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ORIGINAL RESEARCH ARTICLE

Safety of COVID-19 Vaccines Among the Paediatric Population: Analysis of the European Surveillance Systems and Pivotal Clinical Trials

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Abstract

Background and Objectives The European Medicine Agency extended the use of Comirnaty, Spikevax, and Nuvaxovid in paediatrics; thus, these vaccines require additional real-world safety evidence. Herein, we aimed to monitor the safety of COVID-19 vaccines through Covid-19 Vaccine Monitor (CVM) and EudraVigilance surveillance systems and the published pivotal clinical trials.

Methods In a prospective cohort of vaccinees aged between 5 and 17 years, we measured the frequency of commonly reported (local/systemic solicited) and serious adverse drug events (ADRs) following the first and second doses of COVID-19 vaccines in Europe using data from the CVM cohort until April 2022. The results of previous pivotal clinical trials and data in the EudraVigilance were also analysed.

Results The CVM study enrolled 658 first-dose vaccinees (children aged 5–11 years; $n = 250$ and adolescents aged 12–17 years; $n = 408$). Local/systemic solicited ADRs were common, whereas serious ADRs were uncommon. Among Comirnaty first and second dose recipients, 28.8% and 17.1% of children and 54.2% and 52.2% of adolescents experienced at least one ADR, respectively; injection-site pain (29.2% and 20.7%), fatigue (16.1% and 12.8%), and headache (22.1% and 19.3%) were the most frequent local and systemic ADRs. Results were consistent but slightly lower than in pivotal clinical trials. Reporting rates in Eudravigilance were lower by a factor of 1000.

Conclusions The CVM study showed high frequencies of local solicited reactions after vaccination but lower rates than in pivotal clinical trials. Injection-site pain, fatigue, and headache were the most commonly reported ADRs for clinical trials, but higher than spontaneously reported data.

Key Points

From our cohort event monitoring study, after COVID-19 vaccination in the paediatric population, we observed high frequencies of local reactions but no serious adverse events.

Covid-19 Vaccine Monitor study findings confirmed the favourable risk profile of COVID-19 vaccines in the paediatric population.

Fariba Ahmadizar and Nicoletta Luxi contributed equally to the paper as the first authors.

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The members of the ilmiovaccinoCOVID19 collaborating group are listed in the Acknowledgements section.

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1 Introduction

As of early 2022, two COVID-19 vaccines, Comirnaty (Pfizer) and Spikevax (Moderna) have received the indication of use in children/adolescents aged 5–17 years by the European Medicines Agency (EMA) [1–4]. Afterwards, in June 2022, the EMA recommended using the Nuvaxovid (Novavax CZ) vaccine for adolescents aged 12–17 years [5]. In the same month, the US Food and Drug Administration (FDA) approved the extension, for emergency use, of Comirnaty and Spikevax vaccines also in children aged from 6 months to 4 years; whereas EMA approved the same extension some months later, in October 2022 [6]. From key information about adverse events following immunisation (AEFIs) gathered by pivotal randomised clinical trials (RCTs), it emerged that those approved COVID-19 vaccines are safe, immunogenic, and effective against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 5- to 17-year-old children and adolescents [1–3].

The World Health Organization (WHO) strategic advisory group of experts on immunisation (WHO SAGE) Roadmap classifies children as the lower priority group for COVID-19 vaccination; even though COVID-19 and severe related outcomes, e.g., cardiovascular dysfunction, multisystem inflammatory syndrome, and respiratory failures, may occur [4, 7]. Moreover, with the advent of more transmissible virus variants, severe outcomes and hospitalisation cases due to COVID-19 have been more frequently reported in children and adolescents, with higher risks in those with comorbidities. In Europe, over 17,200 COVID-19-related deaths (47% in children aged 0–9 years and 53% in adolescents aged 10–19 years) have been reported since June 2022, according to the latest report by the MPIDR COVerAGE [8].

Individuals under 18 years of age have the lowest vaccine uptake in European countries, with more than 73% of this population not vaccinated as of November 2022 [9]. A global hesitancy in administering COVID-19 vaccines to children and adolescents exists because of doubts about the benefit-risk balance, probably driven mainly by the lack of awareness and solid safety data in children and adolescents. According to the European Centre for Disease Prevention and Control (ECDC) reports, it seems that vaccine uptake in paediatrics has been low due to the circulation of the Omicron variant, for which related infection was milder and the risk of severe outcomes was lower than with previous variants, particularly for children without comorbidities [10].

