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RESEARCH

Incidence of severe and non-severe SARS-CoV-2 infections in children and adolescents: a population-based cohort study using six healthcare databases from Italy, Spain, and Norway

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Abstract

We aim to estimate the incidence rates (IRs) of SARS-CoV-2 infections stratified by disease severity and comorbidities in pediatric population and to describe the COVID-19 vaccination coverage in children with and without comorbidities. A population-based cohort study was conducted in 6 electronic healthcare records databases from Italy, Spain, and Norway. The study lasted from 1 January 2020 to the latest databases' available data in each site, i.e., in Italian ARS Tuscany and PEDIANET: December 2021, in Spanish BIFAP: February 2022; SIDIAP: June 2022, and VID: December 2021. Finally, in Norwegian Health Registries: December 2021. Children and adolescents were included and stratified into three age categories (< 5, 5– < 12, and 12– < 18 years old). IRs (95% confidence intervals) per 100 person-years (PY) for non-severe (positive SARS-CoV-2 test or diagnosis without hospitalization) and severe COVID-19 (hospitalization, intensive care unit admission, and death after COVID-19) are reported. The cumulative COVID-19 vaccination rollout was stratified by population with and without comorbidities. The study population comprised 5,654,040 individuals < 18 years of age (51% females) across the six European databases (median age: 6 years), with 1.4 to 8.5% of them having at least one at-risk comorbidity for severe COVID-19. Incidence rates of severe COVID-19 were low (0–1 per 100 PY) but 3 to 4 times higher among children and adolescents with comorbidities during Omicron BA.1–2 wave in December 2021–January 2022. Percentages of vaccination rollout in the general population were between 13% in PEDIANET-IT and 64% in BIFAP-ICU-ES. In ARS-IT and SIDIAP-IT, vaccination rate in children with comorbidities was slightly lower than that in the general population. *Conclusion*: Severe COVID-19 was rare across databases, but up to 3 to 4 times higher in children with comorbidities during the predominance of Omicron BA.1–2 variant in winter 2021–2022. COVID-19 vaccination coverage was slightly lower in children with comorbidities in ARS (Tuscany) and SIDIAP (Catalonia) data sources. Our findings will inform future public policies aimed to protect the pediatric population, both within these countries and globally.

What is known:
- *Pediatric population is susceptible to SARS-CoV-2 infection.*
- *COVID-19 severity rates in children vary across study settings and context.*

What is new:
- *This study confirms the low severity rates of COVID-19 in the pediatric population based on a large cohort of children and adolescents residing in Spain, Italy, and Norway.*
- *Incidence of severe COVID-19 in children and adolescents with comorbidities was up to 3 to 4 times higher than in the general pediatric population during the SARS-CoV-2 high transmission wave of Omicron BA.1–2 variant in winter 2021–2022 in Italy and Spain.*

Keywords COVID-19 · SARS-CoV-2 · Incidence rate

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Introduction

Epidemiological knowledge of COVID-19 in the pediatric population is essential to implement evidence-based clinical and policy responses to protect children's health. Omicron BA.1–2 SARS-CoV-2 variant has been shown to be more transmissible and less virulent in the adult population [1, 2] but evidence regarding COVID-19 severity outcomes of post-Delta variants in pediatric population remains contradictory [3–6]. Besides, SARS-COV-2 infection has shown to hit more severely to the population with comorbidities, e.g., immunocompromised population [7]. However, this aspect has not been fully studied at younger ages. To determine severity rates in children with and without comorbidities will be an essential input to design public health interventions, including vaccination policies aimed to reach children at-risk to develop severe COVID-19.

Almost six months after the first COVID-19 vaccines were available in Europe, the European Medicines Agency (EMA) authorized the use of COVID-19 vaccines for adolescents 12 to 15 years old in May 2021 [8] and 12 to 17 years old in July 2021 [9]. Later, EMA granted indication extensions to children aged 5 to 11 years old [10, 11] and then to those > 6 months of age [12].

In this study, we aimed to estimate the incidence rates of non-severe and severe COVID-19 in children and adolescents with and without high-risk comorbidities in Spain, Italy, and Norway. Additionally, we described the COVID-19 vaccination coverage in these two populations.

Materials and methods

Study design, study population, and data sources

A population-based dynamic cohort study was conducted in six European electronic healthcare record databases. Children and adolescents < 18 years of age on January 1, 2020, entered the cohort. Follow-up ended at the first COVID-19 diagnosis (outcome), death, disenrollment, or the last available data (see Table 1). Missing age and sex information were a reason for exclusion, as well as having less than one year of look-back information prior to the start of follow-up, except when born during this period.

