

Original Article

## Respiratory virus infections in hospitalized and non-hospitalized children: determinants of severe course of the disease

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### Abstract

**Introduction:** Viral respiratory disease constitutes a great burden worldwide mainly among children. Objective: One pursued to compare disease characteristics of children who required hospitalization from those who did not require hospitalization due to a viral respiratory disease.

**Methodology:** Medical and demographic data were collected through questionnaires and nasopharyngeal aspirates were tested for detection of respiratory disease viruses of in and outpatients up to five years old, presenting acute respiratory infection.

**Results:** Respiratory syncytial virus predominated among hospitalized children while other viruses (Human rhinovirus, Influenza virus, Parainfluenza virus, Adenovirus, and Human metapneumovirus) together predominated among non-hospitalized patients. Although children with underlying risk condition required longer hospitalization, previously healthy children presented severe disease and required hospitalization as well. Also, clinical characteristics were not found that may distinguish RSV infected children who had comorbidities from those previously healthy.

**Conclusions:** Children who were hospitalized due to respiratory distress had well defined characteristics: early age, respiratory syncytial virus infection, bronchiolitis and presence of comorbidity. Nevertheless, rapid respiratory syncytial virus identification among early age children may be of great value in order to avoid medical misconduct, such as unnecessary antibiotic prescription and preventive health care before an eventual clinical worsening encompassing previous health status.

**Key words:** Children; comorbidities; hospitalization; non-hospitalization; respiratory viral disease severity.

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### Introduction

Respiratory diseases caused by viruses constitute one of the most important causes of deaths and hospitalization worldwide, chiefly among early age children and in developing countries [1,2]. Nowadays there are nearly 200 known viral respiratory agents, and the following viruses have been recognized as the leading cause of respiratory disease in children: respiratory syncytial virus (RSV), human Rhinovirus (HRV), Influenza virus, Parainfluenza virus (PIV), and Adenovirus (AdV) [3].

Respiratory infections present a broad range of clinical symptoms and signs with varying degrees of severity. An important question concerning these infections is related to the factors that may potentially lead to severe symptoms, which may require hospitalization. Several overlapping factors must be taken into account involving the virus itself and underlying risk conditions of the host [2,4].

In addition, clinical, virological, host risk factors and demographic information on children with mild respiratory disease and those with a severe condition in hospitalized children are quite different [4]. This evaluation reinforces the importance of forward identification of risk factors in children who may potentially develop severe respiratory disease.

Thus, the investigation of virological, clinical and demographic differences of children who required hospitalization was pursued and compared to those who did not require hospitalization. Subsequently, the identification of a clinical profile of children hospitalized due to a viral respiratory disease was pursued. These findings may assist in the early identification of the factors that aggravate viral respiratory disease for prophylactic intervention in children that may need especial care.

## Methodology

### *Patients and inclusion criteria*

Patients enrolled in the present study were in and outpatients up to five years old presenting acute respiratory infection (ARI) attended at the Clinic Hospital of the Federal University of Uberlândia, Minas Gerais State, Brazil. Patients within five days from the onset of clinical symptoms between 2010 and 2015 were included. Considering the inclusion criteria aforementioned consultant physicians selected a utmost of four children per day to proceed with the collection of the clinical sample. Also additional information was directly acquired from parents either or guardians at the time of collection. Medical and demographic data were collected through questionnaires filled by the physician.

This study was approved by the Ethics and Research Committee of the Federal University of Uberlândia under protocol number 877/11, and a signed informed consent was obtained from each child's parent or foster parent before sample collection.

### *Clinical criteria*

Characteristic ARI symptoms and signs were assigned to the physician and included: runny nose, coughing, wheezing and difficulty in breathing, with or without fever. The clinical diagnosis was in accordance with the 10th Revision on International Classification of Diseases [5]. Infections of the upper respiratory tract (URTI) were diagnosed as common cold, flu, rhinopharyngitis, and lower respiratory tract infections (LRTI) included laryngitis, laryngotracheitis, croup, tracheobronchitis, no sibilant bronchitis, sibilant bronchitis, bronchospasm, bronchiolitis, pneumonia, and bronchopneumonia. If a patient had mixed symptoms of URTI and LRTI it was considered that it presented the latter.

