



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.



Original Article

Investigation of the incidence of immunisation stress-related response following COVID-19 vaccination in healthcare workers

Tomonori Takano^a, Masanori Hirose^b, Yukitaka Yamasaki^a, Masatoshi Hara^c, Tomoyuki Okada^d, Hiroyuki Kunishima^{a,*}^a Department of Infectious Disease, St. Marianna University School of Medicine, Kanagawa, Japan^b Division of General Internal Medicine, St. Marianna University School of Medicine, Kanagawa, Japan^c Division of Cardiology and Health Service Centre, Department of Internal Medicine, St. Marianna University School of Medicine, Kanagawa, Japan^d Department of Otolaryngology and Health Service Centre, St. Marianna University School of Medicine, Kanagawa, Japan

ARTICLE INFO

Keywords:

Adverse events following immunisation
Allergy
Anxiety-related response
Coronavirus disease 2019
Immunisation stress-related response
Vaccination

ABSTRACT

Introduction: Safe vaccination worldwide is critical to end the coronavirus disease 2019 (COVID-19) pandemic. We aimed to evaluate adverse reactions to vaccination using a web-based questionnaire and examine the risk factors for the occurrence of immunisation stress-related response (ISRR).**Methods:** We conducted a questionnaire survey using Google Form® among the employees of St. Marianna University Hospital who had received the COVID-19 vaccine between April 2021 and May 2021, 1 week after the first and second vaccinations. We developed and used a questionnaire to identify individuals with ISRR according to the World Health Organization diagnostic criteria. A generalised linear mixed model was constructed with ISRR onset as the dependent variable, subjects as the random factor, and each parameter as a fixed factor. A multivariate model was constructed using the forced imputation method with factors that were significant in the univariate analysis.**Results:** We enrolled 2,073 and 1,856 respondents in the first and second questionnaire surveys, respectively. Fifty-five and 33 ISRR cases were identified in the first and second vaccinations, respectively. In the univariate analysis, strong pre-vaccination anxiety (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.30–4.12, $p = 0.004$) and history of allergy (OR, 1.6; 95% CI, 1.14–2.24, $p = 0.007$) were significant risk factors. Multivariate analysis also showed that strong pre-vaccination anxiety (OR, 2.1; 95% CI, 1.15–3.80, $p = 0.016$) and history of allergy (OR, 1.5; 95% CI, 1.09–2.15, $p = 0.014$) were significant risk factors.**Conclusions:** Confirmation of allergy prior to vaccination and subsequent action are essential for addressing ISRR.

1. Introduction

More than a year has passed since the severe acute respiratory syndrome coronavirus 2 caused a global outbreak of the coronavirus disease 2019 (COVID-19). Vaccination against COVID-19 has started worldwide; in Japan, it was initiated in February 2021. The Council for International Organizations of Medical Sciences and World Health Organization (WHO) classified adverse events following immunisation (AEFIs) into five categories [1]. However, the WHO noted that these

categories do not adequately assess adverse reactions caused by the stress associated with vaccination. Therefore, in 2019, the WHO proposed a new concept, immunisation stress-related response (ISRR), to include stress-related symptoms [2].

AEFIs other than ISRR occur only post-vaccination, whereas ISRR may occur before, during, or after vaccination [2]. Symptoms include vasovagal reflex symptoms, such as dizziness and loss of consciousness; acute stress reactions, such as breathlessness and hyperventilation; and dissociative neurological symptom reactions (DNSRs), which are

Abbreviations: AEFI, Adverse events following immunisation; CFS, Chronic fatigue syndrome; CI, Confidence interval; COVID-19, Coronavirus disease 2019; CRPS, Complex regional pain syndrome; DNSR, Dissociative neurological symptom reactions; FDA, Food and Drug Administration; ISRR, Immunisation stress-related response; IQR, Interquartile range; OR, Odds ratio; POTS, Postural orthostatic tachycardia syndrome; WHO, World Health Organization.

* Corresponding author. Department of Infectious Disease, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa, 216-8511, Japan.

E-mail address: h2kuni@marianna-u.ac.jp (H. Kunishima).

<https://doi.org/10.1016/j.jiac.2022.02.002>

Received 5 November 2021; Received in revised form 6 January 2022; Accepted 4 February 2022

Available online 9 February 2022

1341-321X/© 2022 Japanese Society of Chemotherapy and The Japanese Association for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

temporary symptoms, such as difficulty in speaking and numbness of the limbs, occurring hours to days after vaccination [3–5].

