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ORIGINAL ARTICLE

Retrospective study of pneumococcal pneumonia during COVID-19 pandemic in a reference pediatric hospital in Brazil

Estudo de coorte retrospectivo sobre pneumonia pneumocócica durante a pandemia de COVID-19 em um hospital pediátrico de referência no Brasil

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ABSTRACT

Introduction: Community-Acquired Pneumonia caused by *Streptococcus pneumoniae* is a significant pediatric health concern worldwide. The advent of COVID-19 and related public health measures markedly altered the epidemiology of respiratory pathogens, including pneumococcus. **Methods:** A retrospective cohort study was conducted from 2018 to 2022 in Brazil to analyze pediatric patients diagnosed with pneumococcal pneumonia. Development of complications and mortality were investigated according to the age, sex, comorbidities and year of admission. **Results:** During the study period, 1,807 patients were admitted with pneumonia; 413 (22.8%) in 2018, 483 (26.7%) in 2019, 204 (11.2%) in 2020, 217 (12%) in 2021 and 490 (27.1%) in 2022. In total, 59 children were hospitalized with confirmed pneumococcal infection. In 2018 there were 14 (23.7%) cases, 5 (8.5%) in 2019, 2 (3.4%) in 2020, 15 (25.4%) in 2021, and 23 (39%) in 2022 (p=0.002). Median age was 32.4 months (1-156) and 17 (28.8%) were males. About 35 (59.3%) patients had complications, 41(69.5%) were admitted in ICU, 30 (50.8%) required invasive mechanical ventilation and 5 (8.5%) died. Antibiotic susceptibility tests revealed MIC≤2 mg/L in 95.4% of the patients. Older age and hospital admissions in 2018 and 2022 correlated with higher incidences of pneumonia-related complications (p=0.007 and p=0.006). Younger children had a higher probability of requiring invasive mechanical ventilation (p=0.004). **Conclusions:** A better understanding of the transmission dynamics and manifestations of S. pneumoniae infections in recent years is essential for the appropriate management of these patients. The COVID-19 pandemic and age stood out as factors impacting the incidence of pneumococcal pneumonia and its complications in Brazilian children.

Keywords: *Streptococcus pneumoniae*; COVID-19; Antimicrobial resistance.

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RESUMO

Introdução: A pneumonia adquirida na comunidade causada por *Streptococcus pneumoniae* é um problema significativo de saúde pediátrica em todo o mundo. O advento da COVID-19 e as medidas de saúde pública relacionadas alteraram significativamente a epidemiologia dos agentes patogênicos respiratórios, incluindo o pneumococo. **Métodos:** Um estudo de coorte retrospectivo foi realizado de 2018 a 2022 no Brasil para analisar pacientes pediátricos com diagnóstico de pneumonia pneumocócica. A evolução de complicações e mortalidade foi investigada de acordo com idade, sexo, comorbidades e ano de internação. **Resultados:** Durante o período do estudo, 1.807 pacientes foram internados com pneumonia; 413 (22,8%) em 2018, 483 (26,7%) em 2019, 204 (11,2%) em 2020, 217 (12%) em 2021 e 490 (27,1%) em 2022. No total, 59 crianças foram internadas com infecção pneumocócica confirmada. Em 2018 ocorreram 14 (23,7%) casos, 5 (8,5%) em 2019, 2 (3,4%) em 2020, 15 (25,4%) em 2021 e 23 (39%) em 2022 (p=0,002). A mediana de idade foi de 32,4 meses (1-156) e 17 (28,8%) eram do sexo masculino. Cerca de 35 (59,3%) pacientes apresentaram complicações, 41 (69,5%) foram internados em UTI, 30 (50,8%) necessitaram de ventilação mecânica invasiva e 5 (8,5%) faleceram. Os testes de sensibilidade aos antibióticos revelaram MIC≤2 mg/L em 95,4% dos pacientes. A idade avançada e os internamentos hospitalares em 2018 e 2022 correlacionaram-se com maiores incidências de complicações relacionadas com pneumonia (p=0,007 e p=0,006). As crianças mais novas tiveram maior probabilidade de necessitar de ventilação mecânica invasiva (p=0,004). **Conclusão:** A melhor compreensão da dinâmica de transmissão e das manifestações das infecções por S. pneumoniae nos últimos anos é essencial para o manejo adequado desses pacientes. A pandemia da COVID-19 e a idade destacaram-se como fatores de impacto na incidência das pneumonias pneumocócicas e suas complicações em crianças brasileiras.