The previous Phase 2–3 trials initially addressed vaccine safety and tolerability outcomes in children [1–3], but mainly included healthy participants with short follow-ups. In the context of the "Covid Vaccine Monitor" (CVM) study, we aimed to measure and report the frequencies of paediatric patient-reported ADRs following the receipt of different COVID-19 vaccines through cohort event monitoring in a real-world setting [11]. We studied our prospectively collected data on ADRs and those reported in the pivotal COVID-19 trials of children and adolescents. Finally, we also disclosed the reports on ADRs with COVID-19 vaccines in paediatric populations using the EudraVigilance data source.

2 Methods

2.1 Cohort Event Monitoring

The Covid-Vaccine cohort event monitoring study is designed as a cohort study in Europe, directly enrolling persons vaccinated for the first time or receiving a booster (of all ages). The protocol for the study is publicly posted on the EU PAS register (EUPAS42504). For this paediatric sub-study, data were obtained from the Netherlands, Italy, Romania, the UK, Portugal, Slovakia, France, and Spain. We estimated rates of ADRs with COVID-19 vaccines in vaccinees aged between 5 and 17 years using prospectively collected data from the CVM study up to the end of data availability (April 2022). The data collection scheme of the CVM study [11] and the reported ADRs coding system are graphically displayed in Fig. 1.

After providing informed consent and registering children, parents or legal representatives were expected to enter the data on behalf of their children, as needed, based on national legislation. Four web apps collecting harmonised data were used in the whole CVM study. However, the paediatric data for this work were only available from two online platforms: the Lareb Intensive Monitoring (LIM—used in the Netherlands, France, Italy, and the UK; managed by Lareb) and ResearchOnline (RO—used in Italy, Portugal, Romania, Slovakia, and Spain; managed by Julius Centre at UMC Utrecht). Data from SafeVac 2.0 and Croatia OPeN apps were unavailable for the paediatric population. Vaccinees could be registered within 48 hours from the first COVID-19 vaccine dose administration. Once registered, vaccinees were asked to complete a baseline questionnaire to collect information regarding demographic characteristics, comorbidities, concomitant drug use, and vaccine exposure (e.g., vaccine brand, date of administration). Six follow-up questionnaires at different time points over six months were sent to the participants to collect information on short- and medium-term ADRs potentially related to the COVID-19 vaccines. The follow-up questionnaires collected information on solicited ADRs, both local (injection-site haematoma, induration, inflammation, pain, pruritus, swelling,

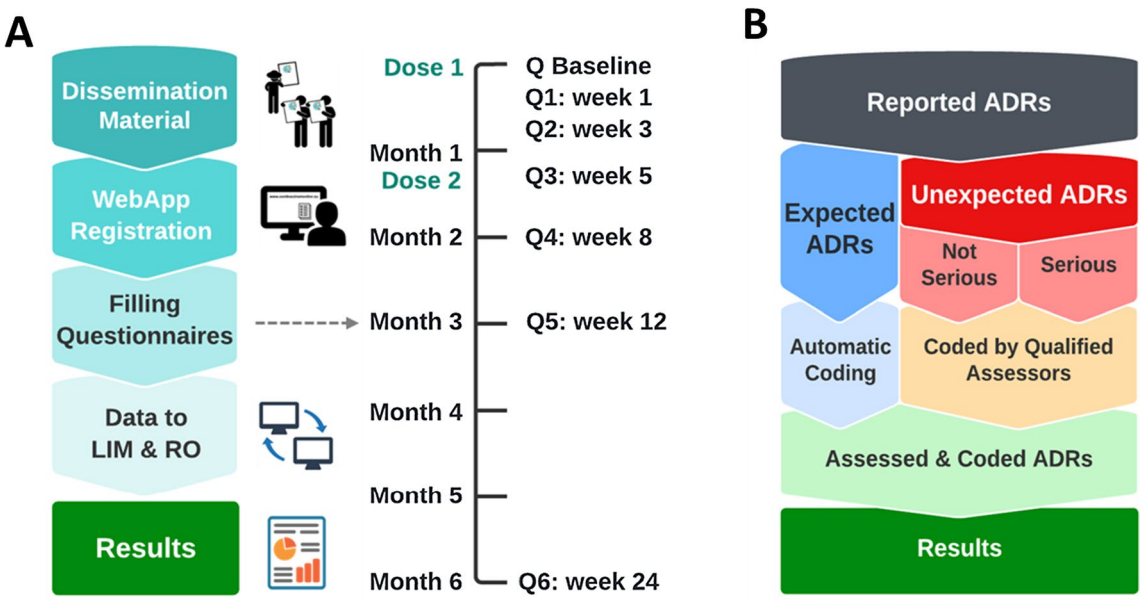

Fig. 1 **A** Key steps of the study projects and timing of the sending of the questionnaires. **B** Reported adverse drug reactions (ADRs) coding system. *LIM* Lareb Intensive Monitoring, *RO* ResearchOnline

