JAMA Dermatology | Brief Report

Assessment of Delayed Large Local Reactions After the First Dose of the SARS-CoV-2 mRNA-1273 Vaccine in Japan

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IMPORTANCE A delayed large local reaction (DLLR) is a delayed-onset adverse skin reaction that may occur after injection of the mRNA-1273 vaccine against SARS-CoV-2.

OBJECTIVE To examine the associations between sex and age and susceptibility of DLLRs after mRNA-1273 vaccination.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cross-sectional study was conducted at the Self-Defense Forces large-scale vaccination center in Tokyo, Japan, from May 24 to November 30, 2021. Participants were recipients of the second dose of the mRNA-1273 vaccine who had received the first dose 4 to 6 weeks earlier. Five experienced dermatologists interviewed participants to assess whether they had experienced symptoms of DLLR after administration of the first dose of the vaccine.

EXPOSURE Receipt of the first dose of the mRNA-1273 vaccine.

MAIN OUTCOMES AND MEASURES The primary outcome was the incidence rate of DLLR stratified by sex and age group. Odds ratios (ORs) were calculated to evaluate the differences between groups. Outcomes were tested for significance using the Pearson χ^2 test with 95% CIs.

RESULTS Of 5893 participants in the study, 3318 (56.3%) were male (median age, 55 years [IQR, 38-68 years]) and 2575 (43.7%) were female (median age, 50 years [IQR, 34-67 years]). A total of 747 participants (12.7%) experienced DLLR symptoms after the first dose of the mRNA-1273 vaccine. Symptoms were mild and not considered as contraindications to the vaccine. The incidence rate was significantly higher among females (22.4% [577 participants]; OR, 5.30; 95% CI, 4.42-6.34) than among males (5.1% [170 participants]; reference). Moreover, the incidence rate was significantly higher among participants aged 30 to 39 years (14.3% [129 participants]; OR, 1.68; 95% CI, 1.25-2.26), 40 to 49 years (15.8% [136 participants]; OR, 1.89; 95% CI, 1.41-2.53), 50 to 59 years (14.9% [104 participants]; OR, 1.76; 95% CI, 1.29-2.40), and 60 to 69 years (12.6% [182 participants]; OR, 1.45; 95% CI, 1.10-1.91) than among participants aged 18 to 29 years (9.0% [81 participants]; reference).

CONCLUSIONS AND RELEVANCE In this cross-sectional study, the first dose of the SARS-CoV-2 mRNA-1273 vaccine was associated with a higher incidence of DLLR among females and among individuals aged 30 to 69 years. The findings suggest that DLLR may be a type IV allergic skin reaction.

Supplemental content

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JAMA Dermatol. 2022;158(8):923-927. doi:10.1001/jamadermatol.2022.2088
Published online June 1, 2022.

A delayed large local reaction (DLLR) is a delayed-onset adverse skin reaction around the injection site after vaccination[1,2] (eFigure 1 in the Supplement). A DLLR typically occurs 7 days after vaccination and has a duration of 4 days.[2] Discrimination of a DLLR from a local site reaction can be based on the time of onset. A local site reaction occurs around the injection site; however, it occurs shortly after vaccination.[2] Although DLLRs may occur after any vaccination,[3] they have been reported as rare[4,5] and almost specific[2,4] adverse skin reactions occurring after receipt of the mRNA-1273 vaccine (Moderna) against SARS-CoV-2. Therefore, a DLLR that occurs after mRNA-1273 vaccination is commonly called "COVID arm" in the US[6,7] and "Moderna arm" in Japan. However, little is known about the pathophysiology of DLLR after mRNA-1273 vaccination.

Vaccinations with mRNA-1273 in Japan started on May 24, 2021, and DLLRs associated with the mRNA-1273 vaccine were reported shortly thereafter.[8] In this retrospective cross-sectional study, we analyzed data from medical examinations in a large-scale population in Japan to assess the associations of sex and age with susceptibility to DLLR. In addition, we analyzed the incidence rate of DLLR stratified by sex and age group and performed multiple linear regression analyses to evaluate the association of sex and age with time of DLLR onset and duration of DLLR.

