



SARS-CoV-2 B.1.1.529 (Omicron) Variant Causes an Unprecedented Surge in Children Hospitalizations and Distinct Clinical Presentation Compared to the SARS-CoV-2 B.1.617.2 (Delta) Variant

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Background: In the midst of successive waves of SARS-CoV-2 variants, the B.1.1.529 (omicron) variant has recently caused a surge in pediatric infections and hospitalizations. This study aimed to describe and compare the symptoms, explorations, treatment and evolution of COVID-19 in hospitalized children during the successive B.1.617.2 (delta) and B.1.1.529 (omicron) waves.

Methods: This observational study was performed in the Pediatric Pulmonology Department of a University Hospital in Paris, France. All hospitalized children aged between 0 and 18 years who tested positive for SARS-CoV-2 using reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swabs from July 15th to December 15th 2021 (delta wave), and from December 15th 2021 to February 28th 2022 (omicron wave) were included.

Results: In total, 53 children were included, 14 (26.4%) during the delta wave and 39 (73.6%) during the omicron wave (almost three times as many hospitalizations in half the time during the latter wave). During the omicron wave, hospitalized patients were mostly aged < 5 years (90 vs. 71% of all the children during omicron and delta waves, respectively), and tended to have fewer underlying conditions (56 vs. 79% during omicron and delta waves, respectively, $p = 0.20$). The omicron variant was also responsible for a different clinical presentation when compared to the delta variant, with significantly higher and often poorly tolerated temperatures ($p = 0.03$) and increased digestive symptoms ($p = 0.01$). None of the three patients who were older than 12 years were fully vaccinated.

Conclusion: The dramatic increase in the hospitalization of children with COVID-19 and the modification of the clinical presentation between the latest delta and omicron waves

require pediatricians to remain vigilant. It should also encourage caregivers to ensure vaccination in children older than 5 years, for whom the BNT162b2 COVID-19 vaccine has been deemed safe, immunogenic, and effective.

Keywords: COVID-19, children, SARS-CoV-2, delta variant, omicron variant, hospitalization

INTRODUCTION

In France and throughout the world, the surge in coronavirus diseases (COVID-19) caused by the variant of concern B.1.1.529 (omicron), reached a peak that was five to six times higher than that caused by any of the previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants (1–3). After an important decrease in the SARS-CoV-2 circulation in June 2021, the French public health agency observed a progression in infections due to the B.1.617.2 (delta) variant that began in mid-July (4). The later switch between the delta and omicron variants began in mid-December 2021 (5). Whereas the incidence of COVID-19 had been far lower in children than in adults, it multiplied in children more than eight times during the period of this change in the SARS-CoV-2 virus variant. Specifically, the incidence of COVID-19 increased from 634/100,000 in the age groups 0–9 and 10–19 years at the delta-wave peak (week 49, 2021) to 4,877 and 6,828/100,000, respectively, in the same age groups at the omicron-wave peak (week 3, 2022) (4).

However, concerns about the high infectivity of the omicron variant have been balanced by its apparent lower severity in adults, with less severe symptoms and decreased hospitalization rates (2, 6, 7). This reduction in disease severity has partly been attributed to the widespread use of COVID-19 vaccines in adults (8, 9).

In contrast, pediatricians observed a surge in pediatric hospitalizations due to COVID-19 during the omicron wave (5, 10, 11). In the United States and South Africa, the peak of child hospitalizations resulted in a patient load that was four times higher than during the delta wave, with the largest increase occurring in children under 4 years of age (12, 13). Further, more children needed hospitalization in the intensive care unit (ICU) and/or invasive ventilation (12, 13). Interestingly, the monthly hospitalization rate in children aged 12–17 years was six times higher in non-vaccinated patients than in fully vaccinated patients (13). Compared to the delta variant, the omicron virus appears to have a predilection for the upper respiratory airways and digestive tract (5, 12). Reports have also described atypical cases of convulsions and cerebral venous thrombosis in children, making this a variant of concern, especially for pediatricians (14, 15).