Palavras-chave: *Streptococcus pneumoniae*; COVID-19; Resistência antimicrobiana.

INTRODUCTION

Community-acquired pneumonia (CAP) is an infection of the lower airways caused by agents from the community environment. It represents a significant global health challenge, particularly among children and adolescents and is a leading cause of respiratory illness, with high morbidity and mortality rates, especially in early childhood. CAP causes about two million deaths per year worldwide, most of them occurring in low and middle income countries[1]. The etiology of CAP is diverse, encompassing a range of viruses and bacteria. Among these, *Streptococcus pneumoniae* emerges as an important pathogen, responsible for approximately 300,000 annual deaths in children under five years old[2]. While most children become colonized with *S. pneumoniae* during their childhood, a small proportion will develop invasive pneumococcal pneumonia, defined as the isolation of *S. pneumoniae* from a normally sterile site[1,2]. In Brazil, the mortality due to pneumococcal pneumonia of children under five years of age decreased by 90% between 1980 and 2010 due to several interventions, including the implementation of the pneumococcal conjugate vaccine (PCV10). However, the disease is still among the main causes of mortality and hospitalization in the country, imposing a substantial burden on the Brazilian Unified Health System[1].

The onset of the COVID-19 pandemic in 2020 led to widespread implementation of public health measures, such as strict physical distancing, improved hygiene practices, and mask-wearing. These preventive measures also had a temporary effect on reducing the circulation of various respiratory pathogens, resulting in a notable decrease in the transmission of pneumococcus[2,3]. This impact was evident in the significant reduction of pneumococcal invasive disease rates in 2020 and early 2021 across different regions[4].

The advent of the COVID-19 vaccine and the employment of non-pharmacological behavioral measures allowed a gradual return to in-person activities throughout 2021-2022. Consequently, the reemergence of the seasonality of respiratory illnesses after a prolonged period of social distancing and mask-wearing was described.[3] A significant surge in pediatric consultations for respiratory diseases was noted in several countries, accompanied by an increase in pneumococcal respiratory disease. In England, for example, following the relaxation of COVID-19 social restrictions, the incidence of pneumococcal disease in children exceeded pre-pandemic levels[4]. In Brazil, there was also a marked increase in respiratory illness in children and an excessive burden on emergency medical services was observed, largely due to an increase in urgent, non-elective consultations[3]. At the same time, there was a significant rise in severe pneumococcal pneumonia, often associated with serious complications such as pleural effusion, parenchymal necrosis and pulmonary abscesses. In addition, disruptions in routine vaccine schedules during the pandemic further weakened the population's collective immunity against pneumococcal disease[3].

The lack of comprehensive Brazilian data on the dynamics of pneumococcal infections in the pediatric population during the pandemic era prompted our study. We aimed to investigate the epidemiological and clinical features of pneumococcal pneumonia at a major pediatric healthcare facility during this period, and identify factors related to complications and deaths in this population.

Methods

From January 2018 to December 2022, a retrospective cohort study was carried out at João Paulo II Children's Hospital in Belo Horizonte, state of Minas Gerais, Brazil, which involved the pre-pandemic period (2018-2019) and the COVID-19 pandemic period (2020-2022). As a state-owned tertiary care facility, the hospital provides comprehensive healthcare services to children and adolescents up to 13 years old, serving a diverse population from throughout the state of Minas Gerais.

