



ORIGINAL ARTICLE

Adverse events after COVID-19 vaccination in the pediatric population in Spain



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Received 18 August 2025; accepted 19 November 2025

Available online 7 February 2026

KEYWORDS

COVID-19;
Vaccines;
Pediatrics;
Adverse drug
reactions (ADRs);
Safety;
Pharmacovigilance

Abstract

Introduction: In December 2021, Spain launched its COVID-19 vaccination campaign for children aged 5–11 years. Although the Comirnaty[®] vaccine exhibited a favorable safety profile in premarketing trials, its rapid deployment and novel mRNA technology raised concerns among the public, leading to parental hesitancy. Real-world postmarketing data are limited but crucial for guiding clinical and public health policy decisions.

Objective: To assess the incidence and nature of adverse drug reactions (ADRs) following pediatric COVID-19 vaccination.

Methods: Prospective, observational and descriptive study conducted at a tertiary care hospital in Spain. The sample consisted of a total of 2126 children aged 5–11 years. Data on ADRs were collected through telephone interviews, health record reviews and institutional registries. An expert committee evaluated each ADR using predefined criteria for causality and severity.

Results: Overall, 35.6% of participants reported at least one ADR, totaling 1437 reactions. Most were mild (99.5%) and resolved spontaneously. Only one case was classified as severe. The most common ADRs were injection site pain (57.1%), fever (11.1%) and headache (5.7%). There was no evidence of increased reactogenicity after the second dose. Of all ADRs, 65.1% were considered «definite» or «probable.»

DOI of original article: <https://doi.org/10.1016/j.anpedi.2025.504088>

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Conclusions: The Comirnaty® vaccine maintains a favorable safety profile in children under real-world conditions, with predominantly mild, self-limiting reactions and minimal need for medical care.

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PALABRAS CLAVE

COVID-19;
Vacunas;
Pediatría;
Reacciones adversas a
medicamentos (RAM);
Seguridad;
Farmacovigilancia

Reacciones adversas a la vacuna COVID-19 en población pediátrica en España

Resumen

Introducción: En diciembre de 2021 comenzó en España la campaña de vacunación contra el COVID-19 en niños de 5–11 años. A pesar del buen perfil de seguridad de la vacuna (Comirnaty®) en los estudios precomercialización, suscitó cierta incertidumbre en la población por su rápida implementación y tecnología novedosa, llevando a los padres incluso a dudar sobre la vacunación de sus hijos. Existen pocos estudios postcomercialización en condiciones reales para evaluar la seguridad y respaldar decisiones clínicas y epidemiológicas fundamentadas.

Objetivo: Evaluar la incidencia y características de las reacciones adversas tras la vacunación pediátrica frente a COVID-19.

Material y métodos: Estudio observacional, ambispectivo y descriptivo, realizado en un hospital terciario. Se incluyeron 2.126 niños de 5 a 11 años. Se recogieron RAM mediante entrevistas telefónicas, revisión de historia clínica y registros institucionales, evaluadas por un comité experto según criterios de causalidad y gravedad preestablecidos.

Resultados: El 35,6% presentaron al menos una RAM, con un total de 1.437 reacciones. La mayoría fueron leves (99,5%) y de resolución espontánea. Solo un caso fue clasificado como grave. Las RAM más frecuentes fueron dolor en el lugar de inyección (57,1%), fiebre (11,1%) y cefalea (5,7%). No se identificó mayor reactividad tras la segunda dosis. El 65,1% de las RAM fueron clasificadas como «definidas» o «probables».

Conclusiones: La vacuna Comirnaty® mantiene un perfil de seguridad favorable en población pediátrica en condiciones reales, con predominio de RAM leves, autolimitadas y con escasa necesidad de atención médica.

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Introduction

In December 2021, Spain began its COVID-19 vaccination campaign for children aged 5–11 years with Comirnaty. The speed with which this vaccine was developed and tested, as well as its novel mechanism of action (via messenger RNA), generated some mistrust and uncertainty in the general population regarding the potential deleterious effects it could have on individuals. These concerns were even more pronounced in relation to children, as they are particularly vulnerable to the effects of drugs, coupled with the fact that, to date, no major consequences of COVID-19 infection had been reported in the pediatric population.¹ This led to significant hesitancy and refusal from parents when it came to vaccinating their children, prompting scientific societies to make statements in support of vaccination,² chiefly based on the important role of the pediatric population in the epidemiological control of this infection.

