



Severity, outcomes, and vaccination status in hospitalized children who tested positive for SARS-CoV-2 during two pandemic waves

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Abstract

Background. The infection with SARS-CoV-2 in children usually manifests as a mild respiratory tract infection. The aim of this study was to evaluate the severity, outcome and vaccination status in children hospitalized for COVID-19 in a single center during two pandemic waves determined by different SARS-CoV-2 variants of concern (VOCs).

Methods. A retrospective study on 656 consecutive pediatric patients was performed from September 1, 2021, to April 30, 2023. The study interval was divided into waves, according to official data on the circulation of Delta and Omicron VOCs. Data collected included sex, age, comorbidities, date of diagnosis, duration of hospitalization, vaccination status, clinical outcome.

Results. The Delta group consisted of 234 children with a mean age of approximately 9 years, while the Omicron group included 422 children with a mean age of around 2.5 years. Most cases were mild, although in the Omicron wave the hospitalization rate was higher and 41.7% of the cases were medium in severity. The presence of comorbidities was not linked to an increase in severity. Vaccination rates were low in both groups, with a mean of 4% for the total of eligible patients.

Conclusion. This pioneering study highlights the nature of COVID-19 in children, focusing on both clinical aspects and public health issues.

Keywords: COVID-19, children, disease severity, vaccination

Background and aims

The global pandemic of SARS-CoV-2 that started in the late 2019 had an unprecedented effect on healthcare systems all over the world, causing anxiety among people of all ages. The severe forms of pneumonia that were often seen in adults [1] raised concerns about what implications this virus would have on children. As in adults, the clinical findings of coronavirus disease (COVID-19) in children can range from asymptomatic infection to mild respiratory tract symptoms, to severe pneumonia with acute respiratory distress syndrome and multiorgan dysfunction [2]. We have now seen an evolution in the process of understanding this disease and

surely local reports describing the nature of the infection have added to the larger picture [3–5].

According to the official data from the Romanian National Institute of Public Health [6], on the 16th of April 2023 (date of interest for the study period), there were no reported deaths in the 0–19 years age group, from a total number of infections for all age groups of 3,393,902. Five percent of these cases are in the 0–9 years age group and 7.5% are in the 10–19 years age group.

During the pandemic, clinical manifestations of the disease also varied among different variants of the SARS-CoV-2. In population-based surveillance [7], the annual COVID-19-associated hospitalization rate among children <18

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years of age in the United States was 48.2 per 100,000 overall, but had variations in different age groups. In Romania, data on hospitalization rates among children are not available. This was one of the primary motivations for initiating research on the local aspects of pediatric COVID-19.

The principle aim of this study was to characterize the differences in clinical features of two different SARS-CoV-2 variants. According to the official data from the Romanian National Institute of Public Health, the fourth wave of the pandemic, due to the Delta variant of concern (VOC) started in Romania at the beginning of September 2021, with a peak in the last week of October [8]. After a decrease in daily new cases in December 2021, the fifth wave started in Romania abruptly after the winter holidays, at the beginning of January 2022 [9]. This was due to the new B.1.1.529 variant, classified as a VOC by the World Health Organization (WHO) on the 26 November 2021 and labeled Omicron [10]. From the 1st week of 2022, Omicron VOC represented more than 60% of the sequenced samples [11]. Available literature [12] sets clinical differences between the two variants: patients with Omicron infection were found to be more likely to present with croup, lower respiratory tract infection and seizures compared with those with Delta infection.

Another focus of this study was to evaluate the anti-SARS-CoV-2 vaccination status of the included children. Romania's vaccination program for adults began in January 2021, while vaccinations for children aged 12 and older started on June 2, 2021. Despite this, the vaccination rate remained very low. In the 5-11 years age group, vaccination was approved starting with February 2022. From an eligible number of almost 1.8 mil children, only 5.358 were vaccinated after 6 months of the program [13].

