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# Self-reported adverse events within the seven days following the Spikevax® (Moderna) vaccination

## Eventos adversos autoinformados en los siete días posteriores a la vacunación con Spikevax® (Moderna)

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## Abstract

**Objective:** Continuous monitoring of COVID-19 vaccines safety may provide additional information to health care professionals and the general population. The aim of the present study was to analyze the local and systemic adverse events following the administration of the Spikevax® (Moderna) vaccine, and to identify the factors related to greater reactogenicity.

**Method:** Using a telephone survey, we interviewed 331 recipient of the Spikevax® vaccine (50.2% men; $Mean_{age}$ = 46.4). Participants characteristics, prior COVID-19 infection and local and systemic adverse events within seven days following the first and second vaccine doses were asked.

**Results:** Injection site pain, fatigue and headache were the most common adverse events. The prevalence and intensity of local events was higher after the first dose, while systemic events were higher in the second one. Most adverse events were mild/moderate; 1.2% of participants needed hospitalization or emergency room visit. Women and participants aged 18-55 years were more likely to experience greater reactogenicity, participants with prior COVID-19 infection had more systemic events after the first dose, and participants with chronic diseases other than hypertension reported fewer systemic adverse events following the second dose.

**KEYWORDS**
COVID-19 vaccines; Adverse events; SARS-CoV-2; Patient safety; Adverse events.

## Resumen

**Objetivo:** La monitorización continua de la seguridad de las vacunas COVID-19 puede aportar información adicional a los profesionales sanitarios y a la población general. El objetivo del presente estudio fue analizar los eventos adversos locales y sistémicos tras la administración de la vacuna Spikevax® (Moderna), e identificar los factores relacionados con una mayor reactogenicidad.

**Método:** Mediante un cuestionario telefónico entrevistamos a 331 receptores de la vacuna Spikevax® (50,2% hombres; $media_{edad}$ = 46,4). Se preguntó acerca de las características de los participantes, infección previa por COVID-19 y eventos adversos locales y sistémicos en los siete días posteriores a la primera y segunda dosis de la vacuna.

**Resultados:** El dolor en el lugar de inyección, la fatiga, y la cefalea fueron los eventos adversos más frecuentes. La prevalencia e intensidad de eventos locales fue mayor en la primera dosis, mientras que los sistémicos lo fueron en la segunda. La mayoría de los eventos adversos fueron leves/moderados; el 1,2% de los participantes necesitaron acudir a urgencias u hospitalización. Las mujeres y participantes de 18-55 años presentaron mayor probabilidad de experimentar mayor reactogenicidad, los participantes con infección previa por COVID-19 presentaron más eventos sistémicos tras la primera dosis y los participantes con enfer-

**PALABRAS CLAVE**
Vacunas COVID-19; Efectos adversos; SARS-CoV-2; Seguridad del paciente; Efectos adversos.

**Conclusions:** Our results are consistent with previous studies, identifying women, people aged 18-55 years and those with previous COVID-19 infection as those who experienced the greatest reactogenicity to the vaccine. A relationship was also found between reactogenicity and suffering from a chronic disease other than hypertension.

medades crónicas distintas de la hipertensión notificaron menos eventos adversos sistémicos tras la segunda dosis.

**Conclusiones:** Nuestros resultados son consistentes con estudios previos, identificando a las mujeres, personas de 18-55 años y con infección previa por COVID-19 como los que mayor reactogenicidad a la vacuna experimentaron. También se encontró una relación entre la reactogenicidad y padecer alguna enfermedad cronica distinta de hipertensión.

## Introduction

The SARS-CoV-2 coronavirus pandemic has caused nearly 430 million confirmed positive COVID-19 cases and 5.9 million deaths worldwide[1]. An unprecedented global effort has focused on the research and development of vaccines against SARS-CoV-2 infection[2]. These efforts have led to several agencies authorising the emergency use of some vaccines; one of the first was the Spikevax® mRNA vaccine (Moderna).

The Spikevax® vaccine is among those approved in Spain to control the spread of the virus[3]. Following the recommendations of the European Medicines Agency (EMA), the Spanish government established a national vaccination campaign divided into phases according to individual risk assessments[4]. By the end of February 2022, more than 16 million doses of the Spikevax® vaccine had been administered in Spain[4]. The phase III clinical trial of the Spikevax® vaccine has reported a relative efficacy of 94.1% in preventing COVID-19. It has also reported transient local and systemic adverse events (AEs) after the administration of the two-dose regimen. Most of these AEs are of mild to moderate severity[5].