and warmth) and systemic events (arthralgia, chills, fatigue, headache, malaise, myalgia, nausea, and fever); in addition, unsolicited events could also be reported by the vaccinee or their parents as uncoded free text. Serious reported events were validated by dedicated and pharmacovigilance-trained personnel who coded all the information provided by the vaccinees. The qualified personnel could also contact the vaccinees if the collected data were inconsistent or lacked essential information. These serious vaccinee-reported ADRs were classified as serious based on the Council for International Organizations of Medical Sciences (CIOMS) criteria [12].

The LIM/RO questionnaires were converted into individual case safety reports (ICSRs) in R3 format. Each country working with a National Competent Authority (NCA) transferred them to its national reporting database. Finally, the ICSRs were sent to the EudraVigilance database. Invalid and incomplete questionnaires were excluded from the analysis. Vaccinees who received Vaxzevria (previously COVID-19 Vaccine AstraZeneca) (3 of 1033 vaccinees) or for whom the vaccine brand was unknown (20 of 1033 vaccinees) were also excluded from our results.

2.2 Randomised Clinical Trials (RCTs)

The information on the safety of COVID-19 vaccines from three previously published RCTs was reported herein.

These studies are: (a) Walter et al in 2022 [1], a Phase 2–3 Randomised Trial in 2268 children aged 5–11 years (1518 received Comirnaty, and 750 received placebo), (b) Frenck et al in 2021 [2], a multinational, placebo-controlled, observer-blinded trial among 2260 adolescents aged 12–15 years (1131 received Comirnaty, and 1129 received placebo) and (c) Ali et al in 2021 [3], a Phase 2–3, placebo-controlled trial in 3726 children aged 12–17 years (2486 received Spikevax vaccine and 1240 received placebo). In these trials, participants recorded solicited local (e.g., redness and injection-site pain) and systemic ADRs (e.g., fever, fatigue, headache, and vomiting) daily for 7 days after each dose. The trial performed by Walter et al also collected data on unsolicited adverse events, including confirmed diagnoses of myocarditis or pericarditis from the first dose through 1 month after the second dose.

2.3 Spontaneous Reporting System

Individual case safety reports of suspected adverse events following COVID-19 vaccine immunisation were retrieved from EudraVigilance up to May 7, 2022 [13]. EudraVigilance is the international spontaneous reporting database maintained by the European Medicines Agency. Individual case safety reports following COVID-19 vaccines for the paediatric population (aged 0–17 years) were selected. As age groups in the EudraVigilance are reported as predefined categories, we could only analyse the age groups 3–11 years and 12–17 years, separately. We found that preferred terms (PTs) related to the local and systemic ADRs were most frequently reported in pivotal trials [1–3], including injection-site reactions, fever, fatigue, headache, chills, malaise, muscle pain, and joint pain (Online Resource 1). We used

the PTs from the Economic European Area (EEA) following the Medical Dictionary for Regulatory Activities (MedDRA) [14].

2.4 Data Analysis

We described the baseline characteristics of the CVM study cohort. We estimated the frequency of local/systemic and serious ADRs following COVID-19 vaccination (first and second doses), self-reported by the vaccinees (or their parents), dividing the number of persons with a reported ADR by the total number of enrolled vaccinees with at least one follow-up questionnaire. The frequencies of solicited local and systemic events in published pivotal RCTs of COVID-19 vaccines in children and adolescents were extracted and reported. We also calculated the reporting rate of ADRs collected in the EudraVigilance database by considering the ICSRs from the EEA as the numerator and the total number of administered doses of Comirnaty and Spikevax in subjects aged <18 years (updated to the first week of May 2022) as the denominator [9]. Data were stratified by age categories (5–11 and 12–17 years), COVID-19 vaccine brands, and ADR seriousness.