The reported incidence of SARS-CoV-2 infection in children when vaccination began in 2021 was in the range of 0.8%–2.1%,³ values that were unrealistic given the known fact that most cases presented with mild symptoms or were even asymptomatic and were therefore not diagnosed. At

the time, the global mortality was 0.08%, with substantial variation between countries⁴: less than 0.0094% in children aged less than 14 years in Spain.⁵ However, the disease was not free of potentially serious consequences,⁶ such as, for example, multisystem inflammatory syndrome in children (MIS-C). Today, we know that following exposure to the virus and active infection, the pediatric population is particularly vulnerable to MIS-C, a clinically heterogeneous syndrome that in some cases (up to 65%) requires advanced life support and that, according to some studies, could be prevented with vaccination.^{7,8}

In the phase II and III trials of Comirnaty⁹ in the pediatric population (which included 2268 children aged 5–11 years, of whom 1517 received the vaccine), the vaccine exhibited a favorable safety profile, as most reactions were mild to moderate, with an incidence of adverse reactions that was similar in vaccinated vs placebo-controlled participants. However, to date, few safety data have been published following mass vaccination of the pediatric population in the real world.

Currently, the need for epidemiological control has decreased; however, vaccination is still recommended for children in risk groups.¹⁰

Therefore, it seems relevant to obtain objective data regarding the safety of the vaccine under real-world conditions, especially if, aside from the data included in the summary of product characteristics,¹¹ there are few post-marketing surveillance studies estimating the incidence of adverse drug reactions (ADRs) following the administration of this vaccine in the pediatric population.

This information could guide decision-making regarding vaccination in this population, both for the prevention of disease and for epidemiological control.

Material and methods

Study sample and design

We conducted an ambispective observational and descriptive study in children vaccinated against COVID-19 in a tertiary care hospital in Madrid. We collected retrospective data for all patients included in the pediatric vaccination register of the hospital (which includes documentation on the ADRs that took place at the point of care within 15 min of the administration of the vaccine), and prospective data (through telephone interviews) on those patients whose parents or guardians provided informed consent to participation.

The sample included patients of any sex aged 5–11 years.

After the administration of the first dose of vaccine, the research team contacted (by telephone) the parents/guardians of the patient to obtain informed consent for the study and, if consent was given, conducted a semi-structured interview to determine whether the child had experienced any adverse events and to obtain details on any such events. If the family could not be reached, the call was repeated up to three times on two different days. Telephone follow-ups were also conducted after the second dose and every dose thereafter, at one month and six months post vaccination, to identify potential adverse events in the medium and long term. To avoid missing information, the team also reviewed all the data on participating patients available in the pediatric vaccination register of the vaccination clinic, which, per hospital protocol, includes exhaustive documentation of possible immediate adverse events of vaccination (identified at the point of care during vaccination or in the 15 following minutes), as well as the health records of the patients in the integrated electronic health record system (HORUS system, which includes records for primary care, specialty care and other health services, such as the such as the 112 emergency medical services line), searching for adverse events notified by pediatric emergency physicians or other health care specialists/professionals (due to suspicion that the reason for an emergency department visit or hospital admission could be related to the vaccine).

For those children in whom adverse events were identified, the team performed a comprehensive review of their health records and searched the hospital's health care information and management systems for additional information.

For all participants, we collected data on variables that would allow the investigation of possible risk factors associated with the development of ADRs (age, sex, body weight, medical history, pharmacological treatments and allergies) in addition to variables related to the adverse events in patients who had experienced them (Appendix A).

All the research team members involved in data collection (interview and review of health records) were health care professionals with expertise in clinical pharmacology and/or pediatrics and specifically trained in the search and identification of ADRs.

For the purpose of this study, we applied the definition of ADR used by the Royal Decree on Pharmacovigilance¹² and the World Health Organization (WHO) as a "noxious, unintended, and undesired response to a medicine that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy, or for the modification of physiological function."

Any event that could be secondary to the administration of the vaccine was evaluated by a committee of experts consisting of two clinical pharmacologists, two pediatricians, and two nurses specialized in pediatric pharmacovigilance. If the event was considered an ADR, the same committee evaluated its causality and severity.

If additional information was needed, the team made another call to the parents and healthcare professionals who had reported the event.

The causality of the event was evaluated by means of the Karch-Lasagna algorithm,¹³ designed to assess aspects such as previous reports in the literature, the temporal sequence between the onset of the event and the administration of the drug, and the outcome of de-challenge (drug removal) or re-challenge (re-exposure). After obtaining the corresponding scores, we classified ADRs into the following categories: unrelated (≤ 0), conditional (1–3), possible (4–5), probable (6–7) and related (≥ 8).