The risk factors for ISRR are classified into physical, mental, and social factors. Particularly, the risk of vasovagal reflex, classified as a physiological factor, has been extensively studied, with age (younger age is associated with higher risk), sex (female sex is associated with higher risk), and weight (lower weight is associated with higher risk) as traditional risk factors [6–8]. Other possible risk factors for ISRR include psychological factors, such as comprehension, prior knowledge of the vaccine, pre-vaccination anxiety, and previous fearful experiences related to needles [2]. Additionally, social risk factors, such as community trust in healthcare and perceptions of immunisation, community and family support for immunisation, and false or misleading news reports and social media messages about immunisation, have been suggested as risk factors [2,9].

Similar to other viral infections, such as measles and influenza, vaccination against COVID-19 is essential for reducing disease severity and ending the epidemic [10–12]. Understanding adverse reactions, including ISRR, is crucial when initiating a new vaccination programme and promoting vaccination in different age groups. However, ISRR associated with COVID-19 vaccination remains to be investigated. This study assessed adverse reactions to vaccination using a web-based questionnaire and investigated risk factors for ISRR.

2. Patients and methods

2.1. Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study design was approved by the Ethics Committee of St. Marianna University School of Medicine (approval number: 5261).

2.2. Survey methods

A questionnaire survey was administered, using Google Form, to employees of St. Marianna University Hospital who had received the COVID-19 vaccine. Specifically, staff members (doctors, paramedical personnel, pharmacists, dieticians, and medical clerks) aged ≥ 20 years who agreed to participate in the questionnaire via a Google Form and were vaccinated at the hospital during the study period were included. The survey was conducted between April 6, 2021 and May 3, 2021. Consent to participate in the survey was obtained by selecting 'Yes' in the 'Consent to Survey' section at the beginning of the questionnaire.

A web-based Google Form survey was conducted 1 week after the first and second doses. ISRR is a new concept, and no previously developed questionnaire on ISRR exists. Therefore, the questionnaire was developed according to the WHO manual on ISRR [2] for assessing AEFIs, including ISRR.

A total of 29 items were assessed in six categories: 'consent to the questionnaire', 'demographic information and allergies', 'local reactions after vaccination', 'systemic reactions after vaccination', 'stress-related reactions', and 'assessment of anxiety'. The severity of physical adverse reactions was graded according to the United States Food and Drug Administration (FDA) Toxicity Grading Scale [13].

2.3. Definition of ISRR

Following the WHO manual on ISRR, we classified ISRR into three categories: i) acute stress response, ii) vasovagal reaction, and iii) DNSRs. Additionally, cases of complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), and suspected chronic fatigue syndrome (CFS) were excluded, and ISRR was determined according to the WHO AEFI reporting manual [1].

Specifically, if symptoms characteristic of i), ii), or iii) were observed at any time before, during, or after vaccination, they were determined to be ISRR according to the AEFI reporting manual [1]. Patients were excluded if drugs had been administered for adverse reactions because of the possibility of anaphylaxis [14], or if they had persistent symptoms at the time of completing the questionnaire, as CRPS, POTS, and CFS could not be ruled out [15–17].

2.4. Vaccine administration procedure

We used the mRNA vaccine, BNT162b2 (Comirnaty, BioNTech/Pfizer). It was administered to the staff once every 3 weeks for a total of two doses, based on the FDA's guidance for emergency vaccine use [18]. Vaccine storage and dispensing into syringes also followed the FDA guidance. Intramuscular injection of the vaccine was performed using a 25-mm long, 25-gauge needle (Top Co. Ltd., Tokyo, Japan), and the COVID-19 vaccine was administered to the deltoid muscle, according to Centers for Disease Control and Prevention guidelines [19].