Table 1 Baseline characteristics in the cohort study according to the questionnaires filled by vaccinees (or their parents)

	5–11 years		12–17 years		Total
	Comirnaty	Spikevax	Comirnaty	Spikevax	
Baseline questionnaire, *n* (%)	340	–	556	19	1033
Baseline + follow-up questionnaire (%)[a]	250 (100)	–	395 (100)	13 (100)	658 (100)
Sex, *n* (%)					
Male	132 (52.8)		167 (42.3)	8 (61.5)	307 (46.7)
Female	118 (47.2)		228 (57.7)	5 (38.5)	351 (53.3)
Comorbidities, *n* (%)					
Yes[b]	55 (22.0)		156 (39.5)	4 (30.8)	215 (32.7)
No	195 (78)		239 (60.5)	9 (69.2)	443 (67.3)
Allergy	29 (11.6)		63 (15.9)	–	92 (14.0)
Cardiovascular disorders	–		–	–	–
Diabetes mellitus	–		1 (0.3)	–	1 (0.2)
Hypertension	–		–	–	–
Immunosuppression	1 (0.4)		4 (1.0)	–	5 (0.8)
Liver disorder	–		1 (0.3)	–	1 (0.2)
Lung disorder	12 (4.8)		22 (5.6)	1 (7.7)	35 (5.3)
Mental disorder	–		9 (2.3)	–	9 (1.4)
Neoplasm malignant	–		–	–	–
Nervous system disorder	1 (0.4)		6 (1.5)	–	7 (1.1)
Renal disorder	4 (1.6)		1 (0.3)	–	5 (0.8)
Other medical situations/disorders	10 (4.0)		35 (8.9)	2 (15.4)	47 (7.1)
Use of any medication, *n* (%)					
Yes	26 (10.4)		64 (16.2)	2 (15.4)	92 (14)
No	223 (89.2)		324 (82)	11 (84.6)	558 (84.8)
Unknown	1 (0.4)		7 (1.8)	0 (0)	8 (1.2)
Prior history of SARS-CoV-2 infection, *n* (%)					
Yes	35 (14.0)		57 (14.4)	1 (7.7)	93 (14.1)
No	215 (86)		334 (84.6)	12 (92.3)	561 (85.3)
Unknown	0 (0)		4 (1.0)	0 (0)	4 (0.6)

Vaccinees with the baseline and at least one follow-up questionnaire completed were included in the analysis. For the characterisation of these vaccinees, percentages (%) were calculated over the number of vaccinees who filled the baseline questionnaire and at least one follow-up questionnaire by column

Q questionnaire

[a]Depicted as the denominators

[b]Vaccinees can report more than one comorbidity or cannot specify the type of comorbidity

3 Results

The CVM study included 915 vaccinees aged between 5 and 17 years who received the first vaccination cycle and completed the baseline questionnaire within 48 hours of the vaccine administration (Table 1). Of these vaccinees, 658 (63.7%) completed at least one follow-up questionnaire and were included in the analysis. We reported 250 (38.0%) and 408 (62.0%) vaccinees in the age groups 5–11 and 12–17 years, respectively. Almost all of them received Comirnaty (98.0%). No substantial differences in gender distribution across age groups were observed. Almost 22% of vaccinees aged 5–11 years and 40% of those aged 12–17 years with Comirnaty had at least one comorbidity with allergy as the most common comorbidity reported in both age groups (12% and 16%), respectively. In both age groups, almost 14% of the vaccinees reported a prior history of diagnosed SARS-CoV-2 infection before vaccination.

As shown in Table 2, overall (n = 658), 45% of vaccinees reported at least one ADR *after the first dose* of Comirnaty, with a higher frequency in vaccinees aged 12–17 years (54.2%; 95% CI 49.2–59.0) when compared to vaccinees aged 5–11 years (28.8%; 95% CI 23.5–34.7). Among the solicited local ADRs, injection-site pain was the most frequently reported event in children (23.2%; 95% CI 18.4–28.8) and adolescents (32.7%; 95% CI 28.2–37.4). Fatigue (6.8% and 22.3%) and headache (6.8% and 16.7%) were the most frequently reported systemic ADRs in children and adolescents, respectively. Only one vaccinee in the 12- to 17-year age group reported an ADR (i.e., paraesthesia

Table 2 Reported ADRs following the first (n = 658) and the second (n = 357) doses of COVID-19 vaccines in the cohort study