Mild diseases consisted of URTI either or considered as such by the attending physician either or occurred in patients who did not require hospitalization due to the respiratory illness. Moderate-to-severe diseases constituted those considered by the consultant physician as moderate or severe either or those patients hospitalized exclusively due to the respiratory disease. Every pneumonia case and children who required supplemental oxygen or mechanical ventilation were also grouped in this category. Bronchiolitis was classified as mild, moderate or severe according to Clinical Score of Respiratory Failure in Bronchiolitis [6]. Clinical scores described by Taussig *et al.* [7] were used to classify other LRTI.

The determination for hospitalization of children diagnosed with ARI were defined by the attending

physician and based on the following clinical parameters: clinical diagnosis of moderate-to-severe disease (based on the criteria aforementioned), either or children with a history of comorbidity (mainly prematurity), either or patients with lower respiratory tract infection, either or need for supplemental oxygenation or mechanical ventilation. There was no criterion that prevailed over another considering the diversity of the clinical history and the response capacity of each patient to the infection.

### *Previous risk conditions*

The risk factors information that may have contributed to respiratory disease severity were collected at medical records and included: prematurity (gestational age up to 35 weeks), congenital heart diseases, non-infections respiratory diseases, smoking on pregnancy, atopic diseases, nervous system diseases, Down syndrome, West syndrome, anemia, short bowel syndrome, cholestatic syndrome, biliary atresia, adenomegaly and nodes' polyarthritis.

### *Viral detection assays*

Nasopharyngeal aspirates were collected and immediately tested by immunofluorescence assay (IFA) for detection of Respiratory Syncytial Virus (RSV), Influenza viruses A and B, Parainfluenza viruses 1, 2 and 3 (PIV), and Adenovirus (AdV) with the Respiratory Panel I Viral Screening and Identification Kit (Merck Millipore, Billerica, MA, USA).

Subsequently to the beginning of the procedures, molecular tests were incorporated and improved to the viral detection routine, being applied to both frozen and future samples. In this case, the protocols were applied separately, therefore, some samples were subjected to the IFI and (RT) PCR tests separately. Thus, reverse transcription-polymerase chain reaction (RT-PCR) was applied for detection of RSV and Influenza viruses A and B [7], PIV 1-3 [8], human Metapneumovirus (hMPV) [9], and HRV [10,11], and PCR for AdV [12]. Viral nucleic acid was extracted from all samples tested by IFI from nasopharyngeal aspirate using Trizol® (Life Technologies Corporation, Carlsbad, CA, USA) according to the manufacturer's instructions.

### *Statistical analysis*

Analyses were performed using qui-square ( $\chi^2$ ) to compare the frequency of groups of infections according to hospitalization status. Qui-square and p values were adjusted through Yates correction using GraphPad Prism® software (GraphPad Software, Inc.,

San Diego, CA, USA). For all tests,  $p < 0.05$  was considered statistically significant.

**Results**

Children up to five years old presenting signs and symptoms of acute respiratory infection with different clinical diagnoses and varying degrees of severity, were enrolled in this study. Viral investigation was performed regardless of hospitalization requirement and viral etiology was confirmed in 430 cases (Table 1).

Upper respiratory tract diseases predominated in non-hospitalized patients (46.3%, 106/229) compared to hospitalized ones (4.0%, 8/201), whereas 82.9% (87/105) of all bronchiolitis and almost all pneumonia cases (96.8%, 30/31) occurred in children, required hospitalization.

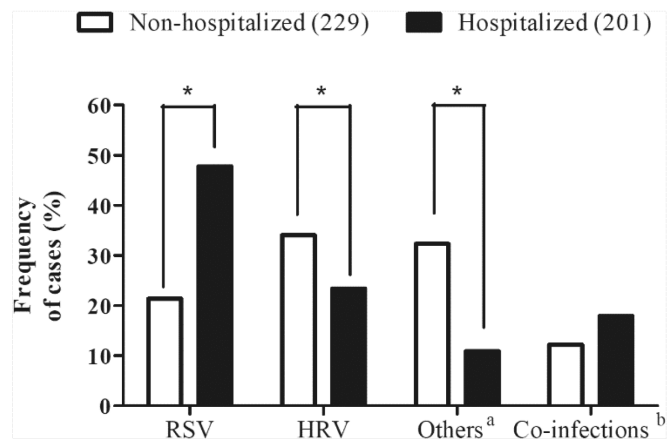
For the non-hospitalized patient group, the number of viral infection cases increased with increasing age in children up to 24 months of age (Table 1; chi-square 35.47;  $p < 0.0001$ ). Similarly, there was also an increment with increasing age in the number of upper respiratory tract infections (URTI) (chi-square 34.06;  $p < 0.0001$ ) and of laryngotracheitis, tracheobronchitis, bronchitis, or sibilant bronchitis in this group (chi-square 17.79;  $p < 0.0001$ ). On the other hand, the number of bronchiolitis cases in this group decreased with increasing age.