Considering the presented situation and the need to better understand the dynamics of SARS-CoV-2 infection in children in our country, we conducted a retrospective study. Our goal was to compare the severity of Delta and Omicron variant infections among hospitalized children. A second point of interest was to establish the immunization status against COVID-19 among those admitted to our center.

Methods

This retrospective study included children under 18 years of age, consecutive hospitalized patients in our center. The hospital is an academic tertiary hospital providing medical services for adults and children with infectious pathology from several neighboring counties. The participants were included based on the following criteria: (1) age under 18 years, (2) a confirmed diagnosis of COVID-19, either through a positive SARS-CoV-2 molecular diagnostic test or a rapid antigen test, and (3) being hospitalized between September 1, 2021, and April 30, 2023. Exclusion criteria were age >18 years and different hospitalization period.

The study interval was divided based on national data on the circulation of SARS-CoV-2 VOCs [8], into the

Delta wave (the period September 1, 2021–January 15, 2022) and the Omicron wave (January 16, 2022–April 30, 2023). Two groups were formed, corresponding to these two waves: group Delta (D) and group Omicron (O). Each group included patients hospitalized during the designated period of time.

Patients' medical records were retrospectively reviewed. Data collected included sex, age, comorbidities, date of diagnosis, duration of hospitalization, vaccination status, clinical outcome. Disease severity was established during the hospitalization, according to the WHO classification [2].

Data were collected in an Excel database (Microsoft 365) and were further on processed using IBM SPSS Statistics for Windows, (Version 29.0.2.0 Armonk, NY: IBM Corp., IBM Corp. Released 2023). Categorical data were presented as counts and percentages. Non-normally distributed quantitative data were presented as median and interquartile range. *p*-values below 0.05 were considered statistically significant for all statistical analyses. Concerning categorical data, chi-squared test or Fisher exact tests were performed in order to compare two independent groups. When assessing more complex relationships, multiple linear regression was used. Two variables, hospital duration and length of disease, were analyzed in relation to the outcome. To address skewed values, a log transformation was applied to hospital duration prior to analysis. A Student's *t*-test was then conducted to compare hospital duration between the Delta and Omicron groups.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local Scientific Research Ethics Committee (No 11972/19.05.2023).

Results

A total of 656 patients aged between 1 month and 18 years were included in the study. The Delta group consisted of 234 children, while the Omicron group included 422 children. The demographic characteristics of these two groups are presented in Table I. In terms of social factors, 69.4% of the children came from urban areas.

The average age of the patients included in the study was 5 years, with a higher mean in the Delta wave (approx. 9 years) and a lower one for the Omicron wave (2 and a half years). A prevalence of male patients was observed.

In terms of disease severity, mild forms predominate in both groups: group Delta (214 mild forms (91.4%), 16 medium forms and one severe form) and group Omicron (242 mild forms, 176 medium forms (41.7%) and 4 severe forms).

The Student's *t*-test yielded a significant *p*-value, indicating a statistically significant difference in hospital duration between the two groups. Additionally, the mean length of the disease was found to be higher for the Delta group, with a significant *p*-value supporting this finding.

Table I. Demographics, COVID-19 severity forms and outcomes.

Characteristic	Total (n=656)	Delta (n=234) 35.67%	Omicron (n=422) 64.32%	p-Value
Demographic data				
Age (months), median (IQR)	60 (7, 120)	117.5 (60, 156)	32.7 (5, 24)	<0.001
Age<1 year, n (%)	237 (36.1)	22 (9.4)	215 (50.9)	<0.001
Age 1-5 years, n (%)	176 (26.8)	41 (17.5)	135 (32)	<0.001
Age ≥5years, n (%)	243 (37)	171 (73)	72 (17.1)	<0.001
Sex (female), n (%)	301 (45.9)	94 (40.2)	207 (49)	>0.05
Severity form, n (%)				
Asymptomatic	3 (0.5)	3 (1.3)	0 (0)	
Mild	456 (69.5)	214 (91.4)	242 (57.3)	
Medium	192 (29.3)	16 (6.8)	176 (41.7)	
Severe	5 (0.8)	1 (0.4)	4 (0.6)	
Outcome				
Length of hospital stay (days), median IQR	4.1 (1, 6)	2.1 (1, 1)	5.2 (4, 7)	<0.001
Disease duration (days), median IQR	7.9 (5, 10)	9.9 (7, 13)	6.8 (5, 8)	<0.001

IQR, interquartile range;

Table II. Comorbidities.