	5–11 years		12–17 years				Total	
	Comirnaty		Comirnaty		Spikevax			
	First dose	Second dose	First dose	Second dose	First dose	Second dose	First dose	Second dose
Vaccinees included in the analysis who received the first and the second doses of the COVID-19 vaccine	250 (100)	123 (100)	395 (100)	226 (100)	13 (100)	8 (100)	658 (100)	357 (100)
At least one ADR, *n* (%)	72 (28.8)	21 (17.1)	214 (54.2)	118 (52.2)	7 (53.8)	3 (37.5)	293 (44.5)	142 (39.8)
Solicited ADRs								
Local ADRs, *n* (%)								
Injection-site erythema	4 (1.6)	0 (0.0)	9 (2.3)	6 (2.7)	2 (15.4)	1 (12.5)	15 (2.3)	7 (2.0)
Injection-site haematoma	0 (0.0)	0 (0.0)	7 (1.8)	1 (0.4)	0 (0.0)	0 (0.0)	7 (1.1)	1 (0.3)
Injection-site induration	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (7.7)	0 (0.0)	2 (0.3)	0 (0.0)
Injection-site inflammation	3 (1.2)	1 (0.8)	24 (6.1)	15 (6.6)	2 (15.4)	4 (50.0)	29 (4.4)	20 (5.6)
Injection-site pain	58 (23.2)	12 (9.8)	129 (32.7)	58 (25.7)	5 (38.5)	4 (50.0)	192 (29.2)	74 (20.7)
Injection-site pruritus	0 (0.0)	0 (0.0)	8 (2.0)	2 (0.9)	0 (0.0)	1 (12.5)	8 (1.2)	3 (0.8)
Injection-site swelling	3 (1.2)	1 (0.8)	30 (7.6)	14 (6.2)	1 (7.7)	3 (37.5)	34 (5.2)	18 (5.0)
Injection-site warmth	1 (0.4)	0 (0.0)	12 (3.0)	12 (5.3)	2 (15.4)	3 (37.5)	15 (2.3)	15 (4.2)
Systemic ADRs, *n* (%)								
Arthralgia	3 (1.2)	1 (0.8)	20 (5.1)	21 (9.3)	0 (0.0)	0 (0.0)	23 (3.5)	22 (6.2)
Chills	3 (1.2)	1 (0.8)	21 (5.3)	26 (11.5)	0 (0.0)	0 (0.0)	24 (3.6)	27 (7.6)
Fatigue	17 (6.8)	8 (6.5)	88 (22.3)	70 (31.0)	1 (7.7)	1 (12.5)	106 (16.1)	79 (22.1)
Headache	17 (6.8)	5 (4.1)	66 (16.7)	63 (27.9)	1 (7.7)	1 (12.5)	84 (12.8)	69 (19.3)
Malaise	9 (3.6)	1 (0.8)	52 (13.2)	47 (20.8)	1 (7.7)	1 (12.5)	62 (9.4)	49 (13.7)
Myalgia	5 (2.0)	1 (0.8)	81 (20.5)	48 (21.2)	4 (30.8)	0 (0.0)	90 (13.7)	49 (13.7)
Nausea	5 (2.0)	2 (1.6)	31 (7.8)	24 (10.6)	0 (0.0)	0 (0.0)	36 (5.5)	26 (7.3)
Body temperature increased	5 (2.0)	3 (2.4)	6 (1.5)	11 (4.9)	2 (15.4)	3 (37.5)	13 (2.0)	17 (4.8)
Pyrexia	2 (0.8)	3 (2.4)	20 (5.1)	16 (7.1)	0 (0.0)	2 (25)	22 (3.3)	21 (5.9)
Hyperpyrexia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
At least one serious ADR, *n* (%)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.3)
At least one unsolicited ADR	10 (4.0)	3 (2.4)	40 (10.1)	20 (8.8)	4 (30.8)	–	54 (8.2)	23 (6.4)

Percentages were calculated based on the total number of vaccinees who filled the baseline questionnaire and at least one follow-up questionnaire and received the first dose of vaccine (N = 658) or the second dose of COVID-19 vaccine (n = 357)

ADR adverse drug reaction

and swelling face) that was classified as serious by PV-trained assessors.

As shown in Table 2, overall ($n = 357$), 40% of vaccinees reported at least one ADR *after the second dose* of Comirnaty; injection-site pain, fatigue, and headache were the most frequently reported local and systemic ADRs, respectively. Only one vaccinee (0.4%; 95% CI 0.1–2.5) in the 12- to 17-year age group reported haematochezia, assessed as a serious ADR.

The previous RCT [1] in children aged 5–11 years reported injection-site pain as the most common local ADR, occurring in 74% (first dose) and 71% (second dose) of the Comirnaty vaccine administration cases (Table 3). Fatigue (34% and 39%) and headache (22% and 28%) were the most frequently reported systemic ADRs after the first and second doses, respectively. Among adolescents, both trials showed similar results, with injection-site pain (86% and 99%), fatigue (60% and 49%), and headache (55% and 47%) as the most frequent local and systemic ADRs after the first dose of Comirnaty (Frenck et al Trial [2]) and after the first dose of Spikevax (Ali et al Trial [3]), respectively. Those ADR percentages were even higher when reported after the second dose of Comirnaty and Spikevax.

