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ORIGINAL ARTICLE

The changing clinical presentation of COVID-19 in children during the course of the pandemic

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Abstract

Aim: To investigate the evolution of clinical symptoms of COVID-19 in children throughout the pandemic.

Methods: In this national prospective surveillance study, symptoms in children hospitalised with COVID-19 were collected from all paediatric hospitals in Switzerland between March 2020 and March 2023. Data was analysed across four time periods, according to the predominantly circulating SARS-CoV-2 variant: T1 (wild-type), T2 (Alpha), T3 (Delta) and T4 (Omicron), as well as by age group.

Results: The study included 1323 children. The proportion of children admitted to an intensive care unit remained stable throughout the pandemic. However, the pattern and frequency of clinical manifestations changed over time. Respiratory symptoms were less prevalent during T1 (wild-type), fever during T2 (Alpha) and rash during T4 (Omicron). In contrast, fever and neurological symptoms were more prevalent during T4 (Omicron). Newly described symptoms during T4 (Omicron) included conjunctivitis, laryngotracheitis and seizures. Fever was more prevalent among neonates and infants whereas respiratory symptoms were more common among infants. Gastrointestinal symptoms were more frequent among toddlers, while both toddlers and school-aged children presented with neurological symptoms more often than other age groups.

Conclusion: Continuous surveillance is required to detect changes in manifestations and there by be prepared for the optimal management of complications in children with COVID-19.

KEYWORDS
Alpha, Delta, gastrointestinal, Omicron, rash, SARS-CoV-2, seizure, variants

Abbreviations: ICU, intensive care unit; IQR, interquartile range; PIMS-TS, paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2.

Nicole Ritz and Petra Zimmermann shared authorship.

For Affiliation refer page on 6

1 | INTRODUCTION

The COVID-19 pandemic has affected millions of people worldwide, including children. Most children experience a mild course, yet they can develop a wide range of symptoms of varying severity, including respiratory, gastrointestinal, dermatological and neurological symptoms.[1–3] As the pandemic progressed, different variants of the virus emerged, including Alpha, Delta and Omicron. Numerous studies have examined the impact of these virus variants on the epidemiology and clinical presentation in adults.[4–6] In children, a decreasing trend in COVID-19 severity was observed during the pandemic,[7–12] but little data is available on the effect of the virus variants on the clinical presentation.

This study investigated the evolution of the clinical presentation of COVID-19 in children and adolescents during the course of the pandemic. Data was analysed according to the predominantly circulating severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) variant and the children's age.

2 | MATERIALS AND METHODS

In a nationwide prospective observational study, data of hospitalised children (0–18 years) with laboratory-confirmed SARS-CoV-2 infection was collected through the Swiss Paediatric Surveillance Unit. Children admitted due to, and with, SARS-CoV-2 infection were included. All 29 paediatric hospitals in Switzerland entered cases on a monthly basis and completed a detailed electronic clinical report form, using REDCap (Vanderbilt University, Tennessee, USA).[13–15]

This study includes data collected between 01 March 2020 and 31 March 2023. According to epidemiologic data from the Swiss Federal Office of Public Health,[16] time periods were defined according to the predominance (>50%) of the respective variant. T1 (wild-type) dated from 01 March 2020 to 06 February 2021. T2 (Alpha) dated from 07 February 2021 to 26 June 2021. T3 (Delta) dated from 27 June 2021 to 21 December 2021. T4 (Omicron) dated from 22 December 2021 to 31 March 2023.

The age groups were defined as follows: neonates (≤28 days), infants (28 days to <1 year), toddlers (1–2 years), pre-schoolers (3–5 years), school-age children (6–11 years) and adolescents (12–17 years). Children who were suspected of having, or were diagnosed with, paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS) were excluded from the analysis. Chi-square and Fisher's exact test were used to compare the groups. A subset analysis was done with data from a centre with a high number of cases and minimal missing data to assess the robustness of the results. All analyses were done with R software version 4.2.2 (R Foundation).

