Characteristics of Children Hospitalized for Acute COVID-19 in France From February 2020 to December 2023

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Abstract: We describe the characteristics of children hospitalized for coronavirus disease 2019 in France with a focus on the post-BA.1 Omicron period (February 2022–December 2023). We identified 3 main groups of children: those ≤90 days old (44.8%), older children with comorbidities (22.1%) and children with multisystem inflammatory syndrome (5.2%). Low vaccination coverage in these groups suggests that this burden could be alleviated with immunization.

Key Words: COVID-19, epidemiology, children, MIS-C

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The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly in December 2019, leading to a pandemic in March 2020. The clinical spectrum and the number of cases of coronavirus disease 2019 (COVID-19) involving children varied greatly as the pandemic progressed. Two main mechanisms may have explained these modifications: changes in the circulating variants and the increasing population immunity against SARS-CoV-2 due to previous infection and vaccination.[1]

At the early stage of the pandemic, COVID-19 in children was underestimated by the lack of tests. At this time, cases were mainly described as asymptomatic to mild infections.[2] In April–May 2020, life-threatening systemic inflammatory responses temporally associated with COVID-19 were reported.[3] This new clinical form was called multisystem inflammatory syndrome in children (MIS-C). During the winter of 2021–2022, the relative proportion of pediatric cases as well as the total number of cases increased with the emergence of the Omicron variant. During the Omicron wave, children younger than 6 months old accounted for a large proportion of the children hospitalized.[4] Since March 2022, MIS-C cases have been less frequent despite several COVID-19 epidemic waves.[5]

Prevention with vaccination against SARS-CoV-2 for children and adolescents is highly effective against hospitalization and MIS-C.[6] In France, vaccination has been recommended for all adolescents (12–17 years) since June 2021, for children (5–11 years) since December 2021, and for younger children (6 months–4 years) who are at risk of severe COVID-19 since December 2022. Full vaccination concerned about 80% of adolescents at 8 months after its implementation. By contrast, vaccine coverage in younger children was very low (<3%) in May 2024 (https://covidtracker.fr/vaccintracker/). In addition, vaccination during pregnancy was proposed to protect both mother and newborns and young infants[7] as this younger age group is at high risk of hospitalization for COVID-19 and is not eligible for vaccination.

Recent population-based epidemiological reports are lacking, particularly since the near disappearance of MIS-C.[5] In France, the surveillance of hospitalized COVID-19 cases by the national public health agency (Santé publique France) has been stopped since June 2023. The aim of this study was to describe the clinical characteristics of children hospitalized for COVID-19 up to December 2023 by using an ongoing national surveillance system in France. Specifically, we decided to focus on children ≤90 days old, older children with comorbidities and children with MIS during the post-BA.1 Omicron period.

MATERIALS AND METHODS

Study Design and Settings

This was a national prospective surveillance study (PANDOR study). Briefly, 60 hospitals throughout France reported all pediatric cases of children hospitalized for acute COVID-19 from February 15, 2020, to December 31, 2023. For each case, a standardized anonymous electronic case report form was completed on

a secure database after patient discharge. This form was transmitted to the investigating center. An estimated 38.5% (95% confidence interval: 35.5–41.5) of children hospitalized in France were enrolled in this study.

Definitions

Confirmed COVID-19 cases were defined as clinical signs and symptoms compatible with a positive SARS-CoV-2 RT-PCR result on a nasopharyngeal swab.

Statistics

Numbers (percentages) were used to describe categorical variables and median [interquartile range (IQR)] to describe continuous variables. Quantitative variables were compared by 1-way analysis of variance and qualitative variables by chi-squared or Fisher exact test. A 2-sided $P < 0.05$ was considered statistically significant. All statistics were performed with STATA 15 (StataCorp 2023, College Station, TX).