Comorbidities	Total (n=656)	Delta (n=234)	Omicron (n=422)	p-value
Cardiovascular, n (%)	21 (3.2)	5 (2.1)	16 (3.8)	<0.001
Diabetes, n (%)	1 (0.2)	0 (0)	1 (0.2)	<0.001
Neurological, n (%)	11 (1.7)	3 (1.3)	8 (1.9)	<0.001
Genetic disorders, n (%)	8 (1.2)	0 (0)	8 (1.9)	<0.001
Pulmonary, n (%)	23 (3.5)	9 (3.8)	14 (3.3)	<0.001
Atopic, n (%)	13 (2)	7 (3)	6 (1.4)	<0.001
Dermatological, n (%)	13 (2)	3 (1.3)	10 (2.4)	<0.001
Hepatic, n (%)	4 (0.6)	0 (0)	4 (0.9)	<0.001
Renal, n (%)	12 (1.8)	4 (1.7)	8 (1.9)	<0.001
Hematological, n (%)	11 (1.7)	2 (0.9)	9 (2.1)	<0.001
Cancer, n (%)	2 (0.4)	0 (0)	2 (0.5)	<0.001
Psychiatric, n (%)	8 (1.2)	3 (1.3)	5 (1.2)	<0.001
Orthopedic, n (%)	6 (0.8)	1 (0.4)	5 (1.2)	<0.001
Gastro-intestinal tract, n (%)	19 (2.9)	4 (1.7)	15 (3.6)	<0.001
Rheumatological, n (%)	2 (0.4)	1 (0.4)	1 (0.2)	<0.001
Immunological, n (%)	4 (0.6)	0 (0)	4 (0.9)	<0.001
Total, n (%)	158 (24)	42 (17.9)	116 (27.4)	<0.001

Table III. Vaccination status, severity of the disease linked to vaccination status.

Vaccination status, n (%) (n=656)	Total	Delta (n=234)	Omicron (n=422)	>0.05
Pre-vaccination	103 (15.7)	87 (37.2)	16 (3.8)	
Not eligible for vaccination	413 (63)	63 (27)	350 (82.9)	
Vaccinated	26 (4)	15 (6.4)	11 (2.6)	
Severity form for vaccinated patients, n (%)				
Mild	23 (88.5)	15 (100)	8 (72.7)	
Medium	3 (11.5)	0 (0)	3 (27.3)	

Pre-vaccination indicates the vaccination status when a patient did not receive any vaccine dose because, at the time of hospitalization, there were no vaccines available on the market for the 5-11 years age group.