Key Points

Question Are sex and age associated with susceptibility of delayed large local reactions (DLLRs) after the first injection of the SARS-CoV-2 mRNA-1273 vaccine?

Findings In this cross-sectional study of 5893 participants, the incidence rate of DLLRs after the first dose of the mRNA-1273 vaccine was significantly higher among females than among males and among participants aged 30 to 69 years than among adults aged 18 to 29 years.

Meaning The findings suggest that DLLR may be a type IV allergic skin reaction.

Methods

This study is reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The study was reviewed and approved by the institutional review board of the Self-Defense Forces Central Hospital, which waived the requirement for informed consent because the study did not involve additional risks to participants; an opt-out method was applied using a leaflet and website. All study protocols were in accordance with the Declaration of Helsinki.

Participants were recipients of the second dose of the mRNA-1273 vaccine who had received a first dose of the same vaccine 4 to 6 weeks earlier. Five experienced dermatologists (T.H., Y. Yamazaki, S.S., Y. Yonekura, and Y.M.) interviewed participants to assess adverse skin reactions after the first dose of the mRNA-1273 vaccine at the Self-Defense Forces large-scale vaccination center in Tokyo, Japan, from May 24 to November 30, 2021.

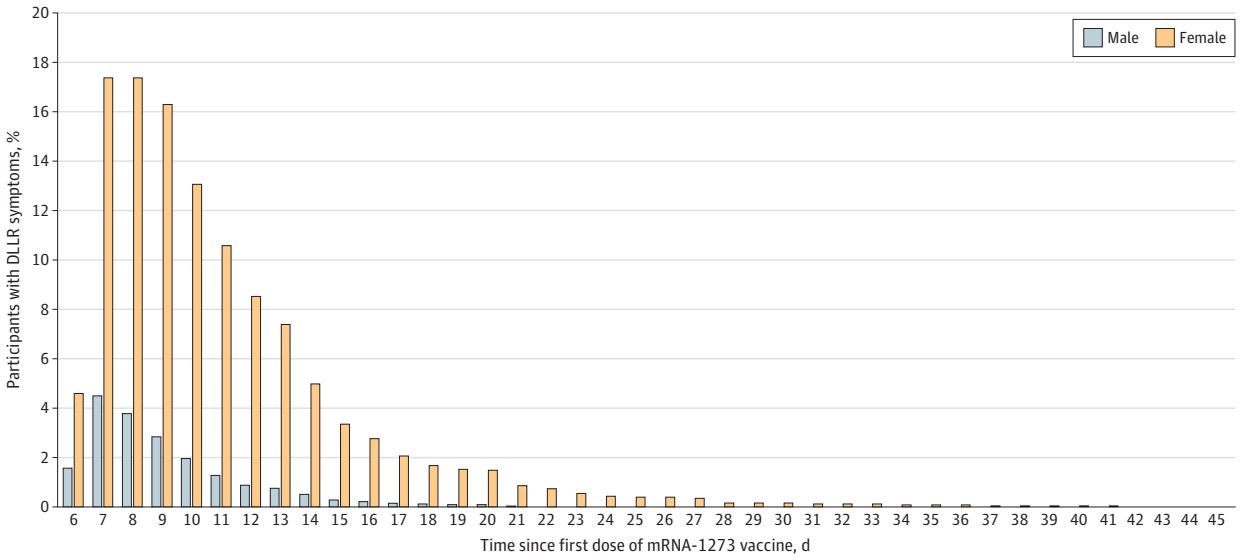
In this study, DLLR was considered if a participant reported erythema, tenderness, itchiness, induration, burning sensation, or swelling around the injection site that existed on or after the sixth day after injection of the first dose of the mRNA-1273 vaccine. Details of the methods are given in the eMethods and eFigure 2 in the Supplement. The primary outcome was the incidence rate of DLLR stratified by sex and age group. Odds ratios (ORs) were calculated to evaluate the differences between groups. To evaluate the association between the time of onset and duration of DLLR (dependent variables) with sex and age (independent variables), multiple linear regression analyses were performed. Outcomes were tested for significance using a 2-sided Pearson χ^2 test with 95% CIs. $P < .05$ was considered significant. Analyses were performed using SPSS, version 22.0J (IBM Inc).

