Impact of Variants, Epidemiological Trends, and Comorbidities on Hospitalization Rates of Unvaccinated Children in Brazil: A Retrospective Study (2020-2022)

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Abstract

This retrospective study aimed to investigate the impact of the emergence of new variants and the epidemiological scenario on hospitalization rates of unvaccinated children (0-12 years) in Brazil. The study included 1,614 children admitted to a hospital between March 2020 and December 2022, with only 101 (6.3%) of them testing positive for COVID-19 via RT-PCR. The frequency of COVID-19 cases increased from 7.5% in 2020 to 9.3% in 2022 with the emergence of the Omicron variant. Children over five years old with comorbidities accounted for the majority of cases (69% [70/101]). Sickle cell anemia was the most frequent comorbidity (20%), and flu disease (36% [36/101]) and decompensation of underlying disease (33% [33/101]) were the main reasons for hospitalization. Co-infection was detected in 11% of cases, with RSV being the most common viral pathogen (71%). Hospital readmission occurred in 26% of cases, with a higher frequency in children over five years old. The death rate was 2.2%, with comorbidities such as cystic fibrosis and congenital heart disease as risk factors. These findings emphasize the need to prioritize vaccination with monovalent Omicron XBB for high-risk groups, including children over five years old with comorbidities, to mitigate the impact of new variants and reduce severe disease outcomes.

Introduction

Since the beginning of the pandemic, epidemiologic data have shown that hospitalization of children and adolescents associated with the severe acute respiratory syndrome (SARS) due to COVID -19 has not significantly impacted this population. They differ from the elderly and adult population with comorbidities, which are specially more susceptible to severe disease progression and complications. (1)

In children, several factors contributed to milder infection, which reduces the number of the significant receptor angiotensin-converting enzyme 2 (ACE2) on the cell surface, resulting in less availability of the receptor, and the presence of other respiratory viruses competing simultaneously and limiting replication of different viruses. In neonates and infants, maternal antibodies provide protective immunity against disease (2,3).

In Brazil, the incidence of SARS associated with COVID -19 totaled 20.846 cases and 856 deaths in the age group between 0 and 19 years by epidemiological week 51 of 2022 (3). In this context, it can also be observed that children were not initially affected by SARS-CoV-2 as much as in the 2009 pandemic caused by H1N1. (4)
It should be noted that the government took several preventive measures to reduce transmission rates in the early stages of the pandemic and after the initial outbreak in Brazil. This dramatically impacted the child population, as schools were closed and classes moved to remote locations, as well as the introduction of social distancing (lockdown), the use of masks, increased availability of Covid-19 testing, and the establishment of field hospitals.

However, after two years of the pandemic, the return of social activities, and the emergence of new variants, among other factors such as mass vaccination of the adult population and the characterization of a new variant of concern called Omicron in late 2021, there has been an increase in confirmed cases of hospitalized children associated with this new variant and its subtype.

Methodology

In this retrospective study, 1614 hospitalizations of children aged up to 12 years at Hospital São Paulo (HSP) were tested for COVID-19 using the polymerase chain reaction method (RT-PCR) from March 2020 to December 2022. Hospitalization data were collected regarding the main reason for hospitalization, underlying medical conditions, indicators of severe disease (length of hospitalization, ICU stay and death), viral load (Ct value), cases of hospital readmission within 6 months, and variant wave.

Coinfection with other respiratory viruses during this period was detected by molecular testing (RT-PCR) for human metapneumovirus (hMPV), human respiratory tract infection (hRSV), influenza A (FLU-A) and B (FLU-B), adenovirus (HAdV), and human rhinovirus (HRV). Simple logistic regression models (for categorical and numerical variables), linear regression and Pearson’s chi-square (numerical variables) were used for statistical analysis.

To evaluate the frequency of this infection in this population, we categorized the age of patients in the following ranges: < 1 year, 1 -| 2 years, 2 -| 5 years and > five years.

Results

The study reports the results of a COVID-19 test in 1614 hospitalized children, the age range of the children ranged from 0 to 12 years, Me= 3.97; Md= 3; SD +/- 3.97 and IQR (1 - 8) years with a confirmation rate of 6.3% (101/1614). Men accounted for 59% of the cases of infection. There was no correlation between sex and positive cases of this population. (Table 1)

Group of 1 -| 2 years of age had the lowest frequency of cases of COVID-19 infection among age groups, demonstrating statistical significance among these ages. Children aged under one year were 2.54 times more likely to be infected, 2 - 5 years of age with 2.44 times more and those older than five years were 2.88 times more likely to be infected by this disease. Age showed a significant difference (p 0.044; OR = 1.10; CI 95% (1.00-1.10)) children over one year of age are 10% more likely to become infected with COVID-19 each year more than life. (Table 1)