To date, few studies have compared children with SARS-CoV-2 infection during the delta and omicron waves. Moreover, for the development of vaccines for children, it is important to precisely describe how children are affected by successive waves (16). Therefore, this study aimed to describe and compare the symptoms, explorations, treatment, and evolution of COVID-19 in children during the delta and omicron waves.

PATIENTS AND METHODS

This observational study was performed in the Pediatric Pulmonology Department of the University Hospital Trousseau, Assistance Publique Hôpitaux de Paris (APHP) Paris, France. According to the information on SARS-CoV-2 circulation in France, the arrival of the B.1.617.2 (delta) variant began in mid-July 2021 and that of the B.1.1.529 (omicron) variant began in mid-December 2021 (5). As such, patients between 0 and 18 years of age hospitalized in this department for COVID-19 between July 15th 2021 (arrival of the delta wave) and February 28th 2022 (end of the omicron wave) were identified using the hospital's "Programme de Médicalisation des Systèmes d'Information" (PMSI) database. This allowed for an exhaustive search of all children testing positive for SARS-CoV-2 by real-time reverse transcription polymerase chain reaction (RT-PCR) using nasopharyngeal swabs, who were admitted to this hospital. The study was approved by the local ethics committee of our institution, which waived the need for patients' consent (Study PED_COVID N°20200717191204).

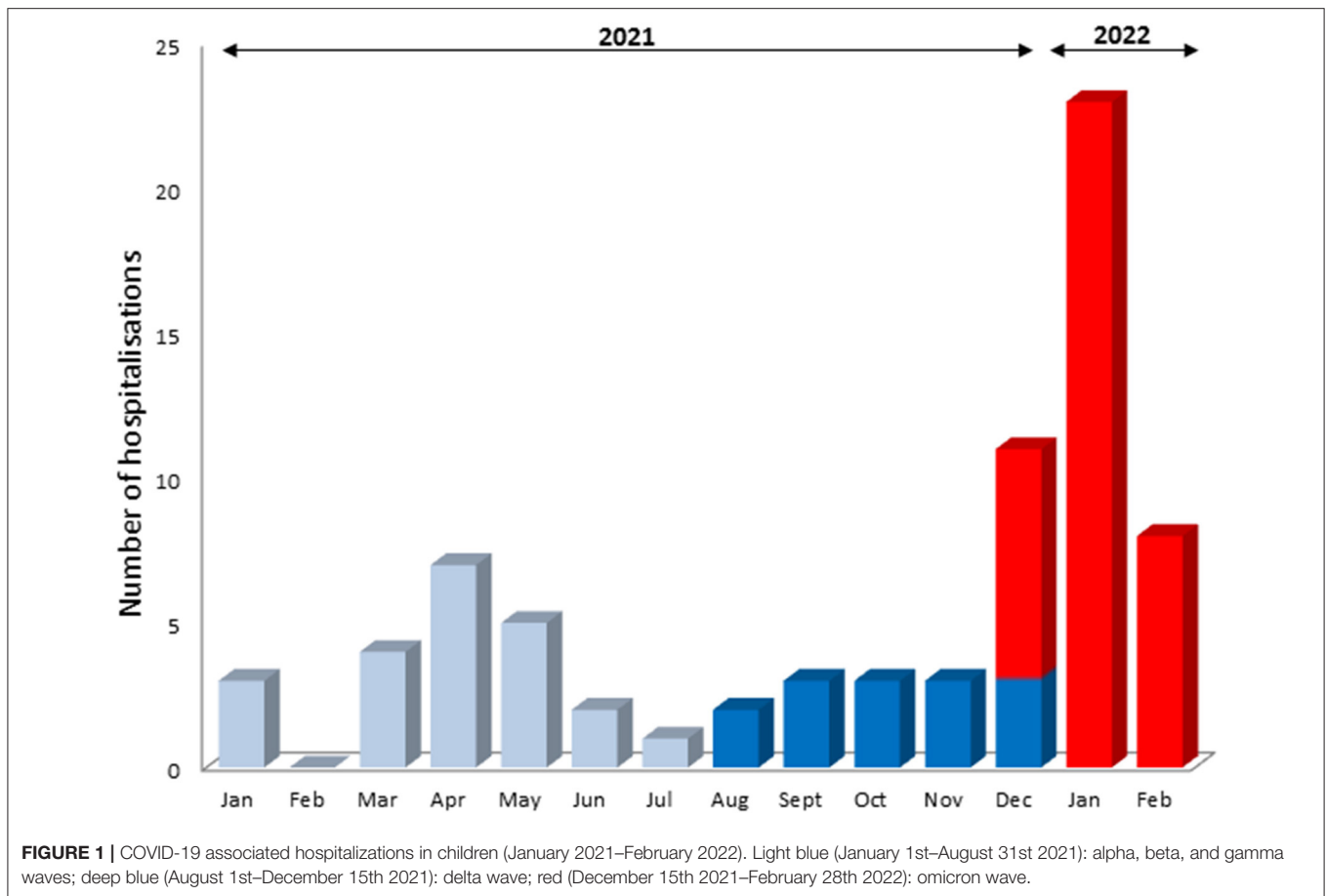
Patient information was retrieved from medical records, including COVID-19 transmission history, clinical, biological (blood tests and viral RT-PCR findings) and radiological information, and the medical evolution. Considering the SARS-CoV-2 variant circulation in France, children hospitalized between July 15th 2021 and December 15th 2021 were included in the "delta-group," and children hospitalized between December 16th 2021 and February 28th 2022 were in the "omicron-group."

