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Impact and Effectiveness of COVID-19 mRNA Vaccination Against COVID-19 Hospitalisation in Paediatrics: A Cohort Study Using Two Linked Data Sources in Spain

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ABSTRACT

Purpose: Despite Spain's > 2 million COVID-19 paediatric cases before 2024, few required hospitalisations (8900). We aimed to estimate the effectiveness of two-dose COVID-19 vaccinations against hospitalisation 'with' and 'for' COVID-19 in paediatrics.

Methods: All individuals aged 5–14 years between January 2021 and February 2022 in two databases in Spain (SIDIAP and BIFAP) vaccinated against COVID-19 (two doses) were matched 1:1 to unvaccinated controls with the same age, sex, region and comorbidities on the dates of vaccination. Individuals with previous SARS-CoV-2 infections were excluded. COVID-19 was identified as the main reason (hospitalisation 'for' COVID-19; SIDIAP) or as one of the reasons (hospitalisation 'with' COVID-19; BIFAP) for hospitalisation with a positive SARS-CoV-2 test ± 30 days. Incidence rate differences and vaccine effectiveness (VE; 95% CI; controlled by inverse probability weights) against hospitalisations 'for' and 'with' COVID-19 were calculated.

Results: The cohorts included 75 361 (SIDIAP) and 178 589 (BIFAP) pairs. Among vaccinated individuals (99.99% with mRNA vaccines) and controls, < 5 and 15 hospitalisations 'for' COVID-19 were identified (SIDIAP), whereas 21 and 32 hospitalisations 'with' COVID-19 (BIFAP), all aged 12–14 years old. Vaccination prevented 2.5 hospitalisations 'for' and 0.5 'with' COVID-19 during the Delta period, and 0.8 hospitalisations 'with' COVID-19 during Omicron predominance per 10⁶ person-days. The VE was 94% (95% CI: 52%–99%; SIDIAP) and 53% (95% CI: 18%–74%; BIFAP).

The results of the current study were presented in the 2024 International Society of Pharmacoepidemiology Annual Meeting (Abstract number 1535); August 24–28, 2024; Berlin, Germany.

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Conclusions: Given the low incidence of hospitalised COVID-19, two-dose series mRNA vaccination showed moderate-high effectiveness with few averted cases. Including hospitalisation ‘with’ COVID-19 underestimated the effectiveness. If paediatric severe COVID-19 remains rare, larger databases are required to understand precisely the effectiveness and impact of new vaccines.

Trial Registration: EU PAS Register number: EUPAS47725

1 | Introduction

Before 2024, around 2 million COVID-19 cases were notified among individuals <15 years old in Spain [1], with the majority attributed to the Omicron variant. The infection rarely led to severe COVID-19, accounting for 8900 cases recorded in the Spanish paediatric population (5–19 years old) [2].

Children were initially classified as a lower-priority population for COVID-19 vaccination by the World Health Organization (WHO) [3]. However, the emergence of more transmissible SARS-CoV-2 variants, particularly Omicron, led to higher hospitalisations among children, especially those with underlying health conditions [4]. In May and July 2021, the European Medicines Agency (EMA) recommended extending the use of two mRNA COVID-19 vaccines, including BNT162b2 or mRNA-1273 molecules, for children aged 12–15 and 12–17, respectively [5, 6]. Later, on 25 November 2021, and 24 February 2022, the indications were expanded to include children aged 5–11 and 6–11, respectively [7, 8]. Importantly, the dosages for those under 12 were lower than those for adults (10 vs. 30 µg for BNT162b2 and 50 vs. 100 µg for mRNA-1273) [7, 8].

In Spain, the recommendation for COVID-19 vaccination of individuals aged 12 and older with vulnerable clinical or social conditions was issued at the end of June 2021 [9]. Vaccination for those aged 12 without vulnerabilities (with two adult doses of any mRNA-based vaccine) and for children aged 5–11 (with two paediatric doses of BNT162b2) spaced at least 8 weeks apart began on 18 October and 7 December 2021, respectively [10, 11].

Nowadays, COVID-19 continues to be a priority for immunisation programmes [12]. In Spain, the COVID-19 vaccination of paediatric groups is still ongoing among children with clinical conditions that increase their risk of severe disease, their cohabitants, as well as those residents of disability centres, nursing homes and other closed institutions [13].

Given the various factors that shaped our response to the pandemic and the ongoing challenges posed by SARS-CoV-2 mutations, along with the limited understanding of post-COVID-19 conditions in children [14], it has been crucial to assess the effectiveness of COVID-19 vaccines (VE). This evaluation is essential for protecting populations and guiding regulatory decisions regarding vaccination campaigns.

In the framework of the ‘Covid Vaccine Effectiveness’ (CoVE) study [15], we assessed the effectiveness of a two-dose series of the original mRNA COVID-19 vaccines in children (5–11 years) and pre-adolescents (12–14 years) on preventing COVID-19 hospitalisations during the Delta and early Omicron variants periods.

2 | Methods

2.1 | Data Sources

We report a retrospective matched cohort study with anonymised data from two electronic health care databases in Spain, the Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (BIFAP) [16] and the Sistema d’Informació per el Desenvolupament de la Investigació en Atenció Primària (SIDIAP) [17].