2.5. Statistical analysis

To examine the effect of several parameters on the onset of ISRR, a mixed model (with participants as a random factor) was used, because there were multiple data sets (maximum two) for the same subject. A generalised linear mixed model (logit link function) was constructed with ISRR onset as the dependent variable, subjects as a random factor, and other variables as fixed factors. We used 10 variables. The following seven variables were selected because they have been suggested as possible risk factors for ISRR [2]: sex, age, pre-vaccination anxiety, previous needle use problems, a history of vasovagal reflex, prior vaccine knowledge, and frequency of social network use. First or second dose, a history of allergy, and a history of epilepsy were selected as the other three variables, because the experience of the first dose may affect the second, patients with allergies tend to be more anxious than those without, and previous studies on subjects with a history of epilepsy and AEFIs did not consider ISRR [2,20]. Statistics were calculated as odds ratios (ORs) and 95% confidence intervals (CIs). Multivariable analysis was performed using the forced imputation method with factors that were significant in the univariate analysis. The analysis aimed to identify predictive factors for ISRR onset. Therefore, events occurring after vaccination were not included in the multivariate analysis. Age and sex were included in the multivariate analysis as classical confounding factors. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using SPSS for Windows, version 24.0 (IBM Japan, Tokyo, Japan).

3. Results

3.1. Results of the AEFI questionnaire excluding ISRR

The main findings of the questionnaire are presented in Table 1. In total, 2,073 participants responded to the first questionnaire, and 1,856 participants responded to the second questionnaire. The total number of vaccinated people in the survey period was 7,662, with a questionnaire response rate of 51.3%. The frequency of Grade ≥ 1 pain at the injection site after vaccination in the ISRR and non-ISRR groups was 100.0% and 95.7%, respectively, for the first dose, and 100.0% and 94.8%, respectively, for the second dose. The frequency of Grade ≥ 1 fever in the ISRR and non-ISRR groups was 1.8% and 0.6%, respectively, after the first dose, and 18.2% and 14.0%, respectively, after the second dose.

3.2. Questionnaire results for ISRR-Related categories and risk factors for ISRR

We classified vaccinees who developed ISRR into three categories: acute stress response, vasovagal reaction, and DNSR. The number of

Table 1
Characteristics of the study participants.

Questionnaire		First dose ISRR group (n = 55)	First dose Non-ISRR group (n = 2,018)	Second dose ISRR group (n = 33)	Second dose Non-ISRR group (n = 1,823)
Sex	Female	50 , 90.9	1,427 , 70.7	24 , 72.7	1,283 , 70.4
Age	Median [IQR]	40.0 [28.0, 51.0]	40.0 [29.0, 51.0]	35.0 [27.5, 49.0]	41.0 [30.0, 52.0]
Do you have any allergies?	Yes	26 , 47.3	483 , 23.9	16 , 48.5	376 , 20.6
Have you ever been diagnosed with epilepsy? Or are you taking any antiepileptic drugs?	Yes	1 , 1.8	16 , 0.8	0 , 0.0	12 , 0.7

n, %; median [IQR].
IQR, interquartile range; ISRR, immunisation stress-related response.

vaccinees who had only an acute stress response was 23 and 13 following the first and second dose, respectively. The number of vaccinees who presented with only vasovagal reactions was 21 and 12 after the first and second dose, respectively, while 7 vaccinees each presented with DNSR after the first and second dose, respectively. The number of vaccinees who presented with both acute stress reaction and vasovagal reaction was 4 and 1 following the first and second dose, respectively. During the study period, there was only 1 case of anaphylaxis which presented with generalised skin rash, swelling of the lips, wheezing, and airway constriction; the patient was treated with medication.

Table 1 shows that the incidence of ISRR was 2.65% after the first dose, and 1.78% after the second dose. In the ISRR group, the proportion of women was 90.9% after the first dose, and 72.2% after the second dose. The incidence of allergy in the ISRR and non-ISRR groups was 47.3% and 23.9%, respectively, for the first dose, and 48.5% and 20.6%, respectively, for the second dose. Table 2 shows that the incidence of strong pre-vaccination anxiety in the ISRR and non-ISRR groups was 20.0% and 5.9%, respectively, for the first dose, and 15.2% and 5.3%,

respectively, for the second dose. The results of the analysis of risk factors for ISRR are shown in Table 3.

Univariate analysis showed that strong pre-vaccination anxiety (OR, 2.3 [95% CI: 1.30–4.12]; p = 0.004) and a history of allergy (OR, 1.6 [95% CI: 1.14–2.24]; p = 0.007) were significant risk factors. In multivariable analysis performed using significant risk factors identified in the univariate analysis, strong pre-vaccination anxiety (OR, 2.1 [95% CI: 1.15–3.80]; p = 0.016) and a history of allergy (OR, 1.5 [95% CI: 1.09–2.15]; p = 0.014) were significant risk factors.

