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ORIGINAL ARTICLE

Community-acquired pneumonia in vaccinated and nonvaccinated children with pneumococcal 10-valent pneumococcal vaccine hospitalized in an university hospital

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Abstract

In Brazil, the main cause of hospitalization in pediatrics is community-acquired pneumonia (CAP), responsible for high morbidity and mortality worldwide. The main etiologic bacterial agent of PAC in children under five is *Streptococcus pneumoniae* (pneumococcus). In 2010, the 10-valent anti-pneumococcal vaccine (PCV10) was implanted in the Brazilian vaccination schedule. The objective was to describe the clinical and evolutionary profile of patients diagnosed with CAP hospitalized in a pediatric university hospital comparing the vaccinated and nonvaccinated population with PCV10 and the possible associations between vaccination and outcome of hospitalization. An observational and retrospective study was performed in the IPPMG/UFRJ wards. A total of 77 hospitalized patients were studied, and 7 did not present data on the vaccination status: 58 (82.9%) with pneumococcal vaccination and 12 (17.1%) nonvaccinated. The median age was 47 months in vaccinated patients and 46,5 months in unvaccinated patients; 53.2% of males and 74% with comorbidities. There was a radiological pattern suggestive of bacterial PAC in 62.3%. The outcome was good in 97.4%, with a mean hospitalization of 9 days. There was no difference between the vaccinated and unvaccinated groups in relation to clinical profile and evolution. It was concluded that the vaccination status of the patients did not interfere in the outcome of the cases.

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INTRODUCTION

Most children have 4 to 6 acute respiratory infections (ARI) per year, mostly in urban areas. ARIs account for a quarter of all illnesses and deaths among children under 5 years of age in developing countries. About 2 to 3% of ARI progress to infection of the lung parenchyma, corresponding to pneumonia[1-3]. Pneumonia is responsible for approximately one fifth of deaths in children under 5 years of age worldwide. Brazil concentrated most cases of pneumonia in children under 5 years of age in the early 2000s[1-4].

Pneumococcal conjugate vaccination has been used since 2000 in the United States of America (USA), first as a 7-valent pneumococcal conjugate vaccine (PCV7) and replaced in 2010 by the 13-valent pneumococcal vaccine (PCV13). In 2010, the 10-valent pneumococcal vaccine (PCV10) was incorporated into the Brazilian vaccination schedule, including the same serotypes as PCV7 (*4,6B,9V,14,18C,19F,23F*) plus serotypes *1, 5 and 7F*.[5] Consequently, there was a reduction in pneumococcal diseases such as meningitis, CAP and colonization of the oropharynx and nasal mucosa by *Streptococcus pneumoniae*[5,6].

The present study aimed to describe the clinical and epidemiological characteristics of hospitalized patients, the frequency of CAP complications and the possible associations between vaccinated and unvaccinated people with PCV10 regarding the outcome of hospital admission.

METHODS

An observational and retrospective study was carried out in the wards of the pediatric university hospital located in the city of Rio de Janeiro and a reference for many areas of activity in this city. The study was conducted from January 2013 to December 2015, analyzing the medical records of all patients aged 2 months to 12 years, hospitalized with a diagnosis of CAP. Those who were discharged in absentia or who were transferred to other health units or who had incomplete data collected were excluded.

The information was recorded in a protocol developed and applied by the resident physicians and trainees of the Pediatric Pulmonology Service. We considered the period from 2013 to 2015 , because before that there was no widespread availability of PCV10 vaccination in the public health network.

The following variables were studied: sex, age, presence of comorbidities (sickle cell anemia, leukemia, AIDS, heart disease, hemoglobinopathies, asthma, neuropathies and others), previous use of antibiotics (use prior to hospital admission), attendance at day care, number of inhabitants under five years of age in the household, presence of indoor smokers, parental education (years of study), radiological alterations (interstitial, alveolar pattern, atelectasis, pneumatocele, hyperinflation, pleural effusion and radiological interpretation: probably bacterial or probably viral) and hospitalization outcome (discharge cured, discharge improved, discharge to the ICU and death).