BIFAP is a not-for-profit research programme funded by the Spanish Agency of Medicines and Medical Devices (AEMPS) that includes primary care data linked to hospital registries. Started in 2001, BIFAP has been progressively and increasingly collecting health data, with annual updates, from several regions located in central and northern Spain. It includes patients’ records of diagnoses through the International Classification of Diseases (ICD-9, ICD-10) and SNOMED-CT code systems linked with information entered by the physicians in free text, primary care prescriptions and dispensing data, vaccinations, lab test results, clinical tests/procedures and lifestyle data such as body mass index (BMI) or smoking status.

SIDIAP is a primary care database set up by the Institute of Research in Primary Care (Institut Universitari D’Investigació en Atenció Primària Jordi Gol [IDIAP Jordi Gol]) and the Catalan Institute of Health (Institut Català de la Salut). It includes information collected since 1 January 2006, during routine visits across 328 primary care centres from the Catalan Health Institute in Catalonia (a region located in eastern Spain), with the participation of 3414 general practitioners (GPs). SIDIAP has pseudonymised records for 5.7 million people (75% of the Catalan population), representative of the Catalan population. SIDIAP data comprise the clinical and referral events registered by primary healthcare professionals and administrative staff in electronic health records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals, primary care laboratory test results and vaccines. SIDIAP can also be linked to the hospital discharges. Health professionals gather this information using ICD-10, ATC codes and structured forms. SIDIAP is listed in the Catalogue of Real-World Data sources and studies by EMA [18].

Both data sources provided information on COVID-19 vaccinations (e.g., product types and vaccination dates), COVID-19 outcomes (e.g., SARS-CoV-2 test results, diagnoses), hospitalisation records and covariates of interest. The data were validated in previous projects (EUPAS 37273, EUPAS 40404, EUPAS 42467). Full details of the conducted COVID-19 VE study are available in the public protocol (EUPAS 47725) [15].

Summary

- Hospitalisations for COVID-19 were rare in paediatrics in Spain during Delta/Omicron periods of the pandemic.
- Vaccination averted ≤ 2.5 hospitalisations for COVID/10⁶ person-days.
- Including COVID-19 recorded as one reason for hospital admission may not reflect severe infections and underestimate the effectiveness calculations.

2.2 | Study Population

The study population consisted of all paediatric individuals aged 5–14 years registered in BIFAP or SIDIAP during the study period. The study focused on the period ranging from the beginning of the vaccination campaign in January 2021 (to capture individuals who, due to their higher risk of severe COVID-19 disease, were vaccinated before the initiation of routine vaccination for the paediatric population) to the latest data available from the data sources (December 2021 for SIDIAP and February 2022 for BIFAP)—encompassing the periods of the Delta and Omicron variants.

Eligible individuals within this population had at least 2 years of prior healthcare data available, which served to identify covariates.

All individuals were defined as not vaccinated (and thus served as a potential control) until the date of the receipt of their first COVID-19 vaccine dose. Individuals were considered to have completed a two-dose series of COVID-19 vaccinations when there was a record of a second COVID-19 vaccine dose (Time 0) occurring at least 19 days after the first dose. The date on which each vaccinated individual received their second dose of the COVID-19 vaccine was defined as Time 0. This same date was assigned as time 0 for their matched control, selected from among unvaccinated individuals as detailed in the Matching section.

2.3 | Studied Vaccines

The study aimed to assess all COVID-19 vaccines available during the study period, meaning those originally authorised in the EU: the BNT162b2 Pfizer vaccine, the mRNA-1273 Moderna vaccine—both of which include mRNA molecules carrying instructions for producing a protein from the original strain of SARS-CoV-2 [19, 20] and the ChAdOx1-S/nCoV-19 [recombinant] vaccine manufactured by AstraZeneca [21], a replication-deficient adenoviral vector vaccine against COVID-19. Records of ChAdOx1-S/nCoV-19 administration in the study population were very rare ($N=5$) and could not be analysed separately. This vaccine was not authorised for use in children or adolescents in Spain, making any recorded administration likely anecdotal or due to a recording error.

2.4 | Matching

From the study participants (see Figure 1), every individual who received a two-dose series of COVID-19 vaccinations was matched (1:1) to a randomly selected individual (with

replacement, meaning the same person could serve as a control for multiple vaccinated individuals) who had not been vaccinated on or before the dates the vaccinated person received their first and second doses (± 7 days). Matched individuals were required to have the same age, sex, geographical region and clinical conditions (e.g., diagnosis of immunodeficiency, malignant tumour, organ transplants, severe renal disease, Down syndrome and prior SARS-CoV-2 infection) as the vaccinated person on the dates of vaccination. Participants with a prior SARS-CoV-2 infection record were excluded from the analysis to avoid confounding the vaccine's effect. The script for the matching process can be found at the following link: https://github.com/VAC4EU/CoVE-Public/blob/main/src/15_execute_matching.R.