In the hospitalized patient group a decrease of number of cases with increasing age was observed (chi-square 177.6;  $p < 0.0001$ ), and early age children (up to three months old) were more affected compared to the other age groups ( $p < 0.0001$ ). In early age group there

was a significant difference of cases in which bronchiolitis largely predominated compared to other clinical manifestations (chi-square 70.59;  $p < 0.0001$ ).

Respiratory syncytial virus (RSV) was the most frequent virus detected among hospitalized children (chi-square 30.47;  $p < 0.0001$ ) (Figure 1), while human rhinovirus (HRV) and other viruses together (influenza virus, PIV, AdV, and hMPV) predominated among non-hospitalized patients (chi-square 15.38;  $p < 0.0001$ ); there was no significant difference in the

**Figure 1.** Frequency of cases of respiratory viral infections in non-hospitalized and hospitalized children up to five years old attended at the Clinic Hospital of the Federal University of Uberlândia (HC-UFU), Midwestern Brazil, from 2010 to 2015.



\*  $p < 0.0001$ ; <sup>a</sup> Influenza virus, parainfluenza virus, adenovirus and human metapneumovirus; <sup>b</sup> HRV and RSV: 34 cases; HRV and FLU: 4 cases; HRV and hMPV: 6 cases; HRV and PIV: 14 cases; HRV and AdV: 6 cases.

**Table 1.** Clinical manifestation of children up to five years old attended at the Clinic Hospital of the Federal University of Uberlândia (HC-UFU), Midwestern Brazil, from 2010 to 2015, according to age and hospitalization requirement.

Age in months	Upper Respiratory Tract Infections <sup>a</sup>	Bronchiolitis	Pneumonia	Others <sup>c</sup>	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
<b>Non-hospitalized n = 229 (53.3%)</b>					
≤ 3	7 (6.6)*	8 (44.4)	-	8 (7.7)	23 (10.0)*
3–6	10 (9.4)	6 (33.3)	-	10 (9.6)	26 (11.3)
6–12	20 (18.9)	3 (16.7)	-	31 (29.8)	54 (23.6)
12–24	38 (35.8)	1 (5.5)	1 (100.0)	26 (25.0)	66 (28.8)
≥ 24	31 (29.4)	-	-	29 (27.9)	60 (26.2)
Total <sup>b</sup>	106 (46.3)	18 (7.9)	1 (0.4)	104 (45.4)	229 (100.0)
<b>Hospitalized n = 201 (46.7%)</b>					
≤ 3	4 (50.0)	56 (64.4)**	22 (73.3)	24 (31.6)	106 (52.7)*
3–6	-	22 (25.3)	3 (10.0)	12 (15.8)	37 (18.4)
6–12	-	9 (10.3)	3 (10.0)	12 (15.8)	24 (11.9)
12–24	1 (12.5)	-	1 (3.3)	19 (25.0)	21 (10.4)
≥ 24	3 (37.5)	-	1 (3.3)	9 (11.8)	13 (6.5)
Total <sup>b</sup>	8 (4.0)	87 (43.3)	30 (14.9)	76 (37.8)	201 (100.0)

<sup>a</sup> Percentage of cases of each age group according to total of cases of each clinical manifestation; <sup>b</sup> Percentage of cases according to total of non-hospitalized and hospitalized cases; <sup>c</sup> laryngotracheitis, tracheobronchitis, bronchitis, and sibilant bronchitis cases; \* Differences at non-hospitalized group according to age from URTI (chi-square 34.06;  $p < 0.0001$ ) and total of cases (chi-square 35.47;  $p < 0.0001$ ), and hospitalized group from total cases (chi-square 177.6;  $p < 0.0001$ ); \*\* Bronchiolitis difference at hospitalized group comparing to other clinical manifestation of  $\leq 3$  months of age children (chi-square 70.59;  $p < 0.0001$ ).

frequency of coinfections cases between hospitalized and non-hospitalized patients.