Previous studies have shown that the main reason given for refusing COVID-19 vaccines is fear of AEs due to vaccination[6,7]. A systematic review of strategies to address concerns about vaccines has shown that the honest reporting of potential side effects is crucial to improve the acceptability of vaccines among citizens[8]. However, currently available data on AEs associated with the Spikevax® vaccine have mainly been published in studies funded by pharmaceutical companies and monitored by third parties. In addition, the EudraVigilance Database pharmacovigilance system does not provide information on the actual prevalence of AEs, because reports are made on the basis of the individual patient and only the most severe AEs are reported. However, the systematic monitoring of local and systemic AEs after vaccination with Spikevax® could be useful to healthcare professionals and the general public.

Our aim was to assess the prevalence and intensity of AEs reported within 7 days after the first and second doses of Spikevax® vaccine and to identify the predictors of such AEs.

## Methods

We invited people scheduled for Spikevax® vaccination for COVID-19 to participate in a descriptive cross-sectional observational study of AEs. This was conducted at a tertiary hospital in the province of Huelva (Spain) from April to June 2021. In this period, individuals in Vaccination Group 7 were scheduled for vaccination for COVID-19, which included people of at least 12 years of age with very high-risk conditions. Inclusion criteria were as follows: a) being at least 18 years of age; being male or female; and being able to communicate correctly and fluently in Spanish both verbally and in writing.

All vaccines were administered by trained nurses. Two doses of Spikevax® vaccine were administered into the deltoid muscle with at least 28 days between doses. A single dose was administered to individuals who had tested positive for SARS-CoV-2 on PCR testing 3 to 6 months prior to the first dose.

On the day of the first dose, information was collected on the participants' gender, age, clinical characteristics, and any prior infection with COVID-19. Clinical characteristics included those considered to be factors for severe COVID-19 infection: smoking, high body mass index (BMI), hypertension, or other chronic diseases. Participants were also asked to provide their telephone number so that they could be interviewed about post-vaccination AEs. Seven days after each vaccination dose, a research assistant monitored vaccine safety using a telephone-based questionnaire. The assistant had experience in conducting surveys and had not been involved in the patient vaccination programme. Participants were contacted up to three times over a 2-day period by telephone to ensure a maximum response rate. The assessment of vaccine safety included the monitoring of self-reported local and systemic AEs, which was conducted by collecting verbal information provided by the participants about any symptoms that occurred within 7 days of each dose. With the help of the interviewer, the participants categorised the AEs according to the phase III clinical trial protocol (mRNA-1273-P301) provided by the makers of the Spikevax® vaccine[9] (Table 1).

This study was approved by the Andalusian Biomedical Research Ethics Coordinating Committee (1555-N-21). Individuals who agreed to participate in the study gave informed consent to the use of their anonymised data, which were stored confidentially and under appropriate standard security conditions. The participants did not receive any incentives for their participation.

Data were analysed using SPSS software (v.24). Descriptive analyses were conducted to show the characteristics of the study sample. Categorical data (prevalences) were compared using Cochran's Q test and differences in AEs severity between the two vaccine doses were compared using the Wilcoxon test. Binary logistic regression models were used to identify predictors of local or systemic AEs after each dose. The data are presented as odds ratios (OR) with 95% confidence intervals. Age grouping (18-55 and > 55 years) was performed to facilitate the comparison of the results with those of previous studies.

## Results

### Participants

A total of 331 people of at least 18 years of age were included between April and June 2021 (range: 18-76 years; Mean = 46.4; SD = 12.6). We excluded 109 people who did not answer the phone, 9 who delayed the second dose, and 5 who only received the first dose due to a recent COVID-19 infection. Table 2 shows the characteristics of the participants.

### Adverse events

In total, 270 (81.6%) participants experienced at least one AE within 7 days after the first dose of Spikevax® vaccine. Of these, 256 (77.3%) reported local AEs and 109 (32.9%) reported systemic AEs. A total of 28.7% of the participants (N = 95) reported experiencing local and systemic events after the administration of the first dose of vaccine.

