

Epidemiology and factors associated with the severity of viral acute lower respiratory infection in children hospitalized in Manaus, Amazonas, in 2017–2018

An observational study

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Abstract

To investigate the epidemiology and factors associated with the severity of viral acute lower respiratory infection (ALRI) in children hospitalized in Manaus, Amazonas, in 2017 to 2018.

Retrospective cohort study of children hospitalized at the Hospital and Emergency Room Delphina Rinaldi Abdel Aziz, in Manaus, from April 01, 2017 to August 31, 2018, with a clinical diagnosis of ALRI and nasopharyngeal aspirates positive for at least 1 respiratory virus.

One hundred forty-six children aged 0.2 to 66 months (median 7 months) were included. Patients were divided into 2 groups according to the disease severity classified by an adapted Walsh et al score: moderate disease, score 0–4, $n=66$ (45.2%) and severe disease, score 5–7, $n=80$ (54.8%). A greater number of viral ALRI cases were observed in the rainiest months. Respiratory syncytial virus was the most prevalent ($n=103$, 70.3%), followed by metapneumovirus ($n=24$, 16.4%), influenza virus ($n=17$, 11.6%), parainfluenza virus ($n=11$, 7.5%), and adenovirus ($n=4$, 2.7%). Co-detections of 2 to 3 viruses were found in 12 (8.2%) patients. The presence of viral coinfection was an independent risk factor for disease severity (adjusted relative risk [RR] 1.53; 95% CI 1.10–2.14). Twelve patients (8.2%) died, all with severe disease. Risk factors for death were shock (adjusted RR 10.09; 95% CI 2.31–43.90) and need for vasoactive drugs (adjusted RR 10.63; 95% CI 2.44–46.31).

There was a higher incidence of viral ALRI in Manaus in the rainy season. Respiratory syncytial virus was the most prevalent virus. The presence of viral coinfection was an independent risk factor for disease severity.

Abbreviations: ALRI = acute lower respiratory infection, CI = confidence interval, RR = relative risk, RSV = respiratory syncytial virus.

Keywords: Amazon region, clinical features, outcomes, respiratory viruses, seasonality

Editor: Yan-Ren Lin.

This study was supported by CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) and Amazonas State University.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Sobrinho FL, Aragon DC, Carlotti AP. Epidemiology and factors associated with the severity of viral acute lower respiratory infection in children hospitalized in Manaus, Amazonas, in 2017–2018: An observational study. *Medicine* 2021;100:18(e25799).

Received: 28 October 2020 / Received in final form: 25 February 2021 / Accepted: 15 April 2021

<http://dx.doi.org/10.1097/MD.00000000000025799>

1. Introduction

Acute lower respiratory infection (ALRI) is a major cause of morbidity and mortality in young children worldwide. It is estimated that 33 million episodes of ALRI caused by respiratory syncytial virus (RSV) occurred in children younger than 5 years in 2015 globally, resulting in 3.2 million hospital admissions and 118,200 deaths.^[1] More than 90% of all RSV-ALRI episodes and 99% of mortality occurred in developing countries.^[2]

ALRIs have marked seasonality, which is quite consistent within most regions, with some variations between different years. In countries with temperate climate, ALRIs occur mainly in the winter, while in equatorial and tropical climates, the circulation of respiratory viruses is highest during the rainy season.^[3] In Brazil, which is a country of continental dimensions, regional differences in seasonality of RSV-associated ALRI were identified.^[4] The peak of the RSV season was observed in the second week of April in the North and Midwest regions, in the first week of May in the Northeast, in the beginning of April in the Southeast and in the first week of June in the South.^[5] However, comprehensive data on ALRI seasonality in Brazil are scarce and a few epidemiological studies have been published so far.^[6–9]

Manaus, the capital of the Brazilian state of Amazonas, is located in the center of the Amazon rainforest. It is the most

populous city in the Brazilian Amazon, with more than 2.2 million inhabitants, and it is also the main financial and commercial center in the North of Brazil. The city has a humid tropical climate, with an annual rainfall index around 2300 mm and constant heat throughout the year. Rainfall is greatest between December and May (rainy season), and decreases considerably between June and November, particularly from July to September (dry season). To our knowledge, no research data on the epidemiology and clinical characteristics of ALRI in children from Manaus have been published. Thus, the aim of this study was to investigate the epidemiology and factors associated with the severity of viral ALRI in children hospitalized in Manaus, in 2017 to 2018.

2. Methods

This was a retrospective cohort study of children with ALRI hospitalized at the Hospital and Emergency Room Delphina Rinaldi Abdel Aziz, in Manaus, from April 1, 2017 to August 31, 2018. The study was approved by the Institutional Research Ethics Board of Amazonas State University (CAAE 85671418.3.0000.5016). The informed consent form was waived because of the retrospective nature of the study. The Hospital and Emergency Room Delphina Rinaldi Abdel Aziz is a 206-bed general hospital which serves as a teaching hospital of the Faculty of Medicine of Amazonas State University. This hospital is a sentinel unit of the surveillance system of respiratory viruses in Brazil.

