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RESEARCH ARTICLE

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Safety of mRNA BNT162b2 COVID-19 (Pfizer-BioNtech) vaccine in children aged 5–11 years: Results from an active pharmacovigilance study in central Italy

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ABSTRACT

This survey investigated on adverse events after vaccination with mRNA BNT162b2 (Comirnaty, Pfizer-BioNTech) vaccine in children aged 5–11 years in central Italy through active surveillance reporting. During December 2021–January 2022, parents of children who undergone vaccination were interviewed using a structured questionnaire. 197 out of 208 contacted parents participated (94.7% response rate), of whom 166 (84.3%) had one child. Of the 229 children, the mean age was 8.9 years, 50.7% were female. 193 (84.3%) had at least one adverse event after the first dose (mean age 9.1 years; 54.4% female), and 146 (73.4%) of 199 after the second (mean age 8.9 years; 54.8% female), which was not administered to 30 children due to previous COVID-19 history. Local symptoms after the first and second dose occurred in 183 (94.8%) and 141 (96.6%) recipients (p = .435), respectively, while systemic reactions in 62 (32.1%) and 34 (23.3%) (p = .074). Mild events were reported by 81.7% and 69.8% children after the first and second dose, followed by moderate (3.9% and 10.6%) and severe (1.3% and 0.5%). After each dose, injection site reactions (79.5% and 68.8%) were the most frequent, followed by headache (13.1%) and lymphadenopathy (8.5%) after the first and second dose, respectively. The adverse events were reported to pediatricians only for 5.7% and 3.9% of children and treated for 17.6% and 15.8%. This is the first report about safety profile through active surveillance of mRNA BNT162b2 among children in Italy, revealing temporary and mild-to-moderate symptoms with no serious events after each vaccine dose.

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Introduction

Routine childhood immunizations are proven to be one of the most effective public health interventions for control of serious consequences of various infectious diseases,[1] including COVID-19. In this context, vaccinating children has benefits either directly preventing severe pediatric COVID-19 cases and post-infectious conditions, or indirectly by protecting others by reducing spread.[2,3] On 29 October 2021, the US Food and Drug Administration (FDA) authorized the mRNA BNT162b2 COVID-19 vaccine (known as Comirnaty, Pfizer-BioNTech) for emergency use in children aged 5 to 11 years of age, which was found to be 90.7% effective in preventing COVID-19, and with a favorable safety profile as no serious side effects were detected.[4] On 25 November 2021, the European Medicines Agency (EMA)'s human medicines committee has recommended an extension of indication for Comirnaty to include use in children aged 5 to 11 years,[5] which showed a positive safety profile and was similar to that in people aged 12 and above in the phase 1 study,[6] and as demonstrated in other age groups[7] apart from its effectiveness.[8] On 1 December 2021, the Italian Medicines Agency further approved the indication of use of Comirnaty vaccine with two doses cycle for the age group of 5–11 years,[9] and vaccination officially started on 16 December 2021.

This active cross-sectional surveillance survey was carried out in central Italy to investigate the safety profile of Comirnaty vaccine among children of 5–11 years through two doses. In addition, to provide essential data to reassure parents of the safety of the vaccine, the study also evaluated the reasons that triggered parents in choosing vaccines, as well as any association between the occurrence of adverse events and both individual and clinical factors of recipients.

Methods

For this study, approval by an ethic committee was not requested as no experimental procedure was applied, and the information were retrospectively provided by participants after signing and providing an informed consent. Furthermore, all data presented were de-identified, coded, and were analyzed anonymously in accordance with ethics guidelines and adhering to Declaration of Helsinki.

During December 2021 and January 2022, parents of children aged 5 to 11 years who went at the hospital vaccinal center in the Molise Region, central Italy, for vaccinating were contacted and asked to sign an informed consent for our study. Between 7 and 10 days after the receipt of both the first and second dose, parents were contacted via telephone by trained interviewers. A structured questionnaire, tested in a pilot study for its validation (data not shown), was administered. Questions referred to children and parental sociodemographic data, as well as information on children preexisting

