COVID-19 vaccines associated with vasovagal malaise: A retrospective study in two mass vaccination centers and analysis of the WHO pharmacovigilance database

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ABSTRACT

The association between COVID-19 vaccines and vasovagal malaise (VVM) has recently been reported in the literature. Our study aimed to describe COVID-19 vaccines associated VVM cases and to identify risk factors of COVID-19 vaccines associated VVM. To this end, we performed a descriptive study of VVM reports associated with COVID-19 vaccines from two French mass COVID-19 vaccination centers. We also extracted reports of VVM associated with all-COVID-19 vaccines in VigiBase®, the World Health Organization (WHO) pharmacovigilance database to analyze demographic data. In the two French mass vaccination center databases, 408 entries reported VVM after the standard administration of tozinameras-Pfizer® (1.63/1,000 vaccinated persons). Of these cases, 213 (52.2%) occurred in women, and 193 (47.3%) occurred in the 18–29 year-old (yo) age group. In 232 cases (56.8%), patients had a history of anxiety related to needles or medical visits, 213 (52.2%) reported a fear of COVID-19 vaccination in particular, and 233 (57.1%) had a history of VVM. In VigiBase®, 336,291 notifications of COVID-19 vaccines associated with VVM were identified in the adult population during the period of analysis. The most reported age class was 18–44 years (52.4%), and women represented 71.7% of the reports. Reporting widely differed depending on the country. This study, performed in real-life conditions, highlights that VVM is associated with all-COVID-19 vaccines. Young age and history of anxiety related in young adults could be a triggering factor of vaccines-associated VVM. Further studies are needed to confirm our results.

Introduction

Vasovagal malaise (VVM) has been reported with various medical procedures, including simple venipuncture,1 the viewing of needles or blood,2 invasive medical procedures2 and vaccination.3 Incidents of VVM are generally not serious, but related to falls can cause injuries. Because VVM has been reported in response to the use of vaccines with different technologies and excipients, these reactions have been attributed to the vaccination process and not to the vaccines themselves.4 In the actual context of the COVID-19 pandemic, messenger ribonucleic acid (mRNA) vaccines have been recommended for the first time and assessing the safety of COVID-19 vaccines is consequently important, including that of COVID-19 mRNA vaccines, which are widely used around the world.5–7 Indeed, in the general population, the words “COVID,” “vaccines” and “mRNA” are a cause of fear, and we believe this fear could be a triggering factor of vaccine-associated VVM.

Furthermore, we also performed a descriptive study in VigiBase8–10 the WHO pharmacovigilance database, of the demographic data of VVM associated with all COVID-19 vaccines marketed before 26 January 2022. This analysis allowed us to study the reporting of VVM associated with all COVID-19 vaccines to determine the precise clinical characteristics of patients suffering from VVM after COVID-19 vaccination.

Materials and methods

Retrospective study in two COVID-19 mass vaccination centers

For this study, all COVID-19 vaccine adverse reactions occurring at the two mass vaccination sites in Caen (Normandy, France) from 1 January to 15 October 2021 were coded into a local database in accordance with local guidelines. The COVID-19 vaccine systematically used was tozinamaran–Pfizer®.

After receiving authorization for the current study by the Ethics Department of University of Caen Normandy (Comité local d’éthique de la recherche en santé – Authorization n°2709,
For our descriptive analyses, reports of VVM were identified with the following MedDRA preferred terms: “Fainting,” “Loss of consciousness,” “Malaise,” “Presyncope,” “Syncope” (version 24.1). Vaccines of interest were the following: mRNA vaccines (elasomeran – Moderna, Tozinameran – Pfizer), COVID-19 vaccines with more traditional technologies (ChAdOx1 – AstraZeneca, NRVV Ad26 – Janssen, NRVV Ad26 and NRVV Ad5 – Sputnik, HB02 – Sinopharm, CZ2020 – Coronavac and NIV-2020-770 – Covaxin). For each vaccine, the following information was described: age class, sex, seriousness, death, and region. The number of report of VVM was compared to the number of report of other adverse reactions.