The data sources used were as follows: for Italy, the Agenzia Regionale di Sanità della Toscana database (ARS-IT) and Pedianet database (PEDIANET-IT) (including adolescents only until 14 years of age) and, for Spain, the Catalonian Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària database (SIDIAP-ES), the Valencian Health System Integrated Database (VID-ES), and the Spanish Pharmacoepidemiological Research Database for Public Health System database (BIFAP-ES) [13]. For Norway, several linked nationwide registries were used (NHR-NO): the Norwegian Surveillance System for Communicable Diseases (MSIS) registry including information about COVID-19 test, the National Patient Register (NPR) (secondary care contacts), the Norway Control and Payment of Health Reimbursement (KUHR) (primary care contacts), the National Prescription and Immunisation Registry, the Cause of Death Registry, and Statistics Norway covering sociodemographic information. BIFAP-ES contained medical records from primary care settings that were linked to hospital discharge diagnoses for a subset of the dataset. This hospital-linked subpopulation [BIFAP-ICU] is part of the primary care population [BIFAP-PC]. Further details are shown in Table 1. These databases were part of the COVID-19 Vaccine Monitoring (CVM) Study, a project funded by the EMA (EMA/2018/23/PE). The study protocol is available on the HMA-EMA Catalog of RWD studies under the registry no. 42467 [14].

Variables and covariates

COVID-19 cases were identified through diagnosis codes, disease registries, and positive SARS-CoV-2 PCR or antigen tests. IT-ARS, ES-SIDIAP, and ES-VID identified COVID-19 cases using codes of the International Classification of Diseases (ICD) 9-clinical modification (CM) (518.91, 480.41, 043.31, 043.21, and 043.11), ICD10 (U10, U07.1, U07.2, B97.2, and B34.2), and ICD10-CM (U10, U07.1, U07.2, B97.2, and J12.82). ARS-IT and BIFAP-ES used a disease registry as well, while PEDIANET-IT used positive SARS-CoV-2 PCRs. NHR-NO used information from MSIS registry to obtain information on SARS-CoV-2 positive tests.

Two COVID-19 severity levels were defined. Non-severe disease was defined as COVID-19 confirmed diagnosis or positive SARS-CoV-2 infection without hospitalization. Severe disease was defined as a combination of (i) hospitalization related to COVID-19 14 days after diagnosis, diagnostic code retrieved in hospital, or patient registry indicating hospitalization; (ii) intensive care unit (ICU) admission related to COVID-19 after 14 days of diagnosis; and (iii) death within 56 days after COVID-19 diagnosis. All COVID-19 vaccines approved by EMA until January 2022 were captured in the databases. Manufacturers, doses, and calendar months of administration were collected for every vaccination episode. When no information about the vaccine manufacturer was available, it was processed as unknown.

Individuals at increased risk of developing severe COVID-19 were identified according to the presence of at least one of the following comorbidities during the look-back period until the start of follow-up (one year), except for newborns: cancer, chronic respiratory diseases, diabetes types I and II, cardiovascular and chronic kidney disease,

Table 1 Data source characteristics and attrition

	IT-ARS	IT-PEDIANET	ES-BIFAP_PC	ES-BIFAP_ICU	ES-FISABIO	ES-SIDIAP	NO-NHR
	Data source characteristics						
Type of data source	Record linkage of inhabitant registry, hospital administrative records, vaccine registry, and COVID-19 registry	Primary care medical records from pediatricians including automatic notifications of discharge letters from hospital and direct linkage COVID-19 molecular swab and vaccination registry	Primary care medical records linked to COVID-19 registry	Primary care medical records with COVID-19 registry and linkage to ICU data	Primary care medical records linked to hospital administrative records. Linkage with inhabitant registry, ICU data, COVID-19 registry, emergency room and vaccine registry	Primary care medical records linked to hospital administrative records	Reimbursement registry for healthcare and patient registry which cover primary and secondary care contacts with linkage to vaccination registry, infections disease registry, cause of death registry and Statistics Norway
Study period end date	31dec2021	31dec2021	28feb2022	28feb2022	31dec2021	30jun2021	31dec21
Coding systems for diagnoses	ICD9CM	ICD9	ICPC, SNOMED	ICPC, SNOMED	ICD10	ICD10	ICD10, ICPC
	Attrition						
Persons in the data source	785,279	49,132	16,316,690	16,316,690	5,997,737	6,968,416	5,664,825
Sex or birth date missing or implausible, no dates of entry or exit	64	0	1975	1975	2342	545,955	0
Other exclusion criteria (> 18 years, death or exit before study start),	263,862	8361	14,209,847	15,381,025	5,066,806	5,460,261	4,532,051
Persons aged 0–17 years in the data source at study start	521,353	40,771	2,104,868	933,690	928,589	962,200	1,132,774
Less than 365 days history at 1/1/2020	9125	107	59,961	24,424	17,832	23,296	110
Pediatric study population	512,228	40,664	2,044,907	909,266	910,757	938,904	1,132,664