Severity was classified according to the Venulet criteria.¹⁴ Thus, ADRs were categorized as mild (did not complicate the primary disease, no treatment was required, suspected drug did not need to be stopped), moderate (clear signs and symptoms observed without involvement of vital organ systems) or severe (fatal or life-threatening, lowering the patient's life expectancy, with impairment of a vital organ-system, or persisting for more than one month).

All the data were recorded using the REDCap (Research Electronic Data Capture) web application.¹⁵

Statistical analysis

All the collected data were exported in a compatible format for subsequent analysis with the software package SPSS, version 25.0.

We conducted a descriptive analysis of the identified ADRs, expressing categorical variables as absolute frequencies and percentages. For quantitative variables, we used measures of central tendency (mean [95% CI] and mode) and of dispersion (standard deviation).

For all tests, we considered a *P* value of .05 or less statistically significant.

Ethical considerations

The study adhered to the principles of the Declaration of Helsinki and Royal Decree 957/2020 regulating observational studies with use of medicines in human subjects. In addition, data collection and handling adhered to Organic Law 3/2018 of December 5 on the Protection of Personal Data and Guarantee of Digital Rights.

Table 1 Demographic characteristics of the sample.

	Count (n)	Percentage (%)	Total
Sex			
Male	1116	52.5	2126
Female	1010	47.5	
Age (years)			
5 years	241	11.3	2126
6 years	223	10.5	
7 years	275	12.9	
8 years	288	13.5	
9 years	333	15.7	
10 years	353	16.6	
11 years	363	17.1	
12 years	50	2.4	
Weight (kg)			
10.1–15	7	0.3	2126
15.1–20	166	8.3	
20.1–25	546	25.3	
25.1–30	444	20.7	
30.1–35	317	14.9	
35.1–40	340	16.1	
40.1–45	164	7.9	
45.1–50	74	3.2	
50.1–55	36	1.6	
55.1–60	18	0.9	
60.1–65	4	0.2	
65.1–70	4	0.2	
70.1–75	3	0.2	
75.1–80	2	0.1	
80.1–82	1	0.1	

The Ethics Committee of the hospital approved the study protocol (Code:22/096-O.M.SP), which was registered in the Spanish Register of Clinical Trials (0020-2022-OBS), and we obtained parental informed consent for all the participants.

The study was monitored by the Clinical Research and Clinical Trials Unit of the hospital.

Results

Between December 19, 2021, and March 2, 2022, a total of 3677 patients were vaccinated, and all of them were included in the hospital's pediatric vaccination registry. This registry is the database that contains the information on ADRs that occur at the point of care within 15 min of vaccination (which would be considered immediate ADRs); we identified 42 patients that experienced a combined total of 59 immediate ADRs.

The registry only contained contact details for 2914 of the total of vaccinated patients, and 480 did not answer the calls. A total of 308 parents refused to consent to participation, so the final sample for the prospective follow-up included 2126 children; all patients who experienced immediate ADRs consented to participation in the prospective follow-up. All of them received Comirnaty 10 micrograms.

Participants were aged 5–11 years, with a mean (SD) age of 109.5 (25.9) months (9.1 years), and 142 months (11.8 years) was the most frequent age; 52.2% of the patients were male (Table 1).

Of the total sample, 16.9% (n=359) patients had a relevant medical history prior to recruitment, 11.6% (n=246) had a history of allergy and 18.3% (n=388) were infected by SARS-CoV-2 (before or during the study). Only 6.2% (n=132) received chronic medication and 9.2% (n=195) took some medication (chronic or otherwise) the same day that they received a dose of vaccine.

Of the total sample, 757 patients had at least one ADR (35.6%; 95% CI, 25.7%–44.4%). A total of 1437 ADRs were identified, with an approximate average of two per patient (mean, 1.88; 95% CI, 1.81–1.96; SD, 1.04), and the frequency of ADRs was similar after both doses (46.8% after the first dose, 53.2% after the second) (Fig. 1).

In terms of severity, based on the Venulet criteria, most ADRs were classified as mild (99.5%), with few classified as moderate (0.4%) and only one as severe (0.1%); 99.4% could be managed at the outpatient level, and 0.6% required hospital admission.