To explore the homogeneity of the reporting of COVID-19 vaccine-associated adverse effects in VigiBase, we searched the number of cases reported for the 01/01/2021 to 01/26/2022 for the following eight countries: France, United States of America, the United Kingdoms, the Popular Republic of China, the Russian Federation, India, Philippines, and Morocco. Those countries were chosen to explore the geographical use of COVID-19 vaccines and the reporting among different pharmacovigilance systems.

Results

Descriptive study based on a French mass vaccination center database (Table 1)

From 01/18/2021 to 10/15/2021, 249,872 COVID-19 vaccine injections were administered at two mass COVID-19 vaccination centers. In total, 521 VVMs after COVID-19 vaccination were reported, and 408 subjects agreed to be included in the analysis (Figure 1). Therefore, 1.63‰ of the vaccinations ended with a VVM. A total of 78.2% (319/408) were associated with the first dose and 52.2% (213/408) of the VVM were observed in women. VVM occurred mainly in younger patients (23.5% and 47.3% in 12–17 and 18–29 age ranges respectively). Age (p = .6), sex (p = .9) or outside temperature (p = .3) did not significantly differ between the 408 subjects included and the 35 subjects who refused to participate. The mean time to onset of the VVM after COVID-19 vaccination was 5.0 ± 4.2 minutes and mean time to recovery was 40.8 ± 236.7 minutes. VVM did not appear before vaccination. Of the patients who presented with COVID-19 vaccine-associated VVM, only six patients (1.5%) needed to be transported to the emergency department. None of the patients required hospitalization. Subjects who experienced a VVM after COVID-19 vaccination frequently reported anxiety with needles or medical examinations, especially with COVID-19 vaccination [56.8% (23/408) and 52.2% (213/408) respectively]. A history of VVM was reported in 57.1% of cases (233/408) (Table 1).

Demographic data in VigiBase

Among the 29,398,228 ICSRs listed in VigiBase on 26 January 2022, 3,006,183 were related to the nine COVID-19 vaccines. According to the selection criteria, 336,291 suffered from VVM after COVID-19 vaccination (11.2%) (Figure 2). In descending order, 163,626 (48.7%) were associated to tozinameran – Pfizer; 83,370 (24.8%) to ChAdOx1 – AstraZeneca; 60,117 (17.9%) to elasomeran – Moderna; 22,161 (6.6%) to
NRVVAd26 – Janssen®; 3,678 (1.1%) to HB02 – Sinopharm®; 2,905 (0.9%) to CZ020 – Coronavac®; 153 (0.05%) to NRVV Ad5 – Sputnik® II; 146 (0.04%) to NRVV Ad26 – Sputnik® I and 135 (0.04%) to NIV-2020-770 – Covaxin®. Most COVID-19 vaccine-associated events were reported in individuals aged 18–44 years (52.4%), and women represented 71.7% of the reports. Adverse events were considered serious in 18.7% of the reports (Table 2). The number of reported cases markedly differed among the COVID-19 vaccines. Furthermore, the reporting pattern appeared very different among the eight countries assessed in the supplementary analysis (Table 3).

**Table 2.** Characteristics of vasovagal malaise events after receipt of COVID-19 vaccine (n = 408) at two mass vaccination sites (Caen, Normandy, France), January 18, 2021–October 15, 2021.