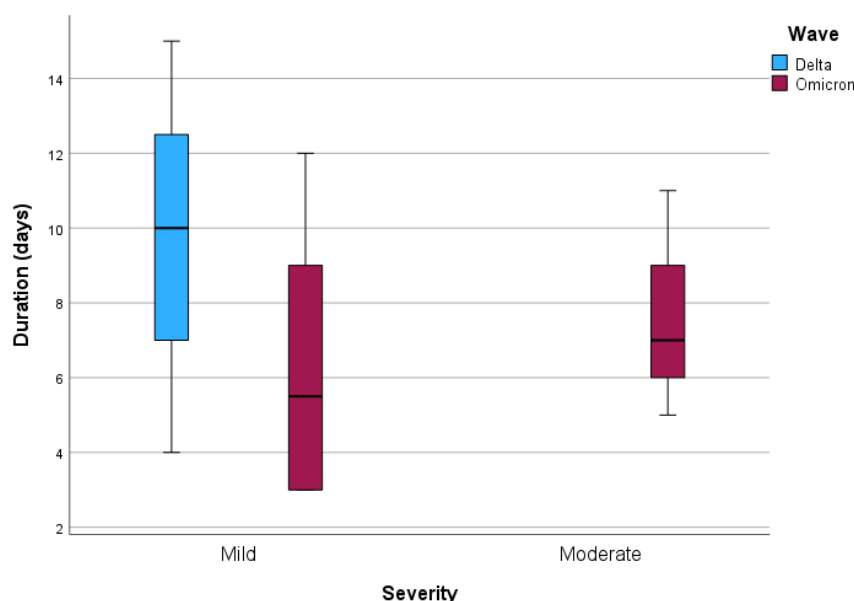


Figure 1. Duration of disease in vaccinated patients, comparison for group Delta and group Omicron and degree of severity. For the boxplot, the box indicates the 25th, 50th (median), and 75th percentiles as the bottom, middle, and top of the box, respectively. The marker inside the box shows the mean. The whiskers extend out relative to the interquartile range.

Comorbidities present in the patients from our study are shown in table II.

The presence of comorbidities increases the likelihood of developing a moderate or severe form of the disease, with an odds ratio of 1.5. While the Pearson correlation coefficient is -0.02, indicating a very weak negative correlation, this finding is not statistically significant, as the two-tailed p-value is greater than 0.05.

Vaccination status of the patients is presented in table III.

We analyzed the duration of disease in vaccinated children in the two groups. The results are shown in figure 1.

For the patients vaccinated in the Delta group, the mean duration was 10 days, the same as for the whole group. In the Omicron group, the mean duration for the vaccinated children with a mild form was 1 day shorter than the group mean.

The risk of developing a more severe form of the disease in unvaccinated patients was analyzed, with an odds ratio of 3.34.

Discussion

This study provides a comparative analysis of pediatric patients hospitalized during the Delta and Omicron waves of COVID-19, focusing on demographic, clinical, and vaccination-related differences. The findings reveal several important distinctions between the two groups.

Firstly, during the Omicron wave, the number of hospitalized cases was larger than during the Delta wave.

This is consistent with data published internationally: for USA, during the Delta wave, 4.6 out of every 1,000 PCR-positive cases in the community were hospitalized within the defined time period, compared to 8.0 per 1,000 during the Omicron wave. When considering only hospital admissions directly attributed to COVID-19, the rates were 3.8 per 1,000 cases for Delta and 5.9 per 1,000 for Omicron [14].

The Omicron group had a significantly younger patient population, with a median age of 32.7 months compared to 117.5 months in the Delta group. This highlights Omicron's greater impact on younger children, particularly those under 1 year of age, who represented 50.9% of the Omicron cohort versus only 9.4% in the Delta group. These findings are consistent with data presented in a review by Powell et al. [15].

In terms of disease severity, mild forms predominate in both groups. However, the Omicron group showed a higher proportion of medium forms (41.7%) and severe forms (0.6%) compared to the Delta group (6.8% medium and 0.4% severe). This indicates a potential shift not necessarily in the clinical presentation, but rather in how well COVID-19 in children was cared for at home. During the Omicron wave, mild forms in older children did not require hospitalization.

The median length of hospital stay was significantly longer in the Omicron group (5.2 days) compared to the Delta group (2.1 days), suggesting more prolonged clinical management. Conversely, the median disease duration was

longer in the Delta group (9.9 days) than in the Omicron group (6.8 days), reflecting differences in disease progression between the two variants. A study by Molteni et al. in UK found a median illness duration of 6 days, with older age correlating with shorter symptomatic disease [16]. In our study, in Delta group, where the mean age was 117.5 months (approx. 9 years), the illness duration was significantly higher than in the Omicron group, where the average age was 2 years (9.9 days vs. 6.8 days), in opposition with the information cited.

When analyzing differences in disease severity and hospital stay duration, it is essential to consider the national health regulations in effect at that time. During the Delta wave, strict measures such as lockdowns, curfews, and restrictions on public gatherings were still enforced. Early in the Delta wave, even asymptomatic cases were occasionally isolated through hospitalization.