Regarding the second dose, 296 (89.4%) participants experienced at least one AE within 5 days of vaccination. Local and systemic events were reported by 223 (67.4%) and 217 (65.6%) participants, respectively. In total, 55.6% of the participants (N = 184) experienced local and systemic events after the second dose of vaccine.

There were more local AEs after the first dose than after the second dose of vaccine ($p < 0.01$), whereas more systemic AEs were reported after the second dose than after the first ($p < 0.001$).

### Types of adverse events, frequency, and intensity

Table 3 shows the prevalence of local and systemic AEs after the first and second dose by sex and age (total sample). Overall, local and systemic AEs were more frequent and more intense in women and in the group aged 18 to 55 years. Reactogenicity data after the second dose showed a decrease in local AEs (injection site pain, $p < 0.001$) or a similar intensity (redness and swelling, $p < 0.001$) compared to those of the first dose. The exception was axillary swelling, which was more intense ($p < 0.05$). The intensity of all the systemic AEs assessed showed a significant increase after the second dose compared to those of the first dose ($p < 0.001$).

**Table 1.** Adverse events and grades of intensity

| Adverse event | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| Pain at injection site | None | Does not interfere with daily activity | Repeated use of OTC pain reliever > 24 h or interferes with activity | Any use of prescription pain reliever or prevents daily activity | Requires emergency room visit or hospitalization |
| Injection site erythema (redness) | < 2.5 cm | 2.5-5.0 cm | 5.1-10.0 cm | > 10.0 cm | Necrosis or exfoliative dermatitis |
| Swelling/induration (hardness) at injection site | < 2.5 cm | 2.5-5.0 cm | 5.1-10.0 cm | > 10.0 cm | Necrosis |
| Axillary (underarm) swelling or tenderness ipsilateral to the side of injection | None | Does not interfere with daily activity | Repeated use of OTC (nonnarcotic) pain reliever > 24 h or some interference with activity | Any use of prescription (narcotic) pain reliever or prevents daily activity | Emergency room visit or hospitalization |
| Headache | None | Does not interfere with daily activity | Repeated use of OTC pain reliever > 24 h or interferes with activity | Any use of prescription pain reliever or prevents daily activity | Requires emergency room visit or hospitalisation |
| Fatigue | None | Does not interfere with daily activity | Some interference with daily activity | Significant; prevents daily activity | Requires emergency room visit or hospitalisation |
| Myalgia (muscle aches throughout the body) | None | Does not interfere with daily activity | Some interference with daily activity | Significant; prevents daily activity | Requires emergency room visit or hospitalisation |
| Arthralgia (Joint aches in several joints) | None | Does not interfere with daily activity | Some interference with daily activity | Significant; prevents daily activity | Requires emergency room visit or hospitalisation |
| Nausea/vomiting | None | No interference with daily activity or 1-2 episodes/24 h | Some interference with daily activity or > 2 episodes/24 h | Impairs daily activity, requires outpatient intravenous hydration | Requires emergency room visit or hospitalisation for hypotensive shock |
| Chills | None | Does not interfere with daily activity | Some interference with daily activity that does not require medical intervention | Impedes daily activity and requires medical intervention | Requires emergency room visit or hospitalisation |
| Fever | < 38.0 °C | 38.0-38.4 °C | 38.5-38.9 °C | 39.0-40.0 °C | > 40 °C |

OTC: over-the-counter.

**Table 2.** Characteristics of participants

| | N (%) |
|---|---|
| Sex | |
| Male | 166 (50.2) |
| Female | 165 (49.8) |
| Age | |
| 18-55 years | 243 (73.4) |
| > 55 years | 88 (26.6) |
| Smokers | 46 (13.9) |
| High body mass index | 32 (9.7) |
| Hypertension | 61 (18.4) |
| Other chronic disease | 124 (37.5) |
| Previous COVID-19 infection | 14 (4.2) |

Although most local and systemic AEs were mild or moderate, four participants reported the need for an emergency room (ER) visit or hospitalisation (Grade 4). An in-depth analysis of these participants revealed the following: a 48-year-old woman with hypertension was hospitalised due to severe muscle and joint pain that made her unable to move and communicate; a 27-year-old woman with chronic disease other than hypertension attended the ER for medical attention after experiencing vomiting and muscle and joint pain; a 23-year-old woman, smoker, with high BMI and chronic disease other than hypertension, attended the ER for muscle pain; and a 46-year-old woman, smoker, attended the ER with a fever of more than 40 °C.