| Characteristics                        | n = 408 |
|----------------------------------------|---------|
| **General characteristics**            |         |
| **Vasovagal malaise reporting date**   |         |
| Pfizer® [n (%)]                        | 408 (100.0%) |
| Dose administered [n (%)]              |         |
| First [n (%)]                          | 319 (78.2%) |
| Second [n (%)]                         | 89 (21.8%) |
| No. of syncpe, cases* [n (%)]          | 97 (23.8%) |
| No. vaccinated, total                  | 249,872 |
| Cases per 1,000 vaccinated, total      | 1.63    |
| **Case characteristics**               |         |
| Women [n (%)]                          | 213 (52.2%) |
| Men [n (%)]                            | 195 (47.8%) |
| Age range, years [n (%)]               |         |
| 12–17 [n (%)]                          | 96 (23.5%) |
| 18–29 [n (%)]                          | 193 (47.3%) |
| 30–39 [n (%)]                          | 55 (13.5%) |
| 40–49 [n (%)]                          | 40 (9.8%) |
| 50–59 [n (%)]                          | 15 (3.7%) |
| 60+ [n (%)]                            | 9 (2.2%) |
| Time delay after COVID-19 vaccination (min) | 5.0 ± 4.2 |
| Time delay to recovery (min)           | 40.8 ± 236.7 |
| Transferred to emergency department [n (%)] | 6 (1.5%) |
| Reported history of anxiety related to needles or medical visits [n (%)] | 232 (56.8%) |
| Reported anxiety of COVID-19 vaccination [n (%)] | 213 (52.2%) |
| History of vasovagal malaise [n (%)]   | 233 (57.1%) |
| **Characteristic vaccination site**    |         |
| Outside temperature (Celsius degrees)  | 22.8 ± 3.6 |
| **Common signs and symptoms**          |         |
| Chest pain [n (%)]                     | 21 (5.1%) |
| Hypotension [n (%)]                    | 6 (1.5%) |
| Light-headness or dizziness [n (%)]    | 333 (81.6%) |
| Nausea/vomiting [n (%)]                | 140 (34.3%) |
| Pallor or diaphoresis [n (%)]          | 322 (78.9%) |
| Seizure-like activity [n (%)]          | 99 (24.3%) |
| Tachycardia [n (%)]                    | 15 (4.0%) [missing = 37] |

*Vasovagal malaise was defined as any of the following occurring in a person during the 15-minute postvaccination observation period at one of the two sites reporting these events: tachycardia, hyperventilation, dyspnea, chest pain, paresthesia, light-headedness, hypotension, headache, pallor, or syncope. Persons with allergic-like symptoms and those who received diphenhydramine or epinephrine were excluded.

**Discussion**

This study was realized to investigate the link between VVM and COVID-19 vaccines under real-world conditions, which we believe could be enhanced by anxiogenic context. We highlighted that VVM is associated with all COVID-19 vaccines and consequently is likely not affected by the technology used. VVM events after COVID-19 vaccination occurred mainly in a young population, especially in people with a history of VVM associated with injections or needle aversion. The impact of sex is probable but requires further discussion.

**Vasovagal malaise and vaccines**

Syncope can occur immediately after vaccination with any vaccine. Syncope can be heralded by presyncopal manifestations, such as lightheadedness, dizziness, diaphoresis, and visual changes, followed by a brief transient loss of consciousness. It occurs more commonly in women and adolescents or young adults than young in young children or elderly individuals. In a review of 697 cases of syncope after different vaccinations (measles-mumps-rubella, different combinations of diphtheria-tetanus-pertussis, hepatitis B, influenza, Haemophilus influenzae type B, and typhoid), when the time to onset was known, 57% occurred within 5 minutes, 80% occurred within 15 minutes, and 88% occurred within 30 minutes after vaccination. Brief tonic-clonic movements were observed in 24% of these individuals. In this study, 10% of the individuals who experienced syncope after immunization required hospitalization for serious injuries, including skull fractures and cerebral hemorrhages. In our study, incidents
after NRVV Ad26 – Janssen* COVID-19 vaccination of 0.8% from March 2 to April 11 based on a review of Vaccine Adverse Events Reporting System (VAERS), the American vaccine safety monitoring program. Although our definition markedly differed, we noted a similar incidence rate. Moreover, 60 reports of syncope after the influenza vaccination were identified during July 1, 2019 – June 30, 2020 (0.5% episodes of syncope after influenza vaccine) in VAERS.19