The study received ethical approval from the Ethics Committee of Northwestern and Central Switzerland (EKNZ 2020-01130).

Key notes

- In this prospective surveillance study, symptoms of 1323 children hospitalised with COVID-19 in Switzerland between March 2020 and March 2023 were analysed according to the predominantly circulating SARS-CoV-2 variant and age group.
- The proportion of children requiring admission to an intensive care unit remained stable.
- Respiratory symptoms were less frequent during the wild-type period, fever was less frequent during the Alpha period and fever and neurological symptoms were more frequent during the Omicron period.

3 | RESULTS

A total of 3600 hospitalised children were reported in Switzerland from T2 (Alpha) to T4 (Omicron). Of these, study-specific clinical report forms were filled in for 181/354 (51%) in T2 (Alpha), 230/508 (45%) in T3 (Delta), and 721/2738 (26%) in T4 (Omicron). During T1 (wild-type), clinical report forms were filled in for 428 children, while the total number of children with COVID-19, both ambulatory and hospitalised, was 2194. After excluding duplicates and cases which were suspected or diagnosed with PIMS-TS, a total of 1323 children (46% female) were included in the study (Table 1). The median age of children was 8 months (interquartile range (IQR) 1–71 months). The study cohort included 13% neonates, 42% infants, 13% toddlers, 7% pre-school children, 12% school-aged children and 13% adolescents. The proportion of infants increased from 29% in T2 (Alpha) to 32% in T3 (Delta) and 48% in T4 (Omicron). In contrast, the proportion of adolescents decreased from 19% in T1 (wild-type) to 17% in T2 (Alpha), 16% in T3 (Delta) and 7% in T4 (Omicron). Most children were Caucasian (68%), followed by Black (5%), Arabic (4%), Asian (2%), and Hispanic (2%). For 20% of the children, ethnicity was reported as either 'other' or 'unknown'. Of the children included in the study, 25% had at least one pre-existing medical condition. Further details can be found in Table 1.

In total, 7% of the 1323 children were admitted to an intensive care unit (ICU), with no differences between T1 (wild-type) to T4 ([Omicron] Table 1, Figure 1). During T2 (Alpha), a significantly higher proportion of children required mechanical ventilation or inotropic support compared with other periods: 5% versus 2% ($p = 0.045$).

Throughout the entire study period, fever was the most common symptom, reported in 67% of children (Table S1). This was followed by respiratory symptoms (including rhinorrhoea/nasal congestion, cough, respiratory distress/tachypnoea, pharyngitis/sore throat, oxygen saturation less than 92% and laryngotracheitis) in 64%. Gastrointestinal symptoms (including vomiting, diarrhoea and abdominal

TABLE 1 Baseline characteristics of the study cohort.