Results

Of 650 532 recipients of the second dose of the mRNA-1273 vaccine at the Self-Defense Forces large-scale vaccination center in Tokyo, 5893 were interviewed (3318 [56.3%] male and 2575 [43.7%] female). The median age of males was 55 years (IQR, 38-68 years; range, 18-92 years), and the median age of females was 50 years (IQR, 34-67 years; range, 18-94 years). A total of 747 participants (12.7%) experienced DLLR symptoms after the first dose of the mRNA-1273 vaccine. Symptoms were mild and not considered as contraindications to the vaccine. The percentage of participants with DLLR symptoms increased on the seventh day after vaccination and gradually decreased thereafter among both males and females (**Figure**). The incidence rate, time of onset, and duration of DLLR overall and stratified by sex and age group are presented in **Table 1**. The incidence rate was significantly higher among females (22.4% [577 participants]; OR, 5.30; 95% CI, 4.42-6.34) than among males (5.1% [170 participants]; reference). Moreover, the incidence rate was significantly higher among individuals aged 30 to 39 years (14.3% [129 participants]; OR, 1.68; 95% CI, 1.25-2.26), 40 to 49 years (15.8% [136 participants]; OR, 1.89; 95% CI, 1.41-2.53), 50 to 59 years (14.9% [104 participants]; OR, 1.76; 95% CI, 1.29-2.40), and 60 to 69 years (12.6% [182 participants]; OR, 1.45; 95% CI, 1.10-1.91) than among participants aged 18 to 29 years (9.0% [81 participants]; reference). Conversely, there was no significant difference in the incidence rates between individuals older than 69 years (10.5% [115 participants]; OR, 1.19; 95% CI, 0.88-1.56) and individuals aged 18 to 29 years.

The mean (SD) time of onset was significantly earlier among males (6.97 [1.26] days) than among females (7.32 [1.44] days) after adjustment for age (β = 0.345 days; 95% CI, 0.105-0.586 days; $P = .005$), whereas there was no association between time of onset and age after adjustment for sex (β = 0.003 days; 95% CI, −0.003 to 0.009 days; $P = .30$) (Table 1 and **Table 2**). The mean (SD) duration of symptoms was significantly shorter among males (4.83 [3.27] days) than among females (5.98 [4.43] days) after adjustment for age (β = 1.535 days;

Figure. Percentage of Participants With Delayed Large Local Reaction (DLLR) Symptoms After the First Dose of the mRNA-1273 Vaccine



A DLLR was considered if a participant reported erythema, tenderness, itchiness, induration, burning sensation, or swelling around the injection site that existed on or after the sixth day after injection. All symptoms resolved by the 22nd day among male recipients and by the 42nd day among female recipients.

Table 1. Incidence Rate, Time of Onset, and Duration of DLLRs After the First Dose of the mRNA-1273 Vaccine by Sex and Age

Characteristic	Participants, No. (%)	Patients with DLLR symptoms, No. (%)	OR (95% CI)	Mean (SD), d		*P* value[a]
				Onset	Duration	
Total	5893 (100)	747 (12.7)	NA	7.24 (1.41)	5.72 (4.22)	NA
Sex						
Female	2575 (43.7)	577 (22.4)	5.30 (4.42-6.34)	7.32 (1.44)	5.98 (4.43)	<.001
Male	3318 (56.3)	170 (5.1)	1 [Reference]	6.97 (1.26)	4.83 (3.27)	
Age group, y						
18-29	896 (15.2)	81 (9.0)	1 [Reference]	7.11 (1.19)	4.48 (3.46)	NA
30-39	900 (15.3)	129 (14.3)	1.68 (1.25-2.26)	7.22 (1.57)	5.09 (3.55)	<.001
40-49	861 (14.6)	136 (15.8)	1.89 (1.41-2.53)	7.13 (1.11)	5.73 (4.28)	<.001
50-59	699 (11.9)	104 (14.9)	1.76 (1.29-2.40)	7.25 (1.03)	5.02 (3.13)	<.001
60-69	1446 (24.5)	182 (12.6)	1.45 (1.10-1.91)	7.46 (1.69)	5.90 (4.05)	.008
>69	1091 (18.5)	115 (10.5)	1.19 (0.88-1.56)	7.13 (1.48)	7.63 (5.65)	.26

Abbreviations: DLLR, delayed large local reaction; NA, not applicable; OR, odds ratio.

