

# Clinical and epidemiological impact of respiratory syncytial virus and identification of risk factors for severe disease in children hospitalized due to acute respiratory tract infection

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## ABSTRACT

**Introduction:** Severe acute respiratory tract infection (ARTI) is a very common cause of hospitalization in pediatrics; respiratory syncytial virus (RSV) is the major etiologic agent. Accurately defining the burden of RSV life-threatening disease (LTD) and its risk factors is a challenge.

**Objectives:** To know the impact of RSV in children hospitalized due to ARTI and describe the risk factors for LTD.

**Materials and methods:** Prospective study in children < 2 years old hospitalized due to ARTI during 2012-2013 at Hospital de Niños "R. Gutiérrez." LTD was defined as requiring non-invasive ventilation and/or mechanical ventilation.

**Results:** 622 studied children, 372 were RSV(+) (59.8 %). Annual rate of hospitalization due to RSV in infants < 1 year old: 956 (95 % CI: 858-1062)/10000 hospitalizations. RSV caused 56/78 (71.8 %) cases of LTD; 42 (75 %) were previously healthy subjects; 32 (76.2 %) were < 6 months old. In the multivariate analysis, RSV was a risk factor for LTD (adjusted odds ratio [aOR]: 2.04; 95 % CI: 1.15-3.63;  $p = 0.014$ ). A differential effect by sex was identified in RSV(+) patients: over-crowding was a risk factor for LTD in males (aOR: 2.36; 95 % CI: 1.07-5.21;  $p = 0.033$ ); breastfeeding was a significant protective factor in females (aOR: 0.342; 95 % CI: 0.13-0.91;  $p = 0.032$ ).

**Conclusions:** RSV caused more than half of ARTI cases and mostly affected previously healthy patients < 1 year old. Males living in over-crowding conditions and females who were not breastfed were at the greatest risk for LTD.  
**Keywords:** respiratory syncytial virus, bronchiolitis, epidemiology, global burden of disease, risk factors.

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## INTRODUCTION

Acute respiratory tract infections (ARTIs) are the most common reason for medical consultation and hospitalization during the winter months.<sup>1-3</sup> In Argentina, ARTIs are the third cause of mortality in children aged 0-5 years.<sup>4-8</sup>

The most frequent etiologic agent of severe ARTI is respiratory syncytial virus (RSV).<sup>1-3,6,7</sup> In industrialized countries, the rate of hospitalization of children with RSV is approximately 1 %, but most severe cases (including 99 % of fatal ones) take place in developing countries.<sup>1,2,5-8</sup> The reported mortality rates in different countries vary greatly.<sup>1,8-10</sup>

Several risk factors for hospitalization in children with ARTI have been described.<sup>11-16</sup> However, there is scarce evidence available on the outcome measures associated with developing a life-threatening disease (LTD)<sup>6</sup> in children with RSV infection. Although different strategies are currently being studied, there is no effective RSV treatment and management still continues to be only supportive.<sup>17-19</sup>

The objective of this study was to describe the characteristics of RSV infections and compare them with the rest of ARTI hospitalizations; estimate the rate of hospitalization, the burden of LTD, and mortality due to RSV; and identify the risk factors for RSV LTD.

## MATERIALS AND METHODS

This was a prospective study for the epidemiological surveillance of hospitalization, clinical course, and mortality due to RSV infection in

children younger than 2 years old seen at Hospital de Niños "Dr. Ricardo Gutiérrez" of Buenos Aires during 2012-2013.

To establish the burden of RSV, the study included all patients younger than 2 years old hospitalized with a diagnosis of severe ARTI at the time of admission. Severe ARTI was defined by the sudden development of cough, tachypnea, wheezing, intercostal retraction and/or rales, with or without fever, oxygen saturation below 93 % on room air, or the presence of these symptoms in infants younger than 1 month old, regardless of their level of saturation.<sup>8</sup>

Patients with respiratory symptoms for more than 10 days prior to hospitalization and newborns who had not been discharged since birth were not included.