Complete vaccination was considered when the child had received the appropriate number of doses for their age.

Descriptive analysis is presented in the form of tables of observed data, expressed as median and interquartile range (Q1 - Q3) for numerical data and as frequency and percentage for categorical data. The inferential analysis for comparison between the two pneumococcal vaccination subgroups 10 (with and without vaccination) consisted of the *Mann-Whitney test* for numerical data and the *chi-square* (χ^2) or *Fisher's exact test* , when appropriate, for qualitative (categorical) data. A non-parametric method was applied, as the numerical variables did not present a normal (Gaussian) distribution, due to the rejection of the hypothesis of normality according to the *Shapiro-Wilks test* . The criterion for determining significance adopted was the level of 5%. Statistical analysis was processed using SAS ® System statistical *software*, version 6.11 (SAS Institute, Inc., Cary, North Carolina).

This study was approved by the CEP of IPPMG-UFRJ (Process 23/11).

RESULTS

A total of 77 hospitalized patients were studied, 7 of which did not present data on the vaccination status and were excluded from the comparative analysis regarding the outcome. Thus, we had 58 children with complete pneumococcal vaccination and 12 without vaccination. There was a lack of information on some variables that are marked in the respective tables.

There were 41 (53.2%) male children and 36 (46.8%) female children. There was no information regarding vaccination in 7 patients. There were 58/70 (82.8%) vaccinated and 12/70 (17.2%) unvaccinated. The median age of the patients was: 47 (IIQ=14-93) months among the vaccinated and 46.5 (IIQ=18-91) months among the non-vaccinated. The mean length of hospital stay was 9 days in both groups. The distribution by sex and the main comorbidities found in both groups are shown in Table 1.

There were reports of previous hospitalization for CAP in 25 (59.5%) vaccinated patients and in 4 (36.4%) of the unvaccinated (p=0.19). The main CAP risk variables identified among the patients are shown in Table 2 and the radiological patterns of CAP in Table 3.

The hospitalization outcome variable was studied in 75 patients. As for the vaccination status, there was information in 68. The results are shown in table 4.

Most patients were discharged, with only one death. There was a statistically significant difference in relation to the number of inhabitants under five years of age in the household, which was higher among those vaccinated.

DISCUSSION

Our study, carried out in a tertiary university hospital, showed a median age of 46 months, that is, children under

Table 1. Comorbidities according to complete vaccination status with PCV10.

Variable	Category	Total		With vaccination		no vaccination		*p* value
		77 children		Total=58/70 children		Total=12/70 children		
		n	%	N	%	n	%	
Sex	Male	41	53.2	30	51.7	6	50.0	091
	Feminine	36	46.8	28	48.3	6	50.0	
comorbidities	Yea	57	74.0	41	70.7	10	83.3	0.49
	No	20	26.0	17	29.3	2	16.7	
Sickle cell anemia	Yea	7	9.1	3	5.2	3	25.0	*0.058*
	No	70	90.9	55	94.8	9	75.0	
Leukemia	Yea	3	3.9	2	3.4	0	0	1
	No	74	96.1	56	96.6	12	100	
AIDS	Yea	2	2.6	2	3.4	0	0	1
	No	75	97.4	56	96.6	12	100	
heart disease	Yea	7	9.1	6	10.3	1	8.3	0.99
	No	70	90.9	52	89.7	11	91.7	
Hemoglobinopathies	Yea	3	3.9	3	5.2	0	0	1
	No	74	96.1	55	94.8	12	100	
Asthma	Yea	6	7.8	4	6.9	1	8.3	0.99
	No	71	92.2	54	93.1	11	91.7	
neuropathies	Yea	22	28.6	16	27.6	3	25.0	1
	No	55	71.4	42	72.4	9	75.0	
Other comorbidities	Yea	31	40.3	25	43.1	4	33.3	0.75
	No	46	59.7	33	56.9	8	66.7	

Chi-square or Fisher's exact test.

Table 2. Risk variables according to complete PCV10 vaccination.