There was no statistically significant association between COVID-19 infection and the following causes, comorbidities, hospitalization, ILI syndrome, ICU and high viral (CT value). (Table 2)

Table 1: Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (%)</th>
<th>Overall (%)</th>
<th>SARS-CoV-2 test result</th>
<th>SARS-CoV-2 test result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 1.614</td>
<td>n = 1.614</td>
<td>Negative (%)</td>
<td>Negative (%)</td>
</tr>
<tr>
<td></td>
<td>n = 1.513 (93.7)</td>
<td>n = 1.513 (93.7)</td>
<td>Sex</td>
<td>Sex</td>
</tr>
<tr>
<td>Sex</td>
<td>Sex</td>
<td>Sex</td>
<td>832 (54.9)</td>
<td>832 (54.9)</td>
</tr>
<tr>
<td>Male</td>
<td>892 (55.2)</td>
<td>892 (55.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>Age-group (years)</td>
<td>Age-group (years)</td>
<td>median 3 (IQR =1-8)</td>
<td>median 3 (IQR =1-8)</td>
</tr>
<tr>
<td>&lt; 1 years</td>
<td>378 (23.4)</td>
<td>378 (23.4)</td>
<td>352 (93.1)</td>
<td>352 (93.1)</td>
</tr>
<tr>
<td>1 -</td>
<td>2 years</td>
<td>354 (21.9)</td>
<td>354 (21.9)</td>
<td>344 (97.1)</td>
</tr>
</tbody>
</table>
The hospitalization time ranged from 1 to 240 days (Me= 13.7; SD +/- 31.85; Md= 6; IQR (4-9) days). The length of stay in the ICU ranged from 1 to 40 days (Me= 9.14; SD +/- 10.84; IQR (3-10) days). Only 17% (17/101) of the patients required ICU (Me= 4.9; SD +/- 4.27; Md= 4; IQR (3-10). Among these cases, 24%
(4/17) of the patients were hospitalized due to decompensation of the underlying disease, and the highest hospitalization rate was due to flu syndrome, representing 47% (8/17) of ICU patients. However, there was no correlation between the time of hospitalization and the ICU admission with age ILI syndrome.

Regarding the viral load (CV) of the patient, CT was used as a proxy, which is inversely proportional to the CVs, that is, the lower the CT, the higher the CV. The general CT of the patients presented Me=27.57 DP+/- 6.71; Md= 29; IQR (22 - 34).

Hospitalization for ILI had CT value of Me=25.17 SD +/- 6.42 Md=25; IQR (20.5- 31), the decompensation of the underlying disease a CT value of Me = 29.27 SD +/- 6.72 Md = 33 IQR (23-35) and for other factors value of Me = 28 SD +/- 6.21; Md=30.5 IQR (24-33.5). There was only a statistically significant association between ILI and CT value (p= 0.028; OR =1.072; CI 95% (1.00 - 1.14)). That is, for each point lower than CT, it is 1.07 times more likely to be hospitalized for ILI.

The last two data evaluated were deaths and hospital cases readmission. Death was approximately 2% (2/101) of the cases, both of which had comorbidities. One case occurred in 2021, the patient had cystic fibrosis; hospitalization was due to the EG and remained in the ICU until death. The other case occurred in 2022; the patient with congenital heart disease was admitted for decompensation of the underlying disease.

Hospital readmission occurred in 26% (26/101) of the cases, with higher frequency in children over 5 years (46%) of the cases (p=0.0047; OR 4.25; CI95% 1.02-17.69).

The frequency of COVID-19 cases among the years analyzed 2020, 2021 and 2022 was 7.5% (23/307), 3.5% (27/762) and 9.3% (51/545), respectively.

In the analyses between years in relation to COVID-19 infection, it shows that in 2020 and 2022 there was a significant association in relation to 2021. (Table 1) That is, children hospitalized in 2020 and 2022 had 2.2 and 2.8 times more chances of this infection occurring than those hospitalized in 2021.

The frequency of cases of viral coinfection during this period was 11% (11/101). Only three of these pathogens were detected. RSV received 64% (7/11), four cases (< 1 year), one case (2 - | 5 years), and two cases (> five years). HRV was detected in three cases, 27% (3/11), when the children were seven months old, and the detection of Flu-A was 9% (1/11) the child was two years old.

The following graph (figure 1) shows positive cases of age groups and their monthly distribution since the beginning of the pandemic. The peaks of cases in children younger than five years correspond to the emergence and spread of new variants in Brazil, while in children older than five years, beyond these peaks, there is a continuous detection for all these periods.