During the study period, we sought hospitalized patients with a diagnosis of pneumonia. All the diagnoses of pneumonia classified from J12 to J18 (all-cause pneumonia), according to the International Classification of Diseases and Related Health Problems (ICD-10) were selected. This group included patients with viral pneumonia, bacterial pneumonia as well as pneumonia with an undefined etiology. Pneumococcal pneumonia was defined as the presence of *S. pneumoniae* in the blood, pleural fluid, or tracheal aspirate samples, obtained via a suction tube from intubated patients and those using non-invasive ventilation systems. Patients with identification of pneumococcus were included in the study group. The isolates were sent to Fundação Ezequiel Dias, the designated State Reference Laboratory, for antimicrobial susceptibility testing, adhering to the protocols outlined by the Clinical Laboratory Standards Institute (CLSI)[5]. Susceptibility to various antibiotics, including oxacillin, erythromycin, clindamycin, vancomycin, levofloxacin, trimethoprim-sulfamethoxazole, and tetracycline, was assessed using the disk diffusion method. Strains resistant to oxacillin were subjected to additional minimum inhibitory concentration (MIC) analysis, utilizing broth microdilution techniques for penicillin and ceftriaxone. The criteria for penicillin susceptibility were set at MIC ≤2 mg/L, while an MIC ≥4.0 mg/L indicated non-susceptibility (either intermediate or resistant) for isolates not involving the central nervous system, according to the CLSI.

Patient medical records underwent a retrospective review for additional data extraction. Variables analyzed included demographic (age, sex), clinical, and laboratory data, length of hospital stay (days), antibiotic therapy, and need for Intensive Care Unit (ICU) admission. Age, gender, year of admission and presence of co-morbidities were the variables studied as possible factors influencing outcomes. Defined outcomes encompassed the development of complicated pneumonia, admission to the ICU, necessity for mechanical ventilation (MV), and death. The diagnosis of complicated pneumonia was defined according to the Brazilian Paediatric Society as the pneumonia that becomes severe despite the use of antibiotics, presenting local complications such as pleural effusion, pleural empyema, lung abscess or necrotizing pneumonia[6]. The data collection was conducted adhering to stringent privacy and confidentiality protocols. Investigated risk factors for these outcomes included age, sex, comorbidities, and year of admission.

Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software, Inc., La Jolla, CA, USA). Descriptive statistics were applied to present results as means with standard deviation, medians or percentages, as suited. Categorical variables were analyzed using the chi-square test. The normality of data distribution was assessed via the Kolmogorov-Smirnov test. For data not normally distributed, comparisons between two groups were conducted using the Mann-Whitney test. In cases of normally distributed data, the unpaired Student's t-test was used for two-group comparisons, and analysis of variance followed by Bartlett's post-test for multiple groups. Correlations between variables were ascertained using either Pearson or Spearman tests. Logistic regression analysis was performed to identify independent risk factors associated with complicated pneumonia, mechanical ventilation, ICU admission and death. Univariate analysis was performed by estimating odds ratios (ORs) and 95% confidence intervals (CI). The p-value was considered significant when less than 0.05.

The study was approved by the Minas Gerais State Hospital Foundation institutional review board (research Ethics Committee reference number 62651022.9.0000.5119). All data were anonymized and securely stored, and a waiver was obtained for the free and informed consent form.