Periods

According to SARS-CoV-2 variants circulating in France (https://www.santepubliquefrance.fr/dossiers/coronavirus-covid-19/coronavirus-circulation-des-variants-du-sars-cov-2#block-270756), the following periods were defined: "original-strain" period from February 15, 2020, to February 14, 2021; "alpha" period from February 15, 2021, to June 27, 2021; "delta" period from June 28, 2021, to December 19, 2021; "BA.1 Omicron" period from December 20, 2021, to February 27, 2022 and "post-BA.1 Omicron" period from February 28, 2022, to December 31, 2023.

Comparison With COVID-19 in Ambulatory Settings

We compared the weekly number of hospitalized COVID-19 cases (from the PANDOR study) with the cases seen in ambulatory settings from the PARI study. PARI is a prospective surveillance study in which data from electronic medical records are automatically extracted in real-time from 125 French ambulatory pediatricians (https://www.infovac.fr/reseau-pari).

Ethics

This study was approved by the *Institut national de la santé et de la recherche médicale* ethics committee and by the institutional review board (IRB00003888) and was registered at ClinicalTrials.gov (NCT04336956).

RESULTS

During the study period, we enrolled 3608 children hospitalized for COVID-19. The median age was 0.9 years (IQR: 0.1–2.1) and 1976 of 3553 (55.6%) were male; 980 of 3486 (28.1%) had at least 1 comorbidity, with chronic respiratory disease the most frequent (Table 1). Figure 1 shows the weekly number of COVID-19 cases requiring hospitalization and those in ambulatory settings.

Changes During the Study Period

We observed major changes in patient characteristics between the study periods. The median age decreased from 2.9 years (IQR: 0.2–10.3) during the original-strain period to 0.3 years