Nasal aspirate specimens were collected within 24 hours of admission from all children included in the study as part of the routine procedures for all patients hospitalized due to this condition (standard of care). The specimens were tested for virus using the direct immunofluorescence (IF) method.<sup>6,7</sup>

Demographic, epidemiological, clinical, and laboratory data were collected since admission and throughout hospitalization using a specially-designed card, which included risk factors for hospitalization reported in the bibliography:<sup>6,11-16</sup> age, sex, smoking in the household, over-crowding (more than three people in the same room), age of caregiver, parental diagnosis of asthma and/or atopy, malnutrition, anemia, absence of breastfeeding, prematurity (gestational age of less than 37 weeks), and presence of underlying disease. Malnutrition was defined according to the weight-for-age percentiles established by the World Health Organization (WHO),<sup>20</sup> and anemia was diagnosed when hemoglobin levels were below -2 standard deviations of the normal level for age.<sup>21</sup> LTD was defined as intensive care needs requiring mechanical ventilation (MV) and/or non-invasive ventilation (NIV). The routine patient management guidelines were not modified for the conduct of this study.

The study was approved by the hospital's Research Ethics Committee and the Health Research Council of the Ministry of Health of the Autonomous City of Buenos Aires. The informed consent was obtained from parents or legal guardians before including the patients in the study. Since this was not an experimental or interventional study, all parents consented to participation.

### Statistical analysis

The characteristics of children with ARTI secondary to RSV were compared to those of children with other types of infection using the  $\chi^2$  test and Student's *t* test, as applicable. Multivariate logistic regression models were developed to assess the risk factors for LTD, both in patients with ARTI in general and those with RSV infection. Outcome measures that had been considered relevant in advance were included in these models if the *p* value in the univariate analysis was lower than or equal to 0.20. Calibration (reliability) was analyzed using the Hosmer-Lemeshow test; and its discrimination capacity, with the area-under-the-curve analysis. A value of *p* < 0.05 was considered significant. The Stata, version 11.2, SE statistical package (StataCorp LP, College Station, TX) was used for analysis.

### RESULTS

Six hundred and twenty-two children were hospitalized with a diagnosis of ARTI and were included in the study; 144 (23.2 %) lived in the Autonomous City of Buenos Aires and 478 (76.8 %), in Greater Buenos Aires. A total of 479 patients (77 %) had been seen in advance due to the cause of their hospitalization; 210 (43.8 %) had visited an emergency department or a health center two or more times. RSV was diagnosed in 372 patients (59.8 %) [RSV(+)]; of these, 292 (78.5 %) were previously healthy subjects.

The characteristics of the study population are detailed in *Table 1* as per their RSV status.

In relation to age, among RSV(+) patients, 204 (54.8 %) were younger than 6 months old; 315 (84.7 %), younger than 1 year old (*Figure 1*). The annual rate of hospitalization due to RSV in infants younger than 1 year old was 956 (95 % confidence interval [95 % CI]: 858-1062) per 10 000 hospitalizations.

The clinical and laboratory manifestations at the time of admission to the hospital are described in *Table 2* and compared to those of RSV(-) patients.

The leukocyte count at the time of admission did not allow to differentiate RSV(+) and RSV(-) patients (*Table 2*). Blood cultures were done in 296 children with ARTI; 2 were positive (0.7%): *Streptococcus pneumoniae* in a 6-month-old infant and *Haemophilus influenzae* in an 8-month-old infant; both were RSV(+), had confirmed pneumonia, and developed LTD. The leukocyte count at the time of admission did not allow

to predict bacteremia in these patients (mean:  $7300 \pm 2828/\text{mm}^3$ ,  $p = 0.17$ ).