4. Discussion

This study aimed to identify risk factors for ISRR to the COVID-19 vaccine. After analysing the questionnaire responses, strong pre-vaccination anxiety and a history of allergy were identified as risk factors for ISRR. We found that among physical adverse reactions, the frequency of pain was high for both the first and second doses, and the frequency of fever was higher for the second dose than for the first dose,

Table 2
Results of ISRR-related questions.

Questionnaire		First dose ISRR group (n = 55)	First dose Non-ISRR group (n = 2,018)	Second dose ISRR group (n = 33)	Second dose Non-ISRR group (n = 1,823)
Please select the anxiety you feel before vaccination. (Select one)	I did not feel anxious	5 , 9.1	633 , 31.4	7 , 21.2	625 , 34.3
	I felt a little anxious	39 , 70.9	1,265 , 62.7	21 , 63.6	1,101 , 60.4
	I had a very strong anxious feeling	11 , 20.0	120 , 5.9	5 , 15.2	97 , 5.3
Do you have any memories of pain or problems related to needles?	No	44 , 80.0	1,870 , 92.7	30 , 90.9	1,732 , 95.0
	Yes	11 , 20.0	148 , 7.3	3 , 9.1	91 , 5.0
Please select one or more of the following if you have ever experienced any when you were vaccinated or had a test or treatment using needles	I have never experienced any of the following	46 , 83.6	1,870 , 92.7	30 , 90.9	1,694 , 92.9
	A feeling of faintness or dizziness	9 , 16.4	85 , 4.2	3 , 9.1	82 , 4.5
	Cold sweats	3 , 5.5	69 , 3.4	0 , 0.0	62 , 3.4
	Nausea or vomiting	3 , 5.5	33 , 1.6	1 , 3.0	27 , 1.5
	Fainting	1 , 1.8	18 , 0.9	0 , 0.0	19 , 1.0
Please select the extent to which you knew or researched about vaccination against COVID-19 in advance. (Select one)	I do not know much about vaccines because I do not have much interest in them and have not done any research on them	2 , 3.6	53 , 2.6	1 , 3.0	46 , 2.5
	I know about vaccines from what I have seen or heard on TV, in newspapers, or in news articles on the Internet	31 , 56.4	1,392 , 69.0	20 , 60.6	1,228 , 67.4
	I am interested and have actively researched about vaccinations using books, the Internet, or social media	21 , 38.2	392 , 19.4	11 , 33.3	403 , 22.1
	I am interested and have actively researched about vaccination through medical papers, academic conferences, and national guidelines	1 , 1.8	181 , 9.0	1 , 3.0	146 , 8.0
How often do you use social networks in your daily life? (Select one)	I do not use social networks at all	2 , 3.6	160 , 7.9	1 , 3.0	140 , 7.7
	I use it a few times a week	2 , 3.6	220 , 10.9	5 , 15.2	221 , 12.1
	I use it at least once a day	16 , 29.1	615 , 30.5	6 , 18.2	570 , 31.3
	I use it many times a day	24 , 43.6	745 , 36.9	19 , 57.6	705 , 38.7
	I always use it when I have time, such as during breaks	11 , 20.0	278 , 13.8	2 , 6.1	187 , 10.3

n, %; median [IQR].
IQR, interquartile range; ISRR, immunisation stress-related response.

Table 3
Odds ratios for each risk factor.

