



OPEN ACCESS

EDITED BY

Andras Bratincsak,
University of Hawaii, United States

REVIEWED BY

Luca Pierantoni,
Sant'Orsola-Malpighi Polyclinic, Italy
Caterina Campoli,
Infectious Disease Unit IRCCS "Policlinico di
Sant'Orsola", Italy

*CORRESPONDENCE

Michaela Semeraro
✉ michaela.semeraro@aphp.fr

[†]Data used in preparation of this article were obtained from the AP-HP Covid Clinical Data Warehouse (CDW). As such, the members of the AP-HP Covid CDW initiative contributed to the design and implementation of the database but did not participate in analysis or writing of this report. A complete listing of members can be found at: <https://eds.aphp.fr/covid-19> and in **Supplementary Material Table S1**.

SPECIALTY SECTION

This article was submitted to Pediatric Cardiology, a section of the journal Frontiers in Pediatrics

RECEIVED 14 September 2022

ACCEPTED 31 January 2023

PUBLISHED 27 February 2023

CITATION

Semeraro M, Pinson P, Populaire M, Dellagi M, Oualha M, Beeker N and Chappuy H (2023) Analysis of the impact of the SARS-CoV-2 infection on the pediatric population hospitalized during the pandemic in the Greater Paris University Hospitals. *Front. Pediatr.* 11:1044352. doi: 10.3389/fped.2023.1044352

COPYRIGHT

© 2023 Semeraro, Pinson, Populaire, Dellagi, Oualha, Beeker and Chappuy. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Analysis of the impact of the SARS-CoV-2 infection on the pediatric population hospitalized during the pandemic in the Greater Paris University Hospitals

Michaela Semeraro^{1,2*}, Pierre Pinson^{2,3}, Margaux Populaire¹, Mourad Dellagi^{2,3}, Mehdi Oualha^{2,3,4} and Nathanael Beeker^{2,3}
Hélène Chappuy^{2,3,4,5} on behalf of AP-HP/Universities/INSERM COVID-19 research collaboration and AP-HP COVID CDR Initiative[†]

¹Centre D'Investigation Clinique-Unité de Recherche Clinique, Hôpital Universitaire Necker Enfants-Malades, GH Paris Centre, Paris, France, ²EA7323 Pediatric and Perinatal Drug Evaluation and Pharmacology, Université Paris Cité, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France, ³Unité de Recherche Clinique, Hôpital Cochin, Paris, France, ⁴Pediatric Intensive Care Unit, Necker-Enfants-Malades University Hospital, Assistance Publique-Hôpitaux de Paris, Paris University, EA7323, Paris, France, ⁵Service D'Urgences Pédiatriques, Hôpital Necker - Enfants Malades, Groupe Hospitalier AP-HP, Centre, EA7323, Université Paris Cité, Paris, France

Background: The clinical characteristics, disease progression and outcome in children affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection appear significantly milder compared to older individuals. Nevertheless, the trends in hospitalization and clinical characteristics in the pediatric population seem to be different over time across the different epidemic waves.

Objective: Our aim was to understand the impact of the different COVID-19 variants in the pediatric population hospitalized in the Pediatric Departments of the Public Hospital in the Greater Paris area by the analysis performed with the Assistance Publique-Hopitaux de Paris (AP-HP) Health Data Warehouse.

Methods: This is a retrospective cohort study including 9,163 patients under 18 years of age, hospitalized from 1 March 2020 to 22 March 2022, in the Paris area, with confirmed infection by SARS-CoV-2. Three mutually exclusive groups with decreasing severity (Pediatric Inflammatory Multisystem Syndrome (PIMS), symptomatic infection, mild or asymptomatic infection) were defined and described regarding demography, medical history, complication of the SARS-CoV-2 infection, and treatment during admission. Temporal evolution was described by defining three successive waves (March–September 2020, October 2020–October 2021, and November 2021–March 2022) corresponding to the emergence of the successive variants.

Results: In the study period, 9,163 pediatric patients with SARS-CoV-2 infection were hospitalized in 21 AP-HP hospitals. The number of patients with SARS-CoV-2 infection increased over time for each wave of the pandemic (the mean number of patients per month during the first wave was 332, 322 during the 2nd, and 595 during the third wave). In the medical history, the most associated concomitant disease was chronic respiratory disease. Patients hospitalized during the third wave presented a higher incidence of pulmonary involvement (10.2% compared to 7% and 6.5% during the first and second waves, respectively). The highest incidence of PIMS was observed during the first and second waves (4.2% in the first and second waves compared to 2.3% in the 3rd wave).