Continuous data were expressed as median [interquartile range (IQR)], while categorical data were expressed as numbers and proportions (%). Descriptive statistics are presented for all study variables. We used Fisher's exact test or Pearson's chi-squared test (with Yates' continuity correction when necessary) to compare categorical and qualitative data and implemented the Wilcoxon rank sum test to evaluate continuous variables. A p -value of <5% was interpreted as evidence of a statistically significant difference. The analyses were performed using SAS software (version 9.4; Cary, NC, USA).

RESULTS

Distribution of the Hospitalizations According to SARS-CoV-2 Waves and to Age

The total number of children hospitalized monthly for COVID-19 between 1 January 2021 and 28 February 2022 is presented in **Figure 1**. During the study period (July 15th 2021 to February 28th 2022), 53 children aged 0–18 years were hospitalized for



COVID-19 in our Pediatric Pulmonology Department. Among them, 14 (26.4%) were included in the delta group and 39 (73.6%) in the omicron group, while the duration of the study period was double that of the omicron wave. Indeed, the first group extended over 5 months (i.e., from July 15th to December 15th, 2021), whereas the second only over 2.5 months (i.e., from December 15th 2021 to February 28th 2022). While all of the 53 included children had positive PCR for SARS-CoV-2 in nasopharyngeal swab, only part of the SARS-CoV-2 variants were identified by Novaplex™ SARS-CoV-2 Variants I and IV Assays (Seegene, South Korea). Among the 14 children of the delta group, 7 (50%) were confirmed SARS-CoV-2 delta variant; and among the 39 children of the omicron group, 22 (56%) were confirmed SARS-CoV-2 omicron variant.

The distribution of hospitalizations according to age group (<5, 5–11, and >11 years) is reported in **Figure 2**. Of the three patients in the omicron group who were older than 12 years, none were fully vaccinated. Two of them had not been vaccinated, and one had received an incomplete vaccination with only one injection 2 weeks prior to the onset of symptoms.

Baseline Clinical Characteristics

The patients' baseline clinical characteristics according to the wave group are detailed in **Table 1**. During the omicron wave, hospitalized patients were mostly aged < 5 years (90 vs. 71%

TABLE 1 | General characteristics of the children hospitalized for COVID-19 during the delta and omicron waves.