	Total, *n* (%)	T1 (wild-type) 01 March 2020 to 06 February 2021, *n* (%)	T2 (Alpha) 07 February 2021 to 26 June 2021, *n* (%)	T3 (Delta) 27 June 2021 to 21 December 2021, *n* (%)	T4 (Omicron) 22 December 2021 to 31 March 2023, *n* (%)
Total	1323 (100.0)	352 (100.0)	133 (100.0)	197 (100.0)	641 (100.0)
Sex					
Female	613 (46.3)	160 (45.4)	63 (47.3)	91 (46.1)	299 (46.6)
Age					
Neonates	172 (13.0)	36 (10.2)	22 (16.5)	35 (17.8)*	79 (12.3)
Infants	559 (42.3)	152 (43.2)	38 (28.6)*	62 (31.5)*	307 (47.9)*
Toddlers	171 (12.9)	24 (6.8)	17 (12.8)	22 (11.2)*	108 (16.8)*
Pre-school children	94 (7.1)	27 (7.7)	11 (8.3)	19 (9.6)	37 (5.8)
School-age	159 (12.0)	46 (13.1)	22 (16.5)	28 (14.2)	63 (9.8)*
Adolescents	168 (12.7)	67 (19.0)*	23 (17.3)	31 (15.7)	47 (7.3)*
Median age in months (IQR)	8.0 (1.0–71.0)	9.0* (1.0–111.25)	21.0* (1.0–114.0)	14.0 (1.0–90.0)	5.0* (1.0–34.0)
Ethnicity					
Caucasian	900 (68.0)	255 (72.4)*	90 (67.7)	136 (69.0)	419 (65.4)
Black	59 (4.5)	23 (6.5)*	10 (7.5)	8 (4.1)	18 (2.8)*
Arabic	56 (4.2)	16 (4.5)	13 (9.8)*	7 (3.6)	20 (3.1)
Asian	26 (2.0)	15 (4.3)*	4 (3.0)	2 (1.0)	5 (0.8)*
Hispanic	23 (1.7)	5 (1.4)	4 (3.0)	3 (1.5)	11 (1.7)
Other/Unknown	259 (19.6)	38 (10.8)*	12 (9.0)	41 (20.8)*	168 (26.2)
Pre-existing comorbidities	335 (25.3)	112 (31.9)*	45 (33.8)*	53 (26.9)	125 (19.5)*
Respiratory	60 (4.5)	23 (6.5)	8 (6.0)	6 (3.0)	23 (3.6)
Haematological/Oncological	46 (3.5)	18 (5.1)	4 (3.0)	5 (2.5)	19 (3.0)
Cardiological	37 (2.8)	12 (3.4)	6 (4.5)	7 (3.6)	12 (1.9)
Diabetes mellitus	12 (0.9)	8 (2.3)*	0 (0.0)	2 (1.0)	2 (0.3)
Immunodeficiency	7 (0.5)	5 (1.4)	1 (0.8)	0 (0.0)	1 (0.2)
Other	224 (16.9)	66 (18.8)*	37 (27.8)*	37 (18.8)	84 (13.1)
ICU admission	91 (6.9)	25 (7.7)	10 (7.5)	19 (9.6)	37 (5.7)
Mechanical ventilation or inotropic treatment	25 (1.9)	8 (2.3)	6 (4.5)*	4 (2.0)	7 (1.1)
COVID-19 vaccination					
1 dose	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
>1 dose	8 (0.6)	0 (0.0)	0 (0.0)	1 (5.1)	7 (1.1)
Reason for hospital admission					
COVID-19	693 (52.4)	125 (35.5)*	46 (34.6)*	104 (52.8)	418 (65.2)*

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

*p value <0.05, chi-squared tests were performed except when cell counts were <5, in which case Fisher's exact tests were done. Mann–Whitney U-tests were used to identify differences between the median ages between time periods.