Discussion: This analysis highlighted the high incidence of hospitalized children in the Greater Paris Area during the third wave of SARS-CoV-2 pandemic corresponding to the Omicron Covid-19 variant, which is probably an expression of a concomitant SARS-CoV-2, while a decreased incidence of PIMS complication was observed during the same period.

KEYWORDS

data warehouse, SARS-CoV-2, children, PIMS, MIS-C multisystem inflammatory syndrome in children, hospitalized child

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic was declared by the World Health Organization on 11 March 2020. Since this time, several waves of infections related to specific variants of the SARS-CoV-2 have emerged. These variants are due to the virus's acquired additional advantageous mutations, potentially altering transmissibility, severity, and escape from natural or vaccine-derived immunity.

Compared to adults, SARS-CoV-2 infection in the children population presented different characteristics and courses (1–3). First data from China suggested that pediatric COVID-19 infections might be less severe than cases in adults, and children might experience different symptoms than adults (4).

In this regard, specific characteristics and consequences of the pandemic in young patients have been described. First of all, since the beginning of the pandemic, several countries reported cases of a rare Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS) also named Multisystem Inflammatory Syndrome in Children (MIS-C), characterized by Kawasaki-like symptoms and toxic shock syndrome (5–7).

The impact of the variants on the clinical courses in adult patients is well known (i.e., the Omicron-variant surge has been characterized by a mild severity of the disease compared to the Delta variant infection (8)), but little is known about the different patterns of clinical characteristics and outcomes in pediatric patients according to the different surges of infection.

The aim of this study was to understand the impact of the COVID-19 variants in the pediatric population presenting with SARS-CoV2 infection hospitalized in the Public Hospitals of the Paris metropolitan area over the different surges of the pandemic and particularly during the last Omicron variant.

Methods

Data source

The Assistance Publique-Hôpitaux de Paris (AP-HP) is the largest hospital entity in Europe, with 39 hospitals (22,474 beds) mainly located in the Greater Paris area.

This retrospective cohort study was conducted using the Assistance Publique-Hopitaux de Paris (AP-HP) Health Data Warehouse (Entrepôt de Données de Santé (EDS), <https://eds.aphp.fr/>; AP-HP Covid Clinical Data Warehouse (CDW)). This

data warehouse contains electronic health records (EHRs) of all inpatients from the 39 greater Paris university hospitals. The clinical data repository has received authorization from the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, number 1980120).

As such, the members of the AP-HP Covid CDW initiative contributed to the design and implementation of the database but did not participate in the analysis or writing of this report. A complete listing of members can be found at <https://eds.aphp.fr/covid-19>.

This analysis follows recommendations provided by the Reporting of Studies Conducted Using Observational Routinely Collected Health Data Statement (9).

This study was approved by the institutional review board (N° CSE: CSE 20–48_COVIDPed; AP-HP CDW Scientific and Ethics Committee number IRB00011591) of the scientific and ethical committee of the AP-HP. All subjects included in this study were informed about the reuse of their data for research, and subjects who objected to the reuse of their data were excluded from this study in accordance with French legislation.

Patients and study groups

We retrospectively retrieved the data of all patients with COVID-19 infection hospitalized in one of the AP-HP hospitals between March 2020 and March 2022 from the EDS-COVID database.

Inclusion criteria were:

1. Full hospitalization in one of the AP-HP pediatric departments between 1 March 2020 and 22 March 2022.
2. SARS-CoV-2 positive diagnosis and/or PIMS diagnosis according to the International Classification of Diseases (ICD-10 code) related to the hospitalization or positive SARS-CoV2 PCR test between 5 days prior to the start of the hospitalization and 15 days after.
3. Minor patient (<18 years old) at the time of hospitalization.

Comorbidities were extracted from ICD-10 codes used during the previous hospitalizations of each patient if available. Outcomes and treatments during hospitalization were obtained from the current hospitalization codes (ICD-10 and technical treatment French codification-CCAM). PIMS outcome code screening was extended up to 28 days after the start of hospitalization considering the delay between SARS-CoV-2 infection and PIMS described in the literature (10).

Correspondence between variables and codes is presented in **Supplementary Material Table S2**.

Age at admission, sex, intensive care unit (ICU) admission, and death during hospitalization were obtained from the hospital administrative data.

Data are presented as mean (standard deviation) and numbers (%).

The study population comprised three retrospective cohorts:

Cohort 1: Patients who had their first SARS-CoV-2 infections or PIMS between March 2020 to September 2020 corresponding to the emergent first historical variant cohort.

Cohort 2: Patients hospitalized during the second wave, October 2020 to October 2021, including the emergent Delta and Alpha/Beta/Gamma variant cohorts in addition to the cohort of patients without a determined variant type.