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diseases and treatment, influenza vaccination, and previous COVID-19 history. The core questions were related to COVID-19 vaccination course, and occurrence, resolution and reporting of any adverse event following each dose. The side reactions after the first and second dose of Comirnaty vaccine were categorized as previously reported.[7,10] Local symptoms included injection site pain, redness, or swelling, lymphadenopathy, and pain in a limb other than that of injection, and systemic reactions were tiredness/asthenia, muscle/joint pain, paresthesia, headache, fever, chills, diarrhea, nausea, vomiting, insomnia, restless, decreased appetite, and rash. In addition, the events were stratified as mild (injection site pain, redness, or swelling, tiredness/asthenia, headache, chills, nausea, insomnia, restlessness, decreased appetite, abdominal pain, and fever <38°C); moderate (lymphadenopathy, muscle/joint pain, localized rash, vomiting, diarrhea, pain in a limb other than that injected, and fever ≥38 and <39°C); or severe (paresthesia, fever ≥39°C, clustered rash).[7,10] Data were anonymously collected and analyzed calculating the relative frequencies of any post-immunization reaction reported by parents. A univariate analysis tested the relationship between at least one adverse events and relevant variables using IBM Statistical Package for Social Science (SPSS) version 28.0 by applying Chi-square or Fisher's Exact tests, at a 0.05 level of significance.

Results

Baseline characteristics of the children enrolled in this study

During December 2021–January 2022, consent to participate was obtained from 208 parents; however, 11 (5.3%) could not be re-contacted and were excluded from data analysis. For the remaining 197 interviewed parents (94.7% response rate), 166 (84.3%) had only one child, and 31 (15.7%) two or more children. Hence, the study included 229 children recipients, with mean age of 8.9 years (standard deviation: 1.8; median: 9, mode: 11), of whom 28.4% (n = 65) aged 11 years old and 50.7% (n = 116) were female. 99% (n = 227) of the children enrolled had undergone the nationally recommended vaccinations, and 43 (18.9%) received other vaccinations in the previous 6 months, largely against seasonal influenza. Of the 229 children, 15 (6.6%) suffered from preexisting pathologies. Fifty-two (22.7%) children suffered from allergies. In the two weeks preceding COVID-19 vaccination, 33 (14.4%) had health problems, including rhinitis (n = 17, 51.5%), and nasal congestion, pain in the pharynx, tonsillitis, and fever (n = 2 each, 6.1%). Before receiving Comirnaty vaccination, 13 children were diagnosed with COVID-19 based on positive results to molecular testing: six during April 2021, four during February 2021, and one each during November 2020, January 2021, and March 2021.

Parent information

Data on education level were obtained for 195 out of 197 parents participating in the study. Maternal education was of degree/postgraduation as reported by 108 (55.5%), followed by secondary school level (n = 59, 30.2%) and primary or low secondary diploma (n = 28, 14.3%). Paternal education was of secondary school diploma (n = 93, 47.7%), followed by degree/postgraduation level (n = 63, 32.3%), and 39 (20.0%) completed primary and lower secondary school.

Information about working activities was collected for 192 parents. Data on maternal professional activity underlined intellectual, scientific, and highly specialized professions (n = 55, 28.6%), followed by executive office professions (n = 48, 25.0%), and students or unemployed (n = 45, 23.4%). The remainder were farmers, plant operators, workers of fixed and mobile machinery, vehicle drivers and unskilled professions (n = 17, 8.9%); law enforcement and qualified professions in commercial activities and services (n = 14, 7.3%); legislators, entrepreneurs, and senior management (n = 9, 4.7%); or employed in technical professions (n = 4, 2.1%).

Regarding paternal professional activity, the most common was executive office professions (n = 55, 28.6%), followed by artisans, farmers, plant operators, workers of fixed and mobile machinery, vehicle drivers and unskilled professions (n = 48, 25.0%); intellectual, scientific and highly specialized professions (n = 30, 15.6%); law enforcement and qualified professions in commercial activities and services (n = 20, 10.4%); legislators, entrepreneurs or belong to senior management (n = 19, 9.9%); technical professions (n = 15, 7.9%); and students or unemployed (n = 5, 2.6%).

The reasons for the 197 enrolled parents agreeing with anti-COVID vaccination for their children was for preventing disease (n = 137, 69.5%), for public health protection (n = 26, 13.2%), and for both motivations (n = 8, 4.1%). Additional reasons were described although were reported in only 1.5%, and included advice by pediatricians and achievement of Green Pass certification.

