	88.6
Headache	19.0	32.0	59.5	77.0
Malaise	25.6	50.9	76.2	85.0
Chills	4.3	14.1	36.6	66.2
Nausea and vomiting	3.2	5.2	13.7	13.5
Diarrhea	2.9	4.5	5.6	8.3
Myalgia	50.7	63.1	53.0	66.5
Joint pain	5.5	17.5	35.6	49.9
Rash	0.5	2.1	1.3	5.0
Reaction to adverse reactions				
Use of antipyretics	25.4	21.0	67.5	73.9
Absence	1.5	17.5	14.0	27.5
Lateness or withdrawal	0.7	6.5	7.1	9.0
Comparison with Influenza Vaccine				
Mild	29.8	5.1	9.7	2.3
No change	27.2	9.9	9.2	2.5
Heavy	43.0	76.7	81.1	88.6
No history of influenza vaccination	N.A.	8.34	N.A.	6.6

†Results of the BNT162b2 post-vaccination survey exclude missing responses.
N.A., not applicable.
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proportion of systemic adverse reactions, satisfaction with vaccination was maintained after the second dose.

Young People's Thoughts about and Adverse Reactions to the Vaccine One Month after the Primary Vaccination

One month after the primary vaccination, we conducted a follow-up survey to assess young people's thoughts and residual adverse reactions. Responses were obtained from 3,447 of the 8,566 participants (40.2% response rate) who received the second vaccination. Approximately 99% of the respondents reported that the adverse reactions disappeared within a week; more than 80% were satisfied with the vaccination and responded favorably to the concepts of a future third vaccination and vaccination for their loved ones. However, roughly 25% of the respondents stated that they would consider the vaccine type when they or their loved ones are vaccinated the next time.

Association between the Presence of Fever and Elevated Antibody Titer

Antibody titer levels increased significantly faster in respondents with fever than in those without fever during the first seven days after vaccination (Fig. 2) [20]; however, no significant difference was found one month post-vaccination. These results indicated that the presence of post-vaccination fever may not be clinically meaningful.

The Importance of a Series of Surveys on Adverse Reactions to the mRNA-1273 Vaccine at Okayama University

The survey conducted by Okayama University on the

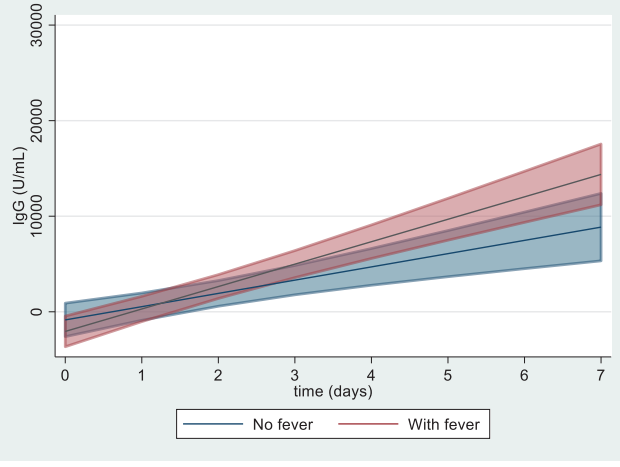

Fig. 2 IgG dynamics in the first week after vaccination by presence or absence of post-vaccination fever.
The red and blue lines show the IgG concentration means predicted by the mixed-effects model in the febrile and nonfebrile groups. The area of each color indicates the 95% confidence interval of the regression curve. Day 0 is a negative value because of the effect of the modeling prediction.
Reproduced from Matsumoto N *et al.* Association between fever and antibody titer trends after a third dose of the mRNA-1273 vaccine. J Epidemiol (2023) 32(12): 567–569 with permission.

post-vaccination adverse reactions of the mRNA-1273 vaccine is significant because it complements the official MHLW surveys. While the MHLW surveys targeted mainly middle-aged men in the Self-Defense Forces [11], the Okayama University surveys included a large number of young people, a demographic not covered in the official surveys.

Consistent with previous studies and national survey results [11,17], the main adverse reactions in these surveys were pain, swelling, redness at the injection site, fever, headache, and malaise. The local and systemic adverse reaction proportion were generally higher after the second vaccination than after the first and decreased with each additional vaccination.

No statistically significant difference in the proportion of adverse reactions by gender or history of allergy was observed in our surveys. In contrast, a lower proportion of fever was observed among participants who were older or had underlying medical conditions compared to young people and those without underlying medical conditions. These results were consistent with those of previous reports, which showed a generally higher occurrence of post-vaccination fever in younger, healthier individuals than in their older and less healthy counterparts [10,19]. Aging-associated immunosenescence is known to contribute to diminished vaccine responses. Various mechanisms related to immunosenescence have been implicated in the decreased vaccine response, including impaired functions of T cells and B cells at different stages of the immune response: *e.g.*, initial antigen-T cell interactions, activation/expansion, differentiation, effector function, germinal center interactions, and memory survival/homeostasis [22]. In fact, older adults and individuals with underlying medical conditions tend to exhibit lower antibody titers following vaccination [23], suggesting that these impaired functions of T cells and B cells may contribute to the reduced risk of post-vaccination fever.

An additional study that measured antibody titers following the third vaccination showed that although antibody titers in the group with fever after vaccination increased faster than those in the group without fever, no significant difference in antibody levels was observed one month after vaccination, suggesting that the presence of fever after vaccination is not a reliable indicator of serum elevation of antibodies. Importantly, however, this study only evaluated the association between adverse reactions and antibody titers after the third vaccination in a small sample; further investigation is required to fully assess this association.

Limitations of Our Series of Surveys on Adverse Reactions to the mRNA-1273 Vaccine at Okayama University

One limitation of this study is that the findings may not be generalizable to other populations because the study was conducted among the personnel of a single institution. The source population may have remained the same, but the proportion of student respondents decreased as vaccination opportunities increased, suggesting that young people who suffered from adverse reactions during previous vaccinations may have avoided additional vaccinations. Furthermore, responses to the self-administered questionnaire lacked an objective perspective; to address this lack, we added a question about the respondents' maximum body temperature on the post-third-vaccination survey. Finally, the small sample size in the supplementary study that examined the association between fever and antibody titers may have limited the statistical power of the analysis.

Conclusions

The Okayama University study provides valuable information on adverse reactions following mRNA-1273 vaccination in a sample that represented more sectors of the population, especially young people, than the samples of the official surveys. By reporting the proportion of adverse reactions in a more broadly representative sample, this survey contributed valuable insight into the safety of mRNA vaccines in the general public. Our findings further highlight the importance of conducting surveys in populations that complement those of public surveys to provide a more representative picture of post-vaccination adverse reactions during a pandemic.

For more information, see the full survey report at:
https://www.unit-gp.jp/eisei/wp/
https://www.pref.okayama.jp/page/797562.html

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