Cohort 3: Patients hospitalized during the third wave, November 2021 to February 2022, corresponding to the Delta and Omicron variant cohorts and patients with a non-determined variant.

For the analysis of the population, we defined three mutually excluded groups with decreasing severity. The first group was represented by pediatric patients with PIMS diagnosis or acute myocarditis. The second group was represented by pediatric patients with a principal diagnosis of SARS-CoV-2 infection, and the third group was defined by a positive PCR test or secondary diagnosis of SARS-CoV2, referred to as clinically mild or asymptomatic infection group.

To assess the differences between waves, we performed chi-squared tests, first on the PIMS distribution within the population, then on the symptomatic SARS-CoV2 within the population, with a significance level of 5%. For each cohort, we performed chi-squared or one-way ANOVA test when appropriate, to compare covariates across waves.

Results

A total of 9,163 pediatric patients hospitalized across 21 APHP hospitals with SARS-CoV-2 infection were included between March 2020 and March 2022: 2,325 patients were included in cohort 1 (mean number of patients detected per month: 332), 3,861 were included in cohort 2 (mean number of patients detected per month: 322), and 2,977 in cohort 3 (mean number of patients detected per month: 595).

Variant genotyping was automatically assigned to the historical variant for the first wave period, while was available (the variant genotyping for 787 patients (9%) of the patients detected during the second and third waves (**Figure 1**). In more detail, in the second cohort, 92 patients presented with the emergent Delta variant cohort, 986 presented with the first historical variant cohort, and 176 patients presented with the Alpha/Beta/Gamma variant while the variant was not available for 2,607 patients. In the third cohort, 411 presented with the Omicron variant and 108 the Delta variant. The rest of the cohort was made up of patients with a non-determined variant.

Distribution according to age group is detailed in **Table 1**. Children between the age of 28 days and 5 years were the most represented in all periods. During the first wave, the least represented age group was patients younger than 28 days old (13.8%), whereas the proportion of this group increased during the other two surges (17.6% and 15.6%, respectively). Globally, the average patient's age decreased throughout the pandemic.

Study group characteristics

Characteristics of the three study groups are described in tables 2 to 4.

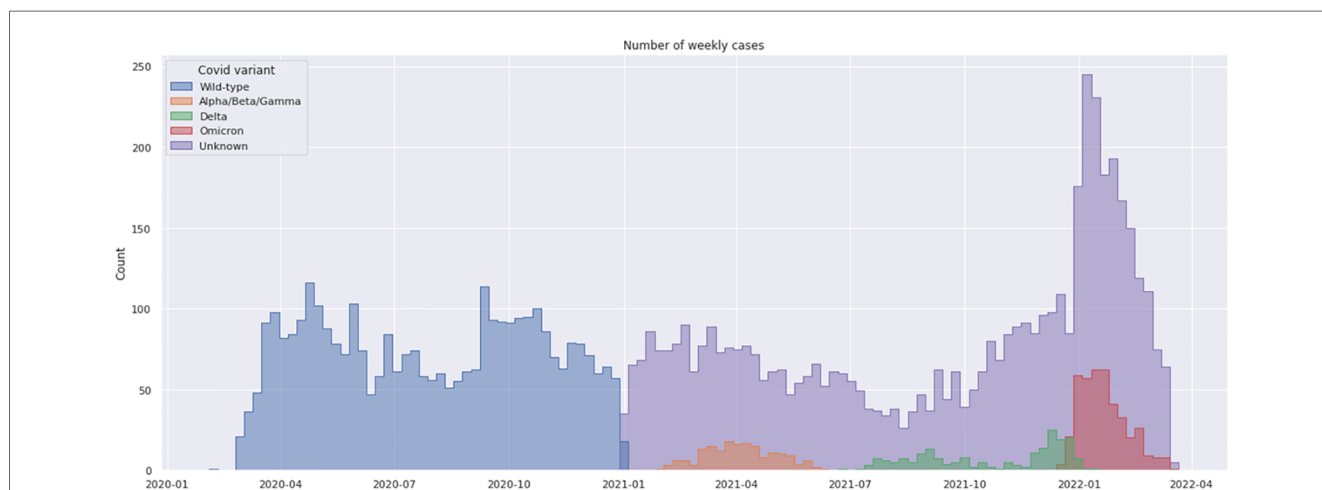


FIGURE 1

Weekly distribution of SARS-CoV2 cases variant genotyping in children hospitalized in the public hospital in the greater Paris area (AP-HP) from March 2020 to March 2022. The blue and violet bars represent the number of cases; the orange, green, and red bars represent the alpha-beta-gamma, delta, and omicron detected genotyping, respectively. For the first wave period (March 2020 - Dec 2020) the genotyping was assigned to the historical variant (wild type).