Vasovagal malaise and COVID-19 vaccines

As mentionned above, Hause et al. have previously described anxiety-related adverse event clusters after NRVV Ad26 – Janssen* vaccination in the United-States of America.19 Five mass vaccination sites reported 64 anxiety-related events, including 17 events of syncope (fainting) after administration of NRVV Ad26 – Janssen*, occurring during April 2021 to the VAERS19. Thirteen (20%) of the patients informed staff members of a history of VVM associated with injections or needle aversion. The prevalence of anxiety-related adverse events ranged from 5.2 to 13.5 per 1,000 vaccinated persons. Among the 64 total cases, a majority [39 cases (61%)] occurred in women with a median age of 36 yo (range = 18–77 yo). As the prevalence of anxiety during the COVID-19 pandemic was higher in women and younger individuals,20 we believe preexisting anxiety could have played a role in the onset of vaccine-associated VVM. Most events resolved within 15 minutes with supportive care. In total, 20% of patients were transported to an emergency department for further medical evaluation, and all were released from medical care on the same day. In addition, a review of all VAERS reports containing the MedDRA terms "syncope" or "syncope vasovagal" after vaccination with NRVV Ad26 – Janssen* during March 2–April 11 2021, identified 653 eligible reports. During March and April 2021, the VAERS reporting rate of syncope after NRVV Ad26 – Janssen* was 8.2 per 100,000 doses among 7.98 million dose of NRVV Ad26 – Janssen* administered in the United States. Only 3% of the 653 syncope/presyncope reports (3%) were classified as serious. Moreover, 123 (19%) reports indicated that the recipient had a history of syncope associated with receiving injections or needle aversion, and 327 (50%) cases occurred in women with a median age of 30 years (range = 18–82 yo). The largest proportion of reported syncopal events after the administration of NRVV Ad26 – Janssen* occurred among persons aged 18–29 yo, and this rate inversely correlated with age.

Reports of syncope were approximately 164 times more common after NRVV Ad26 – Janssen* (8.2 per 100,000) than after influenza vaccination (0.1 per 100,000). The stress of an ongoing pandemic might also increase anxiety surrounding COVID-19 vaccination.19 This Weber bias is well described and is defined as a variation in reporting over time that results in an increase in the number of reports immediately after a drug is marketed (due to incomplete safety profile and increasing exposure).21