The presence of comorbidities was more common in the Omicron group (27.4%) than in the Delta group (17.9%), with cardiovascular diseases (notably heart malformations), gastrointestinal disorders (mainly reflux), and pulmonary comorbidities (primarily asthma) being the most frequently reported in both groups. Comorbidities significantly increased the risk of developing moderate or severe disease, with an odds ratio of 1.5.

Vaccination status was also a critical factor. The proportion of vaccinated children was low in both groups (4%), reflecting the limited availability of vaccines for younger age groups at the time of the study. Among vaccinated children, the mean disease duration in the Delta group was consistent with the overall group mean (10 days), while vaccinated children in the Omicron group with mild forms had a slightly shorter duration compared to the group mean. Unvaccinated patients had a significantly higher risk of developing more severe disease, with an odds ratio of 3.34, emphasizing the protective role of vaccination. Talking about vaccination in Romania is a difficult subject. According to UNICEF, the perception of the importance of vaccination has declined by 10% since the beginning of the pandemic [17]. A meticulous study done by Miko et al. among the population of our city, investigating general vaccine hesitancy found that 30.3% of the responders were hesitant about vaccinating their children and 11.7% of parents reported refusing to vaccinate their child [18]. The presence of mild forms of disease in children was another strong argument against vaccination, fuelled by conspirative theories regarding the mRNA vaccine. Data concerning the local vaccination status of the under 18 years population are scarce. Overall, the percentage of children vaccinated, excluding those who were not eligible, is 4%, with 6.4% vaccinated in the Delta group and 2.6% in the Omicron group. In USA, the percentage of vaccinated children varies from state to state, ranging from <10% to more than 40% [19]. A study done in the Eastern Mediterranean Region yielded a 32% vaccination coverage [20]. The difference in vaccination coverage is important.

As cited by Goldman et al., the hesitancy to vaccinate only increased in the course of the pandemic, with educated and older caregivers being more prone to accept vaccination for their children [21]. The analysis on the data yields a 3.34 higher risk in unvaccinated children to develop a medium form of disease. Considering the costs involved, starting with the psychological implications of the hospitalization and ending with the financial burden, policies should be implemented for better protection against the disease.

The first limitation of the study is the retrospective nature. This study objectively describes the situation at a certain point in the past, but there is no possibility of intervention. Second, the quality and clarity of the data may be influenced by the ways in which clinical and paraclinical parameters have been archived.

This study manages to perform a retrospective analysis on the COVID-19, including a large number of subjects and focuses on two very important features- the severity of the disease and the vaccination status. These data provide the basis for practical measures - in most cases, COVID-19 in children is mild and hospitalization is envisaged only if other factors impose it. Secondly, vaccine policy must be reconsidered, and preventable diseases should benefit from this, given that we lack the test of time regarding long term effects if the SARS-CoV-2 infection in children.

This article comes to add to the information already published on local cases of COVID-19. Most recent national studies targeting the pediatric population include a report on parents' attitudes towards COVID-19 vaccination of children [22], an article on the increased incidence of type 1 diabetes during the pandemic in children [23], a multinational study on the emotional and mental health impact on children after SARS-CoV-2 infection [24] and a case series presentation of patients who required appendectomy simultaneously with SARS-CoV-2 infection [25].

Further studies are needed to explore the long-term effects of these variants on pediatric patients and the efficacy of vaccination in preventing severe outcomes in younger age groups.

Conclusions

This study highlights key differences in pediatric hospitalizations during the Delta and Omicron waves of COVID-19. The Omicron wave had more hospitalizations, particularly among younger children, with longer hospital stays despite shorter illness duration. While most cases were mild, moderate and severe cases were more common in the Omicron group, especially among unvaccinated children and those with comorbidities.

Vaccination proved protective, but hesitancy remains a challenge, requiring stronger public health strategies. Despite its retrospective nature, this study provides valuable insights for refining hospitalization criteria, improving vaccination policies, and guiding future research on long-term effects in children.

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