	Delta wave ^a	Omicron wave ^b	p-value
Patients (n)	14	39	
Age (years): median [IQR]	0.6 [0.1; 6.5]	0.6 [0.3; 1.6]	0.97
Age class (n, %)			0.18
<5 yrs	10 (71%)	35 (90%)	
> 5 yrs	4 (29%)	4 (10%)	
Male (n, %)	10 (71%)	26 (67%)	>0.99
Pre-existing condition, i.e. underlying comorbidity or age < 3 months (n, %)	11 (79%)	22 (56%)	0.14

^aDelta wave: from July 15th to December 15th, 2021.

^bOmicron wave: from December 15th 2021 to February 28th 2022.

during the omicron and delta waves, respectively), and tended to have fewer pre-existing conditions (56 vs. 79% during the same period, respectively, $p = 0.20$). During the delta wave, 5/14 infants (36%) aged <3 months were hospitalized, compared to 8/39 (20%) during the omicron wave.

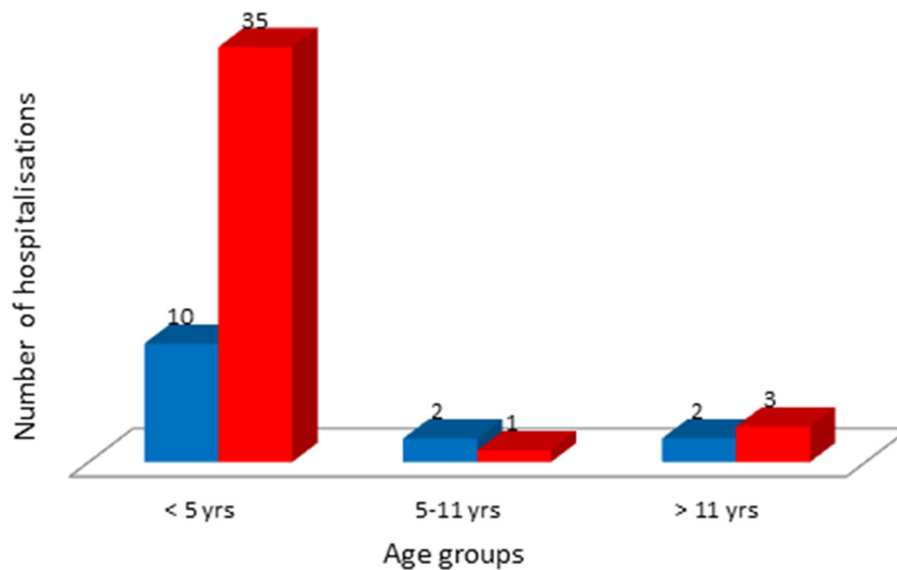


FIGURE 2 | Distribution of children hospitalized for COVID-19 per age class. Deep blue (August 1st–December 15th 2021): delta wave; red (December 15th 2021–February 28th 2022): omicron wave.

In the delta group, the large majority of patients (11/14, 79%) had a pre-existing condition such as asthma, interstitial lung disease, congenital myopathy, obesity, Crohn's disease, and sickle cell disease; and 5 were infants under 3 months of age. In the omicron group, 22/39 (56%) children had an underlying condition: 7 had a respiratory disease (asthma, tuberculosis, cystic fibrosis, bronchodysplasia, interstitial lung disease, Langerhans histiocytosis, and Schwachman-Diamond syndrome), 2 a hematologic disease (sickle cell disease, Hodgkin's lymphoma), 2 a genetic disorder (Prader-Willi, CHARGE syndrome), one a cardiologic defect (pulmonary valvular stenosis), and 8 were infants under 3 months of age.