TABLE 1. Characteristics of Children Hospitalized With COVID-19 by Study Period

	Original Strain Period N = 1082 February 15, 2020, to February 14, 2021	Alpha Period N = 356 February 15, to June 27, 2021	Delta Period N = 394 June 28 to December 19, 2021	BA.1 Omicron Period N = 848 December 20, 2021, to February 27, 2022	Post-BA.1 Omicron Period N = 928 February 28, 2022, to December 31, 2023	Total N = 3608
Male sex	599/1071 (55.9)	193/350 (55.1)	221/384 (57.5)	456/834 (54.7)	507/914 (55.5)	1976/3553 (55.6)
Age (yr), median (IQR)	2.9 (0.2–10.3)	2.4 (0.2–9.7)	0.4 (0.1–5.7)	0.8 (0.2–5.9)	0.3 (0.1–2.1)	0.9 (0.1–2.1)*
Age ≤90 d	326/1082 (30.1)	97/356 (27.2)	173/394 (43.9)	276/848 (32.5)	416/928 (44.8)	1287/3608 (35.7)*
Premature	93/627 (14.8)	25/208 (12.0)	28/259 (10.8)	60/524 (11.4)	90/623 (14.4)	296/2241 (13.2)
Comorbidities	279/1064 (26.2)	85/343 (24.8)	84/375 (22.4)	269/819 (32.8)	263/885 (29.7)	980/3486 (28.1)*
Chronic respiratory disease	76/991 (7.7)	27/320 (8.4)	24/350 (6.9)	66/711 (9.3)	84/801 (10.5)	277/3173 (8.7)
Chronic immune deficiency	22/986 (2.2)	4/315 (1.3)	4/346 (1.2)	12/698 (1.7)	17/785 (2.2)	59/3130 (1.9)
Diabetes	13/984 (1.3)	6/316 (1.9)	2/341 (0.6)	8/670 (1.2)	3/781 (0.4)	32/3092 (1.0)
Sickle cell disease	38/1011 (3.8)	16/330 (4.8)	8/373 (2.1)	58/822 (7.1)	18/904 (2.0)	138/3440 (4.0)*
Obesity	45/1082 (4.2)	16/356 (4.5)	9/394 (2.3)	25/848 (2.9)	10/928 (1.1)	105/3608 (2.9)*
Transplantation	6/974 (0.6)	0/309 (0)	0/336 (0)	2/664 (0.3)	2/776 (0.3)	10/3059 (0.3)
Chronic kidney disease	14/978 (1.4)	4/314 (1.3)	9/343 (2.6)	10/668 (1.5)	20/780 (2.6)	57/3083 (1.8)
Chronic cardiac disease	19/983 (1.9)	3/313 (1.0)	7/343 (2.0)	16/677 (2.4)	18/781 (2.3)	63/3097 (2.0)
Neurologic disease	46/1011 (4.5)	19/330 (5.8)	15/373 (4.0)	62/822 (7.5)	98/904 (10.8)	240/3440 (7.0)*
Congenital disease	44/1013 (4.3)	10/330 (3.0)	16/374 (4.3)	40/821 (4.9)	60/904 (6.6)	170/3442 (4.9)
Other chronic disease	70/1024 (6.8)	16/333 (4.8)	14/361 (3.9)	46/758 (6.1)	62/822 (7.5)	208/3298 (6.3)
Main reason for hospitalization						
MIS-C	343/1082 (31.7)	131/356 (36.8)	81/394 (20.6)	78/848 (9.2)	48/918 (5.2)	681/3598 (18.9)*
Fever	112/1082 (10.3)	38/356 (10.7)	67/394 (17.0)	157/848 (18.5)	179/918 (19.5)	553/3598 (15.4)*
Respiratory symptoms	149/1082 (13.8)	77/356 (21.6)	85/394 (21.6)	183/848 (21.6)	217/918 (23.6)	711/3598 (19.8)*
Pauci-symptomatic	264/1082 (24.4)	60/356 (16.8)	79/394 (20.0)	155/848 (18.3)	243/918 (26.5)	801/3598 (22.3)*
Hospital care						
Antibiotics	432/1005 (43.0)	126/303 (41.6)	135/342 (39.5)	235/749 (31.4)	222/849 (26.1)	1150/3248 (35.4)*
Admission to ICU	288/1013 (28.4)	75/309 (24.3)	72/350 (20.6)	73/771 (9.5)	83/844 (9.8)	591/3287 (18.0)*
Length of hospital stay in days, median (IQR)	4 (2–7)	3.5 (2–7)	2 (1–5)	2 (1–5)	2 (1–3)	2 (1–5)*
Death	7/978 (0.7)	0/301 (0)	4/344 (1.2)	1/750 (0.1)	4/843 (0.5)	16/3223 (0.5)

Data are n (%) unless otherwise specified.
ICU indicates intensive care unit.
*$P < 0.001$.

