Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Vaccine 40 (2022) 5997–6000

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

Vasovagal reactions after COVID-19 vaccination in Japan

Mai Okuyama [a], Saeko Morino [a], Kaori Tanaka [a], Haruna Nakamura-Miwa [a], Sayaka Takanashi [a], Satoru Arai [a], Masaki Ochiai [b], Koji Ishii [b], Motoi Suzuki [a], Akira Oka [c], Tomohiro Morio [d], Keiko Tanaka-Taya [a,e,*]

[a] Center for Surveillance, Immunization, and Epidemiologic Research, National Institute of Infectious Diseases, Tokyo, Japan
[b] Department of Quality Assurance, Radiation Safety, and Information System, National Institute of Infectious Diseases, Tokyo, Japan
[c] Department of Neurology, Saitama Children's Medical Center, Saitama, Japan
[d] Department of Pediatrics and Developmental Biology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Tokyo, Japan
[e] Kanagawa Prefectural Institute of Public Health, Kanagawa, Japan

ARTICLE INFO

Article history:
Received 8 March 2022
Received in revised form 11 July 2022
Accepted 23 August 2022
Available online 25 August 2022

Keywords:
COVID-19 vaccination
Vasovagal reaction
Adverse event following immunization
Adolescents
Young adults
Immunization stress-related responses

ABSTRACT

Coronavirus disease 2019 (COVID-19) vaccine administration started in February 2021 in Japan. As of December 2021, approximately 75% of the population aged ≥12 years had received two doses of vaccine. We conducted a study to investigate vasovagal reactions (VVR) after COVID-19 vaccination using data on adverse events following immunization. The crude reporting rate of VVR (cases/1,000,000 doses) after vaccination was 9.6 in all age groups combined, and was more frequent in the younger age groups: 28.6 and 37.2 in individuals aged 10–19 years and 20–29 years, respectively. In individuals aged 10–29 years, the rate was similar in males and females (33.0 and 34.2, respectively, $p = 0.53$); but was higher after dose 1 than after dose 2 (57.4 and 8.8, respectively, $p < 0.001$). Based on these results, caution needs to be exercised when vaccinating adolescents and young adults, especially with dose 1 of COVID-19 vaccines.

© 2022 The Authors. Published by Elsevier Ltd.

1. Introduction

In Japan, the Immunization Act and related regulations were revised in December 2020, and coronavirus disease 2019 (COVID-19) vaccines were added to the category of "Temporary Vaccinations" [1]. The Ministry of Health, Labour and Welfare (MHLW) of Japan granted special approval for the emergency use of Comirnaty (Pfizer/BioNTech) on February 14, 2021, for individuals aged 16 years and older, and for the emergency use of the Moderna COVID-19 Vaccine (Takeda/Moderna) on May 21, 2021, for individuals aged 18 years and older. The authorization was expanded to 12 years and older for Comirnaty (Pfizer/BioNTech) on May 31, 2021, and for the Moderna COVID-19 Vaccine on July 26, 2021. Vaxzevria (Oxford/AstraZeneca) was also approved on May 21, 2021 for individuals aged 18 years and older, but it was decided to restrict its use to individuals aged 40 years and older, except in special circumstances such as allergy to other COVID-19 vaccines.

The Immunization Act established a system for reporting adverse events following immunization (AEFI) in 2013 and stipulated that if the establisher of a hospital, or clinic, or a medical doctor recognizes a person who underwent a routine vaccination shows symptoms of a disease that are suspected as a result of a routine vaccination, etc. pursuant to the provisions of Order of the MHLW, they must report the details to the Minister of Health, Labour and Welfare pursuant to the provisions of the relevant Order. This law also covers "Temporary Vaccinations". These AEFI reports are aggregated and the Health Sciences Council of the MHLW regularly conducts evaluations by experts. These evaluations are conducted more frequently for COVID-19 vaccines than for other kinds of vaccines.

AEFI have recently attracted attention, especially in adolescents and young adults (AYAs), with respect to the immunization stress-related responses (ISRR) [2]. Vasovagal reactions (VVR), which manifest as dizziness or loss of consciousness, can be triggered by stimulation, including vaccination, and are reported to be more common in AYAs. This study aimed to clarify the features of VVR after COVID-19 vaccination, with a particular focus on AYAs.

Abbreviations: AEFI, adverse events following immunization; AYAs, adolescents and young adults; COVID-19, coronavirus disease 2019; IQR, interquartile range; ISRR, immunization stress-related responses; MHLW, Ministry of Health, Labour and Welfare; VVR, vasovagal reactions.