The adverse reaction classified as serious was a generalized tonic-clonic seizure following the first dose of vaccine in a patient with no previous history of seizures. It resolved without treatment, but the specialist recommended that the second dose of vaccine not be administered. The patient has not experienced any similar episodes since.

In the classification of ADRs by the involved system organ class, the most frequent reactions were those categorized as "general disorders and administration site conditions", followed (in order of decreasing frequency) by nervous system disorders, musculoskeletal disorders, gastrointestinal disorders and blood and lymphatic system disorders. The frequency distribution was similar after administration of each of the doses, except for blood and lymphatic system disorders and general disorders and administration site conditions, whose frequency increased markedly following administration of the second dose. Table 2 presents the frequency distribution of the observed adverse reactions by system organ class.

The most frequent ADR was pain at the site of injection (820 [57.1%]), followed by fever/low-grade fever (both categorized as "general disorders and administration site conditions"), observed in 11.1% of children with ADRs (n=159), and headache (82 [5.7%]). Fatigue (60 [4.2%]), local inflammation or swelling (58 [4%]) and asthenia (55 [3.8%]) were the next most frequently observed ADRs. Table 3 provides a detailed description of the suspected ADRs detected in more than five patients.

In terms of the temporal relationship, most reactions (55.3%) were acute, with 43.1% of subacute to delayed reactions, and no documentation of the temporal relationship for the rest.

With regard to the management of the ADR, most did not require treatment (54.1%); in two cases (0.1%), administration of the second dose was discouraged.

The vast majority of ADRs (99%) had resolved by the end of follow-up. The reactions that had not resolved or were improving over time were lymphadenopathies (n=3), headaches (n=2), skin lesions, abdominal pain, hyperthyrotropinemia under treatment with thyroid-stimulating hormone, changes in taste and nocturnal cough (n=1 for each).

The relationship between the suspected ADRs and the administered vaccine was categorized according to the

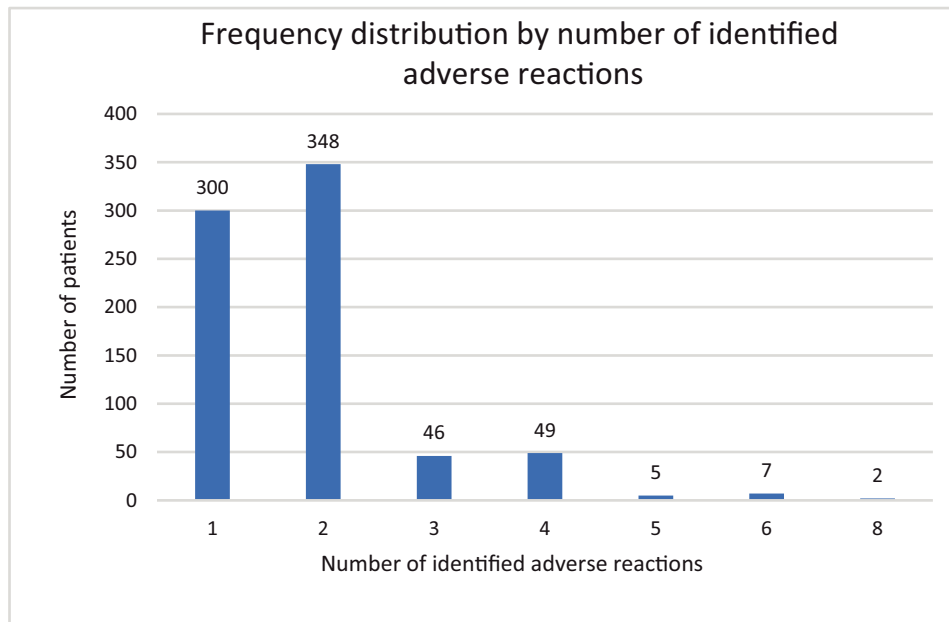


Figure 1 Frequency distribution of patients by number of identified adverse reactions.

Table 2 Frequency distribution of identified adverse reactions by system organ class and the time when they occurred.