First dose and adverse events

Ninety percent (n = 206) of the 229 vaccine recipients received the first dose of Comirnaty on 19 December 2021, and the remaining on 2 January 2022. Only six (2.6%) children received medication before the first dose, mainly (83.4%) self-prescribed, and included paracetamol (50.0%), and non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and antihistamines (16.7% each). No side reactions following the first dose was reported by parents for 36 (15.7%) of the children, thus, 193 (84.3%) had at least one adverse event: among these (mean age 9.1 years, median 9, mode 11), 105 (54.4%) were female. For 136 (70.5%) children, a single adverse event was reported, while two were described by 35 and three by 16 children (18.1% and 8.3%, respectively; mean: 1.2 ± 1, median: 1). Local events occurred among 183 (94.8%) of the 193 children, with one reaction for almost all of them (99.4%), while systemic symptoms were reported for 62 (32.1%) children and were more often one (64.5%) or two (30.6%).

Among 229 children, the most frequent reactions following the first dose of Comirnaty were pain, redness, or swelling at injection site (79.5%), headache (13.1%), and tiredness/asthenia (12.2%); other events were reported at lesser extent (Table 1). For one child (0.4%), glycemia increase was reported. Among children who had at least one event, mild reactions accounted for 96.9% (n = 187), while moderate and severe events for 4.7% (n = 9) and 1.6% (n = 3), respectively. Reactions most appeared after 4–12 h (Table 2a) from the

first dose and generally resolved within 12–24 h and within 24–48 h (Table 2b). Significant differences by gender after the receipt of the first dose were observed for the occurrence of at least one mild event, injection site reactions, and decreased appetite (Table 1).

Treatment for symptoms after the first dose was administered for 34 (17.6%) out of the 193 children who had at least one adverse reaction, and were self-prescribed (n = 28, 73.5%), while only for 11.8% (n = 4) and 5.9% (n = 2) were prescribed by medical doctors and personnel of the vaccinal center, respectively. Drug treatments included paracetamol (n = 30, 88.2%), and NSAIDs, glucocorticoids, food supplements, antihistamines (n = 1 each, 2.9%). Adverse reactions following the first dose were reported to pediatricians only for 11 children. The day after the dose, 50 (21.8%) of children did not go to school, mainly as a precaution (54.0%) or due to symptom onset (24.0%).

Second dose and adverse events

The second dose was received by 199 (86.9%) children, 168 (84.4%) on 9 January 2022.

Among the children who did not receive the second dose, 9 (30.0%) and 18 (60.0%) had COVID-19 before or after the first dose, respectively, while 2 (6.7%) were in quarantine/isolation, and one (3.3%) due to parental choice. Amongst the 18 children who acquired COVID-19, eight were diagnosed one day after the first dose, three each after 14 and 19 days, and two each after 20 and 24 days. COVID-related symptoms were fever (n = 11), pharyngeal pain (n = 4), cold/rhinorrhea (n = 3), headache (n = 3), gastroenteric disorders (n = 2), and asthenia (n = 1).

Only four (2.0%) children had received medication before the second dose, all were self-prescribed, and 3 were treated with paracetamol and one with glucocorticoids.

No side events occurred among 53 (26.6%) children following the second dose, thus, 146 (73.4%) children had at least one adverse reaction. Among the children with symptoms, the mean age was 8.9 years (median 9, mode 11), 80 (54.8%) were female and 107 (73.3%) had one symptom, and 30 (20.5%) two events, with reactions ranging from one to five (mean: 0.98 ± 0.83, median: 1). Local events occurred among 141 (96.6%) of the 146 children, with one reaction for almost all of them (90.8%), while systemic symptoms were reported for 34 (23.3%) children and were more often related to one reaction (85.3%).

Among 199 children who had received the second vaccine dose, the most frequent adverse events were pain, redness, or swelling at the injection site (68.8%), lymphadenopathy (8.5%), headache (8.0%), tiredness/asthenia (4.5%), fever (2.5%), and chills (2.0%); other events were reported less often (Table 1). Among the children who had at least one adverse event (n = 146), mild reactions accounted for 95.2% (n = 139), while moderate and severe events for 14.4% (n = 21) and 0.7% (n = 1), respectively.