Variable N=Total with information	Category	total		w/ vaccination		without vaccination		*p* value
		n	%	N	%	n	%	
Attend daycare (N=33)	Yea	16	48.5	14	51.9	2	40.0	1
	No	17	51.5	13	48.1	3	60.0	
Inhabitants < 5 years in the household (N=63)	0	15	23.8	10	20.4	3	27.3	0.045
	1	43	68.3	37	75.5	5	45.5	
	2	2	3.2	1	2.0	1	9.1	
	3	3	4.8	1	2.0	2	18.2	
household smokers (N=41)	Yea	14	34.1	12	35.3	2	28.6	0.99
	No	27	65.9	22	64.7	5	71.4	
Mother's education (years)(N=40)	2	17	42.5	11	36.7	6	66.7	0.20
	3	19	47.5	16	53.3	2	22.2	
	4	4	10.0	3	10.0	1	11.1	
Father's education (years)(N=32)	1	1	3.1	0	0.0	1	14.3	0.28
	2	12	37.5	10	40.0	2	28.6	
	3	19	59.4	15	60.0	4	57.1	

Chi-square or Fisher's exact test.

Table 3. Radiological patterns according to complete vaccination status with PCV10.

radiological pattern	Category	Total		w/ vaccination		without vaccination		*p*-valor
		n	%	N	%	n	%	
Intersticial (N=77)	Yea	18	23.4	13	22.4	2	16.7	1
	No	59	76.6	45	77.6	10	83.3	
alveolar (N=77)	Yea	42	54.5	33	56.9	6	50.0	0.66
	No	35	45.5	25	43.1	6	50.0	
atelectasis (N=77)	Yea	5	6.5	3	5.2	2	16.7	0.20
	No	72	93.5	55	94.8	10	83.3	
pneumatocele (N=77)	Yea	2	2.6	2	3.4	0	0.0	
	No	75	97.4	56	96.6	12	100.0	
hyperinflation (N=77)	Yea	3	3.9	2	3.4	1	8.3	0.44
	No	74	96.1	56	96.6	11	91.7	
pleural effusion	Yea	11	14.3	9	15.5	2	16.7	1
	No	66	85.7	49	84.5	10	83.3	
Radiological interpretation (N=77)	Probably bacterial	48	62.3	37	63.8	8	66.7	1
	Probably viral	29	37.7	21	36.2	4	33.3	

Legend - PR= radiological standard.

Table 4. Outcome of second full PCV10 vaccination.

Variable	Category	Total		With vaccination		no vaccination		*p* value
		n	%	N	%	n	%	
Outcome of hospitalization	high cured	14	18.7	12	21.4	1	83.3	0.26
	high improved	59	78.7	43	76.8	10	8.3	
	Discharge to ICU	1	1.3	0	0.0	1	8.3	
	Death	1	1.3	1	1.8	0	0.0	

Chi-square or Fischer's exact test.

five years of age predominated. National and international data point to this reality, as younger children are more susceptible to severe CAP. According to the WHO, children under five years of age are hospitalized and progress to death more often, especially those under one year old[7,12]. There was a slight predominance of males and a high frequency of comorbidities in the sample. Two groups of patients were studied: one composed of children with complete PCV10 vaccination and the other without this vaccination and, consequently, more vulnerable to severe pneumococcal infections[16]. More than half of the cases had comorbidities, mainly neurological diseases, which reflects the day-to-day reality of our hospital, which is a reference for chronic diseases. We identified in our series that in both groups these characteristics were similar and the patients did not have different outcomes.

Half of the children attended daycare, which suggests, but does not allow us to infer a cause-effect relationship. It is certain, however, that daily contact with many children favors the transmission of etiological agents, mainly viral in infants, as well as the spread and early colonization of the airways by pneumococcus, increasing the risk of CAP[7,8,16].

Analyzing the vaccinated patients, it was observed that there were a greater number of co-inhabitants under five years of age in the household than among the unvaccinated. Although there is no apparent cause for this finding, it can be assumed that this was due to the small number of vaccinated patients, which affected the analysis.