## Predictors related to local and systemic adverse events

Women and individuals between 18 and 55 years of age were identified as the groups most at risk of developing any local AE after the first dose and systemic AEs after both doses. Participants with a prior COVID-19 infection were more likely to experience systemic AEs after the first dose. An association was found between having a chronic disease other than hypertension and a decreased likelihood of experiencing systemic AEs after the second dose (Table 4).

**Table 3.** Prevalence of participants who developed each adverse event (local or systemic) by dose, gender, and age

| | Dose 1 | | | | Dose 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| **Total (N = 331)** | | | | | | | | |
| Local AEs | | | | | | | | |
| Pain at injection site | 68.3 | 8.5 | 0.3 | 0.0 | 59.5 | 6.0 | 0.0 | 0.0 |
| Redness | 2.4 | 0.9 | 0.0 | 0.0 | 3.9 | 0.6 | 0.0 | 0.0 |
| Swelling | 5.4 | 0.6 | 0.0 | 0.0 | 5.1 | 0.6 | 0.0 | 0.0 |
| Axillary swelling | 0.0 | 0.0 | 0.0 | 0.0 | 1.2 | 0.6 | 0.0 | 0.0 |
| Systemic AEs | | | | | | | | |
| Headache | 13.9 | 1.2 | 0.0 | 0.0 | 27.2 | 5.7 | 0.0 | 0.0 |
| Fatigue | 15.7 | 1.2 | 0.0 | 0.0 | 27.2 | 5.1 | 0.6 | 0.0 |
| Myalgia | 5.1 | 0.9 | 0.0 | 0.0 | 14.2 | 12.7 | 2.7 | 0.9 |
| Arthralgia | 2.4 | 0.9 | 0.0 | 0.0 | 10.0 | 8.5 | 2.4 | 0.6 |
| Nausea/vomiting | 2.4 | 0.0 | 0.0 | 0.0 | 7.6 | 0.9 | 0.0 | 0.0 |
| Chills | 8.2 | 0.0 | 0.0 | 0.0 | 24.5 | 0.6 | 0.0 | 0.0 |
| Fever | 0.9 | 0.3 | 0.0 | 0.0 | 10.9 | 5.7 | 3.6 | 0.3 |
| **Men (N = 166)** | | | | | | | | |
| Local AEs | | | | | | | | |
| Pain at injection site | 66.9 | 3.6 | 0.6 | 0.0 | 59.0 | 2.4 | 0.0 | 0.0 |
| Redness | 1.2 | 0.6 | 0.0 | 0.0 | 1.8 | 0.0 | 0.0 | 0.0 |
| Swelling | 2.4 | 0.0 | 0.0 | 0.0 | 1.8 | 0.0 | 0.0 | 0.0 |
| Axillary swelling | 0.0 | 0.0 | 0.0 | 0.0 | 0.6 | 1.2 | 0.0 | 0.0 |
| Systemic AEs | | | | | | | | |
| Headache | 12.7 | 0.6 | 0.0 | 0.0 | 22.3 | 2.4 | 0.0 | 0.0 |
| Fatigue | 13.9 | 1.2 | 0.0 | 0.0 | 26.5 | 2.4 | 0.0 | 0.0 |
| Myalgia | 2.4 | 0.6 | 0.0 | 0.0 | 13.3 | 9.6 | 1.8 | 0.0 |
| Arthralgia | 1.8 | 0.6 | 0.0 | 0.0 | 7.8 | 6 | 1.2 | 0.0 |
| Nausea/vomiting | 0.6 | 0.0 | 0.0 | 0.0 | 4.2 | 0.0 | 0.0 | 0.0 |
| Chills | 5.4 | 0.0 | 0.0 | 0.0 | 15.7 | 0.6 | 0.0 | 0.0 |
| Fever | 1.2 | 0.6 | 0.0 | 0.0 | 6.6 | 4.2 | 1.8 | 0.0 |
| **Women (N = 165)** | | | | | | | | |
| Local AEs | | | | | | | | |
| Pain at injection site | 69.7 | 13.3 | 0.0 | 0.0 | 60.0 | 9.7 | 0.0 | 0.0 |
| Redness | 3.6 | 1.2 | 0.0 | 0.0 | 6.1 | 1.2 | 0.0 | 0.0 |
| Swelling | 8.5 | 1.2 | 0.0 | 0.0 | 8.5 | 1.2 | 0.0 | 0.0 |
| Axillary swelling | 0.0 | 0.0 | 0.0 | 0.0 | 1.8 | 0.0 | 0.0 | 0.0 |
| Systemic AEs | | | | | | | | |
| Headache | 15.2 | 1.8 | 0.0 | 0.0 | 32.1 | 9.1 | 0.0 | 0.0 |
| Fatigue | 17.6 | 1.2 | 0.0 | 0.0 | 27.9 | 7.9 | 1.2 | 0.0 |
| Myalgia | 7.9 | 1.2 | 0.0 | 0.0 | 15.2 | 15.8 | 3.0 | 1.8 |
| Arthralgia | 3.0 | 1.2 | 0.0 | 0.0 | 12.1 | 10.9 | 3.6 | 1.2 |
| Nausea/vomiting | 4.2 | 0.0 | 0.0 | 0.0 | 10.9 | 1.8 | 0.0 | 0.6 |
| Chills | 10.9 | 0.0 | 0.0 | 0.0 | 33.3 | 0.6 | 0.0 | 0.0 |
| Fever | 0.6 | 0.0 | 0.0 | 0.0 | 15.2 | 7.3 | 5.5 | 0.6 |