TABLE 1 Demography of the pediatric population analyzed.

	FIRST WAVE, MARCH 2020-SEPT 2020	SECOND WAVE, OCT 2020-OCT 2021	THIRD WAVE, NOV 2021-MARCH 2022	P-VALUE
TOTAL	2325	3861	2977	
SEX (MALE)	1 356 (58.3%)	2 131 (55.2%)	1 592 (53.5%)	2e-03
AGE M ± SD	6.1 ± 5.9	5.4 ± 6.0	4.4 ± 5.6	5e-24
AGE	≤ 28D	320 (13.8%)	681 (17.6%)	3e-29
	28D-5Y	1 012 (43.5%)	1 798 (46.6%)	
	6-12Y	542 (23.3%)	637 (16.5%)	
	13-18Y	451 (19.4%)	745 (19.3%)	

Sept: September; Oct: October; Nov: November. Age is expressed by mean (M) with standard deviation (SD). D: days; Y: years. Independence is tested with Chi-squared (χ^2) analysis for categorical data, and one-way ANOVA for quantitative data.

For study group 1, we collected data for PIMS and isolated myocarditis (PIMS/M) occurring after SARS-Cov2 infection (PIMS/M group) (Table 2). Focusing on this group, we observed that the highest number of these complications were registered during the first and second waves (incidence of 4.2%, 4.2%, and 2.4%, respectively, $p = 3e-4$). The PIMS/M patients were mostly within the age group of 5 to 12 years in all the three periods.

The analysis of the clinical characteristics of this group of patients showed that respiratory distress occurred mostly during the first wave (14.3%) compared to the 2 other periods (2.5 and 2.9%, respectively). The third wave was characterized by a lower resort to active respiratory treatments (ventilator support, oxygen support, etc.) compared to the previous surges (i.e., non-invasive ventilation utilized for 27.6% of the patients during the first wave compared to 1.4% during the third wave). Only 57.1% of these patients were admitted to the intensive care (IC) department during the third wave while 80.6% and 65% were hospitalized in the IC unit during the first and second waves, respectively. The percentage of patients who needed inotrope support during the last SARS-Cov2 wave amounted to 14.3% compared to 34.7% of patients during the first wave.

The most represented underlying comorbidities in the personal medical history of pediatric patients presenting PIMS/M were immunologic diseases and cardiac diseases during the first wave (11.2% and 4.1%, respectively), while during the second and third waves, underlying cardiac diseases were the most represented comorbidities (6.1% and 12.9%, respectively), followed by immunologic diseases during the second wave (4.9%) and chronic kidney disease during the third wave (8.6%). Interestingly, during the third wave, the incidence of PIMS/M patients with a history of respiratory diseases increased compared to the other periods (4.3% vs. 1% and 2.5%).

Only two patients hospitalized in one of the AP-HP hospitals presenting PIMS/M died during the pandemic (during the first and second waves).

The number of patients hospitalized with a primary diagnosis of SARS-CoV2 infection (group 2) increased over time as 132

(5.6%), 308 (7.9%), and 442 (14.8%) patients were detected in the three periods of the pandemic ($p = 1e-25$), however, the specific respiratory symptoms decreased as well as admission to the intensive care department (Table 3).

The most represented cohort was pediatric patients with mild or asymptomatic SARS-CoV-2 infection. This third group was homogeneously well represented in all the periods (Table 4). As in symptomatic SARS-Cov2 patients, most of the patients detected in this group were between the age of 28 days to 5 years old in the three periods. The proportional number of patients in this age group increased over time.

The analysis of the patients with symptomatic or mildly symptomatic or asymptomatic SARS-Cov2 infection (groups 2 and 3) showed that 51 patients died within 5 days after the dismissal. These deaths are likely due to other concurrent illnesses not related to the SARS-COV2 infection.

Despite the different clinical presentations of the SARS-CoV-2 infection, the incidence of concomitant diseases was similar in the symptomatic and mild or asymptomatic infected patients with higher involvement in patients with previous respiratory or chronic kidney diseases (Tables 3, 4).

Considering the whole population of SARS-Cov2 hospitalized pediatric patients (groups 2 and 3), the concomitant occurrence of pneumonia was higher during the third wave (10.2% during the third wave compared to 7% and 6.5% in the first and second waves).

Discussion

To our knowledge, this study is one of the largest multicenter retrospective COVID-19 pediatric studies to date on more than 9,100 hospitalized pediatric patients presenting SARS-Cov2 infection in France. Using the AP-HP Covid Clinical Data Warehouse allowed an in-depth analysis of the clinical characteristics of these patients according to the period of hospitalization and the SARS-Cov2 variant identification, if available. The aim of this study was to characterize the impact of the SARS-Cov2 infection on the hospitalized pediatric population in the Great Paris area among the three different waves and, consequently, if possible, to analyze the link with the different subsequent SARS-Cov2 variants.