Results

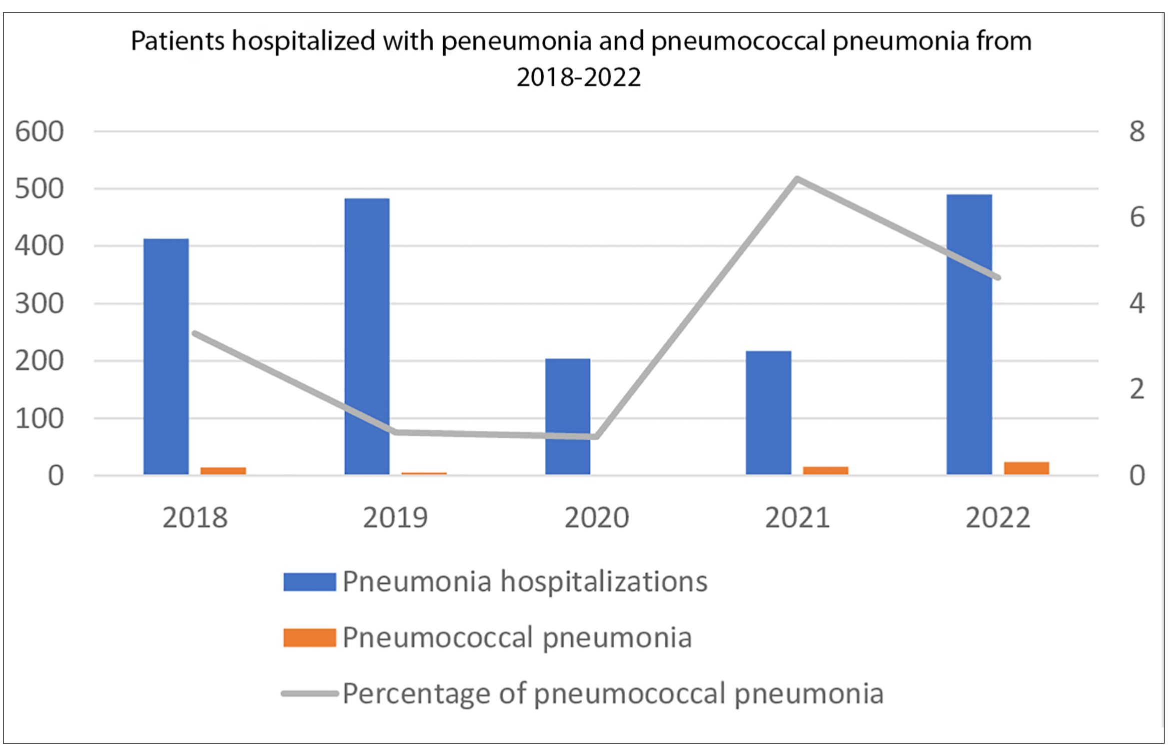
During the study period, 1,807 patients were admitted to HIJPII with a diagnosis of pneumonia. In total, 413 (22.8%) patients were hospitalized in 2018, 483 (26.7%) in 2019, 204 (11.2%) in 2020, 217 (12%) in 2021 and 490 (27.1%) in 2022 (Graph 1).

A total of 59 (3%) patients were diagnosed with pneumococcal pneumonia. Pneumococcal isolates were obtained from blood cultures in 25 (42.4%) patients, from pleural fluid in 21 (35.6%) patients, and from tracheal aspirates in 17 (28.8%) patients. Pneumococcus was isolated from 14 (3.3%) patients admitted in 2018, 5 (1%) in 2019, 2 (0.9%) in 2020, 15 (6.9%) in 2021 and 23 (4.6%) in 2022 (Table 1).

The median age at admission was 16 months, 17 (28.8%) patients were males and 42 (71.2%) females (Table 2). In total, 32 (54.2%) patients had pre-existing medical conditions and the most prevalent were asthma (8), cerebral palsy (5), primary immunodeficiency (2), and cardiac disorders (2). The mean duration of hospitalization was 9 days ranging from 1 to 88 days. Additionally, 17 (28.8%) patients were diagnosed with another infection during their hospitalization including bronchiolitis (10), COVID-19 (3), acute otitis media (2), urinary tract infection (1), and tracheitis (1).

In total, 36 (61%) patients had complications of pneumococcal pneumonia: 27 (45.7%) parapneumonic effusion, 5 (8.5%) atelectasis, 2 (3.4%) pneumothorax, 1 (1.7%) lung abscess, and 1 (1.7%) chronic pleural effusion. All patients with parapneumonic effusion had pleural fluid cytological, biochemical, and microbiological analysis. In total, 41 patients (69.5%) were admitted to the intensive care unit (ICU) and 30 patients (50.85) underwent invasive mechanical ventilation. A total of 5 (8.5%) patients died during hospitalization (Table 2).