Side reactions largely appeared after 4–12 h (Table 3a) from the receipt of the second dose and lasted 12–24 h later (Table 3b). Significant differences by gender were observed for injection site reactions and tiredness/asthenia (Table 1). Treatment for symptoms was carried out for 23 (15.8%) out of 146 children who had at least one adverse reaction and were mainly self-prescribed (n = 20, 86.9%). Drugs included paracetamol (n = 20, 86.9%), and NSAIDs, glucocorticoids (n = 2, 8.7%), and antibiotics (n = 1, 4.3%). Adverse reactions following the second dose were reported to pediatricians only for 4

Table 1. Adverse events among children following the receipt of each dose stratified by sex.

	First dose (N=229)				Second dose (N=199)				Reactions after I *vs* II dose
	Total n (%)	Female (N=116) n (%)	Male (N=113) n (%)	*p*-value	Total n (%)	Female (N=97) n (%)	Male (N=102) n (%)	*p*-value	*p*-value
At least one mild reaction	187 (81.7)	102 (87.9)	85 (75.2)	**.013**	139 (69.8)	77 (79.4)	62 (60.8)	**.042**	**.004**
Injection site pain/ redness/swelling	182 (79.5)	101 (87.1)	81 (71.7)	**.004**	137 (68.8)	75 (77.3)	62 (60.8)	**.012**	**.012**
Tiredness/Asthenia	28 (12.2)	15 (12.9)	13 (11.5)	.742	9 (4.5)	7 (7.2)	2 (2.0)	.074	**.005**
Headache	30 (13.1)	15 (12.9)	15 (13.3)	.939	16 (8.0)	8 (8.2)	8 (7.8)	.916	.092
Chills	3 (1.3)	3 (2.6)	0 (0)	.085	4 (2.0)	3 (3.1)	1 (1.0)	.289	.862
Nausea	3 (1.3)	3 (2.6)	0 (0)	.085	2 (1.0)	1 (1.0)	1 (1.0)	.974	.769
Abdominal pain	5 (2.2)	4 (3.4)	1 (0.9)	.184	0 (0)	0 (0)	0 (0)	not applicable	**.036**
Fever <38°C	5 (2.2)	4 (3.4)	1 (0.9)	.184	4 (2.0)	2 (2.1)	2 (2.0)	.956	.899
Insomnia/Restlessness	9 (3.9)	4 (3.4)	5 (4.4)	.693	1 (0.5)	0 (0)	1 (1.0)	.328	**.019**
Sleepiness	8 (3.5)	6 (5.2)	2 (1.8)	.165	1 (0.5)	1 (1.0)	0 (0)	.303	**.031**
Decreased appetite	4 (1.7)	4 (3.4)	0 (0)	**.046**	1 (0.5)	0 (0)	1 (1.0)	.328	.232
At least one moderate reaction	9 (3.9)	4 (3.4)	5 (4.4)	.140	21 (10.6)	9 (9.3)	12 (11.8)	.568	**<.001**
Muscle/Joint pain	4 (1.7)	3 (2.6)	1 (0.9)	.325	1 (0.5)	0 (0)	1 (1.0)	.328	.232
Lymphadenopathy	1 (0.4)	1 (0.9)	0 (0)	.322	17 (8.5)	9 (9.3)	8 (7.8)	.717	**<.001**
Diarrhea	2 (0.9)	1 (0.9)	1 (0.9)	>.999	1 (0.5)	0 (0)	1 (1.0)	.328	.646
Localized rash	2 (0.9)	0 (0)	2 (1.8)	.150	3 (1.5)	1 (1.0)	2 (2.0)	.590	.542
At least one severe reaction	3 (1.3)	3 (2.6)	0 (0)	.085	1 (0.5)	1 (1.0)	0 (0)	.303	.387
Fever ≥39°C	1 (0.4)	1 (0.9)	0 (0)	.322	1 (0.5)	1 (1.0)	0 (0)	.303	.920
Paresthesia	1 (0.4)	1 (0.9)	0 (0)	.322	0 (0)	0 (0)	0 (0)	not applicable	.351
Clustered rash	1 (0.4)	0 (0)	1 (0.9)	.310	0 (0)	0 (0)	0 (0)	not applicable	.351

Legend: *p*-value were calculated using Chi-square test.