IT-ARS Agenzia Regionale Di Sanità della Toscana database, Italy; *IT-PEDIANET* Italian Societa Servizi Telematici database; *ES_BIFAP_PC* Base de datos para la Investigación Farmacoepidemiológica en el Ámbito Público, Primary care linked to COVID-19 registry, Spain; *ES_BIFAP_ICU* Base de datos para la Investigación Farmacoepidemiológica en el Ámbito Público, Primray care linked to COVID-19 registry and ICU admissions, Spain; *ES-VID* Valencian Health System Integrated Database, Spain; *ES-SIDIAP* Catalonian Sistema d'Informació per al desenvolupament de la Investigació en Atenció Primària database, Spain; *NO-NHR* Norwegian Health Registries, Norway

immunodeficiencies, obesity, and sickle cell disease. These conditions were identified by a combination of diagnosis codes and evidence of use of certain drugs [14].

Statistical analysis

Descriptive characteristics of the population are presented as number (percentage), person-time (PT), or median [interquartile range (IQR)]. The cohort was stratified in age bands as < 5 years, 5– < 12 years, and 12– < 18 years of age. Incidence rates (IRs) of non-severe and severe COVID-19 cases in both the general and the population with comorbidities were calculated by dividing the number of cases (numerator) by the PT of follow-up (denominator). Confidence intervals were obtained by the exact method [15]. All persons were censored 1 to 6 days after the vaccination day. The vaccination rollout (1st dose) per calendar month is presented as cumulative percentages in the study population 5– < 18-year-old.

Data management and quality assessment

Data sources converted their local data into the ConcePTION Common Data Model (CDM) [16]. Converted data was quality-checked for completeness, plausibility, and accuracy (https://github.com/UMC-Utrecht-RWE). A common analysis R-script was centrally developed, and it is publicly available at https://github.com/VAC4EU/CVM/blob/Release_covid_children/p_steps/step_05_12_T2.2_COVID_repeated_events.R. Data providers transferred the aggregated output to the Digital Research Environment (DRE)®, a secure web repository for post-processing steps such as data pooling.

Results

The total study population comprised 5,654,040 children and adolescents < 18 years of age; 51% were females. The median age was 9 years across data sources, except in PEDIANET-IT (6 years). Table 1 shows database characteristics and attrition of the source population. Demographic characteristics at the start of follow-up are presented in Table 2.

The population with at least one comorbidity comprised 420,834 children and adolescents (7.4%). The prevalence of the population with comorbidities varied between 4.7% to 8.5% of the general pediatric population, except for PEDIANET-IT (1.4%). In ARS-IT, BIFAP-ES, and SIDIAP-ES, the median age of those with comorbidities was lower than the median age of the general population. The most frequent comorbidities were chronic respiratory diseases, including asthma.

Incidence rates of COVID-19

Figure 1 and Fig. 2 show monthly IRs of non-severe and severe COVID-19 in the general population and children and adolescents with comorbidities, monthly IRs with confidence intervals are presented in supplementary tables 1 to 4. In Italian databases (ARS-IT and PEDIANET-IT), the highest monthly rates of non-severe COVID-19 in the general population were reported in December 2021 for all age bands (18.0 to 48.7 per 100 PY). The highest rates of severe COVID-19 in children < 5 years of age in the general population ranged from 0.05 in ARS-IT in February 2021 to 0.26 per 100 PY in PEDIANET-IT in December 2021, while in children with comorbidities the highest rates were reached in December 2021 (0.14 and 28/100 PY in ARS-IT and PEDIANET-IT, respectively). In population 5– < 12 years old with comorbidities, rates were higher than in the general population (0.14 and 3.5/100 PY for ARS-IT in February 2021 and for PEDIANET-IT in December 2021, respectively). In adolescents with comorbidities, the highest IR of severe COVID-19 in ARS-IT was reached in August 2021 at 0.4/100 PY and in PEDIANET-IT in November 2020 at 11/100 PY. PEDIANET-IT numbers are affected by the reduced sample size (see 95% confidence intervals in supplementary Table 4).