Out of the 59 pneumococcal strains analyzed, 44 underwent successful susceptibility testing. Of these, 42 strains (95.4%) showed penicillin sensitivity with a minimum inhibitory concentration (MIC) ≤2 mg/L. The remaining 2 strains (4.6%) had an MIC of 4 mg/L. Resistance was noted for sulfamethoxazole/trimethoprim in 31 (52.5%) patients, erythromycin in 29 (49.2%), and clindamycin in 27 (45.8%). No resistance to levofloxacin or vancomycin was observed. Serotyping was performed only on three strains, identifying two as serotype 19A and one as serotype 15C. In total, 24 (40.6%) patients were treated with amoxicillin/clavulanate, 15 (25.4%) patients were treated with ampicillin, 8 (13.5%) patients were treated with



Graph 1. Number of patients hospitalized with pneumonia and pneumococcal pneumonia at João Paulo II Children's Hospital from 2018-2022.

Table 1. Percentage of patients with pneumococcal pneumonia hospitalized at João Paulo II Children's Hospital from 2018-2022.

	Pneumococcal pneumonia				
	Yes		No		
	n	%	n	%	*p*-value
Year					
2018	14	3.3	413	96.7	0.002
2019	5	1.1	483	98.9	
2020	2	1.0	204	99.0	
2021	15	6.5	217	93.5	
2022	23	4.5	490	95.5	

Caption: 95%CI = 95% Confidence interval. Source: Prepared by authors, 2024.

Table 2. Clinical and epidemiological characteristics of patients admitted with pneumococcal pneumonia at João Paulo II Children's Hospital from 2018-2022.

Clinical and epidemiological variables	N (%)
Age (median)	16 months
min	1 months
max	156 months
Sex	
male	17 (28.8%)
female	42 (71.2%)
Year	
2018	14 (23.7%)
2019	5 (8.5%)
2020	2 (3.4%)
2021	15 (25.4%)
2022	23 (39%)
Comorbidities	
yes	32 (54.3%)
no	27 (45.7%)
Pneumococcal isolation blood	25 (42.4%)
pleural fluid	21 (35.6%)
tracheal aspirate	17 (28.8%)
Local complications parapneumonic effusion	25 (45.7%)
atelectasis	5 (8.5%)
pneumothorax	2 (3.4%)
lung abscess	1 (1.7%)
chronic pleural effusion	1 (1.7%)
Mechanical ventilation	
yes	30 (50.8%)
no	29 (49.2%)
ICU	
yes	41 (69.5%)
no	18 (30.5%)
Death	
yes	5 (8.5%)
no	54 (91.5%)

Caption: 95%CI = 95% Confidence interval. Source: Prepared by authors, 2024.

ampicillin/sulbactam, 6 (10.1%) patients with ceftriaxone, 6 (10.1%) with cefepime, 3 (5%) with amoxicillin and 1 (1,6%) with vancomycin.

Outcome analyses revealed that older age and hospital admissions in 2018 and 2022 correlated with higher incidences of complicated pneumonia (p=0.007 and p=0.006 respectively) (Table 3).

We also found that younger children had a higher probability of requiring invasive mechanical ventilation (p=0.004) (Table 4).

There were no significant associations found between age, sex, presence of comorbidities, or year of hospitalization and an increased risk of ICU admission or death within the study timeframe (Tables 5 and 6).

Discussion

The COVID-19 pandemic, emerging in early 2020, dramatically altered the transmission of respiratory pathogens and shifted the epidemiology of respiratory infections in children. Measures to curb the pandemic, including public health interventions, impacted the transmission of respiratory viruses and bacteria, affecting the seasonality and incidence of childhood respiratory diseases and leading to reduced hospitalizations[4]. In this context, many countries, including Brazil, reported a decrease in hospitalization due to pneumonia, as we could observe during the years of 2020 and 2021[4]. In Australia, a 50.5% reduction in invasive pneumonias was recorded in 2020, followed by a marked increase post the easing of pandemic restrictions[7]. In our work, we observed a significant increase in the number of hospitalizations due to pneumonia in 2022, reaching values above those observed in the pre-pandemic years (2018-2019). Social distancing measures and mask mandates were gradually lifted in Brazil between 2021 and 2022, following the control of the COVID-19 pandemic. In the state of Minas Gerais, the re-opening of schools for in-person attendance occurred in a phased manner starting from the second semester of 2021, while mask mandates were officially lifted in April 2022.