Table 2. Description of (a) onset and (b) resolution of adverse reactions after the first dose.

a) Onset	<1 h N (%)	1-4 h N (%)	4-12 h N (%)	12-24 h N (%)	24-48 h N (%)	>48 h N (%)	Total N
Mild							
Injection site pain/redness/swelling	20 (11.0)	59 (32.4)	**80 (44.0)**	19 (10.4)	4 (2.2)		182
Tiredness/Asthenia		5 (17.8)	**12 (42.9)**	9 (32.1)	1 (3.6)	1 (3.6)	28
Headache	1 (3.3)	4 (13.3)	**16 (53.4)**	8 (26.7)		1 (3.3)	30
Chills			**2 (66.7)**			1 (33.3)	3
Nausea	1 (33.3)		**2 (66.7)**				3
Abdominal pain				**2 (40.0)**	**2 (40.0)**	1 (20.0)	5
Fever <38°C			2 (40.0)	**3 (60.0)**			5
Insomnia/Restlessness		2 (22.2)	**4 (44.5)**	3 (33.3)			9
Sleepiness			**6 (75.0)**	2 (25.0)			8
Decreased appetite			**3 (75.0)**		1 (25.0)		4
Moderate							
Muscle/Joint pain		**1 (25.0)**	**1 (25.0)**	**1 (25.0)**		**1 (25.0)**	4
Lymphadenopathy				**1 (100)**			1
Diarrhea				**1 (50.0)**	**1 (50.0)**		2
Localized rash			**2 (66.7)**		1 (33.3)		3
Severe							
Fever ≥39°C				**1 (100)**			1
Paresthesia		**1 (100)**					1
Clustered rash					**1 (100)**		1

b) Resolution	<12 h N (%)	12–24 h N (%)	24–48 h N (%)	48–72 h N (%)	>72 h N (%)	Total N
Mild						
Injection site pain/redness/swelling	22 (12.1)	**75 (41.2)**	74 (40.7)	6 (3.3)	5 (2.7)	182
Tiredness/Asthenia	7 (25.0)	**8 (28.6)**	6 (21.4)	4 (14.3)	3 (10.7)	28
Headache	8 (26.7)	**11 (36.7)**	6 (20.0)	3 (10.0)	2 (6.7)	30
Chills			**2 (66.7)**		1 (33.3)	3
Nausea	1 (33.3)		**2 (66.7)**			3
Abdominal pain		**3 (60.0)**			2 (40.0)	5
Fever <38°C	1 (20.0)	1 (20.0)	**2 (40.0)**		1 (20.0)	5
Insomnia/Restlessness	2 (22.2)	**4 (44.5)**	1 (11.1)		2 (22.2)	9
Sleepiness	2 (25.0)	2 (25.0)	**4 (50.0)**			8
Decreased appetite		**2 (50.0)**		1 (25.0)	1 (25.0)	4
Moderate						
Muscle/Joint pain	**1 (25.0)**		**1 (25.0)**	**1 (25.0)**	**1 (25.0)**	4
Lymphadenopathy			**1 (100)**			1
Diarrhea		**2 (100)**				2
Localized rash		**2 (66.7)**	1 (33.3)			3
Severe						
Fever ≥39°C			**1 (100)**			1
Paresthesia	**1 (100)**					1
Clustered rash		**1 (100)**				1

The highest frequency for each event is reported in bold.

children, who had visit for lymphadenopathy or other symptoms. The day after the second dose, 125 (62.8%) children did not go to the school, but only 15 as a precaution after immunization or for onset of symptoms (n = 10, 8.0% and n = 5, 4.0%, respectively), while the remaining 115 for reasons linked to rules of distance learning at school.

Adverse reactions after 2 doses vaccination

Comparing the adverse reactions after each dose, occurrence of at least one adverse reaction significantly differed ($p = .005$) between the first and second dose, as well as frequency of mild and moderate events, being mild reactions higher after the first dose (81.7% *vs* 69.8%, $p = .004$) and moderate symptoms after the second (3.9% *vs* 10.6%, $p < .001$) (Table 1).

By analyzing the specific symptoms after each dose, occurrence of injection site reactions (79.5% *vs* 68.8%), tiredness/asthenia (12.2% *vs* 4.5%), abdominal pain (2.2% *vs* 0%), insomnia/restlessness (3.9% *vs* 0.5%), and sleepiness (3.5% *vs* 0.5%) were significantly higher after the first than the second dose. Lymphadenopathy was the only symptom more commonly reported after the receipt of the second rather than the first dose (8.5% *vs* 0.4%) (Table 1).