In the Spanish general population, the highest monthly IRs (per 100 PY) of non-severe COVID-19 in children of all ages reached 143 in BIFAP-ES in January 2022, 43.3 in VID-ES (January 2021), and 50.8 in SIDIAP-ES (December 2021). The highest rates of severe COVID-19 disease in children < 5-year-old in the general population were 1.3/100 PY in BIFAP-ES in January 2022, 0.08 in VID-ES (August 2021), and 0.18 in SIDIAP-ES (July 2021). In children with comorbidities, IRs were higher than in the general population (in January 2022 in BIFAP-ES 2.9/100 PY, in January 2021 in VID-ES 0.24/100 PY, and in July 2021 in SIDIAP-ES 0.44/100 PY). The highest rates of severe COVID-19 in children 5– < 12 years decreased to 0.76 in BIFAP-ES in January 2022, 0.03 in VID-ES (December 2021), and 0.67 in SIDIAP-ES in July 2021. In children 5– < 12 years with comorbidities, the incidence of severe COVID-19 was higher than in the general population with rates of 1.1/100 PY in January 2022 in BIFAP-ES, 0.18/100 PY in VID-ES in January 2021, and 0.31/100 PY in SIDIAP-ES in December 2021. The highest incidence of severe COVID-19 in the general adolescent population was reached in January 2022 in BIFAP-ES (0.33/100 PY), in August 2021 in VID-ES (0.10/100 PY), and in December 2021 in SIDIAP-ES (0.28/100 PY). In adolescents with comorbidities, the highest rate for BIFAP_PC-ES was in January 2021: 0.33/100 PY, for BIFAP_ICU-ES was in November 2021: 0.43/100 PY, for VID-ES was in August 2021: 0.21/100 PY. Finally, in SIDIAP-ES, the highest estimate was 0.48/100 PY in July 2021.

Table 2 Demographic characteristics of the pediatric general population and the population with comorbidities as risk factors to develop severe COVID-19

	IT-ARS		IT-PEDIANET		ES-BIFAP_PC		ES-BIFAP_ICU		ES-VID		ES-SIDIAP		NO-NHR	
	Demographic characteristics of the pediatric general study population													
Pediatric Study population (n)	512,228		40,664		2,044,907		909,266		910,757		1,012,820		1,132,664	
Follow-up time (person-years)	861,913		73,672		3,497,779		1,552,515		1,524,587		1,714,628		2,010,144	
Male person-years (%)	48.5%		48.6%		48.6%		48.5%		48.4%		48.5%		48.6%	
Female person-years (%)	51.5%		51.4%		51.4%		51.5%		51.6%		51.5%		51.4%	
Age in years (median, IQR)	9 [5,–13]		6 [3,–9]		9 [5,–13]		9 [5,–13]		9 [5,–13]		9 [5,–13]		9 [4,–13]	
Age in categories (%)														
0–<5	22.3%		38.3%		23.2%		23.5%		22.8%		23.9%		26.0%	
5–<12	41.4%		52.8%		41.4%		41.0%		40.7%		40.3%		40.0%	
12–<18	36.3%		8.9%		35.4%		35.6%		36.5%		35.8%		34.0%	
Pediatric population with comorbidity (n, %)	42,482	(8.3%)	560	(1.4%)	99,622	(4.9%)	43,085	(4.7%)	68,851	(7.6%)	86,163	(8.5%)	80,071	(8.5%)
Cancer	771	(0.15%)	<5		3935	(0.19%)	590	(0.06%)	569	(0.06%)	924	(0.09%)	571	(0.05%)
Chronic lung disease	32,030	(6.25%)	269	(0.66%)	70,300	(3.44%)	30,510	(3.36%)	48,179	(5.29%)	59,516	(5.88%)	64,079	(5.66%)
Diabetes	899	(0.18%)	10	(0.02%)	3519	(0.17%)	1,510	(0.17%)	1,650	(0.18%)	1751	(0.17%)	3335	(0.29%)
Cardiovascular/chronic kidney disease	1774	(0.35%)	14	(0.03%)	5604	(0.27%)	2,150	(0.24%)	1,229	(0.13%)	2951	(0.29%)	7870	(0.69%)
Immunodeficiencies*	12,974	(2.53%)	NA		16,901	(0.83%)	8594	(0.95%)	28	(0.00%)	16,226	(1.60%)	3547	(0.31%)
Other**	282	(0.06%)	269	(0.66%)	8677	(0.42%)	4446	(0.49%)	19,102	(2.10%)	17,365	(1.71%)	4446	(0.39%)
	Demographic characteristics of the pediatric population with comorbidities as risk factors to develop severe COVID-19													
Study population (n)	42,482		560		99,622		43,085		68,851		86,163		80,071	
Follow-up time (person-years)	74,771		1,001		175,420		75,753		117,470		152,461		141,564	
Male person-years (%)	42.8%		41.5%		41.8%		41.8%		43.5%		42.7%		42.6%	
Female person-years (%)	57.2%		58.5%		58.2%		58.2%		56.5%		57.3%		57.4%	
Age in years (median, IQR)	6 [3–11]		8 [5–10]		7 [3–12]		7 [3–12]		9 [4–13]		6 [3–11]		9 [4–13]	
Age in categories (%)														
0–<5	36.9%		20.7%		36.0%		38.1%		26.5%		38.0%		26.3%	
5–<12	39.7%		67.0%		38.1%		36.6%		37.9%		38.9%		38.5%	
12–<18	23.4%		12.3%		26.0%		25.3%		35.6%		23.1%		35.2%	