**Table 3** *(cont.).* Prevalence of participants who developed each adverse event (local or systemic) by dose, gender, and age

| | Dose 1 | | | | Dose 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| **Age 18-55 (N = 243)** | | | | | | | | |
| Local AEs | | | | | | | | |
| Pain at injection site | 71.6 | 10.7 | 0.4 | 0.0 | 61.7 | 7.0 | 0.0 | 0.0 |
| Redness | 3.3 | 0.8 | 0.0 | 0.0 | 4.9 | 0.8 | 0.0 | 0.0 |
| Swelling | 6.2 | 0.8 | 0.0 | 0.0 | 6.2 | 0.8 | 0.0 | 0.0 |
| Axillary swelling | 0.0 | 0.0 | 0.0 | 0.0 | 1.6 | 0.4 | 0.0 | 0.0 |
| Systemic AEs | | | | | | | | |
| Headache | 15.2 | 1.2 | 0.0 | 0.0 | 31.7 | 6.2 | 0.0 | 0.0 |
| Fatigue | 20.2 | 1.2 | 0.0 | 0.0 | 28.0 | 7.0 | 0.8 | 0.0 |
| Myalgia | 6.2 | 0.4 | 0.0 | 0.0 | 18.1 | 12.8 | 3.3 | 1.2 |
| Arthralgia | 3.3 | 0.4 | 0.0 | 0.0 | 12.3 | 7.8 | 3.3 | 0.8 |
| Nausea/vomiting | 2.9 | 0.0 | 0.0 | 0.0 | 8.6 | 0.8 | 0.4 | 0.0 |
| Chills | 8.6 | 0.0 | 0.0 | 0.0 | 28.4 | 0.8 | 0.0 | 0.0 |
| Fever | 0.8 | 0.4 | 0.0 | 0.0 | 14.0 | 5.3 | 4.9 | 0.4 |
| **Age > 55 (N = 88)** | | | | | | | | |
| Local AEs | | | | | | | | |
| Pain at injection site | 59.1 | 2.3 | 0.0 | 0.0 | 53.4 | 3.4 | 0.0 | 0.0 |
| Redness | 0.0 | 1.1 | 0.0 | 0.0 | 1.1 | 0.0 | 0.0 | 0.0 |
| Swelling | 3.4 | 0.0 | 0.0 | 0.0 | 2.3 | 0.0 | 0.0 | 0.0 |
| Axillary swelling | 0.0 | 0.0 | 0.0 | 0.0 | 1.1 | 0.0 | 0.0 | 0.0 |
| Systemic AEs | | | | | | | | |
| Headache | 10.2 | 1.1 | 0.0 | 0.0 | 14.8 | 4.5 | 0.0 | 0.0 |
| Fatigue | 3.4 | 1.1 | 0.0 | 0.0 | 25.0 | 0.0 | 0.0 | 0.0 |
| Myalgia | 2.3 | 2.3 | 0.0 | 0.0 | 3.4 | 12.5 | 0.0 | 0.0 |
| Arthralgia | 0.0 | 2.3 | 0.0 | 0.0 | 3.4 | 10.2 | 0.0 | 0.0 |
| Nausea/vomiting | 1.1 | 0.0 | 0.0 | 0.0 | 4.5 | 1.1 | 0.0 | 0.0 |
| Chills | 6.8 | 0.0 | 0.0 | 0.0 | 13.6 | 0.0 | 0.0 | 0.0 |
| Fever | 1.1 | 0.0 | 0.0 | 0.0 | 2.3 | 6.8 | 0.0 | 0.0 |