Antibiotic therapy was indicated in 262 RSV(+) children (70.4 %); 212 patients (80.9 %) who did not have radiographic images compatible with bacterial pneumonia received it for a median of 6 days (interquartile range [IQR]: 3-10). The most frequently used antibiotics were third-generation cephalosporins ( $n = 193$ , 73.7 %), clarithromycin ( $n = 70$ , 26.7 %), and ampicillin ( $n = 59$ , 22.5 %). Corticosteroids were administered to 202 RSV(+) patients (54.3 %).

Out of 78 ARTI cases that developed LTD, 56 (71.8%) had RSV infection. The possibility of developing LTD was significantly higher in RSV patients: 15.1 % versus 8.8 % in RSV(-) patients,  $p = 0.02$ . The multivariate analysis showed that RSV infection and over-crowding were risk factors for LTD in patients hospitalized due to ARTI (adjusted odds ratio [aOR]: 2.045; 95 % CI: 1.15-3.63;  $p = 0.014$ ; and aOR: 2.812; 95 % CI: 1.68-4.70;  $p < 0.001$ , respectively).

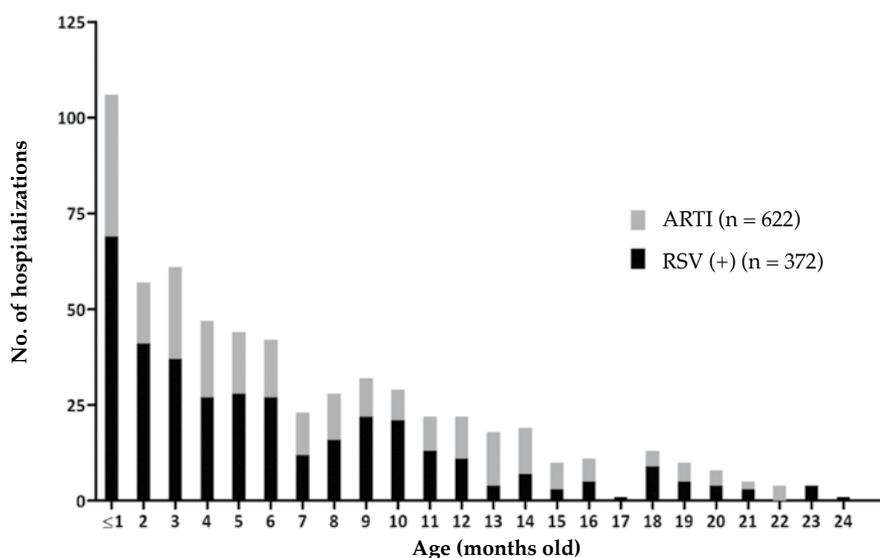
RSV LTD occurred in 18 out of 110 infants younger than 3 months old (16.3 %), in 22 out

TABLE 1. Characteristics of the population ( $n = 622$ )

Characteristic	RSV (+) ( $n = 372$ )	RSV (-) ( $n = 250$ )	<i>p</i> value
Age in months, m (IQR)	5 (2-9)	6 (3-12)	< 0.01
Breastfeeding, n (%)	199 (53.9)	164 (66.1)	< 0.01
Male sex, n (%)	203 (54.6)	154 (61.6)	0.11
Over-crowding, n (%)	104 (28.5)	83 (34.7)	0.10
Smoking in the household, n (%)	175 (47.3)	105 (42.0)	0.20
Parents with asthma, n (%)	146 (39.6)	105 (42.0)	0.47
Malnutrition, n (%)	12 (3.2)	7 (2.8)	0.78
Prematurity, n (%) (a)	41 (11.1)	19 (7.6)	0.15
BPD, n (%) (b)	5 (1.4)	2 (0.8)	0.54
Underlying disease, n (%) (c)	65 (18.2)	68 (28.6)	< 0.01
Recurrent wheezing, n (%) (d)	46 (12.9)	48 (20.2)	< 0.01

RSV: respiratory syncytial virus; m: median; IQR: interquartile range. (a) Prematurity: gestational age of less than 37 weeks. (b) BPD: bronchopulmonary dysplasia. (c) Underlying disease: congenital or acquired immune deficiency, congenital heart disease, blood disorders, cerebral palsy, genetic disorder. (d) Recurrent wheezing: history of 3 or more episodes of wheezing.