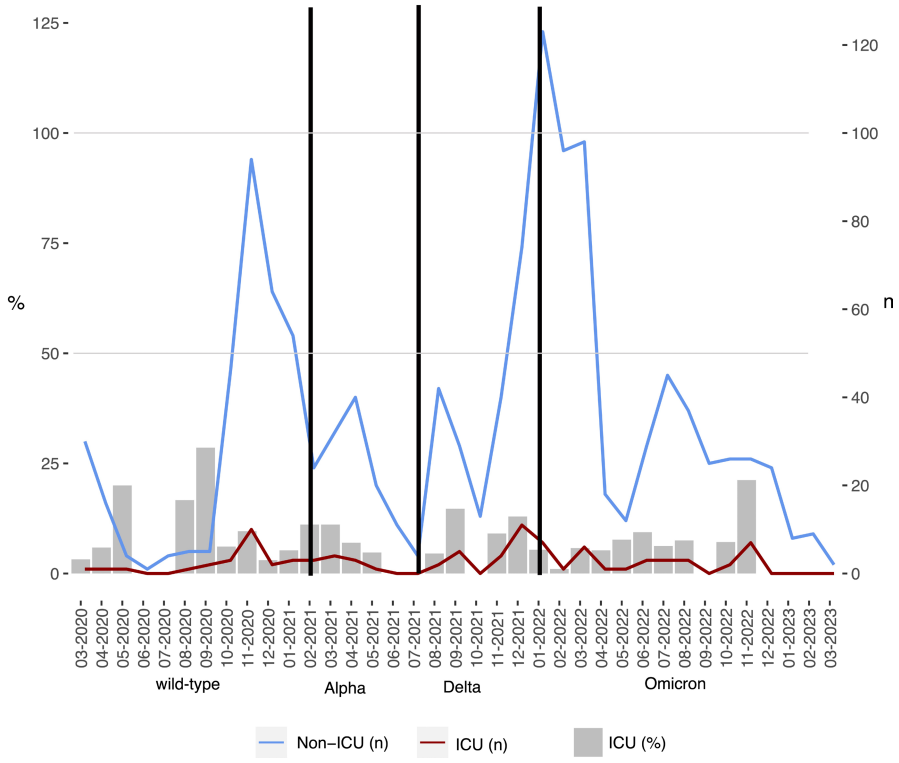

FIGURE 1 Rates and proportions of intensive care and non-intensive care admissions over time.