Discussion

In this cross-sectional study, the characteristics of the population of children up to 12 years of age hospitalized and diagnosed with COVID-19 in HSP were evaluated. It is noteworthy that patients treated and hospitalized in the HSP are very complex. In this analysis, it was found that a portion of the population was eligible to be vaccinated, but none had completed vaccination during hospitalization. Vaccination for children between 5 and 11 years of age had not been approved until the beginning of 2022 and for children between 6 months and four years of age until the end of last year. Since the onset of this pandemic, children have not been as susceptible to the virus as adults or the last pandemic in 2009, which was caused by the H1N1 influenza virus and severely affected children at the time. (5).

However, this scenario has changed, possibly due to the high vaccination coverage in the adult and elderly population, immunization of children older than 12 years until the end of 2021, the end of quarantine and the emergence of new variants.

In this new context, our study children up to 11 years of age became more susceptible to the new circulating variant of omicron. A recent study reported a change in the current pandemic scenario, showing a significant
increase in the proportion of pediatric cases after the emergence of the Omicron variant, rising from > 2% at the beginning of the pandemic to 25% by March 2022 (4).

As observed in our study, most patients were hospitalized for other causes or underlying diseases with an influenza-like illness. Only a few cases required more intensive treatment or had a more severe clinical outcome.

Other studies, such as Zhu’s, report that although most cases are lighter, children with underlying conditions are at higher risk of developing severe symptoms of the disease. (4) In Brazil, one study reported that approximately 40% of the pediatric population had at least one chronic condition, 14.6% (associated with neurological conditions) and 14.2% of children diagnosed with two or more chronic conditions as a risk factor for COVID-19. (5)

Evaluating this population, our findings show that the most affected individuals were children older than five years of age. As age increases, so does the likelihood of infection. This is consistent with other studies, such as Siegel et al., which have shown over time that children aged 12 to 17 years are more susceptible to this infection, followed by the age group of 5 to 11 years and those under four years of age. (6) In the United States, the percentage of general hospitalizations related to COVID-19 in children was 36%, with the highest rate in the > 2 age group (32.7%), followed by 2 to 4 years (8.7%), 5 to 11 years (16.8%). The highest rate was in the age group from 12 to 17 years (41.8%). The rate of ICU admissions was approximately 33%, with only one death. (7)

Data released by the CDC in March of this year through the COVID-NET network, which conducts surveillance of hospitalizations in the United States, show an increase in hospitalizations in the 0-4 age group, with 85% of these cases attributable to COVID-19. Among these cases, 37% had one or more underlying conditions. (8) This differs from our data, which showed that detection was more common in the < 5 age group, and the incidence of underlying disease or comorbidities was approximately 69%.

The cases of coinfection we presented were low (11%) compared with other studies. Wu et al. analyzed COVID-19 coinfections in 74 confirmed children positive for this pathogen. As a result, 34 (45.95%) patients were positive for the cold virus, and 19 (51.35%) had coinfection with pathogens other than SARS-CoV-2. (9).

Our study showed that children older than five years are more likely to test positive for COVID-19. The group with the lowest frequency of this infection was between 1 - 2 years old. Kolla’s study et.al. 2022, suggests that, in children between these ages, vaccines against the tuna virus may confer a protective factor against other viruses, such as SARS-CoV-2, so this probably influenced the lower frequency of cases. The main aged virus vaccines used in this range are quadrivalent viral and poliomyelitis 1 and 3. (10)

Results in the literature usually show a lighter form of the disease in most cases. However, it is worth mentioning that additional research is needed in this population, as the number of cases has changed significantly from the beginning of this pandemic to the current scenario. With the natural evolution of SARS-CoV-2, due to evolutionary pressure, the emergence of new variants and subtypes and the increase in cases among children, such as what happened after the Omicron variant. Therefore, it is difficult to predict the impact of this disease on children over time and its effect on the seasonality of other respiratory viruses and epidemiological control in this population.

In conclusion, after the evolution of SARS-CoV-2, children were finally impacted, as expected compared to other respiratory viruses. We demonstrated that most of the hospitalized cases presented with comorbidities especially patients with sickle cell anemia, a group that was frequently readmitted suggesting that those children should be contemplated with strong program of immunization. Omicron variant caused the highest rate of hospitalization which is implicated in the best formulation should be used among children. In this sense, the new monovalent vaccine with Omicron XBB, may be the best options for them particularly for those with comorbidities.

Institutional Review Board Statement:
The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee from Universidade Federal de São Paulo (UNIFESP)/HSP (process number CEP 29407720.4.0000.5505).

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Conflicts of Interest:

The authors declare no conflicts of interest.

Reference

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Figure 1.docx available at https://authorea.com/users/669938/articles/670169-impact-