In RSV infection cases, the frequency of hospitalized children was 2.3 times higher than non-hospitalized cases, indicating that RSV caused higher degree of severity. Indeed, there was a predominance of moderate-to-severe diseases caused by RSV in hospitalized children (Figure 2A). Yet in HRV infection we observed the frequency of non-hospitalized cases higher than hospitalized children (Figures 1, 2A, and 2B).

In non-hospitalized patients there were no differences between the frequencies in mild cases

compared to moderate-to-severe cases caused by a single virus (Figure 2B). However, in coinfections a slightly higher predominance of moderate-to-severe cases compared do mild diseases was observed. The statistical significant difference was even higher in hospitalized children with coinfections (Figure 2A). RSV in coinfection cases was detected in 33 out of 50 moderate-to-severe cases while it was not detected in any mild cases (n = 14). Also in coinfections HRV was involved in nearly all cases (98.4%, 63/64) and frequently with RSV (51.5%, 33/64). In addition, there was a predominance of moderate-to-severe diseases caused by all viruses studied including coinfections in hospitalized children.

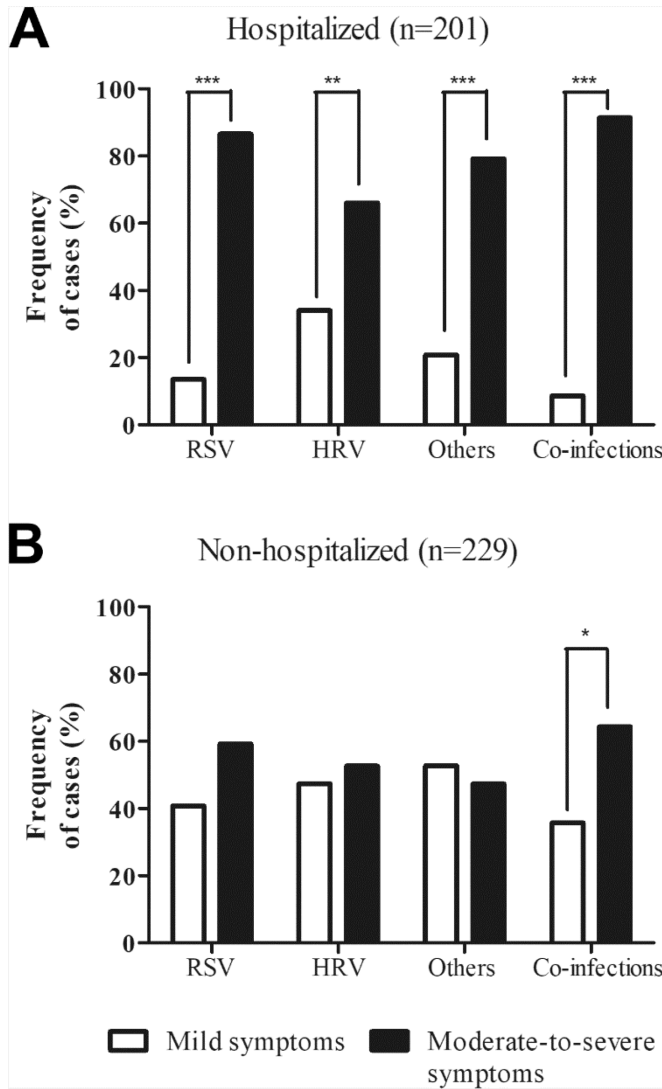
Even though non-hospitalized children presented equivalent frequencies of mild and moderate-to-severe diseases the latter represented an expressive frequency accounting for 53.7% (123/229) of cases. Moreover, the large predominance of moderate-to-severe disease in hospitalized patients (82.1% - 165/201) may imply that these children had even more severe condition either or presented an association with some risk condition that led to hospitalization.

Thus, considering only the group of hospitalized children bronchiolitis largely predominated (43.2% - 87/201) and was caused mostly by RSV (60.9% - 53/87) which was also responsible for most cases of pneumonia (53.3% - 16/30). In addition, RSV predominated in terms of more severe disease among hospitalized children compared to HRV (chi-square 36.24;  $p < 0.0001$ ) and to other viruses (chi-square 58.12;  $p < 0.0001$ ).

In the hospitalized children group approximately half of these children had a previous risk condition unrelated to the infection while other half did not and therefore were considered previously healthy (Table 2). Regarding signs and symptoms cough and dyspnea largely predominated in hospitalized children (90%) regardless of presentation of comorbidities; fever and sibilys were observed in approximately 50% of the cases. In addition, cyanosis cases were slightly more frequent in children with comorbidities and sibilys in previously healthy patients. Although the frequency of more severe disease was lower in children who presented comorbidities (71.6% vs. 91.9%) they required longer hospitalization (> 10 days, 64.7% vs. 21.2%) than in previously health children. Conversely, previously healthy children presented higher frequency of moderate-to-severe disease and had shorter period of hospitalization.