Risk factor	Answer	Univariate analysis of risk factors ^a			Multivariate analysis of risk factors ^b		
		OR	95% CI	p-value	OR	95% CI	p-value
Administration	First dose	Ref.			–		
	Second dose	0.872	0.636 , 1.197	0.397			
Sex	Male	Ref.			Ref.		
	Female	1.256	0.874 , 1.805	0.218	1.078	0.736 , 1.581	0.699
Age	per 1 year	0.996	0.984 , 1.009	0.549	0.998	0.985 , 1.010	0.714
Any allergies	No	Ref.			Ref.		
	Yes	1.594	1.137 , 2.235	0.007	1.532	1.090 , 2.154	0.014
Epilepsy or taking any antiepileptic drugs	No	Ref.			–		
	Yes	1.201	0.221 , 6.524	0.832			
Anxiety	I did not feel anxious	Ref.			Ref.		
	I felt a little anxious	1.279	0.890 , 1.839	0.183	1.208	0.826 , 1.765	0.330
	I had a very strong anxious feeling	2.317	1.303 , 4.120	0.004	2.088	1.148 , 3.798	0.016
Memories of pain or problems related to needles	No	Ref.			–		
	Yes	1.651	0.972 , 2.803	0.063			
History of vasovagal reaction	No history of vasovagal reaction	Ref.			–		
	Have a history of vasovagal reaction	0.737	0.431 , 1.260	0.265			
Knowledge of the COVID-19 vaccine	No knowledge of the vaccine	Ref.			–		
	Passive knowledge of the vaccine	0.853	0.330 , 2.205	0.743			
	Active knowledge from non-academic sources	1.144	0.430 , 3.045	0.787			
Frequency of use of social networks	Active knowledge from academic sources	0.688	0.226 , 2.096	0.510			
	I do not use social networks at all	Ref.			–		
	I use it a few times a week	1.099	0.498 , 2.425	0.815			
	I use it at least once a day	1.146	0.577 , 2.279	0.697			
	I use it many times a day	1.350	0.692 , 2.634	0.378			
	I always use it when I have time, such as during breaks	1.318	0.617 , 2.817	0.476			

*Statistical significance was set at $p < 0.05$.

OR, odds ratio; CI, confidence interval; ref., reference.

^a A generalised linear mixed model (logit link function) was used.

^b A multivariate model was constructed using the forced imputation method with factors that were significant in the univariate analysis and known risk factors.

which is consistent with a previous report of adverse reactions [10].

The key to distinguishing ISRR from anaphylaxis is the time from vaccination to the appearance of symptoms. The acute stress response and vasovagal reaction occur before, during, or within 5 min of vaccination, whereas DNSR occurs few hours to days after vaccination. In contrast, anaphylaxis occurs 5–60 min after vaccination; therefore, we focused on these different time frames in our diagnosis [2]. Thus, in addition to physical findings, time to symptom onset is important for differentiating ISRR from anaphylaxis and other diagnoses.

In this study, the previously identified risk factor ‘strong anxiety before vaccination’ and the new risk factor ‘history of allergy’ were both significant for the incidence of ISRR. Compared to participants with no risk factors, those with strong pre-vaccination anxiety had a 2.1-fold increased risk of developing ISRR, while a history of allergy was associated with a 1.5-fold increased risk of developing ISRR. Studies have reported that it is normal to experience some anxiety before vaccination, with 60% of children and 20% of adults experiencing some degree of fear of the injection [21]. However, a high level of anxiety and fear may lead to ISRR and hesitancy toward vaccination [21,22]. Since ISRR is an AEFI arising from anxiety about immunisation, it is more likely to occur in vaccinees who feel anxious than in those who do not [2]. Therefore, it is important for healthcare providers to identify and respond appropriately to vaccinees who show more anxiety before vaccination.

Other reluctant factors include female sex, young age, low level of education, no underlying medical conditions, and information about vaccines obtained from social networking sites [23,24]. We found that a history of allergy is a new risk factor for ISRR. The prevalence range of allergies is 10–20% globally, depending on the region, and has been gradually increasing in recent years [25–28]. Therefore, it is essential to address individuals with a history of allergy to prevent ISRR. Several studies have attempted to reduce the incidence of allergic reactions in egg-allergic patients, and to examine the safety of vaccinations in this

patient population, even involving dietitians to provide guidance to patients [29,30]. In contrast, the relationship between a history of allergy and the incidence of ISRR has not been investigated. Patients with asthma, among the most common allergy-related diseases, are also known to experience high levels of anxiety and depression [31,32]. Considering that anxiety is a risk factor for ISRR, patients with a history of allergy should be strategically addressed. Effective means of reducing the anxiety and fear that cause ISRR include the attitude of healthcare providers and their communication with the individuals being vaccinated. A friendly, confident, and relaxed approach to vaccination by healthcare providers may reduce fear and anxiety [33].