With regard to the EudraVigilance spontaneous reporting database analyses, 2895 and 17,890 ICSRs concerning vaccinees aged 3–11 and 12–17 years, respectively, were retrieved (Table 4). Identifying the pre-selected ADRs showed that injection-site pain was the most frequently reported local adverse event in children and adolescents (14.6% and 6.6%), with a reporting rate (RR) of 4.7 per 100,000 COVID-19 vaccine-administered doses. As for systemic adverse events, headache (17.3% and 20.2%; RR, 12.0/100,000) and fever (17.3% and 16.6%; RR, 10 dot 1/100,000) were most frequently reported in children and adolescents.

4 Discussion

The herein-presented study shows the results of the CVM study for the cohort event monitoring in vaccinated children and adolescents against COVID-19 and the reporting rates of ADRs retrieved from the EudraVigilance platform for the same paediatric population. Overall, we observed that injection-site pain, fatigue, and headache were the most frequently reported ADRs after the first and second doses of COVID-19 vaccines. Mild to moderate ADRs were common, whereas serious ADRs were uncommon. Generally, higher frequencies of ADRs were reported by vaccinees after receiving the first dose rather than the second dose and in vaccinees aged 12–17 years rather than those aged 5–11 years. We also observed that the local and systemic ADR rates were higher in the pivotal clinical trials than those reported through the CVM and Eudravigilance. This difference may be due to a more systematic follow-up during the trials. However, overall, the rates of the local and systemic reactions after vaccination reported in Eudravigilance were much lower (factor 1000) than for other reported studies.

Even though SARS-CoV-2 infection typically causes less severe illness in paediatrics compared to adults, children and adolescents remain susceptible to transmitting the virus to others, with an increased risk of more severe infection and transmission rate increasing with age [15]. Reported evidence on COVID-19 vaccine safety, including this study, prove their favourable risk profile with no serious ADRs after vaccination, suggesting that COVID-19 vaccines are effectively safe in children and adolescents.

Injection-site pain in the deltoid muscle often occurs in COVID-19 vaccinees within a few hours of injection. Injection-site pain may be related to the extravasation of protein-rich fluid and the produced antigens to the damaged site [16]. The systemic reactions to COVID-19 vaccines, including fatigue and headache, are commonly reported in cohort event monitoring, trials, and spontaneous reports in adults, children and adolescents. Understanding the molecular underpinnings of adverse events following immunisation with COVID-19 vaccines is essential to understanding whether reactogenicity may be decreased while effectiveness is maintained.

Our study has some limitations that should be acknowledged. Most vaccinated adolescents received the Comirnaty vaccine, the first approved vaccine for 12- to 17-year-olds in Europe. Although the Spikevax vaccine has also been authorised in adolescents aged ≥ 12 years, the number of this subset of vaccinees was considerably low. In addition, of the total number of the recruited vaccinees belonging to the paediatric population, only two-thirds filled out at least one of the follow-up questionnaires (responders). We studied the characteristics of one-third of the total vaccinees recruited through the LIM who were excluded due to loss of follow-up (non-responders) compared to the responders. We showed no significant differences between the two groups concerning sex and age distribution at recruitment. We cannot exclude that there was a selective loss to follow-up with those vaccinees who did not fill in the questionnaires since we may expect vaccinees not to fill out the follow-up questionnaires due to severe adverse events, especially in case of hospitalisation. Furthermore, this study is based on the parents' reporting outcomes and follow-up on behalf of the paediatric subject. The assessment of pharmacovigilance specialist personnel was applied only in cases of reported serious events. Unfortunately, we could not recruit more vaccinees, which may result in representing a small sample size prone to less common but severe ADRs being undetected. In general, implementing the goal of the European vaccination campaign was unsuccessful in the paediatric population

Table 3 Characteristics of children and adolescents included in pivotal clinical trials and frequency of ADRs with the first and second doses of COVID-19 vaccines