2.5 | Covariates

The selection criteria for clinical conditions, medication use (including influenza vaccination and other medications) and visits to primary care physicians were based on a presumed higher probability of incurring COVID-19 or severe outcomes. These data, collected up to 2 years before 2021, were utilised as potential confounders in the inverse probability weighted (IPW) analysis (Table 1). Further details can be found in the public repository <https://github.com/VAC4EU/CoVE-Public>, as mentioned in the Data Availability section.

2.6 | Follow-Up Period and Case Definition

The follow-up period for the matched pairs started at Time 0 until the earliest occurrence date of a positive SARS-CoV-2 test within 30 days of a COVID-19 episode recorded in the hospital registries, the last database data extraction, or moving out from the data source. The follow-ups for both matched subjects were also censored when the control received the first dose.

A COVID-19 episode could be recorded as the primary or secondary reason for hospital admission.

In SIDIAP, COVID-19 recorded as the primary reason for admission was captured and considered hospitalisations 'for' COVID-19 in the current study.

In BIFAP, there was no information on whether the diagnosis was the primary or secondary reason for admission; thus, all episodes of COVID-19 recorded in hospital registries were identified and considered hospitalisations 'with' COVID-19 (that do not necessarily indicate severe COVID-19) in the current study.

2.7 | Statistical Analyses

Characteristics are presented as mean (standard deviation [SD]) or overall proportion for each cohort. The proportion of patients with a positive SARS-CoV-2 test who had a recorded hospitalisation within 30 days was estimated. Incidence rates (IRs; 95% confidence intervals [CIs]) and IR differences (IRDs; 95% CI) of

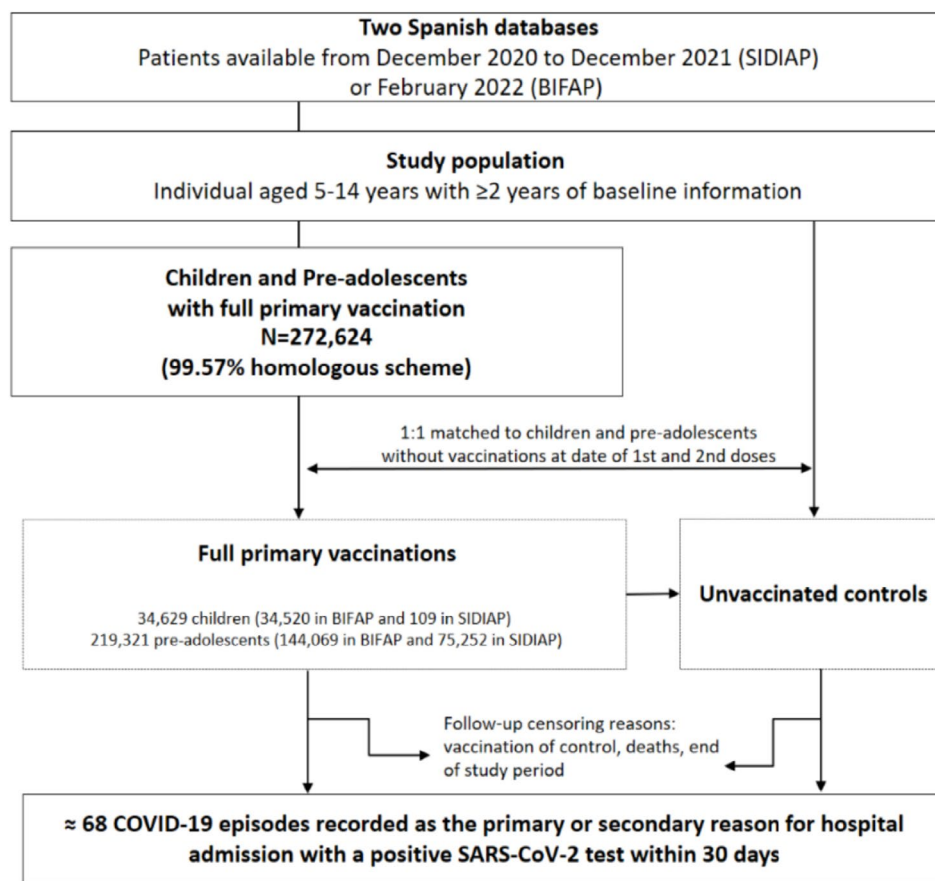


FIGURE 1 | Paediatric vaccinated and control cohorts ascertainment and follow-up to COVID-19.

hospitalisation ‘for’ and ‘with’ COVID-19 have been calculated in SIDIAP and BIFAP, respectively.

We used IPW Cox proportional hazards regression to derive the average hazard ratio (HR; 95% CI) of COVID-19-related outcomes in vaccinated versus unvaccinated controls. The adjusted VE (%) was estimated as 1 minus the adjusted HR multiplied by 100 (corresponding CI calculated as 1%–95%) for each data source overall and by (i) vaccine brands and scheme, (ii) time after vaccination, (iii) age categories (5–11 and 12–14 years old) and (iv) dominant SARS-CoV-2 variants (defined as the variant reaching 50% of the total sequenced specimens at Time 0). Two specific SARS-CoV-2 variant periods were established: Delta (starting from 04/07/2021) and Omicron (starting from 03/01/2022) based on active surveillance data [22]. A sensitivity analysis was conducted, focusing on individuals who had previously been tested for SARS-CoV-2 infection. This approach was used to balance testing availability among compared individuals and to control for surveillance bias.