AEs: adverse events.

## Discussion

The aim of this study was to assess the prevalence and severity of reactogenicity of the Spikevax® COVID-19 vaccine (Moderna) in a sample of individuals who received the vaccine in a tertiary hospital in the province of Huelva (Spain). We found that most Spikevax® vaccine recipients are expected to report at least one AE during the first week after vaccine administration. The most common AEs were injection site pain, fatigue, and predominantly mild or moderate headache. Reactogenicity varied according to the dose (first or second), whether the individual had previously been infected with COVID-19, and certain demographic and clinical characteristics.

We found that local AEs were more common after the first dose, whereas systemic AEs were more frequent and intense after the second dose. This is consistent with previous studies on mRNA vaccines[5,10-12]. The increased systemic reactogenicity after the second dose is thought to be related to immunogenicity after the first dose[13]. Similarly, we found an association between the incidence of self-reported systemic AEs after the first dose of Spikevax® vaccine and the participants with a previous COVID-19 infection. This result is consistent with those of recent studies[11,14,15] and may be due to the fact that after COVID-19 infection people develop a higher IgG antibody response against SARS-CoV-2 after a course of vaccination compared to that of vaccine recipients who have never had a COVID-19 infection[16,17]. However, no differences were found between participants with or without previous COVID-19 infection in relation to systemic AEs reported after the second dose. All the participants had been exposed to the viral antigen either by previous infection or by the first vaccination, which led to

**Table 4.** Predictors of local or systemic adverse events after the first and second doses of Spikevax® vaccine

| Predictors | Univariate analysis for local AEs | | | | Univariate analysis for systemic AEs | | | |
|---|---|---|---|---|---|---|---|---|
| | Dose 1 | | Dose 2 | | Dose 1 | | Dose 2 | |
| | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Sex (male = 0) | 2.08 (1.22, 3.53) | 0.007 | 1.46 (0.92, 2.31) | 0.110 | 1.61 (1.01, 2.56) | 0.043 | 2.37 (1.48, 3.79) | < 0.001 |
| Age (18-55 = 0) | 0.32 (0.18, 0.55) | < 0.001 | 0.61 (0.36, 1.01) | 0.054 | 0.39 (0.22, 0.71) | 0.002 | 0.38 (0.23, 0.62) | < 0.001 |
| Smokers | 0.80 (0.39, 1.64) | 0.550 | 1.12 (0.57, 2.21) | 0.732 | 1.88 (0.99, 3.54) | 0.051 | 1.80 (0.87, 3.69) | 0.109 |
| High body mass index | 1.30 (0.51, 3.28) | 0.579 | 1.07 (0.49, 2.35) | 0.861 | 1.07 (0.49, 2.31) | 0.855 | 0.74 (0.35, 1.57) | 0.440 |
| Hypertension | 1.41 (0.69, 2.87) | 0.341 | 0.99 (0.55, 1.79) | 0.977 | 0.90 (0.49, 1.64) | 0.743 | 1.00 (0.56, 1.79) | 0.998 |
| Other chronic disease | 1.17 (0.68, 2.02) | 0.570 | 1,09 (0.67, 1.75) | 0.724 | 0.95 (0.59, 1.53) | 0.840 | 0.59 (0.37, 0.94) | 0.027 |
| Previous COVID-19 infection | 3.96 (0.51, 30.76) | 0.188 | 0.86 (0.28, 2.65) | 0.801 | 8.19 (2.23, 30.02) | 0.002 | 3.27 (0.72, 14.90) | 0.124 |

AEs: adverse events; CI: confidence interval; OR: *odds ratio*.

a similar response in both groups after the second dose. After the second dose, no significant differences were found in the IgG antibody response to SARS-CoV-2 in participants with or without previous infection[18,19].