FIGURE 1. Age of patients hospitalized due to acute respiratory tract infection and with a diagnosis of respiratory syncytial virus



ARTI: acute respiratory tract infection; RSV: respiratory syncytial virus.

of 119 infants aged 3-6 months old (18.5 %), and in 16 out of 141 infants older than 6 months old (11.3 %) (Figure 2). Forty-two patients with RSV LTD (75 %) were previously healthy subjects; of these, 32 (76.2 %) were younger than 6 months old. The annual rate of hospitalization due to LTD secondary to RSV was 170 (95 % CI: 129-220) per 10 000 hospitalized infants younger than 1 year old.

Among RSV(+) infants who developed LTD, 54 (96.4 %) experienced complications (Table 3).

Among RSV(+) patients, the median length of oxygen requirement was 5 days (IQR: 3-7), which extended to 10 days (IQR: 5-16) in those who developed LTD,  $p < 0.001$ . The median length of hospital stay was 5 days (IQR: 6-9), which was significantly longer in those with LTD: 27 (IQR: 18-46.5),  $p < 0.001$ .

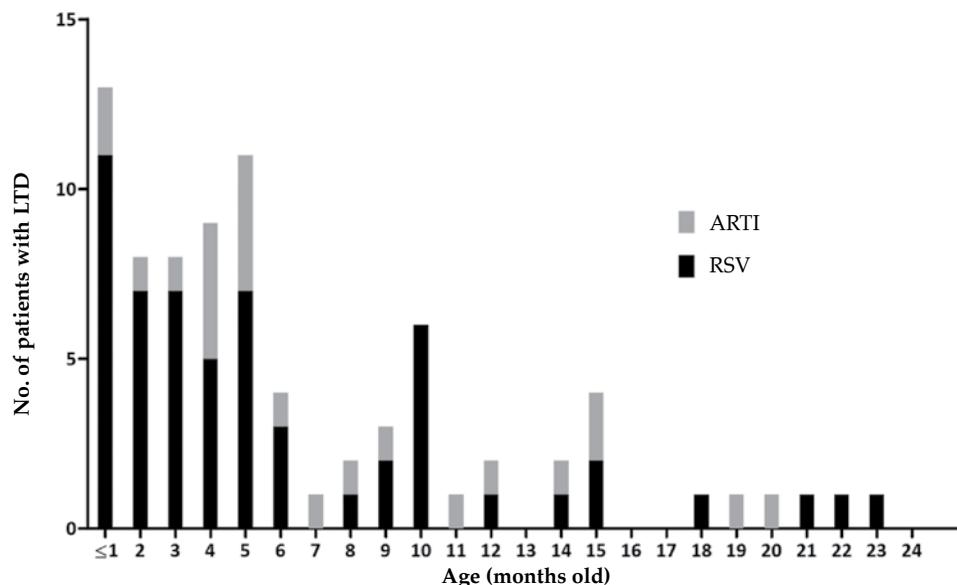
Three out of the 6 patients who died in the study period had RSV infection; all were younger than 1 year old; 2 of them were younger than 4 months old and had an underlying disease

TABLE 2. Clinical and laboratory manifestations at the time of admission, as per respiratory syncytial virus status (n = 622)