Finally, the underestimation of VE in the BIFAP dataset was assessed by applying the proportion of hospitalisation ‘with’ COVID-19 that was confirmed as hospitalisation ‘for’ COVID-19, based on a previous study during the same timeframe in BIFAP [23]. In that study, a manual review of additional information recorded in clinical histories revealed that 63% of non-vaccinated

individuals aged 12–18 years were hospitalised ‘for’ COVID-19, while only 24% of vaccinated individuals were hospitalised ‘for’ COVID-19 [23].

3 | Results

3.1 | Study Population

178 589 Subjects (34 520 children and 144 069 pre-adolescents) with a two-dose series of COVID-19 vaccination (majority with mRNA vaccines and only 5 with the studied adenovirus vaccine) without prior COVID-19 were matched to unvaccinated individuals in BIFAP and 75 361 subjects (109 children and 75 252 pre-adolescents), with mRNA vaccinations, in SIDIAP. Heterologous vaccination was rare (0.3%). Characteristics of the population are displayed in Table 1. The most administered vaccine was BNT162b2 (> 90%) in September 2021 (59% and 66% of total vaccinations in each database).

3.2 | Hospitalisation With and For COVID-19

In BIFAP, there were 21 hospitalisations ‘with’ COVID-19 among vaccinated individuals and 32 among controls, out of 12 651 and 9 703 individuals with a positive SARS-CoV-2 test, respectively.

TABLE 1 | Baseline characteristics among compared vaccinated and matched unvaccinated individuals by two-dose series vaccination schedule.

Data source	SID/AP			BIF/AP		
	Homologous 2-dose serie	Heterologous 2-dose serie	Unvaccinated	Homologous 2-dose serie	Heterologous 2-dose serie	Unvaccinated
Number of participants	75276	85	75361	177921	668	178589
Homologous 2-dose serie (active ingredient)						
mRNA-1273 (mRNA molecule)	7200 (9.6%)			13761 (7.7%)		
BNT162b2 (mRNA molecule)	68076 (90%)			164160 (92%)		
Heterologous 2-dose serie (active ingredient of the 1st dose)						
ChAdOx1-S (adenoviral vector vaccine)					5 (0.7%)	
mRNA-1273 (mRNA molecule)		31 (36%)			133 (20%)	
BNT162b2 (mRNA molecule)		54 (64%)			530 (79%)	
Time to follow-up (days)						
Median	88.0	24.0	88.0	100.0	14.0	100.0
Maximum	235.0	177.0	235.0	297.0	330.0	330.0
Reason for final censoring						
Censoring of the other member of the pair	30388 (40%)	16 (19%)	121 (0.2%)	45150 (25%)	25 (3.7%)	291 (0.2%)
Censoring by 3rd dose	50 (<0.1%)	<5	<5	80 (<0.1%)	<5	<5
Censoring by 1st dose	<5	<5	29505 (39%)	<5	<5	41772 (23%)
Study exit date	44838 (60%)	69 (81%)	45735 (61%)	132691 (75%)	640 (96%)	136526 (76%)
Female	36517 (49%)	52 (61%)	36569 (49%)	86749 (49%)	361 (54%)	87110 (49%)
Age at matching date (years)						
Mean (SD)	12.4 (0.5)	12.3 (0.5)	12.4 (0.5)	11.9 (1.3)	12.2 (0.9)	11.5 (2.1)
Age band at matching date						
05–11	109 (0.1%)	<5	109 (0.1%)	34479 (19%)	41 (6.1%)	34520 (19%)
≥12	75167 (100%)	85 (100%)	75252 (100%)	143442 (81%)	627 (94%)	144069 (81%)
Calendar month-year at matching date						
January 2021	<5	<5	<5	<5	<5	<5
February 2021	<5	<5	<5	<5	<5	<5
March 2021	<5	<5	<5	8 (0.1%)	<5	8 (>0.1%)

(Continues)

TABLE 1 | (Continued)