IT-ARS Agenzia Regionale Di Sanità della Toscana database, Italy; *IT-PEDIANET* Italian Societa Servizi Telematici database; *ES_BIFAP_PC* Base de datos para la Investigación Farmacoepidemiológica en el Ámbito Público, Primary care linked to COVID-19 registry, Spain; *ES_BIFAP_ICU* Base de datos para la Investigación Farmacoepidemiológica en el Ámbito Público, Primray care linked to COVID-19 registry and ICU admissions, Spain; *ES-VID* Valencian Health System Integrated Database, Spain; *ES-SIDIAP* Catalonian Sistema d'Informació per al desenvolupament de la Investigació en Atenció Primària database, Spain; *NO-NHR* Norwegian Health Registries, Norway; *NA* not assessed

*Includes use of immunosuppressants

**Obesity or Sickle cell disease

Fig. 1 Monthly incidence rates of non-severe COVID-19 in the general population and in children with comorbidities

Fig. 2 Monthly incidence rates of severe COVID-19 in the general population and in children with comorbidities

In Norway, the highest IR of non-severe COVID-19 disease was reached in December 2021: 28.6/100 PY in children 0– < 5-year-old, 63.8/100 PY in children 5– < 12 years old, and 40/100 PY in adolescents. Rates of severe COVID-19 were almost zero across all age categories. For the pediatric population with comorbidities, IRs were zero, except for few cases detected in November 2021 (0.04/100 PY).

COVID-19 vaccination

Almost no vaccinated individuals were observed in children < 5-year-old (≈0%) during the observation period. Figure 3 depicts cumulative COVID-19 vaccination uptake (1st dose, all brands) over calendar months, both in the general population and in the population with comorbidities. In 5– < 18-year-old general population subjects, the vaccination cumulative percentage was higher in Spain than in Norway and Italy (56.1% in BIFAP-PC-ES, 64% in BIFAP-ICU-ES, 56% in VID-ES, 54% in SIDIAP-ES, vs 38% in NHR-NO, and 41.8% in ARS-IT, 13% in PEDIANET-IT). Among children with comorbidities, vaccination uptake was: 81% in BIFAP-PC-ES, 100% in BIFAP-ICU-ES, 62% in VID-ES, 56% in SIDIAP-ES, 42% in NHR-NO, 39% ARS-IT, and 13% in PEDIANET-IT. Most children (≥ 79%) received the Pfizer/BioNTech vaccine across all countries.

Discussion

In this study, incidence rates of non-severe and severe pediatric COVID-19 were low but reached the highest level during Omicron BA.1–2 peak in December 2021 and January 2022. In children with comorbidities, incidence rates were higher across all databases and subpopulations in comparison to the rates in the general pediatric population. We report incidence rates of severe COVID-19 as a composite outcome of hospitalization, ICU admission, or death after COVID-19, rates might therefore be higher than individual hospitalization and mortality rates reported elsewhere, although comparable. Previous studies in Italian children 5– < 12-year-old and adolescents 12– < 18-year-old showed a cumulative hospitalization rate of 0.034 and 0.038/100 persons, respectively [17]. In Spanish population, COVID-19 mortality rates were reported as 0.18 and 0.37/100,000 persons in children < 9-year-old and in adolescents 10–19 year-old, respectively [18]. Our results shows low rates of severe COVID-19 during the study period, with incidence peaks following Omicron BA.1–2 waves. This finding is aligned with morbidity and mortality rates reported in 2020 and 2021 in Canada, France, Germany and Italy in children 0–14 years of age [19]. Adolescents > 15-year-old seem more susceptible to Omicron BA.1–2 variant than pre-Omicron ones [2]. In general, low severity rates of COVID-19 among children may be related to factors such as variances in receptor and proteinase expression (ACE2, CD147, glucose-related protein (GRP78), and TMPRSS2) [20], stronger innate and adaptive immunity, more frequent concurrent infections, coronaviruses pre-existing immunity, differences in microbiota, higher levels of melatonin, and lower SARS-CoV-2 intensity of exposure [21].

Underlying medical conditions, such as chronic respiratory disease, immunodeficiencies, obesity, and others, have been described as risk factors for developing severe COVID-19 in children [22–25]. We report between 4.7% and 8.5% of children with at least one high risk comorbidity. Similar to previous publications [25], chronic respiratory diseases, including asthma, were the most prevalent comorbidities. Our findings confirm that SARS-CoV-2 infection in children with comorbidities resulted in higher rates of severe disease than in the general pediatric population in Spain and Italy. Furthermore, during the Omicron BA.1–2 wave in winter 2021–2022, severity rates in children with comorbidities tripled the rates in children aged 5– < 12 years and younger, and rose up to 4 times in adolescents with comorbidities. In general, severe cases of COVID-19 in Norway were rare, confirming previous findings [3].