Physiopathological mechanisms

These syncopal events are thought to be caused by vasovagal or vasodepressor mechanisms.16 This reaction is a well-described...
| Vaccine Family | Total | Age class available | <18 | 18–44 | 45–64 | 65–74 | 75+ | Sex available | Men | Women | Death | Serious | Hospitalization | Life threatening |
|---------------|-------|---------------------|-----|-------|-------|-------|-----|---------------|-----|-------|-------|---------|---------------|----------------|
| COVID-19 mRNA COVID-19 mRNA |       |                     |     |       |       |       |     |               |     |       |       |         |               |                |
| Elasomeran – Moderna* | Malaise - | 531,151 | 486,862 | 9,231 | 199,291 | 164,447 | 68,942 | 44,951 | 527,987 | 161,311 | 366,676 | 5,884 | 8,012 | 35,262 | 88.6% | 751: |
|                     | Malaise + | 60,117 | 5,758 | 370 | 27,106 | 21,441 | 5,237 | 3,426 | 59,886 | 17,948 | 41,938 | 712 | 10,096 | 4,534 | 11.4% | 1,013: |
| Tozinameran – Pfizer* | Malaise - | 1,374,099 | 1,139,320 | 47,306 | 529,519 | 366,307 | 103,209 | 92,979 | 1,357,401 | 411,258 | 946,143 | 21,344 | 317,824 | 123,073 | 89.3% | 26,953: |
|                     | Malaise + | 163,626 | 141,959 | 9,193 | 73,199 | 40,102 | 10,559 | 8,906 | 162,498 | 47,453 | 115,045 | 2,381 | 33,485 | 14,715 | 10.7% | 3,434: |
| COVID-19 Ad |       |                     |     |       |       |       |     |               |     |       |       |         |               |                |
| ChAdOx1 – Astrazeneca* | Malaise - | 631,758 | 57,824 | 1,708 | 243,645 | 235,733 | 70,937 | 26,217 | 616,462 | 191,478 | 424,984 | 4,168 | 210,665 | 30,561 | 90.4% | 8,885: |
|                     | Malaise + | 8,337 | 79,249 | 130 | 36,681 | 33,589 | 6,557 | 2,292 | 82,408 | 19,608 | 628 | 454 | 20,076 | 3,245 | 9.6% | 983: |
| NRVV Ad26 – Janssen* | Malaise - | 110,859 | 89,047 | 1,467 | 44,846 | 33,236 | 6,572 | 2,926 | 10,981 | 49,821 | 59,995 | 2,458 | 21,003 | 9,905 | 89.4% | 2481: |
|                     | Malaise + | 22,161 | 20,509 | 49 | 13,717 | 6,019 | 467 | 257 | 2,211 | 8,706 | 13,404 | 293 | 2,632 | 1,171 | 10.6% | 349: |
| NRVV Ad26 – Sputnik I | Malaise - | 4,013 | 3,902 | 20 | 2,454 | 1,209 | 168 | 51 | 3,971 | 1,562 | 2,409 | 17 | 119 | 67,905 | 16 | 88.9% | |
|                     | Malaise + | 146,35 | 142,35 | 0 | 90,35 | 44,35 | 5,29 | 3,56 | 145 | 45 | 100 | 3 | 17,125 | 7 | 9.5% | 2,11: |
| NRVV Ad5 – Sputnik II | Malaise - | 4,269 | 4,164 | 19 | 2,584 | 1,314 | 189 | 58 | 4,226 | 1,612 | 2,614 | 20 | 151 | 94,940 | 19 | 90.9% | |
|                     | Malaise + | 96,5 | 96,5 | 100 | 96,6 | 96,7 | 95,9 | 93,5 | 96,5 | 97,4 | 96,0 | 87,0 | 90,4 | |
| Others |       |                     |     |       |       |       |     |               |     |       |       |         |               |                |
| HB02 – Sinopharm* | Malaise - | 43,207 | 42,457 | 263 | 28,325 | 10,999 | 2,077 | 793 | 43,073 | 20,959 | 22,114 | 89 | 535 | 243 | 89.3% | 67 | 89.3% |
|                     | Malaise + | 3,678 | 3,631 | 22 | 2,711 | 782 | 74 | 4,2 | 3,669 | 1,417 | 2,252 | 18 | 68 | 11.3% | 29 | 10.7% | 8 | 10.7% |
| CZ020 – Coronavac* | Malaise - | 45,553 | 43,841 | 219 | 21,648 | 1,443 | 459 | 295 | 4,519 | 19,115 | 26,075 | 2103 | 5467 | 2,446 | 89.6% | 339 | 95.5% |
|                     | Malaise + | 2,905 | 2,863 | 17 | 1,728 | 644 | 29 | 245 | 2,881 | 1,104 | 1,777 | 179 | 505 | 8.5% | 284 | 10.4% | 16 | 4.5% |
| NVV-2020-770 – Covavir* | Malaise - | 16 | 10.6% | 1,591 | 7 | 1,036 | 375 | 66 | 107 | 1,598 | 755 | 843 | 80 | 146 | 58 | 98.9% | 1 | 100.0% |
|                     | Malaise + | 135 | 89.4% | 134 | 7.8% | 0 | 120 | 13 | 3.4% | 0 | 1,09 | 135 | 68 | 67 | 1 | 1.2% | 3 | 2.0% | 1 | 1.7% | 0 | 0.0% |

*1: Malaise – are reports of adverse effects without malaise. Malaise + are reports of adverse effects including a malaise