Despite the fact that RSV was the leading cause of respiratory disease in hospitalized patients, lower

**Figure 2.** Severity of symptoms according to virus among non-hospitalized and hospitalized children up to five years old attended at the Clinic Hospital of the Federal University of Uberlândia (HC-UFU), Midwestern Brazil, from 2010 to 2015.



\*  $p = 0.05$ ; \*\*  $p < 0.001$ ; \*\*\*  $p < 0.0001$ .

frequency of more severe disease and longer hospitalization periods were observed in children with comorbidities regardless of the etiology (Table 3).

We also compared other characteristics of infections caused by different viruses (Table 3). Based on the chi-square values a higher predominance of RSV infections (compared to other viruses) was observed in previously healthy children. In all clinical characteristics for children with comorbidities, but fever, frequencies were higher in children infected with RSV infection (mostly in cough and dyspnea cases).

Children hospitalized with previously healthy status also demonstrated to be regularly affected by RSV in all evaluated clinical characteristics compared to other viruses. Moreover, frequency of RSV infections was higher in moderate-to-severe symptoms and in hospitalization for over ten days.

Of one hundred and two hospitalized children with previous risk condition prematurity was the most common condition (45.1% - 46/102), followed by heart diseases (37.2% - 38/102) and non-infectious respiratory disease (21.6% - 22/102). Prematurity predominated compared to non-infectious respiratory disease ( $p = 0.0004$ ), neural disease ( $p < 0.0001$ ) and other comorbidities ( $p < 0.0001$ ). Eleven children who had heart disease, aside thirty-eight, and thirteen who had non-infectious respiratory disease, aside twenty-two, were born prematurely. Thus, if considering prematurity exclusively which corresponds to twenty-two cases, heart disease was the most prevalent comorbidity equivalent to twenty-seven cases or 37.2% ( $p = 0.0140$ ).

Thirty-four aside one hundred and two which corresponds to 31.4% of children who had been hospitalized acquired the respiratory viral infection during the stay at the hospital. HRV was the most common agent detected in these cases from twenty-three to thirty-four corresponding to 67.4%. Heart diseases and non-infectious respiratory diseases were the most common reasons for hospitalization of these children.

## Discussion

One aimed at increasing the knowledge of ARI by evaluating factors that may lead to increased severity of respiratory diseases by comparing virological and clinical characteristics of patients who required and those who did not require hospitalization.

The numbers of hospitalized and non-hospitalized cases were similar and included patients attended at different settings of the hospital and presented a broad range of symptoms involving both URTI and LRTI. Our findings indicate that children who were hospitalized due to respiratory distress had well defined characteristics: early age, RSV as the causative agent, bronchiolitis, and presence of comorbidity. In previous studies performed by our group [4] and by others [3,14] early age has also been shown to be an important risk factor associated with severe disease caused by RSV as well as by HRV.

Increasing frequencies of viral respiratory infections with older age in non-hospitalized patients were observed (Table 1). This observation may be due to increasing social contact of older children mostly at school and kindergarten [15,16], making them more

**Table 2.** Characteristics of the 201 hospitalized children up to five years old attended at the Clinic Hospital of the Federal University of Uberlândia (HC-UFU), Midwestern Brazil, from 2010 to 2015, with viral respiratory disease presenting comorbidities or who were previously healthy.

Characteristics	Children with comorbidities (n = 102)	Previously healthy children (n = 99)	Total (n = 201)	Chi-square and p values <sup>a</sup>
	N (%)*	N (%)*	N (%)*	
<b>Clinical characteristics</b>				
Fever	44 (43.1)	56 (56.6)	100 (49.8)	NS
Cough	92 (90.2)	92 (92.9)	184 (91.5)	NS
Dyspnea	86 (84.3)	92 (92.9)	178 (88.6)	NS
Cyanosis	26 (25.5)	17 (17.2)	43 (21.4)	3.767; 0.0523
Apnea	14 (13.7)	11 (11.1)	25 (12.4)	NS
Sibyls	45 (44.1)	60 (60.6)	105 (52.2)	4.286; 0.0384
<b>Severity of disease</b>				
Mild	29 (28.4)	8 (8.1)	37 (18.4)	23.84; < 0.0001
Moderate-to-severe	73 (71.6)	91 (91.9)	164 (81.6)	3.951; 0.0468
<b>Days of hospitalization</b>				
< 5 days	13 (12.7)	48 (48.5)	61 (30.3)	40.16; < 0.0001
6-10 days	23 (22.5)	30 (30.3)	53 (26.4)	NS
> 10 days	66 (64.7)	21 (21.2)	87 (43.3)	46.55; < 0.0001