No significant differences were observed between the occurrence of at least one adverse event after the vaccine doses and gender, other vaccinations in the previous six months, allergies or pathologies for which children were under treatment, and parental education or employment. Conversely, in-depth analysis after each dose revealed that there were significant differences by gender for reporting of mild events (87.9% in females *vs* 75.2% in males, and 69.8% *vs* 60.8%) and injection reactions (87.1% *vs* 71.7%, and 77.3% *vs* 60.8%), and for the occurrence of decreased appetite (1.7% *vs* 0%) after the first dose.

Discussion

Immunization is an important means of controlling serious infectious diseases.[11] COVID-19 vaccines, including Comirnaty, were safely used in adult populations with the aim to protect from severe disease.[7,12] Globally, during the

Table 3. Description of (a) onset and (b) resolution of adverse reactions after the second dose.

a) Onset	<1 h N (%)	1-4 h N (%)	4-12 h N (%)	12-24 h N (%)	24-48 h N (%)	>48 h N (%)	Total N
Mild							
Injection site pain/redness/swelling	12 (8.8)	34 (24.8)	**72 (52.6)**	15 (10.9)	4 (2.9)		137
Tiredness/Asthenia		2 (22.2)	**4 (44.4)**	3 (33.4)			9
Headache	1 (6.2)	3 (18.8)	**6 (37.5)**	**6 (37.5)**			16
Chills			**3 (75.0)**	1 (25.0)			4
Nausea		**1 (50.0)**	**1 (50.0)**				2
Fever <38°C			1 (25.0)	**3 (75.0)**			4
Insomnia/Restlessness				**1 (100)**			1
Sleepiness				**1 (100)**			1
Decreased appetite		**1 (100)**					1
Moderate							
Muscle/Joint pain				**1 (100)**			1
Lymphadenopathy			2 (11.8)	4 (23.5)	**7 (41.2)**	4 (23.5)	17
Diarrhea						**1 (100)**	1
Localized rash			**2 (75.0)**			1 (25.0)	3
Severe							
Fever ≥39°C				**1 (100)**			1

b) Resolution	<12 h N (%)	12–24 h N (%)	24–48 h N (%)	48–72 h N (%)	>72 h N (%)	Total N
Mild						
Injection site pain/redness/swelling	22 (16.1)	**53 (38.7)**	50 (36.5)	8 (5.8)	4 (2.9)	137
Tiredness/Asthenia		**6 (66.7)**	1 (11.1)	2 (22.2)		9
Headache	4 (25.0)	**10 (62.5)**	2 (12.5)			16
Chills	1 (25.0)	**3 (75.0)**				4
Nausea		**1 (50.0)**	**1 (50.0)**			2
Fever <38°C	1 (25.0)	**2 (50.0)**	1 (25.0)			4
Insomnia/Restlessness			**1 (100)**			1
Sleepiness		**1 (100)**				1
Decreased appetite			**1 (100)**			1
Moderate						
Muscle/Joint pain		**1 (100)**				1
Lymphadenopathy		1 (5.9)	**9 (52.9)**	6 (35.3)	1 (5.9)	17
Diarrhea	**1 (100)**					1
Localized rash		**2 (66.7)**		1 (33.3)		3
Severe						
Fever ≥39°C			**1 (100)**			1

The highest frequency for each event is reported in bold.