* Corresponding author at: Center for Surveillance, Immunization and Epidemiologic Research, National Institute of Infectious Diseases, Toyama 1-23-1, Shinjuku-ku, Tokyo 162-8640, Japan.
E-mail address: ktaya@niid.go.jp (K. Tanaka-Taya).

https://doi.org/10.1016/j.vaccine.2022.08.056
0264-410X/© 2022 The Authors. Published by Elsevier Ltd.

Table 1
Incidence of vasovagal reaction after COVID-19 vaccination according to age – February 17 to December 5, 2021.

			Age (years)								
		Total	10–19[a]	20–29	30–39	40–49	50–59	60–69	70–79	≥80	Unknown
All AEFI reports (cases)[b]	Male	8,401	707	1,626	1,476	1,338	800	748	873	828	5
	Female	21,732	811	3,677	3,799	5,119	3,669	1,834	1,316	1,499	8
	Unknown	73	7	11	17	8	7	10	6	4	3
	Total	30,206	1,525	5,314	5,292	6,465	4,476	2,592	2,195	2,331	16
VVR cases in AEFI reports (cases)[b]	Male	862	184	358	156	91	35	13	14	11	0
	Female	1,021	194	368	163	136	86	38	25	11	0
	Unknown	6	2	3	0	0	0	1	0	0	0
	Total	1,889	380	729	319	227	121	52	39	22	0
Estimated number of doses of vaccine administered (doses)[c]	Male	93,558,102	6,744,237	9,693,469	11,205,134	15,174,540	15,043,145	13,599,631	14,058,933	8,039,013	NA
	Female	103,163,913	6,528,247	9,884,842	11,261,010	15,513,160	15,386,648	14,325,096	16,403,502	13,861,408	NA
	Total	196,722,015	13,272,484	19,578,311	22,466,144	30,687,700	30,429,793	27,924,727	30,462,435	21,900,421	NA
Crude reporting rate of VVR cases (cases/1,000,000 doses)[d]	Male	9.2	27.3	36.9	13.9	6.0	2.3	1.0	1.0	1.4	NA
	Female	9.9	29.7	37.2	14.5	8.8	5.6	2.7	1.5	0.8	NA
	Total	9.6	28.6	37.2	14.2	7.4	4.0	1.9	1.3	1.0	NA
Proportion of VVR cases in AEFI reports (%)[e]		6.3	24.9	13.7	6.0	3.5	2.7	2.0	1.8	0.9	…

[a] COVID-19 vaccine is available to individuals aged 12 years and older; however, in this study, we assessed the number of vaccinations by 10-yearly age groups, including the 10–19-year age group.
[b] This number includes cases in which the vaccine dose (dose 1 or dose 2) was unknown.
[c] This number does not include cases in which the vaccine dose, sex, or age was unknown.
[d] Crude reporting rate of VVR cases (cases/1,000,000 doses): VVR cases in AEFI reports (cases)/Estimated number of doses of vaccine administered (doses) × 1,000,000.
[e] Proportion of VVR cases in AEFI reports (%): VVR cases in AEFI reports (cases)/All AEFI reports (cases) × 100, AEFI, adverse event following immunization; NA, not available; VVR, vasovagal reactions.

2. Methods

Information on AEFI reports submitted by health professionals as of December 5, 2021, and the estimated number of doses of vaccine administered from the material of the Health Sciences Council meeting held by the MHLW on December 24, 2021, were used in this analysis [3]. This Council discussed the reports for the period February 17, 2021, through December 5, 2021, and the data were fixed on December 5, 2021 [3]. We reviewed the reports of cases that mentioned VVR, with or without symptoms such as syncope, and calculated the crude reporting rate of VVR and proportion of VVR cases in all AEFI reports by 10-yearly age groups. In the 10–29-year age group, which included both the 10–19-year age group and the 20–29-year age group, detailed analyses were performed according to age, sex, vaccine dose, outcome, and hospitalization.

Chi-square tests were used to compare the crude reporting rates between groups, and p values <0.05 were considered to be statically significant. Stata version 17.0 (StataCorp, College Station, TX, USA) was used for all analyses.

In this study, cases for which sex, age, or vaccine dose was unknown were excluded for the estimation of vaccination doses because the data were not publicly available. In contrast, AEFI reports included cases for which the vaccine dose and sex were unknown in the analysis to avoid underestimation. In Japan, COVID-19 vaccines were available to individuals aged 12 years and older at the time that this analysis was performed; however, in this study, we assessed the number of vaccinations by 10-yearly age groups, including the 10–19-year age group.

In Japan, Comirnaty (Pfizer/BioNTech) is mainly used for healthcare workers and the older adults (≥65 years of age), and Moderna COVID-19 Vaccine (Takeda/Moderna) is used for workplace vaccination (excluding healthcare workers), mainly for younger people, including university students. The background of recipients of each type of vaccine is thus very different. Because the frequency of VVR is more likely to be influenced by the recipients' background than by the type of vaccine, this analysis was not stratified according to the vaccine type.