Data source	SIDJAP			BIFAP		
	Homologous 2-dose serie	Heterologous 2-dose serie	Unvaccinated	Homologous 2-dose serie	Heterologous 2-dose serie	Unvaccinated
April 2021	<5	<5	<5	<5	<5	<5
May 2021	<5	<5	<5	<5	<5	<5
June 2021	15 (<0.1%)	<5	15 (<0.1%)	38 (<0.1%)	<5	39 (<0.1%)
July 2021	324 (0.4%)	<5	325 (0.4%)	311 (0.2%)	<5	311 (0.2%)
August 2021	15 395 (20%)	<5	15 396 (20%)	12 382 (7.0%)	6 (0.9%)	12 388 (6.9%)
September 2021	44 326 (59%)	10 (12%)	44 336 (59%)	117 032 (66%)	14 (2.1%)	117 046 (66%)
October 2021	8 776 (12%)	15 (18%)	8 791 (12%)	14 127 (7.9%)	9 (1.3%)	14 136 (7.9%)
November 2021	29 19 (3.9%)	20 (24%)	29 39 (3.9%)	4 593 (2.6%)	18 (2.7%)	4 611 (2.6%)
December 2021	35 19 (4.7%)	38 (45%)	35 57 (4.7%)	4 003 (2.2%)	470 (70%)	4 473 (2.5%)
January 2022				1 151 (0.6%)	59 (8.8%)	1 210 (0.7%)
February 2022				24 269 (14%)	91 (14%)	24 360 (14%)
Clinical conditions ^a and prescribed drugs						
Immunodeficiency ^b or use of immunosuppressants-L04 or systemic corticosteroids-H02 at matching date	15 951 (21%)	19 (22%)	15 970 (21%)	20 077 (11%)	72 (11%)	20 149 (11%)
Cancer at matching date	114 (0.2%)	<5	114 (0.2%)	477 (0.3%)	5 (0.7%)	482 (0.3%)
Transplant recipient at matching date	25 (<0.1%)	<5	25 (<0.1%)	9 (<0.1%)	<5	9 (<0.1%)
Severe renal disease at matching date	12 (<0.1%)	<5	12 (<0.1%)	<5	<5	<5
Down syndrome at matching date	24 (<0.1%)	<5	24 (<0.1%)	15 (>0.1%)	<5	17 (>0.1%)
Heart failure at matching date	18 (<0.1%)	<5	19 (<0.1%)	6 (<0.1%)	<5	<5
Diabetes (Types 1 and 2) at matching date	191 (0.3%)	<5	170 (0.2%)	272 (0.2%)	<5	222 (0.1%)
Bladder incontinence at matching date	920 (1.2%)	<5	935 (1.2%)	88 (<0.1%)	<5	75 (<0.1%)
Chronic kidney disease at matching date	60 (<0.1%)	<5	62 (<0.1%)	30 (<0.1%)	<5	35 (<0.1%)
Sepsis at matching date	80 (0.1%)	<5	79 (0.1%)	38 (<0.1%)	<5	48 (<0.1%)
Arthritis and osteoarthritis at matching date	17 153 (23%)	21 (25%)	14 921 (20%)	11 25 (0.6%)	<5	787 (0.4%)
Cerebrovascular diseases at matching date	29 (<0.1%)	<5	44 (<0.1%)	13 (>0.1%)	<5	13 (>0.1%)
Malignant tumours without metastasis for Charlson at matching date	109 (0.1%)	<5	107 (0.1%)	476 (0.3%)	5 (0.7%)	480 (0.3%)

(Continues)

TABLE 1 | (Continued)

Data source	SIDIAF			BIFAP		
	Homologous 2-dose serie	Heterologous 2-dose serie	Unvaccinated	Homologous 2-dose serie	Heterologous 2-dose serie	Unvaccinated
Hypertension at matching date	156 (0.2%)	< 5	142 (0.2%)	54 (<0.1%)	< 5	43 (<0.1%)
Coronary artery disease at matching date	5 (<0.1%)	< 5	< 5	28 (<0.1%)	< 5	27 (<0.1%)
Analgesics at matching date	7085 (9.4%)	10 (12%)	6568 (8.7%)	20137 (11%)	77 (12%)	15013 (8.4%)
Corticosteroids at matching date	1103 (1.5%)	< 5	1053 (1.4%)	3411 (1.9%)	13 (1.9%)	3553 (2.0%)
Nonsteroidal anti-inflammatory drugs at matching date	11950 (16%)	13 (15%)	11288 (15%)	28701 (16%)	113 (17%)	21977 (12%)
Psychotropics or psycholeptics at matching date	873 (1.2%)	< 5	755 (1.0%)	2095 (1.2%)	16 (2.4%)	1725 (1.0%)
Statins at matching date	27 (<0.1%)	< 5	19 (<0.1%)	85 (<0.1%)	< 5	16 (<0.1%)
Antibiotics at matching date	4183 (5.6%)	9 (11%)	4085 (5.4%)	11288 (6.3%)	46 (6.9%)	9584 (5.4%)
Antiviral medications at matching date	75 (<0.1%)	< 5	93 (0.1%)	175 (<0.1%)	< 5	152 (<0.1%)
Number of drugs at matching date						
0	57073 (76%)	63 (74%)	52579 (76%)	132228 (74%)	485 (73%)	143591 (80%)
1	10900 (15%)	11 (13%)	9900 (14%)	27502 (15%)	112 (17%)	19823 (11%)
2	5321 (7.1%)	8 (9.4%)	5033 (7.3%)	13922 (7.8%)	54 (8.1%)	11154 (6.2%)
3	1168 (1.6%)	< 5	1237 (1.8%)	3255 (1.8%)	11 (1.6%)	2823 (1.6%)
4	258 (0.3%)	< 5	244 (0.4%)	752 (0.4%)	5 (0.7%)	899 (0.5%)
5	69 (<0.1%)	< 5	53 (<0.1%)	245 (0.1%)	< 5	274 (0.2%)
6	5 (<0.1%)	< 5	8 (>0.1%)	16 (>0.1%)	< 5	23 (>0.1%)
7				< 5	< 5	>
Influenza vaccination (in the previous 4 years)	6886 (9.1%)	12 (14%)	5316 (7.1%)	16294 (9.2%)	46 (6.9%)	8046 (4.5%)
Number of COVID-19 tests ever before matching date when available; mean (SD)	1.7 (1.5)	1.7 (1.6)	1.4 (1.4)	0.7 (1.1)	0.8 (1.1)	0.5 (1.0)

^aThe code list defining the covariates is available in the public repository (<https://github.com/VAC4EU/CoVE-Public>).