Vaccination uptake was extensive among children 5– < 18-year-old (around 51% at the end of the series), excluding PEDIANET-IT (13%). In all data sources but in ARS-IT (Tuscany) and SIDIAP-ES (Catalonia), vaccine coverage was slightly higher in the general population than in children with comorbidities. This finding could denote different prioritization policies and strategies to reach children with pre-existing risk factors to develop severe COVID-19 by national and local authorities. Moreover, it has also been shown higher vaccine hesitancy figures in parents of children with comorbidities, e.g., transplant recipients [26–28]. In general, our results emphasize the need to design and implement policies and strategies to protect children with comorbidities against severe COVID-19. Furthermore and given the results obtained in the Norwegian database, this study also highlights the need for research across different geographic regions with diverse responses to the COVID-19 pandemic in terms of children protection.

The accuracy of data sources to detect SARS-CoV-2 infection as they are mostly based on diagnoses and registries of PCR/antigen tests is a main strength of this study. There are, however, limitations to be acknowledged. First, ICU admissions could not be estimated for each data source, and hospitalization after COVID-19 was estimated using primary and secondary diagnosis. Therefore, there may be some misclassification, but review of records showed that secondary diagnoses of COVID-19 were related to the cause of hospitalization. Second, comorbidities were identified during the look-back period. Potential new comorbidities appearing after the start of follow-up were not captured, which may lead to some misclassification of the population. Finally, incidence rates were

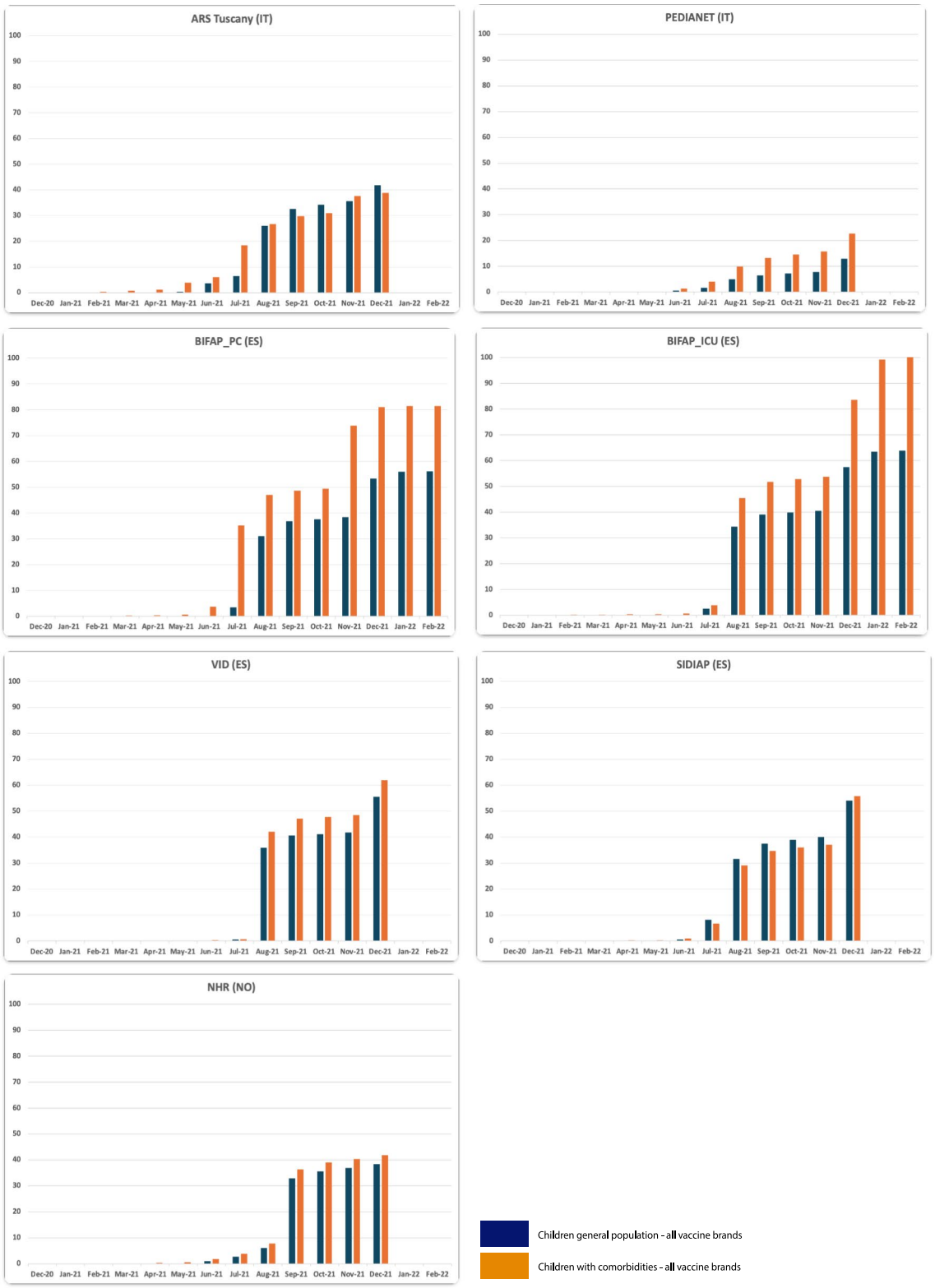

Fig. 3 Cumulative percentage of COVID-19 vaccination uptake (1st dose, all brands) over calendar months in the general pediatric population and in children with comorbidities

not stratified by vaccination status. We avoided this analysis due to missing clinical information to properly adjust variables among vaccinated and non-vaccinated children.