NS: non-significant; <sup>a</sup> chi square values were calculated comparing “children with comorbidities” vs. “previously health children” for each clinical characteristics; \* Percentage calculated according to total of each category: comorbidity (102) or previously health (99) .

prone to acquire pathogens that cause respiratory diseases.

Also, we found that severe disease decreased with increasing age. By experiencing viral respiratory infections since early age children develop immunity [17] and thereby it can fight the infection more properly. It is particularly well documented for RSV infections [18] that the virus is most involved in respiratory tract infections. Moreover, respiratory tract development as well as immunological system are well defined with increasing age, which may also contribute for older children to face more promptly respiratory infections.

For children that required hospitalization due to viral respiratory disease bronchiolitis was the main diagnosis affecting mostly children up to three months of age. Bronchiolitis has been reported as one of the main reasons for infant hospitalization mostly in developing countries and early age as an important condition of vulnerability due to respiratory infections [3,19]. Moreover, unfavorable socioeconomic

conditions may have contributed to aggravate the disease taking into account that low socioeconomic status has often been mentioned as a factor to be taken into consideration regarding the outcomes of respiratory diseases in children [1,2]. Nevertheless, considering that an individual and detailed socioeconomic analysis was not possible to be performed in the present study this aspect of our data must be carefully evaluated. Indeed, Desselberger [20] raised a wide range of factors concerning socioeconomic conditions for the effectiveness of the rotavirus vaccine comparing developed and low-income countries, which would be useful on further analysis for better measure ARI socioeconomic impact.

Regarding virological findings RSV was the agent most related to hospitalization (figures 1 and 2) followed by HRV. RSV is the leading cause of severe disease mostly in early age children [2,3], and bronchiolitis due to RSV infection is one of the most important causes of infant hospitalization [3,14]. Thus, as we will discuss later, RSV infection among early age

**Table 3.** Comparison of clinical characteristics between RSV infections and other infections in hospitalized children up to five years old attended at the Clinic Hospital of the Federal University of Uberlândia (HC-UFU), Midwestern Brazil, from 2010 to 2015, with viral respiratory disease presenting comorbidities or were previously healthy.