The planning and implementation of mass immunisation campaigns involve problems that do not arise with conventional clinic immunisations. In mass immunisation campaigns, health care providers are under pressure to vaccinate a large number of people in a short time. Thus, communication with vaccinees may be reduced and ISRR occurrence is likely [2]. The vaccines may also be administered in crowded venues with a lack of privacy. Because of the limited number of health care providers available for post-vaccination follow-up, post vaccination, patients often wait together in a single space, which may result in AEFI, including ISRR, for clusters of people [34]. Additionally, in cases where adverse reactions occur, the media only broadcasts information that gives a negative impression of the vaccine and rarely reports on its safety and efficacy, which also increases anxiety levels in vaccinees [35]. Such negative impressions may spread further via the media and social networks [36], reinforcing people’s fear of vaccines [37]. In fact, we have experienced the spread of adverse reactions to the surrounding population during mass vaccinations in our institution [2]. Thus, to prevent clusters during mass immunisation campaigns a relaxed vaccination environment should be created by providing privacy for vaccinators and by placing local health care providers at the venue [38].

To create a safe environment for vaccination at the level of

government programmes, planning a communication strategy in advance is required, including the best way to send out information [39]. Physical risk factors may be addressed in the following ways: in individuals with a history of, or at risk for vasovagal reflexes, vaccines should be administered with the patient in the supine position; furthermore, patients should be advised to maintain a sitting position for a few minutes after vaccination [2]. Finally, studies have shown that exercises, such as stretching, are effective in preventing the onset of the vasovagal reflex [40].

4.1. Limitations

This study was based on questionnaire data, which confirmed that symptoms had disappeared by the time of completing the questionnaires; however, the presence of abnormalities in blood test results, magnetic resonance imaging, or electroencephalography scans was not confirmed. Therefore, we followed the WHO AEFI causality checklist, but were not able to fully exclude diseases, such as transit ischaemic attack and ischaemic heart disease, which cause temporary weakness and chest pain, but subsequently improve. Additionally, vaccination in this study was limited to healthcare workers aged ≥ 20 years. ISRR may involve a variety of factors, such as age, sex, and region. Therefore, further investigation of risk factors is warranted at a global scale. In this study we checked only for the presence of food and drug allergies and did not collect any data regarding the degree or severity of allergy. Further research is needed to determine whether there is a relationship between the occurrence of ISRR and the degree and severity of allergies.

5. Conclusions

In addition to the existing risk of ISRR, a history of allergy may increase the risk of ISRR. Therefore, it is essential to be aware of this factor when administering vaccines, including the COVID-19 vaccine, to ensure safe vaccination. In order to continue vaccination efforts safely and consistently, healthcare providers should have a good understanding of ISRR and should be trained to act calmly in the event of an ISRR.

Author contributions

TT and HK designed the study and took responsibility for the integrity of the data and the accuracy of data analysis. MHA (Dr. Hara), TO, YY, and TT developed the questionnaire and prepared the data. MHI (Dr. Hirose) and YY performed the statistical analyses. TT conducted the data analyses and drafted the first draft of the manuscript. All authors critically revised the manuscript and approved the final version.

Author statement

All authors meet the ICMJE authorship criteria.

Data availability statement

Owing to the sensitive nature of the results of this study, raw data will remain confidential and will not be shared.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None.

Acknowledgements

We would like to thank the pharmacists and healthcare providers who prepared the vaccinations. We would like to thank Editage (www.editage.com) for their writing support.