	Walter et al (5–11 years)		Frenck et al (12-15 years)		Ali et al (12–17 years)	
	Comirnaty	Placebo	Comirnaty	Placebo	Spikevax	Placebo
	N = 1518	*N* = 750	*N* = 1131	*N* = 1129	*N* = 2486	*N* = 1240
Sex						
Male, *n* (%)	799 (52.6)	383 (51.1)	567 (50.1)	585 (51.8)	1283 (52)	632 (51)
Age, years						
Mean ± SD	8.2 ± 1.93	8.1 ± 1.97	13.6 ± 1.11	13.6 ± 1.11	14.3 ± 1.6	14.2 ± 1.6
Median (range)	8.0 (5–11)	8.0 (5–11)	14 (12–15)	14 (12–15)		
Race (*n*, %)						
White	1204 (79.3)	586 (78.1)	971 (85.9)	962 (85.2)	2085 (84)	1041 (84)
Black	89 (5.9)	58 (7.7)	52 (4.6)	57 (5.0)	83 (3)	42 (3)
American Indian/Alaskan Native			4 (0.4)	3 (0.3)	12 (<1)	7 (1)
Asian	90 (5.9)	47 (6.3)	72 (6.4)	71 (6.3)	142 (6)	79 (6)
Native Hawaiian/Pacific Islanders			3 (0.3)	0	2 (<1)	0
Multiracial	109 (7.2)	49 (6.5)	23 (2.0)	29 (2.6)	118 (5)	50 (4)
Not reported	26 (1.7)	10 (1.3)	6 (0.5)	7 (0.6)	17 (<1)	12 (<1)
Hispanic/Latinx						
Yes	319 (21)	159 (21.2)	132 (11.7)	130 (11.5)	280 (11)	152 (12)
No			997 (88.2)	996 (88.2)	2188 (88)	1076 (87)
Not reported			2 (0.2)	3 (0.3)	18 (1)	12 (1)
Country						
USA	1073 (70.7)	531 (70.8)	1131 (100)	1129 (100)	2486 (100)	1240 (100)
Finland	158 (10.8)	81 (10.4)				
Spain	162 (10.7)	78 (10.4)				
Poland	125 (8.2)	60 (8)				
Baseline SARS-CoV-2 status						
Positive	133 (8.8)	65 (8.7)	46 (4.1)	47 (4.2)	147 (6)	69 (6)
Negative	1385 (91.2)	685 (91.3)	1028 (90.9)	1023 (90.6)	2167 (87)	1075 (87)
Unknown	0	0	57 (5)	59 (5.2)	172 (7)	96 (8)
Obese, *n* (%)	174 (11.5)	92 (12.3)	–	–	170 (7)	94 (8)
Coexisting conditions*, *n* (%)	312 (20.6)	152 (20.3)	–	–	–	–
Safety analysis						
Local reactions						
Dose 1						
Redness (%)	15	6	6	1	14.3	0.6
Swelling (%)	10	3	7	1	17.3	1
Injection-site pain (%)	74	31	86	23	98.5	34.9
Dose 2						
Redness (%)	19	5	5	1	22.4	0.9
Swelling (%)	15	3	5	1	22.5	1
Injection-site pain (%)	71	29	79	18	97.5	30.5
Systemic reactions						
Dose 1						
Fever (%)	3	1	10	1	2.9	1.1
Fatigue (%)	34	31	60	41	49.2	38.1
Headache (%)	22	24	55	35	46.9	39.9
Chills (%)	5	5	28	10	18.6	11.2
Vomiting (%)	2	1	3	1	11.4	8.9
Diarrhoea (%)	6	4	8	7	–	–

Table 3 (continued)

	Walter et al (5–11 years)		Frenck et al (12-15 years)		Ali et al (12–17 years)	
	Comirnaty	Placebo	Comirnaty	Placebo	Spikevax	Placebo
	N = 1518	*N* = 750	*N* = 1131	*N* = 1129	*N* = 2486	*N* = 1240
Muscle pain (%)	9	7	24	13	27.9	17.4
Joint pain (%)	3	5	10	7	15.6	12
Dose 2						
Fever (%)	7	1	20	1	14.2	1.2
Fatigue (%)	39	24	66	25	74.5	29.7
Headache (%)	28	19	65	24	74.9	31.4
Chills (%)	10	4	42	7	43	8
Vomiting (%)	2	1	3	1	23.9	8.7
Diarrhoea (%)	5	5	6	4	–	–
Muscle pain (%)	12	7	32	8	51.8	12.7
Joint pain (%)	5	4	16	5	31.2	9.5

ADR adverse drug reaction

*Coexisting conditions included obesity, chronic lung disease, asthma, prematurity, feeding tube dependent, blood disorders, sickle cell disease, immunocompromised condition, neurologic disorders, congenital heart disease, chronic metabolic disorders, diabetes, and cardiovascular disease

Table 4 Number of ICSRs retrieved from EudraVigilance regarding local and systemic reactions by age group and COVID-19 vaccine brand