3. Results

From February 17 to December 5, 2021, approximately 200 million doses of COVID-19 vaccine (Pfizer/BioNTech, Takeda/Moderna or Oxford/AstraZeneca) are estimated to have been administered to people in Japan. During that period, 30,206 AEFI reports were submitted, of which 1,889 were cases of VVR. The crude reporting rate of VVR was 9.6 cases/1,000,000 doses in all age groups combined, 28.6 in the 10–19-year age group and 37.2 in the 20–29-year age group. The crude reporting rate of VVR was higher in the 10–29-year age group than in individuals aged 30 years and above (30–39-, 40–49-, 50–59-, 60–69-, 70–79- and ≥80-year age groups combined) (33.8 vs 4.8 cases/1,000,000 doses, $p < 0.001$). The proportion of VVR cases in the AEFI reports was 6.3% in all age groups combined, 24.9% in 10–19-age group, and 13.7% in 20–29-age group (Table 1).

In the 10–29-year age group, there were 1,109 cases of VVR, with a median age of 21 years (interquartile range [IQR]: 19–24 years). Of these cases, 542 (48.9%) were in males, 562 (50.7%) were in females and the sex was unknown in 5 individuals (0.5%). Regarding the dose, 962 (86.7%) were administered as dose 1,141 (12.7%) were administered as dose 2, and the dose was unknown in 6 individuals (0.5%). The crude reporting rate of VVR did not differ significantly by sex (33.0 and 34.2 cases/1,000,000 doses in males and females, respectively, $p = 0.53$); but was significantly higher after dose 1 than after dose 2 (57.4 and 8.8 cases/1,000,000 doses, respectively, $p < 0.001$). Of the 962 VVR cases reported after dose 1,477 (49.6%) were in males, 480

Table 2
Characteristics of individuals aged 10–29 years[a] with vasovagal reactions reported after COVID-19 vaccination – February 17 to December 5, 2021 (N = 1,109).

		No. of cases[b] (%) N = 1,109	Estimated number of doses of vaccine[c] (doses)	Crude reporting rate of VVR cases (cases/1,000,000 doses)
Age, median (IQR), years		21 (19–24)	…	…
Sex	Male	542 (48.9)	16,437,706	33.0
	Female	562 (50.7)	16,413,089	34.2
	Unknown	5 (0.5)	…	…
Vaccine doses	Dose 1	962 (86.7)	16,761,058	57.4
	Dose 2	141 (12.7)	16,089,737	8.8
	Unknown	6 (0.5)	…	…
Outcome	Recovering	192 (17.3)	…	…
	Recovered	882 (79.5)	…	…
	Unrecovered	4 (0.4)	…	…
	Unknown	31 (2.8)	…	…
Hospitalized		20 (1.8)	…	…

[a] COVID-19 vaccine is available to individuals aged 12 years and older; however, in this study, we assessed the number of vaccinations by 10-yearly age groups, including the 10–19-year age group.
[b] This number include cases in which the vaccine dose, sex, or age was unknown.
[c] This number does not include cases in which the vaccine dose, sex, or age was unknown, IQR, interquartile range; VVR, vasovagal reactions.

(49.9%) were in females, and 5 (0.5%) were in individuals of unknown sex, and the crude reporting rate of VVR was 56.9 and 57.3 cases/1,000,000 doses in males and females, respectively. Of the 141 VVR cases reported after dose 2, 61 (43.3%) were in males, and 80 (56.7%) were in females, and the crude reporting rate of VVR was 7.6 and 10.0 cases/1,000,000 doses in males and females, respectively.

The outcomes were 192 (17.3%) recovering, 882 (79.5%) recovered, 4 (0.4%) unrecovered, and 31 (2.8%) unknown. All four unrecovered cases occurred after dose 1, of which 1 was in the 10–19-age group and 3 were in the 20–29-age group; and 1 was in a male and 3 were in females. Twenty of the individuals with reported VVR (1.8%) were hospitalized (Table 2).

4. Discussion and conclusion

This study determined the incidence rate of VVR after COVID-19 vaccination based on AEFI reports. The incidence of VVR was highest in the 10–19-year and 20–29-year age groups. Similarly, the proportion of reported AEFI due to VVR was highest in the 10–19-year and 20–29-year age groups, especially in the 10–19-year age group. The proportion of AEFI attributable to VVR was inversely related to age. In the analysis of the 10–29-year age group, the incidence of VVR did not differ according to sex, but was approximately 6.5 times higher with dose 1 than with dose 2. The reason for the higher incidence with dose 1 may be that people had less anxiety and fear of vaccination with dose 2 because of having experienced dose 1, or because of measures may have been taken to prevent a VVR with dose 2, such as administering it with the subject in a supine position, if the subject had experienced a VVR with dose 1. The outcome data were as of December 5, and most cases, including hospitalized cases, were recovered or recovering.