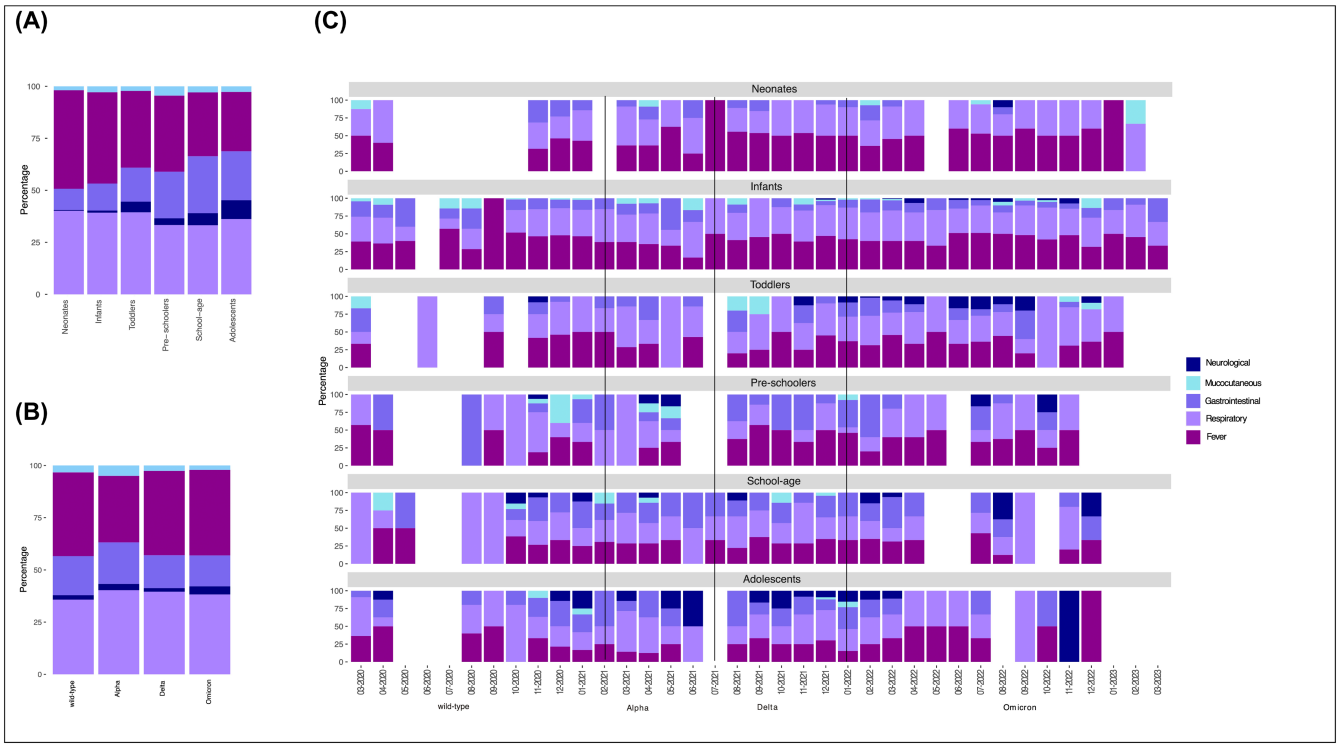

FIGURE 2 Clinical presentation of COVID-19 over time among hospitalised patients of different age groups. Panel A shows percentages of symptoms among different age groups, panel B displays percentages of symptoms across different time periods and panel C shows percentages of symptoms among different age groups and across different time periods.

pain) occurred in 28% of children. Neurological symptoms (including seizures, headache and anosmia/dysgeusia) and mucocutaneous symptoms (including rash and conjunctivitis) were reported in 5% of children.

Respiratory symptoms were less prevalent during T1 (wild-type) compared with T2 (Alpha) to T4 (Omicron): 59% versus 65% ($p = 0.023$). During T2 (Alpha), fever was reported less frequently compared to the other periods: 48% versus 69% ($p \leq 0.001$). During

T4 (Omicron), fever and neurological symptoms were more prevalent: 70% versus 64% ($p = 0.034$); 7% versus 4% ($p = 0.016$); Seizures were particularly more frequent during T4 (Omicron) compared to before: 5% versus 1% ($p \leq 0.001$). Rash was less frequent in T4 (Omicron) than during T1 (wild-type) to T3 (Delta): 3% versus 6% ($p = 0.012$). Finally, conjunctivitis and laryngotracheitis, which had only been reported in zero and two children before, were both reported in 1% of the children during T4, respectively.

A comparative analysis of symptom manifestations across different a groups showed age-specific differences (Table S1, Figure 2). Infants were more likely to present with fever and respiratory symptoms than other age groups: 80% versus 57% ($p \leq 0.001$); 72% versus 58% ($p \leq 0.001$). In toddlers and in adolescents, neurological symptoms were significantly more often reported: 9% versus 4% ($p = 0.008$); 12% versus 4% ($p \leq 0.001$). School-age children, on the other hand, more often presented with gastrointestinal symptoms: 42% versus 26% ($p = 0.001$), and neurological symptoms: 9% versus 4% ($p = 0.030$).

The subset analysis showed that a centre with 229 cases and only three missing cases exhibited a comparable age distribution (14% neonates, 41% infants, 14% toddlers, 6% pre-school children, 12% school-aged children, and 13% adolescents) and similar results to the overall results: 13% of the children were admitted to the ICU, 66% had respiratory symptoms, 29% had gastrointestinal symptoms, 6% had neurological symptoms, and 2% had mucocutaneous symptoms (Table S1).

4 | DISCUSSION

This study investigated trends in the clinical presentation of COVID-19 in children throughout the course of the pandemic, during which different virus variants predominated. In contrast to comparable studies from the United States and Germany, which reported a decrease in severity and rates of admissions to ICU in children during the course of the pandemic,[7,10,11,17] as well as a decrease in severity and rate of admission to ICU in adults,[18] in our study, the proportion of children requiring admission to an ICU did not differ between different time periods.[7,10] However, international comparisons are challenging due to variations in vaccine coverage rates, the proportion of children with pre-existing medical conditions, and admission criteria for ICUs across different countries. The need for mechanical ventilation or inotropic support is a more objective measure than ICU admissions. We observed slightly higher rates for these during the prevalence of the Alpha variant. However, it is important to note that the absolute numbers of children requiring mechanical ventilation or inotropic support in our study were relatively small.