*2: seriousness criteria include among others caused/prolonged hospitalization* and life threatening* adverse effects

**Life threatening**
Table 3. Number of reports of COVID-19 vaccines associated adverse effects per country shared to VigiBase® during the period of the study in a list of eight countries.

|                          | France | USA  | UK   | PRC | RF  | India | Philippines | Morocco |
|--------------------------|--------|------|------|-----|-----|-------|-------------|---------|
| **COVID-19 mRNA**        |        |      |      |     |     |       |             |         |
| Elasomeron – Moderna*    | 20,147 | 379,628 | 36,290 | 0   | 0   | 0     | 4,444       | 0       |
| Tozinameran – Pfizer*    | 86,213 | 585,174 | 166,102 | 0   | 0   | 1     | 11,912      | 1,653   |
| **COVID-19 Ad**          |        |      |      |     |     |       |             |         |
| ChAdOx1 – Astrazeneca*   | 28,245 | 3   | 264,727 | 0   | 0   | 22,481 | 34,135      | 13,511  |
| NRVV Ad26 – Janssen*     | 1,438  | 77,373 | 10   | 0   | 0   | 0     | 3,850       | 731     |
| NRVV Ad26 or Ad5 Sputnik*| 1      | 0    | 1    | 0   | 0   | 74    | 852         | 0       |
| **Others**               |        |      |      |     |     |       |             |         |
| HB02 – Sinopharm*        | 0      | 0    | 0    | 0   | 0   | 0     | 181         | 19,993  |
| CZ02 – Coronavac*        | 0      | 0    | 0    | 0   | 0   | 0     | 32,336      | 0       |
| NIV-2020-770 – Covaxin*  | 0      | 0    | 0    | 0   | 0   | 1,575 | 0           | 0       |
| **TOTAL**                | 136,615 | 1,044,118 | 464,636 | 3   | 0   | 24,136 | 87,314      | 36,314  |
| **Total reporting**      | 207,441 | 2,241,045 | 565,736 | 264,345 | 0   | 74,757 | 91,016      | 37,441  |

aROR: adjusted reporting odds ratio; CI: confidence interval
Multivariate analysis: results were adjusted on age class, sex, region and qualification of reporter. Analysis population: reports with COVID-19 vaccines from 01/01/2021 to 26/01/2022 (reference: Influenza vaccines)
*1: In rare cases, reporting is not precise enough to identify a specific vaccine (i.e., “COVID-19 vaccine mRNA 5")
*2: not restricted to covid-19 vaccines
USA: United States of America UK: United Kingdom PRC: People’s Republic of China RF: Russian Federation

syndrome consisting of sympathetic nervous system stimulation, often in a setting of fear or emotional distress, followed by sudden onset of hypotension that often results in syncope or presyncope.1,12 Syncopal seizures unrelated to epilepsy also occur as a result of a relative cerebral anoxia,22 and electrocardiographic monitoring of patients undergoing vasovagal syncope has shown that a period of at least 5 seconds of asystole is a common occurrence.7 Vasovagal reactions are known to be elicited by a variety of stimuli, including simple venipuncture, or seeing of blood or invasive medical procedure, such as vaccination.1,2,12

As VVM and hypersensitivity reactions occur soon after the administration of vaccines, observation for at least 15 minutes is recommended for individuals receiving vaccines in French mass COVID-19 vaccination centers before being discharged.23 In this study, the time delay of VVM occurrence was 5.0 ± 4.2 minutes. Based on our data, this national protocol seems to be adapted to this phenomenon and agrees with the literature. Brown et al. described that syncope after immunization can occur in 88.8% of cases within 15 minutes.12