Clinical Presentation and Explorations at COVID-19 Onset

The clinical presentation at COVID-19 onset is described in **Table 2**. The omicron variant caused significantly more digestive symptoms, such as diarrhea (33% vs. 0) during the omicron and delta waves respectively ($p = 0.01$), and refusal to eat (46 vs. 7%) during the omicron and delta waves respectively ($p = 0.01$). No patient in the omicron group presented with hemoptysis, compared to three patients (21%) in the delta group ($p = 0.01$). Body temperature was significantly higher during infections with the omicron variant than in those with the delta variant [39.2°C (38.9; 39.4) vs. 38.5°C (38.5; 38.7), respectively; $p = 0.02$]. Although not statistically significant, the proportion of children with poor symptom tolerance and deterioration of general health status was higher in the omicron group (59 vs. 36%) during the omicron and delta waves respectively, $p = 0.21$.

Detailed information on the main explorations performed at admission is provided in **Table 3**. Six children (50%) were co-infected with other respiratory viruses during the delta wave and 22 (63%) during the omicron wave (details on the different

viruses are provided in **Table 3**). Chest X-ray and thoracic CT-scan, when abnormal, were similar in both groups, with features of lung consolidation without specific localization. One patient in the delta group presented with pleural effusion and one in the omicron group with bilateral pneumothorax. No pulmonary embolisms were observed during these waves in our department.

Management and Evolution

The management and clinical evolution are detailed in **Table 4**. Two patients (14%) required nutritional support during the delta wave and 11 (28%) during the omicron wave. During the latter period, the median [IQR] duration of nutritional support was 2 [1.25; 3] days. There were no differences in patient management or disease evolution between the two groups. Two patients (one during the delta wave and one during the omicron wave) were already on home oxygen therapy and non-invasive ventilation due to chronic respiratory insufficiency prior to hospitalization for COVID-19. For both, oxygen or ventilation needs increased respectively during 2 and 11 days before returning to previous support levels.

DISCUSSION

This study compared the incidence and clinical symptoms of children hospitalized for COVID-19 during the delta and omicron waves. During the omicron wave, there was a major increase in the number of hospitalizations, with almost three times as many hospitalizations in half the time when compared to the delta variant, with the vast majority of children younger than 5 years. There were also distinct clinical characteristics, with higher temperature and poorly tolerated fever and a predilection for upper respiratory airways and digestive symptoms during the omicron wave.

TABLE 2 | Clinical presentation of the children hospitalized during the delta and omicron waves at COVID onset.

	Delta wave ^a	Omicron wave ^b	p-value
General symptoms			
Fever (n, %)	11 (79%)	29 (74%)	>0.99
Poor fever tolerance (n, %)	2 (18%)	8 (28%)	>0.99
Fever duration [days, median (range)]	1 (1; 15)	2 (1; 9)	>0.99
Fatigue/deterioration of general status (n, %)	5 (36%)	23 (59%)	0.21
Respiratory symptoms			
Cough (n, %)	9 (64%)	26 (67%)	>0.99
Dyspnea (n, %)	9 (64%)	20 (51%)	0.53
Hemoptysis (n, %)	3 (21%)	0	0.02
Upper respiratory airway			
Acute rhinitis (n, %)	6 (43%)	23 (59%)	0.36
Pharyngitis (n, %)	1 (7%)	7 (18%)	0.67
Laryngitis (n, %)	0	3 (8%)	0.56
Digestive symptoms			
Vomiting (n, %)	1 (7%)	9 (23%)	0.26
Diarrhea (n, %)	0	13 (33%)	0.01
Refusal to eat (n, %)	1 (7%)	18 (46%)	0.01
Initial vital signs			
Highest temperature (°C) [median (IQR)]	38.5 [38.5; 38.7]	39.2 [38.9; 39.4]	0.03
Respiratory rate (/min) [median (IQR)]	42 [24; 54]	46 [35; 50]	0.53
Oxygen saturation (%) [median (IQR)]	98 [94; 99]	98 [95; 99]	0.93
Cardiac rate (/min) [median (IQR)]	135 [123; 151]	143 [133; 157]	0.31

^aDelta wave: from July 15th to December 15th, 2021.

^bOmicron wave: from December 15th 2021 to February 28th 2022.