[a] *P* value for the Pearson χ^2 test for the association between each characteristic and incidence.

95% CI, 0.901-2.169 days; $P < .001$). The duration of DLLR was also associated with age after adjustment for sex (β = 0.041 days; 95% CI, 0.024-0.057 days; $P < .001$).

Discussion

According to a phase 3 clinical trial of the mRNA-1273 vaccine that included 30 420 participants in the US,[9] delayed injection-site reactions with onset on or after the eighth day of vaccination occurred in 244 recipients (0.8%) after the first dose and in 68 recipients (0.2%) after the second dose. More recent studies on recipients who reported DLLR symptoms after the first or second dose of the mRNA-1273 vaccine revealed cumulative incidence rates of 1.1% among female recipients in the US (no DLLR symptoms among 675 male recipients)[4] and 0.16% in the general population in Germany.[5] Although DLLR has been reported as a rare adverse event associated with the mRNA-1273 vaccine in the US and Europe, a previous Japanese study reported an incidence of 1.5%

Table 2. Multiple Linear Regression Analysis for Onset or Duration of Delayed Large Local Reaction After the First mRNA-1273 Dose by Sex and Age

	Covariate			
	Female sex		Age	
Dependent variable	β (95% CI)	*P* value[a]	β (95% CI)	*P* value[a]
Onset, d	0.345 (0.105 to 0.586)	.005	0.003 (−0.003 to 0.009)	.30
Duration, d	1.54 (0.901 to 2.169)	<.001	0.041 (0.024 to 0.057)	<.001

[a] *P* value for multiple linear regression covariate (sex and age).

among males and 12.5% among females.[10] In the current study, DLLR occurred among 5.12% of males and 22.4% of females; therefore, our results support previous findings that DLLR is a common adverse event in Japan. The difference in the incidence rate in our study compared with others is possibly attributable to Japanese recipients being more aware of skin symptoms after vaccination. Thus, the incidence rate of DLLR may be underestimated in the US and Europe. To maximize the sensitivity of our study, only dermatologists with experience in examining individuals with DLLR interviewed the participants for details of skin symptoms, including delayed-onset erythema, tenderness, itchiness, induration, burning sensation, and swelling around the injection site. Thus, the incidence rate in this study may be higher than that previously reported in a Japan.[10] Because the incidence rates of DLLR were low in previous studies,[4,5,9] it has been difficult to assess the association between susceptibility and demographic characteristics. Therefore, we performed association analyses in a large-scale population to examine the factors associated with the onset of DLLR. The incidence rate was significantly higher among females than among males, supporting the findings of a previous Japanese study.[10] In addition, we found later onset and longer duration of DLLR among females. To our knowledge, this is the first study to report this information. Sex differences in body weight and immune responses associated with hormonal and environmental factors[11] may partially explain the differences in susceptibility, time of onset, and duration of DLLR.

In this study, we found for the first time, to our knowledge, that DLLR occurred more frequently among individuals aged 30 to 69 years than among individuals aged 18 to 29 years. However, there was no significant difference in the incidence rate between individuals older than 69 years and those aged 18 to 29 years. These findings are similar to the prevalence for allergic contact dermatitis associated with several antigens, such as formaldehyde, and suggest that DLLR is a type IV allergic skin reaction.[12] Both DLLR and allergic contact dermatitis manifest as spongiosis of the epidermis and superficial perivascular and perifollicular T-cell infiltrate with eosinophils,[13-15] and the histopathological similarities may support this scenario.

Limitations

This study has limitations. It did not include people who did not receive a second dose of the mRNA-1273 vaccine; therefore, selection bias may exist. Recall bias may not be excluded because information regarding adverse skin reactions was self-reported.

Conclusions

This cross-sectional study revealed a higher incidence rate of DLLR after the first dose of the mRNA-1273 vaccine among females than among males and among individuals aged 30 to 69 years than among individuals aged 18 to 29 years. In addition, females had later onset and longer duration of DLLR than males. The association between demographic characteristics and susceptibility of DLLR suggests that the condition is a type IV allergic skin reaction.