Conclusions

This study included over 5.6 million children in six data sources in Italy, Spain, and Norway. Rates of severe COVID-19 were low in all data sources but up to 3 to 4 times higher in children with comorbidities, mainly during the predominance of the Omicron BA.1–2 SARS-CoV-2 variant in winter 2021–2022. COVID-19 vaccination coverage was slightly lower in children with comorbidities in ARS-IT (Tuscany) and SIDIAP-ES (Catalonia) data sources. Our findings will inform future vaccination efforts and public policies aimed to protect the pediatric population, both in these countries and globally.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00431-024-05864-1.

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Authors' contributions MS, CED, RG and FR contributed to the study design. Analysis scripts were prepared by RG and DM. Data preparation and running of analysis scripts were performed by EB, PG, MM, FV, LS, JJC, AU, ECM, JZ, AL, and HN. The first draft of the manuscript was written by CED and FR. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The data that support the findings of this study are available from the authors but restrictions apply to the availability of these data, and so are not publicly available. Data are, however, available from the authors upon reasonable request.

Declarations

Ethics approval Most data partners that provided data for the hereinpresented results had passed the local ethical review process for the whole COVID-19 Vaccine Monitor study (EUPAS42467); Norwegian data (NHR): Regional Committee for Research Ethics (approval number 155294/REK Nord) and the Data Protection Officer at the University of Oslo (approval number 523275); Valencian data (VID): Comité Ético de Investigación con Medicamentos del Hospital General Universitario de Elche (approval number: PI-90/2021); Catalonian data (SIDIAP): Comitè Ètic d'Investigació amb medicaments (CEIm) de l'IDIAP Jordi Gol (approval number: 21/199-PCV); and BIFAP (several Spanish regions): Comité de Ética de la Investigación con Medicamentos del Hospital Universitario de la Princesa and Comité Científico de BIFAP (approval number: CEIm 14/21). There was no need of ethical committee approval for Italian databases (ARS and PEDIANET). This research adhered to the rules and principles of the European Network of Centers of Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct.

Consent to participate This research was conducted using secondary heathcare data. Informed consent to participate was not obtained. The whole COVID-19 Vaccine Monitor study (EUPAS42467) was conducted following the ENCePP Code of Conduct.

Competing interests The authors declare no competing interests.

References

1. Shao W, Zhang W, Fang X et al (2022) Challenges of SARS-CoV-2 Omicron variant and appropriate countermeasures. J Microbiol Immunol Infect 55(3):387–394. https://doi.org/10.1016/j.jmii.2022.03.007
2. Hu FH, Jia YJ, Zhao DY et al (2023) Clinical outcomes of the severe acute respiratory syndrome coronavirus 2 Omicron and Delta variant: systematic review and meta-analysis of 33 studies covering 6 037 144 coronavirus disease 2019-positive patients. Clin Microbiol Infect 29(7):835–844. https://doi.org/10.1016/j.cmi.2023.03.017
3. Chun JY, Jeong H, Kim Y (2022) Identifying susceptibility of children and adolescents to the Omicron variant (B.1.1.529). BMC Med 20(1):451. https://doi.org/10.1186/s12916-022-02655-z
4. Whittaker R, Greve-Isdahl M, Bøås H et al (2022) COVID-19 Hospitalization among children <18 years by variant wave in Norway. Pediatrics 150(3):e2022057564. https://doi.org/10.1542/peds.2022-057564
5. Butt AA, Dargham SR, Loka S et al (2022) Coronavirus Disease 2019 disease severity in children infected with the omicron variant. Clin Infect Dis 75(1):e361–e367. https://doi.org/10.1093/cid/ciac275
6. Iuliano AD, Brunkard JM, Boehmer TK et al (2022) Trends in disease severity and health care utilization during the early Omicron variant period compared with previous SARS-CoV-2 high transmission periods - United States, December 2020-January 2022. MMWR Morb Mortal Wkly Rep 71(4):146–152. https://doi.org/10.15585/mmwr.mm7104e4
7. Evans RA, Dube S, Lu Y et al (2023) Impact of COVID-19 on immunocompromised populations during the Omicron era: insights from the observational population-based INFORM study. Lancet Reg Health Eur 13(35):100747. https://doi.org/10.1016/j.lanepe.2023.100747.
8. European Medicines Agency. First COVID-19 vaccine approved for children aged 12 to 15 in EU. First COVID-19 vaccine approved for children aged 12 to 15 in EU | European Medicines Agency (europa.eu). Accessed 14 Dec 2023
9. European Medicines Agency. COVID-19 vaccine Spikevax approved for children aged 12 to 17 in EU. https://www.ema.europa.eu/en/news/covid-19-vaccine-spikevax-approved-children-aged-12-17-eu. Accessed 14 Dec 2023