According to the World Health Organization (WHO) data, the omicron variant has been responsible for five to six times more confirmed SARS-CoV-2 infections in Europe and America (1). Although it has been suggested that the omicron variant is associated with lower hospitalization rates due to a suspected reduction in disease severity, this wave has caused an important increase in the number of hospitalizations in children (1, 7, 11–13). This is in line with the surge in the number of hospitalizations for COVID-19 observed in our pediatric pulmonology department, which almost tripled between the two waves in half of the time. The higher infectivity of the omicron variant has been attributed to an exceptional number of mutations in the spike glycoprotein-binding human ACE2, resulting in increased infectivity of nasal epithelial cells and ACE2-positive cells (3, 17). These alterations in virus conformation influence antibody neutralization and facilitate viral immune escape, making it a variant of concern (3, 18).

In the light of these findings, questions have arisen regarding the vaccine efficacy. Although studies have suggested a decrease in vaccine-induced immunity after the second dose, others have shown that boosters can restore neutralizing immunity (19–21). Lauring et al. showed in adults that three doses of mRNA vaccine were necessary to obtain the same protection for the

TABLE 3 | Results of the main explorations performed at admission of the children hospitalized for COVID-19 during the delta and omicron waves.

	Delta wave ^a	Omicron wave ^b	p-value
Nasopharyngeal result on PCR assay			
Positive for SARS-CoV-2 (n, %)	14 (100%)	39 (100%)	
Positive for ≥1 other respiratory viruses (%) [*]	6/12 (50%)	22/35 (63%)	0.75
Respiratory Syncytial virus (n)	3	2	
Rhinovirus (n)	0	10	
Influenza virus (n)	0	3	
Parainfluenza (n)	2	2	
Coronavirus (n)	1	3	
Bocavirus (n)	0	6	
Adenovirus (n)	0	1	
Metapneumovirus (n)	0	1	
Thoracic imaging			
Chest radiography			
Number of patients, % of abnormal results	5 (60%)	26 (38%)	0.63
Computed tomography			
Number of patients, % of abnormal results	6 (100%)	3 (33%)	0.08
Blood tests [median (IQR)]			
WBC (x10 ⁹ /L)	7.5 [4.5; 9.4]	10.5 [7.1; 14.3]	0.26
Lymphocytes (x10 ⁹ /L)	2.4 [1.9; 2.6]	3.2 (1.4; 5.4)	0.32
Neutrophils (x10 ⁹ /L)	1.5 [0.7; 5.4]	3.1 [1.8; 8.0]	0.26
Hemoglobin (g/dL)	11.5 [10.7; 12.5]	11.1 [10.0; 11.8]	0.29
Platelets (x10 ⁹ /L)	318 [241; 387]	312 [256; 388]	0.73
CRP (mg/L)	8 [5; 20]	7 [0; 42]	0.72

^{*} These analyses were performed by means of Allplex Respiratory Panel Assays (Seegene).

^aDelta wave: from July 15th to December 15th, 2021.

^bOmicron wave: from December 15th 2021 to February 28th 2022.

omicron variant as that provided for other variants after two doses (22). Similar results were observed in immunocompetent adolescents (12–17 years old), where vaccine efficacy toward the omicron variant was restored after three doses (23). In our study, none of the three patients older than 12 years hospitalized during the omicron wave were fully vaccinated. This result, along with the observation by others that children were more susceptible to infections/reinfections during the omicron wave despite vaccination or previous infection, requires that children be vaccinated when possible, and this includes the need for the booster dose (13, 24). This is supported by the 6-fold increase in the monthly hospitalization rate in non-vaccinated adolescents compared to that in vaccinated children during the omicron wave (13).

Along with the increased number of child hospitalizations, the symptoms observed at COVID-19 onset were somewhat different when subsequently infected by the omicron variant or by the delta and previous variants (12, 25–28). In Italian children, an analysis of online search trends suggested increased upper respiratory airway symptoms and possibly poorly tolerated fever, whereas dyspnea and anosmia/ageusia seemed less frequent (25). The latter finding could also be an indicator of the younger age of infected children and their inability to report such

TABLE 4 | Management and evolution of the children hospitalized for COVID during the delta and omicron waves.