Our study reflects a similar decline in pneumococcal pneumonia hospitalizations in 2020 related to the

Table 3. Associations between clinical and epidemiological variables and complicated pneumococcal pneumonia in children hospitalized at João Paulo II Children's Hospital from 2018-2022.

	Complicated pneumonia						
	yes		no				
	n	**%**	**n**	**%**	*p*-value	**OR**	**IC 95%**
Sex							
male	8	22.2	9	37.5	0.25	0.47	0.15-1.49
female	28	77.8	15	62.5			
Year							
2018	10	27.8	4	16.7	**0.006**		
2019	3	8.3	2	8.3			
2020	2	5.6	0	0.0			
2021	3	8.3	12	50.0			
2022	18	50.0	6	25.0			
Co-morbidities							
yes	17	47.2	16	66.7	0.18	0.45	0.15-1.31
no	19	52.8	8	33.3			
Age (months)							
					0.007		
median	20		8				

Caption: 95%CI = 95% Confidence interval. Source: Prepared by authors, 2024.

Table 4. Associations between clinical and epidemiological variables and mechanical ventilation in children hospitalized with pneumococcal pneumonia at João Paulo II Children's Hospital from 2018-2022.

	Mechanical ventilation						
	Yes		No				
	n	**%**	**n**	**%**	*p*-value	**OR**	**IC 95%**
Sex							
male	10	33.3	7	23.3	0.56	1.64	0.53-5.12
female	20	66.7	23	76.7			
Year							
2018	6	20.0	8	26.7	0.31		
2019	2	6.7	3	10.0			
2020	2	6.7	0	0.0			
2021	10	33.3	5	16.7			
2022	10	33.3	14	46.7			
Co-morbidities							
yes	16	53.3	17	56.7	1.0	0.88	0.32-2.42
no	14	46.7	13	43.3			
Age (months)							
					0.006		
Median	9		20				

Caption: 95%CI: 95% Confidence interval. Source: Prepared by authors, 2024.

Table 5. Associations between clinical and epidemiological variables with admission to the intensive care unit (ICU) of children hospitalized with pneumococcal pneumonia at João Paulo II Children's Hospital from 2018-2022.

	ICU						
	Yes		No				
	n	%	n	%	*p*-value	OR	CI 95%
Sex							
male	10	24.4	7	36.9	0.37	0.55	0.17-1.78
female	31	75.6	12	63.1			
Year							
2018	10	24.4	4	21.0	0.52		
2019	3	7.3	2	10.5			
2020	2	4.9	0	0.0			
2021	12	29.3	0	0.0			
2022	14	34.2	10	52.6			
Co-morbidities							
yes	22	53.7	11	57.9	0.78	0.84	0.28-2.53
no	19	46.3	8	42.1			
Age (months)							
					0.11		
median	16.0		20.0				

Caption: 95%CI = 95% Confidence interval. Source: Prepared by authors, 2024.

Table 6. Associations between clinical and epidemiological variables with death of children hospitalized with pneumococcal pneumonia at João Paulo II Children's Hospital from 2018-2022.

	Death						
	Yes		No				
	n	%	n	%	*p*-value	OR	CI 95%
Sex							
male	0	0.0	17	30.9	0.31	...	...
female	5	100.0	38	69.1			
Year							
2018	2	40.0	12	21.8	0.18		
2019	0	0.0	5	9.1			
2020	1	20.0	1	1.8			
2021	1	20.0	14	25.5			
2022	1	20.0	23	41.8			
Co-morbidities							
yes	3	60.0	30	54.5	1.0	1.25	0.19-8.08
no	2	40.0	25	45.5			
Age (months)							
					0.11		
median	16.0		20.0				

Caption: 95%CI = 95% Confidence interval. Source: Prepared by authors, 2024.

COVID-19 pandemic, when a reduction in pathogen circulation was observed. However, this trend reversed in 2021-2022, with rates surpassing pre-pandemic levels (2018-2019). Similar patterns have also been observed in other countries. For instance, in England, an initial increase in pneumococcal pneumonia among younger children in 2021 was succeeded by a rise across all age groups[4]. It is important to also consider that since the beginning of the COVID-19 pandemic in 2020, a drop in vaccination coverage in Brazil has been observed. This may have contributed to the increase in number of cases of pneumococcal infection in children after the release of distancing measures and masks.