Fatigue was the most common systemic AE after the first (16.9%) and second dose (32.9%). This rate is lower than that reported in the literature: 37.2% and 65.3%, respectively, in clinical trials[5], and 32.5% and 60.0%, respectively, among V-Safe Active Surveillance System participants in the US[10]. It may be the case that the effect of vaccines regarding fatigue may be overestimated in clinical trials, given that at least one in four participants who received placebo also reported experiencing fatigue[5]. In addition, differences in findings between previous studies and the present one may be due to the nature of data collection. For example, participants in the study by Chapin-Bardales *et al.* voluntarily accessed the V-Safe Active Surveillance System and answered questions about the AEs[10]. It is possible that the participants who experienced more AEs were more motivated to access and report them. In contrast, the present study was conducted using telephone interviews, which allowed data to be collected from all participants who received both doses and answered the calls regardless of their level of vaccine reactogenicity. However, further research is needed to estimate the prevalence of AEs related to COVID-19 vaccination. The most frequent local AE was injection-site pain after the first dose (77.1%) and the second dose (65.5%). Although this finding is consistent with those of previous studies[5,10], the rates are also lower than those previously reported. In this regard, the literature clearly shows that genetic, sociological, and psychological factors may explain individual differences in pain perception[20].

Although most of the reported AEs were mild or moderate, 1.2% of participants required emergency room visits or hospitalisation within 7 days of receiving the Spikevax® vaccine. These individuals reported AEs related to muscle and joint pain, vomiting, and fever: in one these cases, the participant required hospitalisation due to muscle and joint pain that made them unable to move and communicate. Although this is a low percentage of participants, these potential AEs should be systematically monitored for given that some patients may experience high reactogenicity after vaccination. This information could facilitate the identification of AEs that, although uncommon, may occur after vaccination.

We found differences in the proportion and intensity of AEs according to the participants' characteristics, which is in line with the results of clinical trials and previous studies. Overall, AEs were more common and more intense in women and in participants aged between 18 to 55 years. Both groups were more likely to report local AEs after the first dose and systemic AEs after both doses of the Spikevax® vaccine. Although it has been reported that, in general, women are more likely to report AEs after administration of vaccines and medications[14,21,22], no reason or mechanism has yet been offered to explain this phenomenon. It has been suggested that this association is complex and may include many contributing factors[23]. More research is needed to understand these differences. An association has been found between the decreased likelihood of reporting AEs and increasing age and immunosenescence[24]. In addition, we found that participants with a chronic disease other than hypertension were significantly less likely to report vaccination-related systemic AEs after the first dose. To our knowledge, no previous studies have compared differences between people with or without chronic conditions in relation to the reactogenicity of COVID-19 vaccines. For this reason, the results of this study should be interpreted with caution. Nevertheless, this finding could be explained by these participants associating their symptoms with the chronic disease instead of associating them with the vaccination. Another potential explanation is that any medication taken to manage their disease may alleviate symptoms related to vaccination. More research is needed on AEs in patients with a chronic illness other than hypertension.

The present study has limitations that need to be addressed. Firstly, although a trained research assistant interviewed participants, information on AE is subjective and may depend on the individual's pain threshold. A second limitation is the follow-up period, given that AEs were not assessed beyond 7 days post-vaccination. However, AE related to COVID-19 vaccination usually occur within the first 24 to 48 hours and only rarely manifest later than that[25]. Finally, some statistical bias may exist due to the small number of participants reporting previous COVID-19 infection.

Despite these limitations, our results suggest that COVID-19 vaccines are safe in the short term and that there are some factors that correlate with their reactogenicity. We hope that these results will help public health professionals to identify individuals most likely to experience increased reactogenicity to the Spikevax® COVID-19 vaccine and, consequently, to adequately inform recipients about possible short-term AE. These findings are also of interest in understanding its short-term safety profile in a setting other than that of a clinical trial. Communicating this information to the general public could help counteract the negative effects of misinformation about vaccine safety and could reduce the prevalence of people who remain hesitant to get vaccinated[8].

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## Conflict of interests

No conflict of interests.

## Contribution to the scientific literature

The results could be of use in the identification of individuals with increased reactogenicity to the Spikevax® vaccine.

This information may help predict adverse reactions and improve treatments.

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