10. European Medicines Agency. EMA recommends approval of Spikevax for children aged 6 to 11. https://www.ema.europa.eu/en/news/ema-recommends-approval-spikevax-children-aged-6-11. Accessed 14 Dec 2023
11. European Medicines Agency. Comirnaty COVID-19 vaccine: EMA recommends approval for children aged 5 to 11. https://www.ema.europa.eu/en/news/comirnaty-covid-19-vaccine-ema-recommends-approval-children-aged-5-11. Accessed 14 Dec 2023
12. European Medicines Agency. EMA recommends approval of Comirnaty and Spikevax COVID-19 vaccines for children from 6 months of age. https://www.ema.europa.eu/en/news/ema-recommends-approval-comirnaty-spikevax-covid-19-vaccines-children-6-months-age. Accessed 14 Dec 2023
13. Maciá-Martínez MA et al (2020) Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP): A data resource for pharmacoepidemiology in Spain. Pharmacoepidemiol Drug Saf 29:1236–1245
14. EUPAS42467 study protocol. https://www.encepp.eu/encepp/viewResource.htm?id=42637. Accessed 15 Dec 2023
15. Ulm K (1990) A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 131(2):373–375. https://doi.org/10.1093/oxfordjournals.aje.a115507
16. Thurin NH, Pajouheshnia R, Roberto G et al (2022) From Inception to ConcePTION: genesis of a network to support better monitoring and communication of medication safety during pregnancy and breastfeeding. Clin Pharmacol Ther 111(1):321–331. https://doi.org/10.1002/cpt.2476
17. Martella M, Peano A, Politano G et al (2023) Paediatric hospitalizations over three waves of COVID-19 (February 2020 to May 2021) in Italy: determinants and rates. PeerJ 11:e15492. https://doi.org/10.7717/peerj.15492
18. Tagarro A, García-Salido A, Martínez EV et al (2021) Low COVID-19 mortality in Spanish children. Lancet Child Adolesc Health 5:e24–e25
19. Yuan L, Sun C, Zeng Z et al (2024) Children aged 0–14 years had a far lower mortality risk during the entire COVID-19 pandemic in four major industrial countries: an observational study. Eur J Pediatr 183:2645–2653. https://doi.org/10.1007/s00431-024-05522-6
20. Ahmed IS, Tapponi SL, Widatallah ME et al (2023) Unmasking the enigma: an in-depth analysis of COVID-19 impact on the pediatric population. J Infect Public Health 16:1346–1360
21. Zimmermann P, Curtis N (2021) Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. Arch Dis Child 106:429–439
22. Moreira A et al (2021) Demographic predictors of hospitalization and mortality in US children with COVID-19. Eur J Pediatr 180:1659–1663
23. Otto WR et al (2020) The epidemiology of severe acute respiratory syndrome coronavirus 2 in a pediatric healthcare network in the United States. J Pediatric Infect Dis Soc 9:523–529
24. Hernández-García M, Solito C, Pavón Ortiz A et al (2023) Characteristics and risk factors associated with SARS-CoV-2 pneumonias in hospitalized pediatric patients: a pilot study. Children (Basel) 10(10):1703. https://doi.org/10.3390/children10101703
25. Kompaniyets L, Agathis NT, Nelson JM et al (2021) Underlying medical conditions associated with severe COVID-19 illness among children. JAMA Netw Open 4(6):e2111182. https://doi.org/10.1001/jamanetworkopen.2021.11182
26. Zheng Z, Lu Y, Wang M et al (2023) Low COVID-19 vaccine coverage and guardian acceptance among pediatric transplant recipients. J Med Virol 95(1):e28377. https://doi.org/10.1002/jmv.28377
27. Stefanizzi P, Bianchi FP, Moscara L et al (2023) Determinants of compliance to influenza and COVID-19 vaccination in a cohort of solid organ transplant patients in Puglia, Southern Italy (2017–2022). Hum Vaccin Immunother 19(3):2266932. https://doi.org/10.1080/21645515.2023.2266932
28. Keens M, Guttoo P, Stanek JR et al (2022) An exploration of COVID-19 Impact and vaccine hesitancy in parents of pediatric hematopoietic stem cell transplant (HCT) recipients. Bone Marrow Transplant 57(4):547–553. https://doi.org/10.1038/s41409-022-01587-9

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