Studies of VVR after vaccination have the limitation of not using a standard case definition or surveillance system. Therefore, the characteristics of VVR, especially those not accompanied by syncope, as in this study, are unclear. Although reports of VVR with syncope have been published, the reported frequency has varied from 0.054 to 88 cases per 100,000 doses [2]. According to the Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting system used in the United States, 77.5% of reported cases of syncope after vaccination occurred in females and most individuals were in the 11–18-year age group during the period from 2005 to 2007 [4]. However, the type of vaccine was not reported, and the incidence rate could not be determined because the total number of doses administered in each age group was unknown [4]. VVR are generally more common in females than in males. It is unclear why the crude reporting rates among males and females were similar in the younger age groups in this study. It is possible that both males and females were equally anxious because COVID-19 vaccines were new, and were the first mRNA vaccines to be used in Japan. Comirnaty (Pfizer/BioNTech) for use in children aged 5–11 years old was approved on January 21, 2022. Only a limited number of vaccinations have been administered to children in this age group to date, so children should continue to be monitored carefully following vaccination.

In 2019, the Global Advisory Committee on Vaccine Safety advocated the concept of ISRR, which is a response to the stress that some individuals may feel when receiving an injection, and covers the spectrum of manifestations, including VVR [2,5]. The ISRR manual describes approaches for prevention, diagnosis, and management of VVR [2]. The prognosis of VVR is good, but it sometimes causes injury, and individuals undergoing vaccination experience fear. Clinicians need to acquire knowledge about VVR and pay attention when administering vaccines, particularly when administering vaccines to AYAs.

This study has some limitations. First, the national AEFI surveillance system, based on spontaneous reporting, is aimed at documenting severe adverse events. The reported incidence may not include milder cases of VVR without complications. Second, there are no set definitions for the conditions reported, so it is not possible to determine whether the VVR was accompanied by symptoms such as syncope, or whether it is occurred with other AEFI such as anaphylaxis, ISRR, and other conditions. Third, the results are based on an analysis of the data that were available at a point in time and a follow-up period was not established by the national AEFI surveillance system, so any additional information reported on the cases after the data were collected, including information on outcomes, was not included in the analysis. Fourth, we conducted the analysis based on the assumption that individuals who were vaccinated but did not have VVR reported, did not develop VVR. There may have been reporting bias and some cases may not have been reported, so the incidence of VVR may have been underestimated.

In conclusion, we showed that the incidence of VVR after COVID-19 vaccination in Japan is predominantly in AYAs and is

inversely related to age; is higher with dose 1 than with dose 2; and does not differ according to sex in AYAs. Considering these results, healthcare professionals should be well prepared to manage VVR and careful when administering COVID-19 vaccines to AYAs. It is extremely rare for a particular vaccine to be administered to individuals of such a wide age range in such a short period, and the results, including AEFI, need to be examined in detail for future reference. Vaccination of AYAs is an important issue in Japan and should be closely monitored on an ongoing basis.

Funding

This work was supported by the Ministry of Health, Labour, and Welfare Program, Grant No JPMH20HA2007 and the Research Program on Emerging and Re-emerging Infectious Diseases from Japan Agency for Medical Research and Development, AMED.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank Ms. Ayaka Asano, Ms. Toshie Yoshida, Ms. Aya Iwasaki, and Ms. Rie Kitamoto for data management and technical assistance.

References

[1] Yamamoto N, Takahashi Y, Hayashi S. Legal and regulatory processes for Japan's COVID-19 immunization program. Vaccine 2021;39:6449–50. https://doi.org/10.1016/j.vaccine.2021.09.002.
[2] World Health Organization. Immunization stress-related responses. 2019. https://www.who.int/publications/i/item/978-92-4-151594-8 [accessed 17 January 2022].
[3] Ministry of Health, Labour and Welfare. Committee on the Vaccine Adverse Reaction Review and Drug Safety of the Pharmaceutical Affairs and Food Sanitation Council Committee (joint meeting), Health Sciences Council. 24 December 2021. https://www.mhlw.go.jp/stf/shingi2/0000208910_00036.html [accessed 17 January 2022].
[4] Centers for Disease Control and Prevention. Syncope after vaccination – United States, January 2005–July 2007. MMWR Morb Mortal Wkly Rep 2008;57:457–60.
[5] World Health Organization. Immunization stress-related responses: A synopsis of the manual for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization. 2019. https://apps.who.int/iris/handle/10665/330276 [accessed 17 January 2022].