The greater Paris area has experienced five SARS-Cov2 infection surges (11): from March to May 2020, from September to November 2020, from March to May 2021, from July to September 2021, and from December 2021 to January 2022. For our analysis, we preferred to merge the periods characterized by a predominant SARS-Cov2 variant in order to better compare the impact and clinical characteristics in the pediatric population.

The spread of SARS-CoV-2 infection in the pediatric population, and in more detail, the incidence of the Omicron variant has been previously reported in the literature. Data from a pediatrics cohort in the United States suggested that hospitalization for symptomatic SARS-CoV-2 infection increased with the emergence of the Omicron variant, particularly in younger children (12). In another large cohort of pediatric

TABLE 2 Characteristics of pediatric patients hospitalized with pediatric inflammatory multisystem syndrome (PIMS) or acute myocarditis after SARS-Cov2 infection.

		First wave, March 2020-sept 2020	Second wave, Oct 2020-Oct 2021	Third wave, Nov 2021-March 2022	p-value	
	TOTAL (N,%)	98, 4.2%	163, 4.2%	70, 2.3%	3e-04	
Demography	Sex (male)	41 (41.8%)	104 (63.8%)	39 (55.7%)	3e-03	
	Age m ± sd	8.4 ± 5.1	8.2 ± 4.6	8.3 ± 4.5	0.91	
	Age	≤ 28d	0 (0.0%)	1 (0.6%)	0 (0.0%)	0.77
		28d-5y	33 (33.7%)	54 (33.1%)	23 (32.9%)	
		6-12y	42 (42.9%)	79 (48.5%)	36 (51.4%)	
13-18y		23 (23.5%)	29 (17.8%)	11 (15.7%)		
Medical history	Heart disease	4 (4.1%)	10 (6.1%)	9 (12.9%)	0.07	
	Chronic respiratory diseases	1 (1.0%)	4 (2.5%)	3 (4.3%)	0.40	
	Immunological diseases	11 (11.2%)	8 (4.9%)	3 (4.3%)	0.09	
	Cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00	
	Chronic kidney diseases	1 (1.0%)	6 (3.7%)	6 (8.6%)	0.04	
	Obesity	2 (2.0%)	2 (1.2%)	2 (2.9%)	0.68	
	Neurological and musculoskeletal disorders	0 (0.0%)	0 (0.0%)	1 (1.4%)	0.15	
Complications during the hospitalization	Acute respiratory failure hypoxia	14 (14.3%)	4 (2.5%)	2 (2.9%)	2e-04	
	Pneumonia	10 (10.2%)	4 (2.5%)	3 (4.3%)	0.02	
	Length of stay m ± sd	8.6 ± 6.9	6.2 ± 5.0	6.1 ± 4.5	2e-03	
	Admission to intensive care	79 (80.6%)	106 (65.0%)	40 (57.1%)	3e-03	
	Death close to SARS-CoV-2 diagnosis	1 (1.0%)	1 (0.6%)	0 (0.0%)	0.70	
Treatment	Non-invasive ventilation	27 (27.6%)	14 (8.6%)	1 (1.4%)	3e-07	
	ECMO	1 (1.0%)	2 (1.2%)	0 (0.0%)	0.66	
	Oxygen supply	22 (22.4%)	19 (11.7%)	4 (5.7%)	5e-03	
	Inotropes/vasopressors	34 (34.7%)	34 (20.9%)	10 (14.3%)	5e-03	

ECMO, extracorporeal membrane oxygenation.

patients in the United States (7,201 infected children), the incidence of SARS-COV2 with the Omicron variant predominated in children under the age of 5 years old (13). The REACT-1 cohort in England found a significantly higher incidence of the Sars-Cov2 Omicron infection in children (5 to 17 years old) compared to the previous variant infections (14).

Parts of these results are similar to our analysis where pediatric patients, less than 5 years old, are highly represented in the last period of the pandemic (71% of the 2,977 patients hospitalized during the third wave). The role of the incoming SARS-Cov2 vaccination for older children during the third wave is to be

taken into account considering the higher incidence in very young patients (15).

In our study, the total number of pediatric patients hospitalized for symptomatic SARS-Cov2 infection increased over time (442 in the third wave vs. 132 and 308 in the first and second wave) with lung involvement, especially during the first period (21.2%). Nevertheless, considering the entire pediatric cohort (groups 2 and 3), a higher incidence of pulmonary involvement was observed during the third wave. Concomitant seasonal virus infections have to be considered in the analysis of the Omicron SARS-Cov2 infected pediatric patients (16) since SARS-CoV2

TABLE 3 Characteristics of pediatric patients hospitalized with a principal diagnosis of SARS-CoV-2 infection.