early phase of the pandemic, incidence and severity of COVID-19 were very low in children, probably because of the higher rate of asymptomatic or paucisymptomatic cases, hence, the understanding of their role in disease propagation was limited.[13,14] In Italy, in the spring 2020, the strict measures imposed by the government strongly affected interactions between children and adolescents, because schools were closed, and social activities were prohibited. Nevertheless, during summer 2020, cases increased, especially among people of 15-19 years of age, most likely due to vacation, and opening of school allowed virus spread more rapidly among secondary and high school students than in the general population.[15] The launch of the vaccination against COVID-19 started in December 2020, for healthcare workers and the vulnerable people, and later included the healthy general population of 12 years of age and over. During the beginning of December 2021, the Omicron (B.1.1.529) variant of concern of SARS-CoV-2 rapidly emerged and exponentially increased, replacing the Delta variant in multiple countries, including in Italy. A surge in the incidence was possibly due to an increased transmissibility combined with the ability of the variant to evade immunity conferred by past infection or vaccination.[16] Therefore, the rationale for vaccinating children against COVID-19 with Comirnaty, which was the single vaccine approved for use in this category, occurred because of a rise of incidence in this age group, and was administered because both primary and booster vaccination were proved to be safe for other age groups, with only mild-moderate transient adverse events.[4,6,7] The safety of vaccinations is important, especially among children. However, the adverse events related to the use of vaccines occur at a very low frequency and are generally irrelevant when compared to risks associated with non-vaccination.[17] Furthermore, serious adverse events reported after childhood and adolescence vaccinations, including for hepatitis B and measles-mumps-rubella vaccines, are rare.[18]

To date, this is the first report of a safety profile for Comirnaty used amongst children of 5–11 years of age in Italy evaluated through active surveillance. Studies conducted elsewhere to investigate on adverse reactions among children aged 5–11 years using Comirnaty included a phase 1 study,[6] and another based on data reported to the Vaccine Adverse Event Reporting System (VAERS), a passive vaccine safety surveillance system co-managed by the Centers for Disease Control and Prevention (CDC) and FDA.[19] In contrast to the passive system for reporting adverse events, active monitoring is a very important component of immunization programs, since can rapidly and more accurately support the safety of vaccines, and adequately respond to potential emerging concerns. Additional studies were available for Comirnaty in age

groups other than that targeted in the present survey, mainly on 12–17-year-old subjects underlining that the current options are safe, and more effective than in adult groups.[20]

The results of this study revealed that adverse events after the first dose were more commonly mild and transient (injection site pain, redness or swelling). These findings were in line with the benefits of Comirnaty demonstrated in children aged 5 to 11, as well as among adolescents of 16 years and older that outweighed the risks as stated by the European Medicine Agency.[5,21]

From the start of vaccination with Comirnaty in Italy, considering all the reported adverse reactions (89,315 reports) to the pharmacovigilance system of the Italian Medicines Agency,[22] the reporting rate was evaluated as 101 cases per 100,000 doses administered. Eighty-four percent of adverse reports were described as non-serious and only 16.1% as serious, which occurred almost exclusively in people aged between 30 and 59 years. The age groups with the lowest number of reports were in children, adolescents, and the elderly.[22] To date, 439 reports of adverse reactions for Comirnaty administration in the age group 5–11 years were registered (approximately 0.3% of total reports), with a rate of 21 cases per 100,000 doses administered.[22] Almost all (94.0% of total reports) were attributed to the first dose, in line with the results of our survey (84.3%) while adverse reactions related to the second dose were identified at a higher rate through active surveillance as compared to the national passive reporting system (73.4% vs 6.0%).[22] Furthermore, 87.2% of reports among children were classified as non-serious and 12.8% as serious, with no deaths, in agreement with data presented in this study revealing a high proportion of mild events either after the first or second dose (96.9% and 95.2%) compared to those severe (1.6 and 0.7%).

Combining both doses, the distribution of reports to the national pharmacovigilance system highlighted that the five most frequent events for Comirnaty vaccine administration among 5–11 years children were injection site pain, headache, fever, tiredness/asthenia, vomiting and nausea, which were followed by itching, urticaria, and abdominal pain,[22] and were in line with those observed through active surveillance in this study. Indeed, the top five reactions were injection site pain, redness or swelling, headache, tiredness/asthenia, lymphadenopathy, and fever, followed by insomnia/restlessness, sleepiness, chills, localized rash, nausea, abdominal pain, decreased appetite, and muscle/joint pain. Therefore, in our study, while fever was less commonly reported as compared to data available from the Italian Medicine Agency, the occurrence of lymphadenopathy was more commonly reported here, especially after the receipt of the second dose, and is not yet reported among the vaccine adverse events in children. The survey revealed that the higher number of the reactions, either after the first or the second dose, were described in female subjects, with the only exception of moderate reactions occurring more frequent among males after the second dose, although this was not statistically significant. Indeed, in our study, mild reactions including injections site pain, redness or swelling were significantly more reported in female children after both doses, as well as decreased appetite after the first dose. These findings could be related to gender differences, as recently reported in a large study,[23] remarking the consistent excess in the rates of adverse events in females in all age groups following immunization with the Pfizer-BioNTech COVID-19 vaccine. Data suggest the need to assess and report vaccine adverse events by gender and that differences should be considered when determining dosing schedules.[23]