	RSV (+) (n = 372)	RSV (-) (n = 250)	p value
<b>Clinical outcome measures</b>			
Days of progression until admission, m (IQR)	3.5 (2-5)	4 (2-6)	0.26
Wheezing, n (%)	239 (64.2)	163 (65.2)	0.80
Respiratory pauses / apnea, n (%)	22 (5.9)	20 (8.0)	0.31
Pertussis-like syndrome, n (%)	4 (1.1)	3 (1.2)	0.88
Fever, n (%)	254 (68.3)	162 (64.8)	0.37
Vomiting, n (%)	92 (24.7)	82 (32.8)	0.03
Diarrhea, n (%)	45 (12.1)	33 (13.2)	0.68
Pneumonia, n (%)	50 (13.4)	24 (9.6)	0.15
<b>Laboratory outcome measures</b>			
Leukocyte count (/mm <sup>3</sup> ), (n) mean ± SD	(n = 256) 12 597 ± 5658	(n = 146) 13 142 ± 5711	0.36
Anemia, n (%)	135/251 (53.8)	68/143 (47.5)	0.23
Positive blood cultures, n (%)	2/187 (1.1)	0/109	-

RSV: respiratory syncytial virus; m: median; IQR: interquartile range; SD: standard deviation; pneumonia: diagnosed based on clinical course and X-ray image showing condensation and/or air bronchogram.

FIGURE 2. Patients hospitalized due to acute respiratory tract infection who developed a life-threatening disease, by age and respiratory syncytial virus status



LTD: life-threatening disease; ARTI: acute respiratory tract infection; RSV: respiratory syncytial virus.

(bronchopulmonary dysplasia, heart disease). The annual rate of mortality due to RSV was 91 (95 % CI: 19-266) per 10 000 infants younger than 1 year old hospitalized due to this virus.

In RSV(+) patients, both over-crowding conditions and breastfeeding had a differential effect on the course of disease based on sex. Specifically, over-crowding was significantly associated with the development of LTD in male patients hospitalized due to RSV (aOR: 2.36; 95 % CI: 1.07-5.21;  $p = 0.03$ ); none of the other studied outcome measures was associated with a similar morbid effect (Table 4). In turn, breastfeeding played a significant protective role in female patients (aOR: 0.342; 95 % CI: 0.13-0.91;  $p = 0.03$ ) (Table 4).

## DISCUSSION

The results of this study confirm the critical, preponderant role of RSV as an etiologic agent in severe ARTI in young children. The characteristics of the population included in this study make results adequately representative, even for other regions of the world.<sup>22</sup>

This study, which is in line with the estimations of a meta-analysis published by Nair et al.,<sup>1</sup> and a multicenter study carried out in the Metropolitan Area of Buenos Aires,<sup>6</sup> shows that the burden of RSV is noteworthy. RSV caused more than half of ARTI cases requiring hospitalization in children younger than 2 years old; most were previously healthy subjects. The primary outcome measure was defined as the need for intensive care, with MV and/or NIV requirement –which was considered a more assessable and less variable piece of information than oxygen saturation– unlike in other multicenter studies, where oxygen saturation at the time of admission was used due to the lack of an intensive care unit and the limited access to ventilators in some of the participating sites.<sup>6</sup>

Compared to the rest of the patients hospitalized due to ARTI, the age of RSV(+) children was significantly younger; also, they showed a smaller prevalence of associated morbidities or of a history of recurrent wheezing. More than half of patients hospitalized due to ARTI were  $\leq 6$  months old (57.5 %); most were younger than 1 year old (79.1 %; 84.7% of all admissions due to RSV). No differences were observed in terms of the sex of children hospitalized due to ARTI, both RSV(+) and RSV(-), or those who developed LTD. It was observed that patients hospitalized due to ARTI had a considerable prevalence of anemia and a concerning percentage of them had not been breastfed, which was significantly higher among those hospitalized due to RSV.