**Proposals to avoid vasovagal malaise after COVID-19 vaccination**

To avoid VVM and its consequences after COVID-19, we suggest identifying subjects at risk with an in-depth interview prior to vaccination. The following risk factors could be identified: as past medical history of acute VVM after immunization and a fear of needles or medical context in general. Particular attention should be given to young persons. When a patient is identified with risk factors of VVM, intervention to reduce pain and prevent syncope should be provided. Many authors have previously proposed intervention in this matter.24,25 For example, soothing background music has been proposed by Kuntz et al.24 Moreover, exposure-based psychological interventions and applied muscle tension have shown evidence of benefit in the reduction of needle fear in pediatric and adult population.25 In contrast, drinking water does not seem to be associated with a decrease of postvaccination presyncope in particular in adolescents.26 Finally, the site capacity and layout of the mass COVID-19 vaccination site must be adapted to permit the isolation of people feeling unwell and decrease the risk of multiple anxiety events.27

**Strengths and limitations**

The present study has several strengths. The study of local data could provide details on COVID-19 vaccine-associated risk factors associated with the onset of VVM, with hundreds of patients included in the study, but only with mRNA-based COVID-19 vaccine Tozinameran – Pfizer*. Furthermore, the study in VigiBase® allowed us to describe the reporting of VVM with all-COVID-19 vaccines. However, as discussed above, the marketing of COVID-19 vaccines widely differs between countries, the pharmacovigilance system is poorly developed in a wide range of countries, and geopolitical interest might have played a role in the reporting of COVID-19 vaccine-associated adverse effects to VigiBase®. Thus, we could not
conducted a disproportionality analysis that would have been biased. Moreover, our study was limited due to the use of a pharmacovigilance database. Underreporting is the most important limitation in pharmacovigilance, but this phenomena did not appear to change the results and significance of a case/non-case study.28 Missing data is another limitation in pharmacovigilance database extractions. Therefore, we selected a sensitive definition for VVM in VigiBase*. However, this definition may have lack specificity.

Furthermore, the seriousness of the adverse event was assessed based on pharmacovigilance guidelines, which might, in rare cases, differ from other seriousness scales, such as the Common Terminology Criteria for Adverse Events (CTCAE).29,30 Because COVID-19 vaccines are new drugs which are highly mediatized, a reporting bias might exist. The retrospective design could also provoke a memory bias. Moreover, comparing patients who experienced VVM at the two mass vaccination centers to those who did not present VVM was impossible, as the latter were not retrospectively contacted in accordance with the authorization granted for the study. Moreover, data regarding the history of generalized anxiety were not collected in our study. Indeed, adolescent girls are usually affected by VVM, and episodes are associated with anxiety or are a component of an anxiety disorder. Episodes often recur, and the diagnosis of anxiety disorder may be missed and ascribed to cardiac events or another life-threatening disorder.11 The cumulative incidence of syncope in Framingham is approximately 50% in men and women 80 years-old, but VVM was only responsible for 21.2% of all episodes.31,32 These two COVID-19 mass vaccination centers were selected based on the convenience of investigators, but they also represent 2/3 of the activity of COVID-19 mass vaccination centers in the area of the study for the considered period. Moreover, these centers were opened at the start of the national vaccination campaign in January and March 2021, and before primary care vaccination (general practitioners, nurses and pharmacists) was available.

Conclusion

This study, performed in real-life conditions, described the clinical characteristics of VVM associated to all-COVID-19 vaccines. From a practical point of view, the present study suggests that patients with a history of VVM and/or needle aversion and in particular young people are at higher risk of VVM following COVID-19 vaccination. Moreover, the technology of the vaccine is likely not an important factor in the development of VVM. Prior to vaccine administration, we suggest the identification of patients at higher risk of VVM to adapt the medical procedure and reduce the risk of VVM. After the vaccination, all patients should be observed for 15 minutes. This protocol will help promote the vaccination and avoid serious injuries potentially caused by the VVM.

Abbreviations

| ADR | adverse drug reaction |
| aROR | adjusted reporting odds ratio |
| ATC | anatomical therapeutic chemical classification |

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Disclosure statement

The authors declare that they have no conflict of interest to disclose.

Funding

The author(s) reported that there is no funding associated with the work featured in this article.

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