References

- [1] World Health Organization. Causality assessment of an adverse event following immunisation (AEFI): user manual for the revised WHO classification. 2018.
- [2] World Health Organization. Immunization stress related responses: a manual. <https://www.who.int/publications/i/item/978-92-4-151594-8>; 2019. 8 July 2021.
- [3] McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev* 2007;87:873–904. <https://doi.org/10.1152/physrev.00041.2006>.
- [4] van Lieshout JJ, Wieling W, Karemaker JM, Eckberg DL. The vasovagal response. *Clin Sci (Lond)* 1991;81:575–86. <https://doi.org/10.1042/cs0810575>.
- [5] McMurtry CM. Managing immunization stress-related response: a contributor to sustaining trust in vaccines. *Can Comm Dis Rep* 2020;46:210–8. <https://doi.org/10.4745/ccdr.v46i06a10>.
- [6] Romme JJCM, van Dijk N, Boer KR, Dekker LR, Stam J, Reitsma JB, et al. Influence of age and gender on the occurrence and presentation of reflex syncope. *Clin Auton Res* 2008;18:127–33. <https://doi.org/10.1007/s10286-008-0465-0>.
- [7] Fu Q, Witkowski S, Okazaki K, Levine BD. Effects of gender and hypovolemia on sympathetic neural responses to orthostatic stress. *Am J Physiol Regul Integr Comp Physiol* 2005;289:R109–16. <https://doi.org/10.1152/ajpregu.00013.2005>.
- [8] Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, et al., ESC Scientific Document Group. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;39:1883–948. <https://doi.org/10.1093/eurheartj/ehy037>.
- [9] de Figueiredo A, Simas C, Karafillakis E, Paterson P, Larson HJ. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: a large-scale retrospective temporal modelling study. *Lancet* 2020;396:898–908. [https://doi.org/10.1016/S0140-6736\(20\)31558-0](https://doi.org/10.1016/S0140-6736(20)31558-0).
- [10] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. C4591001 clinical trial group. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med* 2020;383:2603–15. <https://doi.org/10.1056/NEJMoa2034577>.
- [11] McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS, Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps. In: 2013: summary recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep*, vol. 62; 2013. p. 1–34.
- [12] World Health Organization. Vaccines against influenza WHO position paper—November 2012. *Wkly Epidemiol Rec* 2012;87:461–76.
- [13] US Food & Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical>; 2007. 8 July 2021.
- [14] Hause AM, Gee J, Johnson T, Jazwa A, Marquez P, Miller E, et al. Anxiety-related adverse event clusters after Janssen COVID-19 vaccination—five US mass vaccination sites. *MMWR Morb Mortal Wkly Rep* 2021;70:685–8. <https://doi.org/10.15585/mmwr.mm7018e3>. April 2021.
- [15] Harden NR, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, et al. Validation of proposed diagnostic criteria (the “Budapest Criteria”) for complex regional pain syndrome. *Pain* 2010;150:268–74. <https://doi.org/10.1016/j.pain.2010.04.030>.
- [16] Institute of Medicine. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness. Committee on the diagnostic criteria for myalgic encephalomyelitis/chronic fatigue syndrome, US. National Academies Press.
- [17] Sheldon RS, Grubb BP, Olshansky B, Shen WK, Calkins H, Brignole M, et al. Heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm* 2015;12:e41–63. <https://doi.org/10.1016/j.hrthm.2015.03.029>. 2015.
- [18] Pfizer. BioNTech COVID-19 vaccine. Global information about pfizer-BioNTech COVID-19 vaccine (also known as BNT162b2). www.cvdvaccine.com; 2021. A, 8 July 2021.
- [19] Centers for Disease Control and Prevention. Moderna COVID-19 vaccine: what healthcare professionals need to know. 8 July 8 2021, <https://www2.cdc.gov/vaccines/ed/covid19/moderna/40140.asp>; 2021.
- [20] Top KA, Brna P, Ye L, Smith B. Risk of seizures after immunization in children with epilepsy: a risk interval analysis. *BMC Pediatr* 2018;18:134. <https://doi.org/10.1186/s12887-018-1112-0>.
- [21] Taddio A, Ipp M, Thivakaran S, Jamal A, Parikh C, Smart S, et al. Survey of the prevalence of immunization non-compliance due to needle fears in children and adults. *Vaccine* 2012;30:4807–12. <https://doi.org/10.1016/j.vaccine.2012.05.011>.
- [22] McMurtry CM, Pillai Riddell RP, Taddio A, Racine N, Asmundson GJ, Noel M, et al. Far from ‘just a poke’: common painful needle procedures and the development of needle fear. *Clin J Pain* 2015;31(Suppl). <https://doi.org/10.1097/AJP.0000000000000272>. S3–S511.
- [23] Schwarzingier M, Watson V, Arwidson P, Alla F, Luchini S. COVID-19 vaccine hesitancy in a representative working-age population in France: a survey