		First wave, March 2020-sept 2020	Second wave, Oct 2020-Oct 2021	Third wave, Nov 2021-March 2022	p-value	
	TOTAL (N,%)	132, 5.6%	308, 7.9%	442, 14.8%	1e-25	
Demography	Sex (male)	65 (49.2%)	153 (49.7%)	248 (56.1%)	0.15	
	Age m ± sd	7.2 ± 7.0	4.6 ± 6.2	3.3 ± 5.1	8e-11	
	Age	≤28d	16 (12.1%)	59 (19.2%)	64 (14.5%)	3e-10
		28d–5y	51 (38.6%)	154 (50.0%)	285 (64.5%)	
		6–12y	23 (17.4%)	39 (12.7%)	52 (11.8%)	
13–18y		42 (31.8%)	56 (18.2%)	41 (9.3%)		
Medical history	Heart disease	4 (3.0%)	8 (2.6%)	11 (2.5%)	0.94	
	Chronic respiratory diseases	22 (16.7%)	45 (14.6%)	52 (11.8%)	0.27	
	Immunological diseases	3 (2.3%)	8 (2.6%)	16 (3.6%)	0.62	
	Cancer	5 (3.8%)	8 (2.6%)	14 (3.2%)	0.79	
	Chronic kidney diseases	18 (13.6%)	18 (5.8%)	39 (8.8%)	0.03	
	Obesity	2 (1.5%)	7 (2.3%)	4 (0.9%)	0.31	
	Neurological and musculoskeletal disorders	2 (1.5%)	9 (2.9%)	13 (2.9%)	0.65	
Complications during the hospitalization	Acute respiratory failure hypoxia	20 (15.2%)	16 (5.2%)	19 (4.3%)	2e-05	
	Pneumonia	28 (21.2%)	37 (12.0%)	57 (12.9%)	0.03	
	Length of stay m ± sd	8.6 ± 6.9	6.2 ± 5.0	6.1 ± 4.5	0.03	
	Admission to intensive care	45 (34.1%)	63 (20.5%)	112 (25.3%)	1e-02	
	Death close to SARS-CoV-2 diagnosis	5 (3.8%)	0 (0.0%)	1 (0.2%)	1e-05	

infection has similar symptoms to winter respiratory viruses. However, in our cohort, the symptoms could originate from several viruses without the possibility of attribution to SARS-CoV-2. On the other hand, a recent study underlined that children without previous SARS-CoV-2 immunization could present a more severe Omicron variant Covid-19 disease than children with previous immunization (17).

Interestingly, the analysis of the medical records showed that chronic respiratory diseases (i.e., asthma) were associated with a higher incidence of SARS-CoV-2 infection. The association of chronic kidney diseases with SARS-CoV-2 infection is probably due to a selection bias in patients in an exclusive hospital setting. Further studies need to focus on this population in order to state if chronic kidney disease patients are exposed to a higher risk of infection.

Pediatric Inflammatory Multisystem Syndrome correlated to SARS-CoV-2 infection is an exclusive complication of COVID-19 infection in the pediatric population (18). These patients have

been already well-characterized in the literature (19, 20). In our analysis, we showed that pediatric patients presenting PIMS or acute myocarditis following SARS-CoV-2 infection were well represented in the three periods with higher incidence during the first and the second wave. Interestingly, in accordance with our results, a German study comparing the incidence of PIMS over the pandemic and the incidence of the different variants revealed a lower occurrence of PIMS correlating with the Omicron variant of SARS-CoV-2 infection (21). This is also concordant with other results from studies performed in the United Kingdom (22), Denmark (23), and Australia (24) which also found a lower incidence of PIMS during the dominant Omicron variant of SARS-CoV-2. This is probably due to the viral antigen changes and the subsequent host immune-inflammatory pathway activations. Further investigations is needed to complete these analyses since this complication could occur with a variable delay from the time of infection. Nevertheless, the diagnosis and management of

TABLE 4 Characteristics of pediatric patients hospitalized with mild or asymptomatic SARS-CoV-2 infection. .