	Comirnaty			Spikevax		
	3–11 years	12–17 years	Reporting rate in the paediatric population per 100,000 doses administered	3–11 years	12–17 years	Reporting rate in the paediatric population per 100,000 doses administered
Total *n* ICSRs (%)	2895 (100)	17,890 (100)	60.6	42 (100)	1549 (100)	79.9
Local adverse reactions, *n* (%)						
Redness	36 (1.2)	182 (1.0)	0.6	3 (7.1)	23 (1.5)	1.3
Warmth	2 (0.1)	108 (0.6)	0.3	3 (7.1)	5 (0.3)	0.4
Injection-site pain	423 (14.6)	1174 (6.6)	4.7	8 (19)	48 (3.1)	2.8
Itch	2 (0.1)	33 (0.2)	0.1	1 (2.4)	3 (0.2)	0.2
Haematoma	3 (0.1)	44 (0.2)	0.1	0 (0.0)	2 (0.1)	0.1
Swelling	23 (0.8)	252 (1.4)	0.8	3 (7.1)	6 (0.4)	0.5
Systemic adverse reactions, *n* (%)						
Chills	91 (3.1)	1240 (6.9)	3.9	5 (11.9)	60 (3.9)	3.3
Fatigue	303 (10.5)	2382 (13.3)	7.8	6 (14.3)	136 (8.8)	7.1
Fever	502 (17.3)	2974 (16.6)	10.1	5 (11.9)	466 (30.1)	23.7
Headache	500 (17.3)	3607 (20.2)	12.0	7 (16.7)	330 (21.3)	16.9
Joint pain	65 (2.2)	545 (3.0)	1.8	2 (4.8)	48 (3.1)	2.5
Malaise	136 (4.7)	1794 (10)	5.6	2 (4.8)	94 (6.1)	4.8
Muscle pain	86 (3.0)	1365 (7.6)	4.2	6 (14.3)	87 (5.6)	4.7
Serious ADRs, *n* (%)						
Yes	557 (19.2)	5442 (30.4)	–	6 (14.3)	379	–
No	2338 (80.8)	12,448 (69.6)	–	36 (85.7)	1170	–
Not available	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–

(i) All the percentages are calculated based on the total number of ICSRs by age category. (ii) To calculate the reporting rate, the total number of doses administered of Comirnaty (*N* = 34,310,333) and Spikevax (*N* = 1990,861) vaccines in the population < 18, used as the denominator to calculate the Reporting Rate is available at https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab (updated to May 5, 2022). iii) Data from EudraVigilance were updated up to May 7, 2022

ADRs adverse drug reactions, *ICSR* Individual Case Safety Report

[17], where the goal was to rapidly raise the population's immunity. In some countries, the CVM study started when the vaccination campaign was already in an advanced stage. In addition, a 6-month follow-up is not yet available for most vaccinees. All the information collected in CVM is transferred to EudraVigilance, so ICSRs retrieved from EudraVigilance may include reports from CVM.

5 Conclusion

This study's results support the favourable risk profile of COVID-19 vaccines for the paediatric population [18], as previously documented in pivotal clinical trials, showing a high frequency of local adverse events and almost no serious adverse events. We observed a higher frequency of mild adverse events reported by a) vaccinees following the first dose administration compared to the second dose and b) in vaccinees aged 12–17 years than in those aged 5–11 years. European Medicines Agency invested much effort and funding to build infrastructure to rapidly investigate the post-marketing benefit-risk profile of COVID-19 vaccines under conditional authorisation. In the future, we can benefit from these structured, organised, and validated data collection systems beyond the COVID-19 pandemic emergency, as they can easily be adapted for other specific needs.

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Conflict of interest Miriam Sturkenboom is head of a department that conducts studies for regulatory agencies and pharmaceutical companies, with research grants to the institution; this includes Pfizer, Janssen and AstraZeneca. All studies are conducted using the ENCePP code of conduct. Gianluca Trifirò has served in the last three years on advisory boards/seminars funded by SANOFI, Eli Lilly, AstraZeneca, Abbvie, Servier, Mylan, Gilead, Amgen; he was the scientific director of a Master's program on pharmacovigilance, pharmacoepidemiology and real-world evidence which has received a non-conditional grant from various pharmaceutical companies; he coordinated a pharmacoepidemiology team at the University of Messina until October 2020, which has received funding for conducting observational studies from various pharmaceutical companies (Boehringer Ingelheim, Daichii Sankyo, PTC Pharmaceuticals). He is also the scientific coordinator of the academic spin-off "INSPIRE srl" which has received funding for conducting observational studies from contract research organizations (RTI Health Solutions, Pharmo Institute N.V.). None of these listed activities is related to the topic of the manuscript. Fariba Ahmadizar is the principal investigator of a Janssen COVID-19 vaccine safety study. None of the other authors has any conflicts of interest that are directly relevant to the content of this article.

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