Characteristics	RSV (n = 41)	HRV (n = 33)	Others <sup>a</sup> (n = 11)	Coinfections (n = 17)	Total (n = 102)	Chi-square; p values
	n (%)	n (%)	n (%)	n (%)	n (%)	
<b>Children with previous comorbidities (n = 102)</b>						
Cough	41 (100)	26 (78.8)*	10 (90.9)**	15 (88.2)**	92 (90.2)	31.77; < 0.0001
Dyspnea	41 (100)	22 (66.7)*	8 (72.7)**	15 (88.2)**	86 (84.3)	35.66; < 0.0001
Fever	14 (34.1)	15 (45.5)	10 (90.9)	5 (29.4)*	44 (43.1)	NS
Cyanosis	14 (34.1)	4 (12.1)*	5 (45.5)*	3 (17.6)*	26 (25.5)	12.65; 0.0055
Apnea	8 (19.5)	3 (9.1)	1 (9.1)*	2 (11.8)	14 (13.7)	8.580; 0.0354
Sibyls	19 (46.3)	12 (36.4)*	5 (45.5)**	9 (52.9)*	45 (44.1)	10.47; 0.0150
Mild disease	10 (24.4)	12 (36.4)	5 (45.4)	2 (11.8)*	29 (28.4)	10.43; 0.0152
Moderate-to-severe disease	31 (75.6)	21 (63.6)	6 (54.5)**	15 (88.2)*	73 (71.6)	26.11; < 0.0001
OTI+MV	7 (17.1)	6 (18.2)	3 (27.3)	2 (11.8)	18 (17.6)	NS
<b>Hospitalization length</b>						
< 5 days	4 (9.8)	4 (12.1)	1 (9.1)	4 (23.5)	13 (12.7)	NS
5-10 days	12 (29.3)	4 (12.1)*	4 (36.4)*	3 (17.6)*	23 (22.5)	9.722; 0.0211
> 10 days	25 (61.0)	25 (75.8)	6 (54.5)*	10 (58.8)*	66 (64.7)	21.47; < 0.0001
<b>Previously healthy children (n = 99)</b>						
Cough	51 (92.7)	12 (85.7)**	12 (100)**	17 (94.4)**	92 (92.9)	60.15; < 0.0001
Dyspnea	51 (92.7)	13 (92.9)**	11 (91.7)**	17 (94.4)**	92 (92.9)	60.26; < 0.0001
Fever	31 (56.4)	7 (50.0)*	6 (50.0)*	12 (66.7)*	56 (56.6)	18.76; < 0.0001
Cyanosis	11 (20.0)	2 (14.3)*	2 (16.7)*	2 (11.1)*	17 (17.2)	14.94; 0.0019
Apnea	9 (16.4)	1 (7.1)*	0 (0.0)	1 (5.6)*	11 (11.1)	12.08; 0.0024
Sibyls	35 (63.6)	8 (57.1)**	5 (41.7)**	12 (66.7)**	60 (60.6)	43.84; < 0.0001
Mild disease	3 (5.5)	4 (28.6)	1 (8.3)	1 (5.6)	9 (9.1)	NS
Moderate-to-severe disease	52 (94.5)	10 (71.4)**	11 (91.7)**	17 (94.4)**	90 (90.9)	66.59; < 0.0001
OTI+MV	8 (14.5)	1 (7.1)*	1 (8.3)*	2 (11.1)*	12 (12.1)	11.69; 0.0085
<b>Hospitalization length</b>						
< 5 days	25 (45.5)	8 (57.1)**	6 (50.0)**	9 (50.0)**	48 (48.5)	21.81; < 0.0001
5-10 days	13 (23.6)	5 (35.7)*	4 (33.3)*	8 (44.4)	30 (30.3)	NS
> 10 days	17 (30.9)	1 (7.1)**	2 (16.7)**	1 (5.6)**	21 (21.2)	37.16; < 0.0001

\* p < 0.05; \*\* p < 0.0001; <sup>a</sup> Influenza virus, Parainfluenza virus, Adenovirus and human Metapneumovirus; NS: non-significant; IOT+VM: orotracheal intubation and mechanical ventilation.

patients along with diagnosis of bronchiolitis would be predictive of especial care regardless of child hospitalization requirement in the first moment of the infection.

Related to HRV, forty-two aside forty-seven (89.4%) of hospitalized children infected with this virus presented LRTI and thirty-one of them (66.7%, aside forty-seven) had moderate-to-severe symptoms. Despite being known as the causative agent of common cold HRV has been increasingly related to LRTI [4,19] even in hospitalized children [21].

Even though the group performed the molecular characterization of some HRV samples (unpublished data), no evidence was found of a correlation of HRV-C and severe disease. Based on VP4 conserved region sequencing [12] it was possible to characterize just a few samples of HRV (42): 21 samples belonged to HRV-A and 19 to species C – most of them related to common cold cases, that is, eight cases corresponding to 42,1% where two of them were enteroviruses. Difference in severity between the HRV-A and HRV-C was not found. However, one believes that these results may not be representative given the amount of virus that could be sequenced, and thus HRV-C may be underrepresented in their possible role with severe disease. Thus, the possibility that this species may be responsible for serious diseases caused by HRV cannot be excluded considering what has been widely reported [22-24].

Nevertheless, in these cases of severe illnesses among hospitalized patients caused both by RSV and HRV infections show that viral respiratory diseases indeed led patients to hospitalization, considering that our study solely enrolled children with respiratory distress caused by viruses. Despite the fact that frequency of moderate-to-severe disease was lower in patients who presented comorbidities, they stayed longer in the hospital as previously reported [4]. However, the previous health status also must be considered when treating children with respiratory viral diseases especially when there is involvement of RSV and HRV in the infections.

Indeed, we found similar numbers of hospitalized children with comorbidity and with previous healthy status (Table 2). In both groups, we observed a stronger influence of RSV on some of the clinical characteristics, severity of disease and hospitalization length over the infections caused by other viruses (Influenza virus, Parainfluenza virus, Adenovirus, and Human metapneumovirus). The differences were found by observing higher chi-square values at all parameters evaluated. RSV is a well-known agent that leads to

increased disease severity under several and well-determined risk conditions. Similarly, other studies have shown that this virus also contributes to severe disease in previously healthy children as well [14,25], indicating that RSV is an important cause of child disease regardless of their previous health status.