System organ class	Number of adverse reactions		Total
	After first dose	After second dose	
General disorders and administration site conditions	560	643	1.203
Nervous system disorders	42	44	86
Musculoskeletal and connective tissue disorders	22	26	48
Gastrointestinal disorders	21	17	38
Blood and lymphatic system disorders	9	19	28
Immune system disorders and infection	8	7	15
Psychiatric disorders	3	2	5
Respiratory, thoracic and mediastinal disorders	1	3	4
Cardiac disorders	1	1	2
Metabolism and nutrition disorders	1	1	2
Skin and subcutaneous tissue disorders	1	1	2
Renal and urinary disorders	1	0	1
Reproductive system and breast disorders	1	0	1
Sensory organ disorders	1	0	1
Vascular disorders	1	0	1
Total	673	764	1.437

Karch-Lasagna criteria as “related” in 37.8% of cases (n=543), “probable” in 27.1% (n=389), “possible” in 18.5% (n=266) and “conditional” in 15.3% (n=220), with the remaining events considered “unrelated” (1.3% [n=19]).

Discussion

The population vaccinated at our hospital was similar to the populations included in the clinical trials and post-authorization surveillance studies conducted by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA).^{9,16,17} The mean age of

patients vaccinated in clinical trials of the vaccine before its authorization⁹ was 8.2 years (9.1 years in our patients), and the mean age of patients with notified ADRs in post-authorization surveillance studies^{16,17} was 8 years, with similar characteristics in terms of the sex distribution and previous medical history.

The main reason why some patients were not included in the study was the difficulty in reaching them by telephone. This factor was unrelated to their clinical characteristics, motivations, or any other variable that could affect the study findings. Therefore, we consider that the inability to contact them did not introduce bias into the results, as their exclusion was based solely on logistical limitations and not

Table 3 Frequency of adverse drug reactions classified by the time course.

Event	Number of ADRs	‰ of ADRs	‰ of 2126 vaccinated children	After first dose	After second dose	Total
Pain at the site of injection	820	570.633	3.857	382	438	820
Fever	159	110.647	0.748	77	82	159
Headache	82	57.063	0.386	38	44	82
Fatigue	60	41.754	0.282	23	37	60
Swelling at the site of injection	58	40.362	0.273	22	36	58
Asthenia; general malaise	55	38.274	0.259	27	28	55
Pain in the extremity	32	22.269	0.151	17	15	32
Dizziness	30	20.877	0.141	22	8	30
Lymphadenopathy	26	18.093	0.122	8	18	26
Nausea; vomiting	26	18.093	0.122	17	9	26
	12	8.351	0.056	4	8	12
Cold symptoms	11	7.655	0.052	5	6	11
Myalgia	10	6.959	0.047	2	8	10
Chills	6	4.175	0.028	1	5	6
Diarrhea	5	3.479	0.024	1	4	5
Abdominal pain	5	3.479	0.024	2	3	5

Abbreviations: ADR: adverse drug reaction; ‰: frequency per 1000 patients.

Table 4 Comparison of frequency of adverse reactions identified in the sample to those described in the Comirnaty summary of product characteristics.

System organ class	Event	Estimated frequency in summary of product characteristics		Estimated frequency in vaccinated cohort	
		Percentage of affected patients (%)	Frequency classification	Percentage of affected patients (%)	Frequency classification
Blood and lymphatic system disorders	Lymphadenopathy	0.1–0.01	Frequent	0.012	Frequent
[1,0]Immune system disorders	Hypersensitivity reaction	0.001–0.01	Infrequent	0.002	Infrequent
Metabolism and nutrition disorders	Anaphylaxis		Unknown		Unknown
[1,0]Psychiatric disorders	Decreased appetite	0.001–0.01	Infrequent		Unknown
[5,0]Nervous system disorders	Irritability	> 0.1	Very frequent		Unknown
	Insomnia	0.001–0.01	Infrequent	0.001	Infrequent
	Somnolence	> 0.1	Very frequent	0.001	Rare
	Headache	> 0.1	Very frequent	0.039	Frequent
	Dizziness	0.001–0.01	Infrequent	0.014	Frequent
	Lethargy	0.001–0.01	Infrequent		Unknown
	Acute peripheral facial paralysis	0.0001–0.001	Rare		Unknown
	Paresthesia; hypoesthesia		Unknown		Unknown
[1,0]Cardiac disorders	Myocarditis	< 0.0001	Extremely rare		Unknown
	Pericarditis	< 0.0001	Extremely rare		Unknown
[1,0]Gastrointestinal disorders	Diarrhea	> 0.1	Very frequent	0.002	Infrequent
	Nausea; vomiting	0.1–0.01	Frequent	0.012	Frequent
[1,0]Skin and subcutaneous tissue disorders	Hyperhidrosis; night sweats	0.001–0.01	Infrequent		Unknown
	Erythema multiforme		Unknown		Unknown
[2,0]Musculoskeletal and connective tissue disorders	Arthralgia	> 0.1	Very frequent	0.001	Rare
	Myalgia	> 0.1	Very frequent	0.005	Infrequent
	Pain in the extremity	0.001–0.01	Infrequent	0.015	Frequent
Reproductive system and breast disorders	Heavy menstrual bleeding		Unknown		Unknown
[9,0]General disorders and administration site conditions	Pain at the site of injection	> 0.1	Very frequent	0.386	Very frequent
	Fatigue	> 0.1	Very frequent	0.028	Frequent
	Chills	> 0.1	Very frequent	0.003	Infrequent
	Fever	> 0.1	Very frequent	0.075	Frequent
	Swelling at the site of injection	> 0.1	Very frequent	0.027	Frequent
	Redness at site of injection	0.1–0.01	Frequent	0.006	Infrequent
	Itching at site of injection	0.001–0.01	Infrequent	0.001	Rare
	Asthenia; malaise	0.001–0.01	Infrequent	0.026	Frequent
	Extensive swelling in the extremity of vaccine administration		Unknown		Unknown
	Facial swelling		Unknown	0.001	Rare