Despite the global decline in pneumococcal disease during the pandemic, nasopharyngeal carriage of pneumococcus remained constant[8]. This presents a paradox, as nasopharyngeal carriage is typically a precursor to pneumococcal diseases, implying that factors other than carriage may significantly influence pathogenesis. During the pandemic, a notable global reduction in respiratory viruses was also observed, coinciding with decreased pneumococcal disease rates[8,9]. This suggests a potential interplay between viral infections and invasive bacterial diseases, supported by evidence showing that viral respiratory tract infections can predispose children to secondary bacterial pneumonia[8]. In Brazil, the specific correlation between viral circulation and pneumococcal pneumonia remains unclear. However, a resurgence in Respiratory syncytial virus (RSV) and influenza infections following the relaxation of isolation measures was also observed, beginning in 2021[10]. The study by Dias et al. (2024)[10] reveals an atypical behavior of influenza and RSV viruses in 2021 and 2022 in Brazil, breaking from their usual seasonal patterns. An increase in the number of influenza cases could be observed in the second half of 2021 and 2022 and a steady circulation of RSV was observed during both years.

Our study showed that 61% of patients hospitalized with pneumococcal pneumonia had complications. It is known that only about 3% of community-acquired pneumonia become complicated, but this percentage tends to be higher in hospitalized children[11]. These results are similar to data found in other countries. In Israel, a study showed that 57% of hospitalized children developed complications and in Canada this rate was as high as 51%[12]. In particular, we noticed that the year 2022 marked an increase in pneumococcal pneumonia complications, reaching levels above those observed in 2018, before the COVID-19 pandemic. Another study carried out in Brazil also found higher rates of complication such as pleural effusion, empyema and necrotizing pneumonia in children hospitalized with CAP from 2020 to 2022[1]. The same way the interaction between viruses and circulating bacteria in the post-pandemic period may be responsible for an increase in number of pneumococcal pneumonia hospitalizations, it may also have been responsible for an increase in complications observed during this period.

We were able to observe low rates of pneumococcal resistance to penicillin in our study. This highlights the ongoing effectiveness of ampicillin or penicillin G when local epidemiologic data document a lack of substantial high-level penicillin-resistance for invasive *S. pneumoniae*[13]. Lima et al. (2024)[1] had already observed in Brazilian children that ampicillin was still the most prescribed antibiotic in about 45% of children before and during the COVID-19 pandemic. Nevertheless, the trend towards decreasing sensitivity among pneumococcal strains emphasizes the need for continued monitoring of serotype distribution and patterns of antimicrobial resistance[9]. In addition, we observed high rates of pneumococcal resistance to other antimicrobials such as sulfamethoxazole/trimethoprim, erythromycin and clindamycin. Another study in Brazil has also observed a gradual increase in resistance to these antibiotics from 2017 to 2019[14].

Limitations of our study include the potential for overestimating pneumococcal infection rates due to the isolation of pneumococcus from tracheal aspirates, which might represent colonization rather than infection. The inability to distinguish colonizing from pathogenic organisms is a key limitation for the use of theses specimens. Another limitation of the study was the small number of patients in whom it was possible to detect *S. pneumoniae*. This occurred possibly because the majority of children who were referred to our hospital due to pneumonia were probably already in use of antibiotics before admission.

This study is the first one to illustrate the behavior of pneumococcal pneumonia in Brazil and its relationship with the COVID-19 pandemic. As has been observed in other countries, we have seen an increase in the number of cases and severity of pneumococcal pneumonia from the moment children returned to their activities. Our work contributes to a better understanding of the transmission dynamics and manifestations of *S. pneumoniae* infections in Brazilian children in recent years, an essential step for the proper management of these patients.

Author's Contributions:

We describe contributions to the papers using the taxanomy (CRediT) provide above:

All authors contributed to all the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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