Severe ARTIs due to RSV appear to be more common in developing countries than in industrialized ones.<sup>1,6,8,9</sup> In a prospective study for the surveillance of hospitalizations due to RSV in infants in the United States, no RSV-associated deaths were observed,<sup>23</sup> while 3 out of 372 children with RSV infection died in our hospital during the study period. In the Argentine multicenter study mentioned above,<sup>6</sup> the annual rate of mortality due to RSV in infants younger than 1 year old who were hospitalized was 3 (95 % CI: 1-6) per 10 000 infants in the same age range that lived in the study region. To illustrate the size of RSV impact, this rate was four times higher than that reported for influenza A (H1N1) virus in the year of the H1N1 epidemics in this population.<sup>6</sup> The same group observed an annual rate of mortality due to RSV of 9.4 per 10 000 live births (95 % CI: 5.5-13.3), which was the leading cause of mortality beyond the post-neonatal period.<sup>8</sup>

No clinical or laboratory characteristics were identified that would allow to establish differences between RSV(+) children and the rest.

TABLE 3. Complications in patients with life-threatening disease, as per respiratory syncytial virus status ( $n = 78$ )

Complications, n (%)	RSV (+) (n = 54)	RSV (-) (n = 22)	p value
Health care-associated infection	22 (39.3)	13 (59.1)	0.12
Ventilator-associated pneumonia	18 (33.3)	9 (40.9)	0.50
Urinary tract infection	11 (20.4)	8 (36.4)	0.13
Gastroenteritis	1 (1.8)	4 (18.2)	0.03
Atelectasis	11 (20.4)	3 (13.6)	0.54
Deep vein thrombosis	8 (14.8)	4 (18.2)	0.90
Pneumothorax	3 (5.6)	5 (22.7)	0.03

RSV: respiratory syncytial virus

Although secondary bacterial infection has been described in patients with RSV,<sup>24</sup> as well as in our study, it is striking that there was a high number of patients with RSV infection who received long-term antibiotic therapy without conclusive signs of consolidated pneumonia. Several clinical studies demonstrated the ineffectiveness of macrolides and corticosteroids in infants with bronchiolitis.<sup>19,25</sup>

Most children hospitalized due to ARTI who developed LTD were previously healthy subjects and had RSV infection.

In a multivariate analysis that included traditional risk factors for hospitalization,<sup>6</sup> two outcome measures had a significant impact on the risk for RSV LTD: living in over-crowding conditions and lack of breastfeeding. The influence of an environment with a high bacterial load on the severity of RSV infections has already been reported.<sup>6,26</sup> Over-crowding might be related to a greater exposure to bacterial lipopolysaccharides. To date, there are no studies that have described this condition as a

TABLE 4. Risk factors for life-threatening disease in patients hospitalized due to respiratory syncytial virus

Risk factors for life-threatening disease in female patients hospitalized due to respiratory syncytial virus (n = 169)									
	LTD	NO LTD	Univariate analysis			Multivariate analysis			
			OR	95 % CI	p	OR	95 % CI	p	
<i>Socioeconomic outcome measures</i>									
Over-crowding (n,%)	9 (40.9)	37 (25.7)	2.002	0.79-5.07	0.143	1.968	0.74-5.20	0.173	
Smoking in the household (n,%)	10 (45.4)	73 (50.0)	0.833	0.34-2.05	0.691	-			
Age of caregiver, years old (mean, SD)	25.4 (6.4)	25.9 (7.4)	0.990	0.93-1.06	0.765	-			
<i>Inherited outcome measures</i>									
Asthma in the father / mother (n,%)	6 (27.3)	56 (38.1)	0.609	0.22-1.65	0.329	-			
Atopy in the father / mother (n,%)	6 (27.3)	30 (20.5)	1.450	0.52-4.02	0.475	-			
<i>Patient's outcome measures</i>									
Malnutrition (n,%)	3 (13.6)	4 (2.7)	5.645	3.48-7.32	0.031	3.872	0.74-20.3	0.109	
Breastfeeding (n,%)	7 (31.8)	86 (59.3)	0.320	0.12-0.83	0.020	0.342	0.13-0.91	0.032	
Age, months old (mean, SD)	7.6 (6.4)	7.0 (5.7)	1.016	0.94-1.09	0.680	1.017	0.94-1.10	0.670	
Prematurity (n,%)	2 (9.1)	17 (11.6)	1.032	0.95-1.11	0.434	-			
Underlying disease (n,%)	5 (22.7)	18 (12.2)	0.759	0.16-3.54	0.725	-			
Bronchopulmonary dysplasia (n,%)	1 (4.8)	3 (2.1)	2.300	0.23-23.2	0.480	-			

LTD: life-threatening disease; OR: odds ratio; CI: confidence interval; SD: standard deviation.