According to the literature, a greater number of inhabitants under 5 years of age in the household would be a risk factor for the occurrence of CAP in children[8,11].

The frequency of indoor smokers, around 30%, reflects the national average at the time, and shows that one third of children were subject to passive smoking in both groups[8-10]. Postnatal exposure to smoking has been associated with an increased frequency of lower respiratory tract diseases in childhood. Although the mechanisms are still unclear, it is believed to cause changes in the structure and function of mucosal surface cells. It can also affect local bacterial colonization, selectively altering the adherence of respiratory pathogens to the mucosal surface, which has an indirect effect on the development of local immunity[11,16]. A cross-sectional study carried out in schools in northern Greece in 2005 showed that

upper and lower respiratory tract infections occurred more frequently in children exposed to tobacco[29]. Also in Fortaleza, in 1997, it was shown that exposure to maternal secondhand smoke significantly increased the probability of acquiring ARI[16].

The group of unvaccinated patients showed a higher frequency of mothers with lower education, although without statistical significance. This finding points to the importance of education and knowledge in valuing the correct vaccination of the child[7,8,16]. On the other hand, the father's education did not show such a tendency, that is, it was not related to low education. The father's schooling would be less important in our country, probably because the one who takes care of the child is most of the time the mother.

Just over half of our patients had previous hospitalizations for CAP and, of these, 24% had been hospitalized for more than six months (results not shown). This profile reiterates the characteristic of our hospital's special clientele, with more frequent hospitalizations.

The analysis of the radiological pattern showed that 62% of the patients presented alterations compatible with bacterial CAP , that is, alveolar infiltrate, pleural effusion or both[4,12]. Thus, it is possible to demonstrate, once again, the severity of CAP cases and the correct indications for hospital admissions in our series. Although the radiological interpretation in order to differentiate bacterial from viral CAP is a controversial aspect, the presence of alveolar infiltrate and effusion are quite reliable in this regard[12,13].

As for complications, similarly to the literature, pleural effusion was the most frequent complication and pneumatoceles were the most uncommon in 14% of cases. Interstitial infiltrates, hyperinflation and atelectasis, more suggestive of a viral etiology, occurred less frequently, as already discussed. There was no difference between the vaccinated and unvaccinated groups, therefore, there was apparently no greater severity of CAP among vaccinated patients. However, there are conflicting reports in the literature from countries that have had PVC10 in their routine for a longer time. These report less frequent and more severe severe CAP, probably due to the selection of more aggressive pneumococcal serotypes that are not contained in the vaccine[14,15].

Regarding the time and types of antibiotics used, we did not observe any difference between the two groups: in both groups, antibiotics derived from penicillin were more used, which reflects the criteria established in our institution, aiming at their judicious use (data not shown). At the study site, a CAP treatment flowchart was created jointly by the hospital's pulmonology, emergency and infectology services[4,12]. Even so, we can observe that, contrary to international studies, patients with complete vaccination did not present more severe cases of CAP that required the use of broader-spectrum antibiotics[14,15]. Studies show that the resistance of pneumococcus to penicillin and derivatives in our country is very low, reiterating its indication for the treatment of CAP[17].

The average length of stay was nine days in both groups, showing that the presence of comorbidities and the patients' vaccination status did not interfere with the evolution of the cases.

As for the outcome, we had only one death, which allows us to consider that there was good care provided to patients, due to the lack of difference in the evolution of the cases, regardless of their vaccination status. This statement contradicts international reports of the occurrence of greater severity of CAP in the post-vaccination era[14,15,18]. Theoretically, mass vaccination would favor the appearance of strains not contained in the vaccine that could cause more severe conditions, which are difficult to handle. Our results show that PCV10 vaccination was not related to increased CAP severity. We need to expand our sample and observe over time whether we will have a similar effect on our population.

The limitations of our study involve aspects inherent to the difficulties in collecting data from medical records and through research protocols in retrospective studies. In addition, there was a small number of patients involved in the unvaccinated group, since our sample depended on the hospital's free demand, being influenced by strikes and operational difficulties.

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