		First wave, March 2020-Sept 2020	Second wave, Oct 2020-Oct 2021	Third wave, Nov 2021-March 2022	p-value	
	TOTAL (N,%)	2,095 (90.1%)	3,390 (87.8%)	2,465 (82.8%)	0.19	
Demography	Sex (male)	1 250 (59.7%)	1 874 (55.3%)	1 305 (52.9%)	2e-05	
	Age m ± sd	5.9 ± 5.8	5.3 ± 6.0	4.5 ± 5.6	1e-14	
	Age	≤28d	304 (14.5%)	621 (18.3%)	399 (16.2%)	9e-22
		28d-5y	928 (44.3%)	1 590 (46.9%)	1 337 (54.2%)	
		6-12y	477 (22.8%)	519 (15.3%)	384 (15.6%)	
13-18y		386 (18.4%)	660 (19.5%)	345 (14.0%)		
Medical history	Heart disease	41 (2.0%)	90 (2.7%)	68 (2.8%)	0.17	
	Chronic respiratory diseases	371 (17.7%)	756 (22.3%)	434 (17.6%)	2e-06	
	Immunological diseases	82 (3.9%)	142 (4.2%)	99 (4.0%)	0.87	
	Cancer	104 (5.0%)	117 (3.5%)	114 (4.6%)	0.01	
	Chronic kidney diseases	280 (13.4%)	366 (10.8%)	214 (8.7%)	3e-06	
	Obesity	49 (2.3%)	75 (2.2%)	36 (1.5%)	0.06	
	Neurological and musculoskeletal disorders	26 (1.2%)	73 (2.2%)	45 (1.8%)	0.05	
Complications during the hospitalization	Acute respiratory failure hypoxia	30 (1.4%)	44 (1.3%)	43 (1.7%)	0.37	
	Pneumonia	136 (6.5%)	211 (6.2%)	249 (10.1%)	2e-08	
	Length of stay m ± sd	4.5 ± 7.2	4.5 ± 6.6	4.4 ± 5.7	0.75	
	Death close to SARS-CoV-2 diagnosis	14 (0.7%)	16 (0.5%)	16 (0.6%)	0.56	

PIMS patients improved over time and this is probably a significant reason why the severity of the disease seems to be less important during the last wave.

Several limitations of this study should be noted since some variables were not available in the database for the analysis, and potential inaccuracies can be present in the electronic health records. Although these findings should be interpreted with caution, this study illustrated the impact of the SARS-Cov2 infection on the hospitalized pediatric population providing valuable information on the characteristics and frequency over time. The robustness of the data analyzed rests on one of the largest multicenter retrospective SARS-Cov2 pediatric studies. Further analysis is needed to improve our knowledge of the new emerging variants and to monitor the frequency of reinfection.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by N° CSE: CSE 20-48_COVIDPed; AP-HP CDW Scientific and Ethics Committee number IRB00011591. The authors have the necessary regulatory agreements (n° 1980120) to use the patient data from the National Commission on Informatics and Liberty (CNIL), aimed at ensuring the application of data privacy laws.

Author contributions

MS: primary author, designed the study plan; analysis of the data, writing the bulk of the manuscript. PP, MD, and NB: AP-HP Covid Clinical Data Warehouse extraction and analysis, statistical analysis, image acquisition, and image edition. MP: drafted the manuscript, and contributed to the analysis of the data. MO and HC: critical revision of the manuscript, contributed to the analysis of the data, and designed the study plan. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fped.2023.1044352/full#supplementary-material>.