^bImmunodeficiency definition included congenital and acquired immunodeficiencies and those caused by haematological cancers, patients undergoing solid organ transplantation and autoimmune diseases; or treatment with immunosuppressants (ATC L04) or systemic corticosteroids (ATC H02) treatment.

TABLE 2 | Incidence rate, rate difference and vaccine effectiveness (VE) of hospitalisation ‘with’ (in BIFAP database) or ‘for’ (in SIDIAP database) COVID-19 among children and pre-adolescents.

Datascource	Unvaccinated			Vaccinated			Rate difference/100000 pd	95% LCI	95% UCI	VE adjusted	95% LCI	95% UCI	
	Unvaccinated person-days	Unvaccinated recorded in hospital	Unvaccinated IR/100000 pd	Vaccinated person-days	Vaccinated recorded in hospital	Vaccinated IR/100000 pd							
Overall	BIFAP	19012187	32	0.17	19013282	21	0.11	-0.06	-0.13	0.02	53%	18%	74%
Overall	SIDIAP	5482136	15	0.27	5482788	<5	0.02	-0.25	-0.40	-0.11	94%	52%	99%
1st-dose (mRNA molecule)	BIFAP	17440133	27	0.15	17440792	21	0.12	-0.03	-0.11	0.04	46%	3%	70%
1st-dose (mRNA molecule)	SIDIAP	5047437	14	0.28	5048075	<5	0.02	-0.26	-0.41	-0.11	93%	49%	99%
Individuals with previous negative test	BIFAP	2270541	8	0.35	2270712	<5	0.18	-0.18	-0.47	0.12	52%	-60%	86%
Individuals with previous negative test	SIDIAP	2514326	10	0.40	2514520	<5	0.04	-0.36	-0.62	-0.10	90%	23%	99%
Age ≥ 12	BIFAP	16131895	32	0.20	16132990	21	0.13	-0.07	-0.16	0.02	54%	18%	74%
Age ≥ 12	SIDIAP	5471041	15	0.27	5471693	<5	0.02	-0.26	-0.40	-0.11	94%	52%	99%
Delta	BIFAP	13094135	10	0.08	13094095	<5	0.03	-0.05	-0.10	0.01	61%	-29%	88%
Delta	SIDIAP	5481653	15	0.27	5482305	<5	0.02	-0.25	-0.40	-0.11	94%	52%	99%
Omicron	BIFAP	5951612	22	0.37	5952630	17	0.29	-0.08	-0.29	0.12	50%	5%	74%

In SIDIAP, there were fewer than five hospitalisations ‘for’ COVID-19 among vaccinated individuals and 15 among controls out of 1546 and 2784 individuals with a positive SARS-CoV-2 test, respectively.

Thus, overall, SARS-CoV-2 infections led to hospitalisation in rare cases: 0.25% of infections among vaccinated individuals and controls (see Table 2). All hospitalisation cases were among pre-adolescents, with the majority occurring during the Omicron variant period.

3.3 | Impact and Vaccine Effectiveness of the Two-Dose Series Vaccination

During the study period, among controls aged 5–14 years, the incidence of hospitalisations ‘with’ COVID-19 was 1.7 cases per million person-days in BIFAP and hospitalisation ‘for’ COVID-19 was 2.7 in SIDIAP. We estimated that vaccination prevented 0.6 hospitalisations ‘with’ COVID-19 (BIFAP) and 2.5 ‘for’ COVID-19 (SIDIAP) per million person-days.

About relative reduction, the VE was 53% (95% CI: 18%–74%) against hospitalisation ‘with’ COVID-19 (BIFAP) and 94% (95% CI: 52%–99%) against hospitalisation ‘for’ COVID-19 (SIDIAP). In BIFAP, a statistically significant VE (i.e., 50%; 95% CI: 5%–74%) against hospitalisation ‘with’ COVID-19 was observed only from January to February 2022, which accounted for most cases (see Table 2).

The low number of cases collected did not allow for an estimation of waning immunity.

Sensitivity analysis indicated higher incidences of hospitalisation among individuals who were tested for SARS-CoV-2 before the beginning of the study, as well as a slight overestimation of the VE by 1%–4% in the main analysis. Only the SIDIAP data confirmed a statistically significant VE against hospitalisation ‘for’ COVID-19 in the sensitivity analysis (90%; 95% CI: 23%–99%), which was similar to the main analysis; however, the limited number of hospitalisations (< 5 among vaccinated children) led to imprecise estimations (see Table 2).