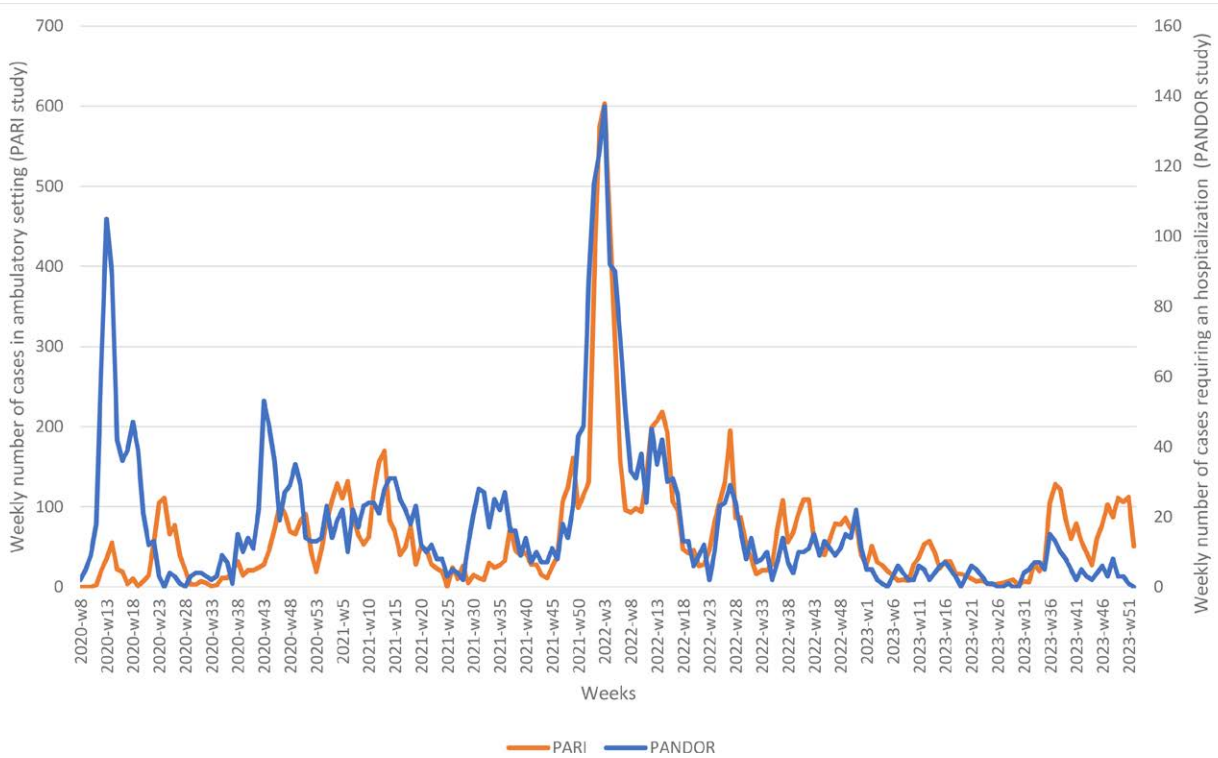

FIGURE 1. Number of children with COVID-19 requiring hospitalization (PANDOR study) and in ambulatory settings (PARI study) per week. full color online

(IQR: 0.1–2.1) during the post-BA.1 Omicron period. Both hospitalization length (median from 4 to 2 days) and proportion of hospitalizations in intensive care units (28.4%–9.8%) decreased over the study period. The proportion of children with MIS decreased from 31.7% (343/1082) to 5.2% (48/918) between the 2 periods.

Children Hospitalized During the Post-BA.1 Omicron Period

We identified 3 populations representing 72.1% of the children hospitalized during the post-BA.1 Omicron period: children ≤90 days, older children with comorbidities and children with MIS.

Children ≤90 days of age accounted for 44.8% (416/928) of the hospitalizations; 131 of 416 (31.4%) were <1 month old. Among these children, 178 of 413 (43.1%) had pauci-symptomatic COVID-19 and 111 of 413 (26.9%) were hospitalized for fever and 74 of 413 (18.2%) for a respiratory disease. By contrast, among the children included in the PARI study, patients <1 month represented <1% (24/3496) and children <3 months of age accounted for 5.9% (206/3496). Fever was reported in 338 of 407 children (83.0%) compared with 739 of 842 (87.8%) before the post-BA.1 Omicron period. Antibiotics were prescribed in 13.9% (54/389) of these cases, and the median hospitalization duration was 1 day (IQR 1–2). Before this period, 26.1% (211/809) of children of the same age received antibiotics while their median length of hospitalization was 2 days (IQR: 1–3.5). Parental COVID-19 vaccination status was known for 102 children ≤90 days old. For 46 of 102 children (45.1%), both parents were vaccinated; for 18 of 102 (17.7%), only 1 parent was vaccinated and for 38 of 102 (37.2%), no parents were vaccinated.

Older children with comorbidities represented 208 of 928 children (22.1%). Their median age was 5.4 years (IQR: 1.0–8.6): 30 of 191 (15.7%) required intensive care and 125 of 128 (97.7%) were not vaccinated against COVID-19.