References

- Parkar S, Pethani A, Zehra SMEJ, Khan F, Kazi Z, Hilal K, et al. Epidemiological, clinical, and radiological comparison of adult and pediatric features in COVID-19: a scoping review. *J Pak Med Assoc.* (2022) 72(2):305–11. doi: 10.47391/PPMA.3269
- Zhu F, Ang JY. COVID-19 Infection in children: diagnosis and management. *Curr Infect Dis Rep.* (2022) 24(4):51–62. doi: 10.1007/s11908-022-00779-0
- CDC COVID-19 Response Team. Coronavirus disease 2019 in children - United States, February 12–April 2, 2020. *MMWR Morb Mortal Wkly Rep.* (2020) 69(14):422–6. doi: 10.15585/mmwr.mm6914e4
- Kelvin AA, Halperin S. COVID-19 in children: the link in the transmission chain. *Lancet Infect Dis.* (2020) 20(6):633–4. doi: 10.1016/S1473-3099(20)30236-X
- Flood J, Shingleton J, Bennett E, Walker B, Amin-Chowdhury Z, Oligbu G, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS): prospective, national surveillance, United Kingdom and Ireland, 2020. *Lancet Reg Health Eur.* (2021) 3:100075. doi: 10.1016/j.lanpe.2021.100075
- Payne AB, Gilani Z, Godfred-Cato S, Belay ED, Feldstein LR, Patel MM, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. *JAMA Netw Open.* (2021) 4(6):e2116420. doi: 10.1001/jamanetworkopen.2021.16420
- Guenver C, Oualha M, Levy C, Antona D, Madhi F, Toubiana J, et al. Educational setting and SARS-CoV-2 transmission among children with multisystem inflammatory syndrome: a French national surveillance system. *Front Pediatr.* (2021) 9:745364. doi: 10.3389/fped.2021.745364
- Taylor CA, Whitaker M, Anglin O, Milucky J, Patel K, Pham H, et al. COVID-19-Associated hospitalizations among adults during SARS-CoV-2 Delta and omicron variant predominance, by race/ethnicity and vaccination Status - COVID-NET, 14 states, July 2021–January 2022. *MMWR Morb Mortal Wkly Rep.* (2022) 71(12):466–73. doi: 10.15585/mmwr.mm7112e2
- Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, et al. The REporting of studies conducted using observational routinely-collected health data (RECORD) statement. *PLoS Med.* (2015) 12(10):e1001885. doi: 10.1371/journal.pmed.1001885
- Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis.* (2020) 20(11):e276–88. doi: 10.1016/S1473-3099(20)30651-4
- Dinh A, Dahmane L, Dahoumane M, Masingue X, Jourdain P, Lescure FX. Impact of omicron surge in community setting in greater Paris area. *Clin Microbiol Infect.* (2022) 28(6):897–9. doi: 10.1016/j.cmi.2022.02.015
- Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND, Xu R. Comparison of outcomes from COVID infection in pediatric and adult patients before and after the emergence of omicron. *medRxiv.* (2022). doi: 10.1101/2021.12.30.21268495
- Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND, Xu R. COVID Infection severity in children under 5 years old before and after omicron emergence in the US. *medRxiv.* (2022). doi: 10.1101/2022.01.12.22269179
- Elliott P, Eales O, Bodinier B, Tang D, Wang H, Jonnerby J, et al. Dynamics of a national omicron SARS-CoV-2 epidemic during January 2022 in England. *Nat Commun.* (2022) 13(1):4500. doi: 10.1038/s41467-022-32121-6
- Infectious Diseases CO. COVID-19 Vaccines in infants, children, and adolescents. *Pediatrics.* (2022). 150(3):e2022058700. doi: 10.1542/peds.2022-058700
- Fratty IS, Reznik-Balter S, Nemet I, Atari N, Klier L, Sherbany H, et al. Outbreak of influenza and other respiratory viruses in hospitalized patients alongside the SARS-CoV-2 pandemic. *Front Microbiol.* (2022) 13:902476. doi: 10.3389/fmicb.2022.902476
- Edward PR, Lorenzo-Redondo R, Reyna ME, Simons LM, Hultquist JF, Patel AB, et al. Severity of illness caused by severe acute respiratory syndrome coronavirus 2 variants of concern in children: a single-center retrospective cohort study. *J Pediatric Infect Dis Soc.* (2022):piac068. doi: 10.1101/2021.10.23.21265402
- Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA.* (2020) 324(3):259–69. doi: 10.1001/jama.2020.10369
- Harwood R, Allin B, Jones CE, Whittaker E, Ramnarayan P, Ramanan AV, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national delphi process. *Lancet Child Adolesc Health.* (2021) 5(2):133–41. doi: 10.1016/S2352-4642(20)30304-7
- Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *Lancet Child Adolesc Health.* (2020) 4(9):669–77. doi: 10.1016/S2352-4642(20)30215-7
- Sorg AL, Schönfeld V, Siedler A, Hufmagel M, Doehardt M, Diftloth N, et al. SARS-CoV-2 variants and the risk of pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 among children in Germany. *Infection.* (2022):1–7. doi: 10.1007/s15010-022-01908-6
- Cohen JM, Carter MJ, Cheung CR, Ladhani S, for the evelina paediatric inflammatory multisystem syndrome temporally related to SARS-CoV-2 (PIMS-TS) study group. Lower risk of multisystem inflammatory syndrome in children with the Delta and omicron variants of severe acute respiratory syndrome coronavirus 2. *Clin Infect Dis.* (2022) 76(3):e518–e21. doi: 10.1093/cid/ciac553
- Holm M, Espenhain L, Glenthøj J, Schmidt LS, Nordly SB, Hartling UB, et al. Risk and phenotype of multisystem inflammatory syndrome in vaccinated and unvaccinated danish children before and during the omicron wave. *JAMA Pediatr.* (2022) 176(8):821. doi: 10.1001/jamapediatrics.2022.2206
- Lopez L, Burgner D, Glover C, Carr J, Clark J, Boast A, et al. Lower risk of multi-system inflammatory syndrome in children (MIS-C) with the omicron variant. *Lancet Reg Health West Pac.* (2022) 27:100604. doi: 10.1016/j.lanwpc.2022.100604