If we apply the misclassification rate of hospitalisations ‘for’ COVID-19 observed in a previous study [23] to the number of hospitalisations ‘with’ COVID-19 found in BIFAP (all cases among pre-adolescents), the confirmed hospitalisations ‘for’ COVID-19 in our study would yield a total of five among vaccinated individuals and 20 among controls, resulting in IRs of 0.03 and 0.12 per 100 000 person-days, respectively. Therefore, among individuals aged 12 and older, the corrected IRD would be 0.09 per 100 000 person-days and the corrected unadjusted VE would be 75%. In contrast, the observed crude VE for pre-adolescents was 34% (with a 95% CI of –14% to 62%), indicating an underestimation of 41%.

4 | Discussion

The vaccination with a two-dose series of original COVID-19 mRNA vaccines (primarily BNT162b2) among children and

pre-adolescents showed some protection against hospitalisation ‘with’ and ‘for’ COVID-19 when compared to matched unvaccinated individuals in Spain during the Delta variant period and the initial weeks of the Omicron variant. However, hospitalisation was a rare outcome in that population and the vaccine effectiveness (VE) that we could estimate was imprecise.

The VE value against hospitalisation for COVID-19, observed in the SIDIAP database, was consistent with the $\geq 90\%$ rates reported in Spain before and during October 2021 [24]. Using hospitalisations ‘with’ COVID-19 in the BIFAP database, vaccination was found insufficient in preventing cases, with a VE of only 53%. The low VE observed aligns with estimates from Spanish national sources in November 2021, which reported a VE of 49% [24], however, it may be underestimated due to the broad definition of the outcome used in this database. Hospitalisation ‘with’ COVID-19 may indicate incidental diagnoses, differing from the ‘for’ COVID-19 category, which identifies cases where COVID-19 was the primary reason for hospitalisation (as captured in SIDIAP). After making corrections, the VE was found to be similar to the effectiveness reported in other non-randomised studies (VE: 70.8%; 95% CI: 38.5%–86.1%) [25], which supports a moderate level of certainty in the evidence.

It has been reported that the effectiveness of COVID-19 vaccines against hospitalisation is greater than their effectiveness against infection [25–27]. However, this finding comes with uncertainties due to the lower number of hospitalisations among the youngest. The high efficacy of BNT162b2 against SARS-CoV-2 infections found in randomised controlled trials during the Delta period was not replicated in observational studies [25]. Also, the reduction of the effect could be due to the evolving virus and its epidemiology and/or the precision and sensitivity of COVID-19 cases notified/recorded during the pandemic [28].

The benefit–risk evaluation of vaccination among children and pre-adolescents has been complex and widely debated. Despite the numerous clinical studies addressing the safety, tolerability [29–31] and effectiveness [6–8, 32, 33] of approved COVID-19 vaccines in children, vaccine uptake among those under 18 in the European Union/European Economic Area population remained below 25% [34]. The lower incidence of severe infection in the paediatric population (estimated to be 15–18 times lower than in adults in the current CoVE study [35, 36]) was a significant factor in that debate.

Furthermore, we observed that the rate of infections in unvaccinated children and pre-adolescents during the Omicron period was three to five times higher than during the Delta variant period, which led to more than a fourfold increase in hospitalisations.

In our current study, the two-dose vaccination series showed effectiveness against COVID-19 hospitalisations. However, the absolute reduction in cases was relatively low in two distinct epidemiological contexts: low contagious rates combined with high hospitalisations during the Delta period and higher contagious rates with lower hospitalisations during the Omicron period, where hospitalisations were already rare.

We present several metrics aimed at improving the understanding and communication of vaccine value to the population, that is, the absolute and relative effectiveness, as recommended elsewhere [37]. If SARS-CoV-2 virulence among youths were to increase in the future, new studies would be necessary to investigate the virus' pattern regarding age, season and its endemic nature [38] as well as to assess whether the benefits of vaccination continue to outweigh the risks. Our work provides important insights to support decision-making for pre-adolescents in this context.

The utility of our findings is also methodological. Regarding outcome definitions and study size, we quantified the underestimation of VE when including outcomes with low predictive value, such as COVID-19 being potentially recorded as a secondary diagnosis upon hospital admission. This misrepresentation can significantly distort the interpretation of the benefit-risk balance. Also, we highlight the importance of having a sufficient study size to adequately address questions about vaccine effects in the paediatric population, especially those related to rare outcomes or specific vulnerable groups. In such studies, efforts should be made to ensure comparability between exposure arms to avoid limitations related to participant numbers.

Finally, future evaluations of VE should rely on a clear awareness of potential confounders in each epidemiological scenario. These parameters are crucial for utilising study findings as evidence in vaccination decision-making.

The current analysis did not include booster doses, which were not recommended for children and adolescents during the study period. However, booster doses have the potential to restore protection against severe Omicron infections, with reported efficacy of 55% (95% CI: 50%–60%) for children [25]. Moreover, the diminishing effectiveness over time after 4 months [39] is crucial information for decision-making regarding the frequency and time of doses required.