	Delta wave ^a	Omicron wave ^b	p-value
Symptoms prior to hospitalization			
Duration (days): median (IQR)	3 (2; 3.8)	3 (2, 4)	0.63
Hospitalization duration (days): median (IQR)	2.5 (2.0; 3.8)	3.0 (2.0; 4.8)	0.29
Intensive Care Unit (n, %)	0	4 (10%)	0.56
Oxygen therapy (n, %)	5 (36%)	12 (31%)	0.75
Oxygen therapy duration [days, median (IQR)]	2.0 (1.0; 2.0)	3 (1.5; 9.0)	0.18
Non-invasive ventilation (n, %)	0	3 (8%)	>0.99
Invasive ventilation (n, %)	0	2 (5%)	>0.99
Nutritional support (n, %)	2 (14%)	12 (31%)	0.31

^aDelta wave: from July 15th to December 15th, 2021.

^bOmicron wave: from December 15th 2021 to February 28th 2022.

symptoms. Indeed, we found that hospitalized children were mostly aged under 5 years (90% during the omicron wave and 71% during the delta wave). We observed similar symptoms at the onset of infection to those reported by Cloete et al. in South African children (12). As such, we found that omicron caused significantly higher temperatures, diarrhea, and refusal to eat. The rate of underlying conditions was also in agreement with that reported by Cloete et al., with only 56% of the children hospitalized during the omicron wave vs. 79% during the delta wave. Similar to other studies, this study observed slightly more frequent upper respiratory airway symptoms during omicron waves (29, 30). The higher susceptibility to target upper airways could be a real concern in young children, a population prone to severe upper airway infections due to a smaller respiratory tract (29). A recent retrospective cohort study showed results similar to ours, with adults infected by the omicron variant being younger, with less frequent comorbidities and dyspnea, and more frequent upper respiratory airway symptoms (31). Finally, although these symptoms were not observed in this study, others have highlighted the risk of convulsions and venous cerebral thrombosis in children infected with the omicron variant (12, 15). Nevertheless, neurological signs have already been described in previous waves and should remain a cause of concern in children (27, 28).

The main limitation of this study is its retrospective and monocentric nature, which led to small number of inclusions. However, the scarce literature on the infections caused by the omicron variant in children makes it important to report the

clinical features in the pediatric population and the specificities compared to previously described waves.

In conclusion, during the omicron wave, there was a major increase in the number of hospitalizations of children for COVID-19. These children were mostly under 5 years of age, younger than during previous waves (27). Unfortunately, children under 5 years of age cannot benefit from the vaccination as available SARS-CoV-2 vaccines are recommended for older children. Although the BNT162b2 COVID-19 vaccine has been deemed safe, immunogenic, and effective in preventing COVID-19 infection (16), concerns have arisen regarding the risk of myocarditis, especially in adolescents (32–35). This could explain why vaccination rates remain low in children aged 5–11 years old (36). For example in France, although the BNT162b2 COVID-19 vaccine is available for the children aged 5–11 years old since December 22, 2021, only 5% received at least one dose as of April 29, 2022. Thus, describing the continuous evolution of COVID-19 symptoms and severity in children is essential for improving vaccination adherence.

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 the Local Ethics Committee of our institution, which waived the need for patients' consent (Study PED_COVID N°20200717191204). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JT, BP, and HC were involved in the methodology, formal analysis, investigation, data curation, writing the original draft, reviewing and editing the manuscript, designing of tables and graphs, and verified the underlying data. AS, GA, LBe, LBi, AD-A, GT, and NN data were involved in data provision and reviewing and editing the manuscript. All authors had full access to all data in the study and accept responsibility for the decision to submit for publication.

¹Le tableau de bord de la vaccination. Available online at: <https://solidarites-sante.gouv.fr/grands-dossiers/vaccin-covid-19/article/le-tableau-de-bord-de-la-vaccination>.

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