on criteria that could affect the validity or representativeness of the sample.

When comparing the frequency of the ADRs observed in our cohort with the reported frequency in the summary of product characteristics,¹¹ we found agreement for some

ADRs, such as pain at the site of injection, lymphadenopathy, hypersensitivity reactions, insomnia, nausea and vomiting.

However, there were other reactions for which the reported incidence was higher in the summary of product characteristics¹¹ compared to the observed frequency

in our cohort. Among the reactions labeled as very common in the summary of product characteristics, we found a lower frequency in some ADRs, including irritability, somnolence, headache, diarrhea, arthralgia, myalgia, fatigue, chills, fever and swelling at the site of injection. The absence of detected episodes of irritability is particularly salient, as the reported frequency of reaction in controlled trials exceeded 10%.

ADRs with an incidence of less than 0.1% (facial paralysis, pericarditis, myocarditis) may not have been identified in the cohort due to the sample size (too low to detect ADRs with an incidence of less than 1/1000).

The incidence of dizziness, pain in the extremity of administration and asthenia (all of them mild reactions that resolve spontaneously) was higher in the study cohort compared to the incidence reported in the summary of product characteristics.¹¹ Table 4 presents a detailed comparison of the incidence of ADRs.

In addition to ADRs whose frequency in the cohort we were unable to compare with the incidence reported in the summary of product characteristics¹¹ (anaphylaxis, paresthesia/hypoesthesia, erythema multiforme and menstrual bleeding, swelling of the vaccinated extremity), there were ADRs identified in our patients that were not reported in the summary of product characteristics, out of which we ought to highlight dyspnea, cold symptoms and abdominal pain, with an estimated incidence in our cohort of 1/1000 to 1/100, that were categorized as “uncommon”.

Apart from the data included in the summary of product characteristics, there is little post-authorization data on the incidence of ADRs following administration of this vaccine.¹⁸

In the preauthorization pediatric clinical trials controlled with placebo,⁹ the most frequent local ADR was pain at the site of injection (71% after the second dose and 74% after the first dose), and fatigue and headache were the most common general disorders (0.9% and 0.3%). The incidence of severe adverse events was 0.1%, the same incidence observed in our cohort.

These studies detected a higher incidence of systemic ADRs (general disorders) after administration of the second dose compared to the first. However, in our cohort, there was no evidence of an increased risk of adverse reactions with the second dose. Nevertheless, the existing evidence suggests that when patients experience ADRs, they usually develop more than one, rather than an isolated event. This also differs from the evidence in the adult population, where greater reactogenicity for systemic reactions has been observed after the second dose compared to the first.

Conclusion

Considering the number and characteristics of the adverse reactions reported, our study shows that the Comirnaty vaccine maintains a favorable safety profile in real-world clinical practice, with a low frequency of adverse reactions that, in addition, are mild and self-limiting in most cases.

Although our findings were generally consistent with the previous literature, we identified some peculiarities in the

pediatric cohort under study, and we did not observe an increase in reactogenicity after the second dose.

Funding

This study did not receive external funding.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Acknowledgments

The authors would like to express their gratitude to Dr. Ramos Amador, Dr. Laredo Fernandez, Dr. Mariano Lázaro, and the members of the Pediatric COVID Vaccination Working Group at Hospital Clínico San Carlos for their valuable contributions and commitment to the development of this work.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.anpedi.2025.504088>.

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