ARTICLE INFORMATION

Accepted for Publication: April 20, 2022.

Published Online: June 1, 2022. doi:10.1001/jamadermatol.2022.2088

Author Contributions: Dr Higashino had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: Higashino, Yamazaki, Senda, Yonekura, Imai, Miura.
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Supervision: Kawano, Miura.

Conflict of Interest Disclosures: None reported.

Meeting Presentation: This article was presented at the 121st Annual Meeting of the Japanese Dermatological Association; June 2, 2022; Kyoto, Japan.

Additional Contributions: We thank the patients for granting permission to publish this information. We also thank the participants in the study. Hiroshi Nakashima, MD, PhD (Department of Preventive Medicine and Public Health, National Defense Medical College), provided assistance with manuscript revision and peer review. There was no financial compensation for these contributions.

REFERENCES

1. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed large local reactions to mRNA-1273 vaccine against SARS-CoV-2. *N Engl J Med*. 2021;384(13):1273-1277. doi:10.1056/NEJMc2102131

2. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. *J Am Acad Dermatol*. 2021;85(1):46-55. doi:10.1016/j.jaad.2021.03.092

3. Kelso JM, Greenhawt MJ, Li JT, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol*. 2012;130(1):25-43. doi:10.1016/j.jaci.2012.04.003

4. Jacobson MA, Zakaria A, Maung Z, et al. Incidence and characteristics of delayed injection site reaction to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine

(Moderna) in a cohort of hospital employees. *Clin Infect Dis*. 2022;74(4):591-596. doi:10.1093/cid/ciab518

5. Hoff NP, Freise NF, Schmidt AG, et al. Delayed skin reaction after mRNA-1273 vaccine against SARS-CoV-2: a rare clinical reaction. *Eur J Med Res*. 2021;26(1):98. doi:10.1186/s40001-021-00557-z

6. Johnston MS, Galan A, Watsky KL, Little AJ. Delayed localized hypersensitivity reactions to the Moderna COVID-19 vaccine: a case series. *JAMA Dermatol*. 2021;157(6):716-720. doi:10.1001/jamadermatol.2021.1214

7. Kempf W, Kettelhack N, Kind F, Courvoisier S, Galambos J, Pfaltz K. 'COVID arm'—histological features of a delayed-type hypersensitivity reaction to Moderna mRNA-1273 SARS-CoV2 vaccine. *J Eur Acad Dermatol Venereol*. 2021;35(11):e730-e732. doi:10.1111/jdv.17506

8. Higashino T, Yamazaki Y, Senda S, Horinosono H, Miura Y. Delayed large local reaction to mRNA-1273 vaccine. Article in Japanese. *Jpn J Dermatol*. 2021;131(9):2045-2049. doi:10.14924/dermatol.131.2045

9. Baden LR, El Sahly HM, Essink B, et al; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403-416. doi:10.1056/NEJMoa2035389

10. Hibino M, Ishihara T, Iwata M, Doi Y. Delayed injection site reaction after mRNA-1273 vaccination in Japan: a retrospective, cross-sectional study. *Open Forum Infect Dis*. 2021;8(10):ofab497. doi:10.1093/ofid/ofab497

11. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol*. 2016;16(10):626-638. doi:10.1038/nri.2016.90

12. Lynch MD, McFadden JP, White JM, Banerjee P, White IR. Age-specific profiling of cutaneous allergy at high temporal resolution suggests age-related alterations in regulatory immune function. *J Allergy Clin Immunol*. 2017;140(5):1451-1453.e5. doi:10.1016/j.jaci.2017.03.054

13. Larson V, Seidenberg R, Caplan A, Brinster NK, Meehan SA, Kim RH. Clinical and histopathological spectrum of delayed adverse cutaneous reactions following COVID-19 vaccination. *J Cutan Pathol*. 2022;49(1):34-41. doi:10.1111/cup.14104

14. Ackerman AB. *Histologic Diagnosis of Inflammatory Skin Diseases*. Lea & Febiger; 1978.

15. Kimber I, Dearman RJ. Allergic contact dermatitis: the cellular effectors. *Contact Dermatitis*. 2002;46(1):1-5. doi:10.1034/j.1600-0536.2002.460101.x