Risk factors for life-threatening disease in male patients hospitalized due to respiratory syncytial virus (n = 203)

Risk factors for life-threatening disease in male patients hospitalized due to respiratory syncytial virus (n = 203)									
	LTD	NO LTD	Univariate analysis			Multivariate analysis			
			OR	95 % CI	p	OR	95 % CI	p	
<i>Socioeconomic outcome measures</i>									
Over-crowding (n,%)	16 (48.5)	42 (25.3)	2.779	1.29-5.98	< .001	2.362	1.07-5.21	0.033	
Smoking in the household (n,%)	20 (60.6)	72 (42.6)	2.072	0.98-4.44	0.061	2.001	0.40-4.43	0.087	
Age of caregiver, years old (mean, SD)	26.8 (6.4)	25.7 (6.9)	1.022	0.98-1.08	0.437	-			
<i>Inherited outcome measures</i>									
Asthma in the father / mother (n,%)	15 (44.1)	69 (40.8)	1.144	0.54-2.40	0.722	-			
Atopy in the father / mother (n,%)	7(21.9)	47 (27.8)	0.727	0.29-1.79	0.489	-			
<i>Patient's outcome measures</i>									
Malnutrition (n,%)	0	5 (3.0)	-			-			
Breastfeeding (n,%)	14 (42.4)	92 (54.4)	0.617	0.29-1.31	0.209	0.660	0.30-1.45	0.301	
Age, months old (mean, SD)	4.7 (4.0)	6.1 (5.1)	0.932	0.85-1.02	0.120	1.017	0.94-1.10	0.670	
Prematurity (n,%)	3 (9.1)	19 (11.2)	0.789	0.22-2.84	0.717	0.943	0.86-1.03	0.186	
Underlying disease (n,%)	9 (26.5)	33 (19.5)	1.484	0.63-3.48	0.364	-			
Bronchopulmonary dysplasia (n,%)	1 (3.0)	0	-			-			

LTD: life-threatening disease; OR: odds ratio; CI: confidence interval; SD: standard deviation.

significant risk factor for LTD, specifically, in male infants hospitalized due to RSV. Further studies are required to analyze the phenomena leading to such differential association by sex. In turn, the protective role of breastfeeding was particularly significant in female children, which was consistent with the evidence found in other studies.<sup>27</sup>

This study has certain limitations. RSV infections peak every 4 to 5 years,<sup>6</sup> and a study period that covered more winters would detect a greater or smaller burden of disease. Anyhow, the rates reported here are not much different from those described in 2008;<sup>6,28</sup> therefore, our data probably reflect the typical impact of RSV-associated ARTIs in our setting. This study was done in children hospitalized at a single center; regional differences in terms of environmental exposure, genetic variations or cultural practices may have an effect on results. Finally, the study design prevented us from analyzing the impact of studied outcome measures on the risk for hospitalization.

Public health strategies aimed at modifying the risk factors described here and other outcome measures that may be identified in the future should be explored in order to reduce the impact of life-threatening ARTIs. Also, knowledge on the factors related to the extreme severity of this condition may contribute to establish customized preventive measures and decide on an early and timely hospitalization for patients at a higher risk.

## CONCLUSIONS

RSV was the most frequent etiologic agent in severe ARTIs, causing more than half of all cases and affecting mostly previously healthy patients younger than 1 year old. Males living in overcrowding conditions and females who were not breastfed were at the greatest risk for LTD. ■

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