4.1 | Limitations and Strengths

Some limitations should be mentioned. First, effectiveness against hospitalisations 'with' COVID-19 might not always accurately reflect severe infections as aforementioned. Second, the limited number of hospitalisations with/for COVID-19 hampered the analysis of both, the duration of the effectiveness and the effectiveness across clinical subgroups. This issue is common and highlighted by 4226 screened references investigating child populations, which allowed to estimate the global VE (resulted in 70.8%; 95% CI: 35.5%–86.1%) against COVID-19-related hospitalisations but did not provide insights into its duration [25]. Additionally, aligned with that extensive review of studies [25] with no or rare death events reported, we did not find any deaths during the 56 days following a positive SARS-CoV-2 test among children and pre-adolescents. So, VE against fatal COVID-19 could not be performed. Finally, we collected up to 42 covariates, which were incorporated into the statistical models to minimise both measured and, indirectly, unmeasured confounding. However, we cannot rule out a potential healthy vaccinee effect, as the reference group consisted of unvaccinated individuals. This factor might lead

to an overestimation of VE if the control group delayed vaccination when feeling unwell.

Despite these limitations, the designed matching criteria have been maximised to reach an excellent balance of co-medications and comorbidities among the compared groups. Additional evaluation of the algorithms utilised to identify the studied outcomes [23] allowed us to correctly interpret the different estimates observed, highlighting the relevance of quality and validation studies in research with electronic health records.

5 | Conclusions

The 2-dose vaccination series with the mRNA vaccine BNT162b2 in pre-adolescents has shown moderate to high effectiveness, with only a few COVID-19 hospitalisations averted due to the low incidence of severe cases. When evaluating the benefits of preventing severe COVID-19 against the risks of adverse events from the updated vaccines, it is crucial to consider both absolute and relative metrics. This approach provides a clearer understanding of the vaccine's overall value. If hospitalisations for COVID-19 continue to be rare among paediatric populations, large-scale studies will be necessary to assess the impact of new vaccines and guide decision-making more precisely and timely.

5.1 | Plain Language Summary (PLS)

Real-world data and evidence on children are needed to assess the effect of the vaccines as clinical trials may not be representative of this specific sub-population. In Spain, COVID-19 vaccination continues for children at high risk of complications. We estimated the effectiveness of two-dose mRNA COVID-19 vaccinations against hospitalisation for COVID-19 in children aged 5–14 years between January 2021 and February 2022. We utilised the information recorded in two public primary care databases linked to hospital registries from different regions in Spain to identify vaccinated children and compared them with unvaccinated children of the same age, sex, region and diseases. We observed very few hospitalisations for COVID-19, all aged 12–14 years. For this reason, even though the vaccination showed high effectiveness (94%), few cases (<2.5) were averted per million children vaccinated per day. We also confirmed that the effectiveness was reduced (53%) when including all patients with COVID-19 as a primary or secondary admission reason. Due to the rarity of this event in the young population, even larger studies are required to understand more precisely the number of cases prevented with new COVID-19 vaccines in this age group.

Author Contributions

Belén Castillo-Cano: methodology, investigation, writing – original draft. **Fabio Riefolo:** investigation, writing – review and editing. **Felipe Villalobos:** data access provider, investigation, writing – review and editing. **Mar Martín-Pérez:** data access provider, investigation, writing – review and editing. **Davide Messina:** software, data curation, writing – review and editing. **Roel Elbers:** software,

formal analysis, writing – review and editing. **Dorieke Brink-Kwakkel**: software, formal analysis, writing – review and editing. **Carlo Alberto Bissacco**: data curation, writing – review and editing. **Elena Segundo**: data access provider, writing – review and editing. **Luis Carlos Saiz**: investigation, writing – review and editing. **Leire Leache**: writing – review and editing. **Elisa Barbieri**: writing – review and editing. **Tiago Vaz**: software, data curation, writing – review and editing. **Rosa Gini**: software, data curation, methodology, writing – review and editing. **Olaf Klungel**: writing – review and editing. **Elisa Martín-Merino**: methodology, investigation, writing-review and editing.

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During the preparation of this work, the authors used Grammarly Pro, an AI-assisted technology, in order to improve the English edition and readability. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Ethics Statement

The independent ethics committee of Hospital Universitario de la Princesa from Spain approved the study with the registry number 4915. The Comitè Ètic d’Investigació amb medicaments (CEIm) de l’IDIAP Jordi Gol approved this study with the registry number 22/180-EOm.

Conflicts of Interest

All the authors declare financial support was provided by the European Medicines Agency and the following financial interests/personal relationships which may be considered potential competing interests: Fabio Riefolo is an employee of TEAMIT Institute, a research management organisation that participates in financially supported studies for the European Medicines Agency and related healthcare authorities, pharmaceutical companies and the European Union. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Felipe Villalobos is a salaried employee at Fundació Institut Universitari per a la recerca a l’Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), which receives institutional research funding

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Data Availability Statement

We have shared the link to an open/public repository including the script we developed for programming and the code list defining the variables in the manuscript: <https://github.com/VAC4EU/CoV-E-Public>.

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