Comirnaty vaccine has proved to be effective and safe since the initial safety evaluation study,[12] although some adverse events were reported, including axillary lymphadenopathies ipsilateral to the vaccine injection, which were rare as recorded in 0.3% of patients, and should be considered as reactive cases.[24] After the receipt of Comirnaty vaccine, lymphadenopathies in other locations such as supraclavicular were also reported,[25] although there were more reports associated with mRNA-1273.[26] In the phase 1 study,[6] lymphadenopathy was reported in 0.9% of 5-to-11-year-old Comirnaty recipients, which was an incidence like that found in 12-to-15-years adolescents (0.8%), but higher than that observed in adults (0.3%).[12,27] Data on lymphadenopathy in pediatric population are limited but, in the FDA authorization document, swollen lymph nodes were reported after vaccination in recipients aged 5 through 11 years, which were followed for safety for at least 2 months after the second dose.[4] Furthermore, two males aged 16 and 13 years were recently reported as presenting supraclavicular lymphadenopathy 2 weeks after receiving the first COVID-19 vaccination, and both had the lymphadenopathy on the same side as the vaccination,[24] as occurred in the children surveyed in this study. Other reports describe the possibility that COVID-19 vaccines could potentially trigger an uncommon but potential serious inflammatory response,[7,28] as described for other vaccines.[29] Also mRNA-1273 vaccine (Spikevax, Moderna) received provisional approval in some countries outside the United States for use in children aged 6 to 11 years.[30–32] During May 2022, the results of the ongoing phase 2–3 trial were further published, which evaluated the safety, immunogenicity, and efficacy of two doses of vaccine, as compared with placebo.[33] Reactogenicity events were mild to moderate and most included injection site pain, fatigue, and headache, and the incidence of local and systemic adverse events was similar or lower in children 6 to 11 years of age than in young adults (18 to 25 years of age). Axillary (or groin) swelling/tenderness was also reported after the receipt of the first dose administered at 50 μg and 100 μg (10.8% and 14.6%, respectively), and after the second dose (12.1% and 17.0%).

Therefore, based on these results, the present active surveillance survey describes the lack of serious safety concerns after receiving Comirnaty vaccine among children aged 5–11 years, which is consistent with the available literature data, as no unexpected patterns were observed, being reported generally mild or moderate and temporary adverse reactions. Parents and guardians should be advised to get children vaccinated with Comirnaty and that side reactions are expected, without severe outcomes. The risk of harm to children from COVID-19 infection remains much higher than that derived from vaccine side events. In conclusion, vaccination of children significantly minimizes the risk of COVID-19 and potential sequelae, maximizes their chances of returning to usual social activities, and mitigates the effects of pandemic on their families.

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Author contribution

G.R. designed and managed the project; critically revised all the versions of the manuscript; gave final approval of the version to be published; and has agreed to be accountable for all aspects of the work. M.L.S. contributed to organize the data collected; helped drafting the manuscript; gave final approval of the version to be published; and has agreed to be accountable for all aspects of the work. A.D.A., R.D.D., M.I., A.P., N.S., A.S., C.A., A.N., M.A.D.P., and F.C. substantially contributed to recruit and interview participants; conducted data collection; gave final approval of the version to be published; and has agreed to be accountable for all aspects of the work. R. R. helped develop the structured questionnaire; gave final approval of the version to be published; and has agreed to be accountable for all aspects of the work. A.L. contributed to realization of the work for recruiting participants at vaccinal center; gave final approval of the version to be published; and has agreed to be accountable for all aspects of the work. M.T. had substantial contributions to the data analysis and interpretation; write the original manuscript and critically revised it; gave final approval of the version to be published; and has agreed to be accountable for all aspects of the work.

Ethics statement

For this study, ethical approval was not requested as no experimental procedure was applied, and information was retrospectively provided by participants after signing an informed consent. Furthermore, all data presented were de-identified, coded and were analyzed anonymously in accordance with ethics guidelines.

Disclosure statement

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