- experiment based on vaccine characteristics. *Lancet Public Health* 2021;6:e210–21. [https://doi.org/10.1016/S2468-2667\(21\)00012-8](https://doi.org/10.1016/S2468-2667(21)00012-8).
- [24] Nomura S, Eguchi A, Yoneoka D, Kawashima T, Tanoue Y, Murakami M, et al. Reasons for being unsure or unwilling regarding intention to take COVID-19 vaccine among Japanese people: a large cross-sectional national survey. *Lancet Reg Health West Pac* 2021;14:100223. <https://doi.org/10.1016/j.lanwpc.2021.100223>.
- [25] Ebert CS, Pillsbury HC. Epidemiology of allergy. *Otolaryngol Clin* 2011;44:537–48. <https://doi.org/10.1016/j.otc.2011.03.001>. vii, vii.
- [26] Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and severity of food allergies among US adults. *JAMA Netw Open* 2019;2:e185630. <https://doi.org/10.1001/jamanetworkopen.2018.5630>.
- [27] Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120:638–46. <https://doi.org/10.1016/j.jaci.2007.05.026>.
- [28] Gerez IFA, Lee BW, van Bever HPV, Shek LP. Allergies in Asia: differences in prevalence and management compared with Western populations. *Expet Rev Clin Immunol* 2010;6:279–89. <https://doi.org/10.1586/eci.09.82>.
- [29] Bégin P, Filion C, Graham F, Lacombe-Barrios J, Paradis J, Paradis L, et al. Consultation with registered dietitian to prevent accidental reactions to food: insight from an egg allergy influenza vaccination cohort. *Eur J Clin Nutr* 2017;71:287–9. <https://doi.org/10.1038/ejcn.2016.241>.
- [30] Grohskopf LA, Alyanak E, Broder KR, Blanton LH, Fry AM, Jernigan DB, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2020–21 influenza season. *MMWR Recomm Rep* 2020;69:1–24. <https://doi.org/10.15585/mmwr.rr6908a1>.
- [31] Sastre J, Crespo A, Fernandez-Sanchez A, Rial M, Plaza V. Investigators of the CONCORD. Anxiety, depression, and asthma control: changes after standardized treatment. *J Allergy Clin Immunol Pract* 2018;6:1953. <https://doi.org/10.1016/j.jaip.2018.02.002>. –9.
- [32] Dafaucé L, Romero D, Carpio C, Barga P, Quirce S, Villasante C, et al. Psychodemographic profile in severe asthma and effect of emotional mood disorders and hyperventilation syndrome on quality of life. *B.M.C. Psychol* 2021;9:3. <https://doi.org/10.1186/s40359-020-00498-y>.
- [33] Kurudirek F, Arıkan D. Effects of therapeutic clowning on pain and anxiety during intrathecal chemotherapy in Turkey. *J Pediatr Nurs* 2020;53. <https://doi.org/10.1016/j.pedn.2020.01.015>. e6–e13.
- [34] Loharikar A, Suragh TA, MacDonald NE, Balakrishnan MR, Benes O, Lamprianou S, et al. Anxiety-related adverse events following immunization (AEFI): a systematic review of published clusters of illness. *Vaccine* 2018 Jan 4;36:299–305. <https://doi.org/10.1016/j.vaccine.2017.11.017>.
- [35] Okuhara T, Ishikawa H, Okada M, Kato M, Kiuchi T. Newspaper coverage before and after the HPV vaccination crisis began in Japan: a text mining analysis. *B.M.C. Public Health* 2019;19:770. <https://doi.org/10.1186/s12889-019-7097-2>.
- [36] Suragh TA, Lamprianou S, MacDonald NE, Loharikar AR, Balakrishnan MR, Benes O, et al. Cluster anxiety-related adverse events following immunization (AEFI): an assessment of reports detected in social media and those identified using an online search engine. *Vaccine* 2018;36:5949–54. <https://doi.org/10.1016/j.vaccine.2018.08.064>.
- [37] Larson HJ, Sahinovic I, Balakrishnan MR, Simas C. Vaccine safety in the next decade: why we need new modes of trust building. *B.M.J. Glob Health* 2021;6:e003908. <https://doi.org/10.1136/bmjgh-2020-003908>.
- [38] Goralnick E, Kaufmann C., Gawande A.A., Mass-vaccination sites - an essential innovation to curb the Covid-19 pandemic. *N Engl J Med*. 2021 May 6;384(18):e67. <https://doi.org/10.1056/NEJMp2102535>.
- [39] World Health Organization. Vaccine safety events: managing the communications response A guide for ministry of health EPI managers and health promotion units [online] Available at: https://www.euro.who.int/_data/assets/pdf_file/0007/187171/Vaccine-Safety-Events-managing-the-communications-response.pdf; 2013. July 8, 2021.
- [40] Lee VY, Booy R, Skinner SR, Fong J, Edwards KM. The effect of exercise on local and systemic adverse reactions after vaccinations—Outcomes of two randomized controlled trials. *Vaccine* 2018;36:6995–7002. <https://doi.org/10.1016/j.vaccine.2018.09.067>.