During this period, only 5.2% (48/918) of cases were MIS-C as compared with >30% during the original-strain and alpha-variant periods. Vaccination coverage in children with MIS was 9.4% (3/32).

DISCUSSION

We observed several modifications in the clinical characteristics of children hospitalized for COVID-19 while the dominant variant changed. During the most recent period, post-BA.1 Omicron, several groups representing about three quarters of children were identified: children ≤90 days old (44.8%), older children with comorbidities (22.5%) and children with MIS (5.2%).

Two main factors may explain the changes in clinical characteristics observed over the study period as illustrated by the proportion of MIS-C and of children admitted to intensive care unit. First, the severity of COVID-19 may have been lowered by the acquisition of natural and vaccine-induced immunity over time.[8] Because of the low vaccine uptake and low COVID-19 incidence in pregnant women, the population of young children remained immunologically naive. This mechanism may explain the increased proportion of hospitalized children <3 months of age during the post-BA.1 Omicron period. Second, the change in circulating variants may also explain the change in symptoms associated with COVID-19.[9]

Although data were only available for a minority of children <90 days old, our results suggest a low parental vaccine coverage. These findings are in line with other reports in France in pregnant women (https://www.assurance-maladie.ameli.fr/etudes-et-donnees/2022-vaccin-covid-19-femmes-enceintes). Of note, vaccine coverage in our study and in data from the French social security system only indicates that at least 1 dose of vaccine has been received regardless of the number of doses and the delay since the last dose. This result suggests that hospitalizations for children ≤90 days old could be prevented by increasing vaccine coverage

in pregnant women. SARS-CoV-2 vaccines have been described as safe for both mothers and children. Similarly, vaccine coverage was extremely low in older children and adolescents. In older children, a bivalent vaccine may have prevented half of symptomatic COVID-19 cases in children and adolescents during the post-BA.1 Omicron period.[10] In addition, SARS-CoV-2 vaccines are effective against MIS-C.

By contrast to the patients in outpatient settings, children ≤90 days of age represented almost half of the children enrolled during the post-BA.1 Omicron period. Their care may have improved as suggested by the major decrease in antibiotic prescription while the proportion of infants with fever remained >80% during the study period. The recent guidelines for well-appearing febrile infants <60 days old published by the American Association of Pediatrics does not include viral testing in the algorithm.[11] A recent systematic review and meta-analysis of febrile infants ≤90 days old with COVID-19 suggest that this population, especially infants >28 days old, are at very low risk of bacterial infection, and the authors even suggested that they may receive care without any blood testing.[12] This situation highlights the need for rapid SARS-CoV-2 testing. Triple antigen tests (SARS-CoV-2, influenza and respiratory syncytial virus) have shown interest in this context. Most of the children ≤90 days old in our study received no antibiotics, and their median hospitalization length was 1 day, which suggests that clinicians had already adapted their care for this specific population.

Several limitations need to be discussed. Testing policies may have change over the long study period. However, these changes are more likely to occur in ambulatory care than in hospitalized patients. Furthermore, we cannot exclude that reporting varied over time. However, the similar evolution of COVID-19 cases requiring hospitalization and those in ambulatory settings discounts this hypothesis. Furthermore, children visiting hospitals which did not take part in the surveillance network were not analyzed and the absence of other source of data prevents us from comparison between the cases described. The number of participating centers, their distribution throughout France and the correlation between hospitalized and ambulatory patients are reassurance about the robustness of data.

Maintaining a surveillance of pediatric COVID-19 hospitalizations is critical because the burden of SARS-CoV-2 infection is persistent and evolutive. Of note, the major discrepancy in the proportion of children <3 months of age between hospitals and ambulatory-based network underlines the complementary nature of these 2 surveillance systems. The burden could be relieved by vaccinating pregnant women and at-risk children combined with early diagnosis and adapted care of children ≤90 days old.

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