Interestingly, García *et al.* [26] found that most children hospitalized with bronchiolitis were previously healthy and had more severe disease compared to children hospitalized with bronchiolitis caused by non-RSV pathogens. Similarly, was demonstrated that moderate-to-severe disease cases due RSV infection were more predominant in previously healthy children compared to those with comorbidity (94.5% *vs.* 75.6%; 10.63;  $p = 0.0011$ ). In addition, respiratory disease in hospitalized children with comorbidities may be influenced in a similar manner regardless of the viral agent involved. In this regard, a correlation between coinfections and increased disease severity was not found [4,27].

Due to the high number of cases in several clinical characteristics, severity of symptoms as well as length of hospitalization, RSV seems to play the most important role in viral respiratory diseases compared to other viruses, considering chi-square and  $p$  values (Tables 2 and 3). Early age is considered to be an important predictor for disease severity rather than other comorbidities and coinfections.

Overall, previously healthy children infected with RSV and who were hospitalized presented differences in almost all clinical characteristics compared to other virus infections. These differences were stronger when compared with children who presented comorbidities considering higher Chi-square values. These results, as yet above discussed, deserve attention for the potential risk of acquiring RSV infection in children encompassing previous risk factors, as reported elsewhere [3,14].

## Conclusions

The present study is believed to have provided strong means to better guide physicians to treat children with viral respiratory diseases. Despite extensive literature, unnecessary antibiotic prescription, extended periods of hospitalization, considerable levels of morbidity and mortality and high treatment costs [1,2,28,29] still remains striking. Thus, constant surveillance and improvement of this approach is necessary by collecting information consistent with what has been widely debated and, consequently, by the applicability of appropriate measures at a public

hospital. This may be of great value in order to changing some paradigms in medical conduct that still remains.

In this context, although RSV infection profile was well determined, hallmark clinical characteristics was not found that may clearly distinguish children who had comorbidities and those previously healthy. Only cyanosis (predominated in children with comorbidity) and sibyls (predominant in previously healthy children) could be determined as different between these groups. Thus, the identification of clinical features alone seems not to be enough to guide a medical conduct to predict a likely severe illness. Therefore, viral identification is of utmost importance.

Still, although the predominance of most clinical features is attributed to RSV, the association of factors that can predict the possibility of severe disease is multifactorial and complex. However, the presence of RSV alone is considered to be an aggravating factor regardless of the child's previous health status.

In this regard, we found that RSV was responsible for more severe disease compared to other viruses in previously healthy group children. Thus, relying only on comorbidity may also not be enough to mitigate the impact of this type of infection on children. Therefore, in addition to comorbidities characterization and clinical evaluation, early age and mainly rapid identification of the respiratory agent as reported elsewhere [20,29] should be taken into account in the medical management. Indeed, early viral diagnosis can be useful even to mitigate inappropriate use of antibiotics [30]. Accordingly, prophylactic treatment with Palivizumab®[31] may be applied to early age children encompassing previous clinical status, infected with RSV, avoiding further complex clinical interventions. Eventually, the determination of the causes that lead to severe illness in children remains current even in the context of the SARS-COV-2 pandemic, as COVID-19 is apparently not serious in children up to five years of age [32] also considering that there is still no vaccines available to prevent RSV infections. Therefore, the clinical and epidemiological surveillance of viral respiratory diseases in children should not be obscured or misunderstood in this context.

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### Authors' contributions

Lourenço Faria Costa conceptualized and designed the study, performed the experiments, analyzed the results, drafted the manuscript, and approved the final manuscript as submitted. Hélio Lopes da Silveira performed the analysis of all clinical cases regarding comorbidities and clinical status and helped with the clinical criteria of severity of infections, he has also revised and approved the final manuscript as submitted. Divina Aparecida Oliveira Queiróz helped with the design of the study, oversaw the experimental work and the analyses of the results, revised and approved the final manuscript as submitted. Orlando Cesar Mantese performed the analysis of all clinical cases regarding comorbidities and clinical status, and helped with the clinical criteria of severity of infections, revised and approved the final manuscript as submitted. Jonny Yokosawa helped with the design of the study, oversaw the experimental work and the analyses of the results, revised and approved the final manuscript as submitted.

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