Consistent with our findings, several studies have reported an increase in children presenting with seizures during the circulation of the Omicron variant.[19–21] However, it is noteworthy that cases of seizures occurring at age 5 years and beyond, which fall outside of the typical age range for febrile seizures in children, were reported in both our and in previous studies.[19–21] The underlying pathophysiology for this surge in seizure cases remains unclear, but they could have been associated with viral co-infections during the period when lockdown restrictions were eased and Influenza infections resurged.[22] Viral co-infections have been reported to result in a more severe disease compared infection with SARS-CoV-2 only.[23] Similarly, and consistent with our findings, an increase of laryngotracheitis symptoms have also been reported during the Omicron wave in previous studies. A possible explanation could be the increased replication of the Omicron variant in the upper respiratory tract.[24–27] The higher frequency of fever observed in infants in our study could partly be attributed to clinicians hospitalising them more readily when presenting with fever, rather than it being inherently more common in this age group.

In Switzerland, COVID-19 vaccines were licensed for children aged 12 years and above in August 2021 and 45% of eligible children had received at least one vaccine dose during the circulation of the Omicron variant.[16] In our study, less than 1% of children were vaccinated. A number of factors could explain the reduced incidence of hospitalisation among adolescents in our study during the Delta and Omicron variant period. These include an increasing vaccination coverage in this age group and/or an increased coverage in parents, as well increasing immunity due to previous infection. Nevertheless, it is also plausible that the decline in numbers was attributed to changes in mitigation measures. One of the aforementioned studies form the United States also observed a decline in the proportion of teenagers in later phases of the pandemic, in a manner similar to our findings.[7]

4.1 | Strengths and limitations

The strengths of our study included the systematic nationwide data collection and the longitudinal design allowing analysis of trends over time. The limitations were that the data on viral variants were not case-specific but based on the predominance of the respective variants from national surveillance data. Furthermore, during both the wild-type and Omicron periods, electronic clinical report forms were completed for less than 30% of the hospitalised children. Thus, underreporting could have introduced a potential bias, however, we did not find evidence for this in the subset analysis. Despite a higher rate of ICU admission in the chosen centre compared with the overall sample, which is explained by the fact that only less than half of the 29 centres have an ICU. However, the age group distribution and occurrence of symptoms closely mirrored the overall sample and confirmed the robustness of the results. Including children admitted due to, and with, SARS-CoV-2 infection in our cohort could have influenced the results, but making clear distinctions between these two reasons for admitting patients may not be possible in many instances. Nonetheless, our intention was to analyse the clinical presentation of SARS-CoV-2 cases over the course of the pandemic, which prompted us to encompass all cases. Lastly, numerous other aspects changed throughout the course of

the pandemic, including mitigation measures and possibly hospitalisation admission criteria.

5 | CONCLUSION

This is the first study, which investigated the clinical manifestations of COVID-19 symptoms in nationwide surveillance data. The ICU admission rate remained constant during the study period from 01 March 2020 to 31 March 2023. However, we found that the clinical features of children hospitalised with COVID-19 changed during the course of the pandemic. This was particularly noticeable with the emergence of the Omicron variant. Continuous surveillance is required to be aware of, and detect, the current clinical spectrum of disease to optimally manage children infected with SARS-CoV-2, including the development and implementation of targeted preventive measures like vaccination campaigns and infection control strategies.

AUTHOR CONTRIBUTIONS

Juliane Wurm: Formal analysis; visualization; writing – original draft; writing – review and editing. **Anita Uka:** Conceptualization; writing – review and editing. **Vera Bernet:** Writing – review and editing. **Michael Buettcher:** Writing – review and editing. **Eric Giannoni:** Writing – review and editing. **Lisa Kottanattu:** Writing – review and editing. **Nina Schöbi:** Writing – review and editing. **Abdelaziz Zemmouri:** Writing – review and editing. **Nicole Ritz:** Conceptualization; funding acquisition; supervision; writing – review and editing. **Petra Zimmermann:** Conceptualization; funding acquisition; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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