All children 0 to 5 years of age hospitalized with a clinical diagnosis of ALRI and nasopharyngeal aspirate positive for at least 1 respiratory virus were eligible for the study. The clinical diagnosis of ALRI was defined by the presence of cough, tachypnea, respiratory distress with prolonged expiratory time and wheezing or crackles on auscultation. Laboratory confirmation of viral etiology included detection of viral antigens by immunofluorescence or amplification of specific nucleic acid sequences by real-time polymerase chain reaction in samples of nasopharyngeal aspirates collected at hospital admission. Specimens were routinely tested for RSV, metapneumovirus, influenza viruses A and B, parainfluenza viruses 1, 2 and 3, and adenovirus. Patients with a clinical diagnosis of ALRI, with negative viral detection in respiratory samples, were excluded.

Demographic, clinical, and outcome data were collected from patients' health records. Shock was diagnosed when there were signs of poor tissue perfusion, including altered mental status, cold extremities with capillary refill greater than 2 seconds, or warm extremities with capillary refill less than 1 second, and reduced diuresis (<1 ml/kg/h).^[10] Patients were divided into 2 groups according to the disease severity classified by a numeric score adapted from Walsh et al.^[11] The score was obtained by attributing 1 point each for the presence of wheezing associated with upper respiratory symptoms, requirement for hospitalization, length of hospital stay longer than 5 days, requirement for oxygen, and requirement for oxygen for more than 5 days, and adding 2 points for need for ventilation support.^[12] Patients with scores between 0 and 4 were considered to have moderate disease, while those with scores between 5 and 7 were categorized as having severe disease.

2.1. Statistical analysis

Analysis was made using SAS 9.4 (SAS Institute Inc, Cary, NC). Data were expressed as median (range) or absolute frequency (%). The sample size was defined based on the number of hospital

admissions of patients with ALRI with positive viral detection during the study period. Continuous variables were compared by Mann–Whitney *U* test, and categorical variables were compared by Fisher exact test. To identify risk factors for disease severity and mortality, relative risks (RR) and 95% confidence intervals (CI) were obtained after adjusting log-binomial regression models. Initially, simple log-binomial regression models were fitted, resulting in crude RRs. Subsequently, the adjustment of multiple log-binomial regression models resulted in adjusted RRs, considering age and gender as covariates. A 5% significance level was considered in all analyses.

3. Results

Over the study period, 264 children aged 0 to 5 years old were admitted to the Emergency and Pediatric Unit of the Hospital and Emergency Room Delphina Rinaldi Abdel Aziz, in Manaus, with ALRI. The study population comprised 146 patients who had at least 1 respiratory virus detected in respiratory specimens; 118 patients with negative viral detection in nasopharyngeal aspirates were excluded. The median age of the study population was 7 months; 88.3% of patients were less than 2 years old. The most frequently detected virus was RSV (70.5%), followed by metapneumovirus (16.4%), influenza virus (11.6%), parainfluenza virus (7.5%), and adenovirus (2.7%). Co-detections were found in 12 (8.2%) patients: RSV + influenza B ($n=6$), RSV + influenza A ($n=3$), RSV + parainfluenza 2 ($n=1$), metapneumovirus + parainfluenza 3 ($n=1$), and metapneumovirus + parainfluenza 3 + adenovirus ($n=1$). Twenty-eight children (19.2%) had comorbidities. The most common underlying diseases were cerebral palsy ($n=10$), asthma ($n=8$), and congenital heart disease ($n=5$). The severity score ranged from 2 to 7 (median 5). Sixty-six (45.2%) patients with a severity score ≤ 4 were grouped into the moderate disease group and 80 (54.8%) patients with a severity score 5 to 7 were grouped into the severe disease group. Patients with severe disease had higher heart rate and lower oxygen saturation at hospital admission, longer duration of mechanical ventilation, and longer hospital length of stay compared with those with moderate disease (Table 1).

The distribution of severe and moderate ALRI cases and the virus types according to the months of the year are shown in Figures 1 and 2. A greater number of cases of viral ALRI were observed in the rainiest months (Fig. 3), particularly between April and June.

Twelve children (8.2%) died, all of them with severe disease. Their median age was 3.5 months (range 0.6–32 months); 10 (83.3%) patients were less than or equal to 12 months old. Four patients (33.3%) who died had comorbidities: cerebral palsy ($n=3$) and congenital heart disease ($n=1$). Eleven patients (91.6%) had a single virus type detected in their respiratory samples (RSV in 9 patients, parainfluenza virus 3 in 1 patient, and metapneumovirus in 1 patient), and 1 patient had dual viral co-detection (RSV + influenza virus A). Ten patients (83%) had shock and required inotropes and/or vasopressors. The causes of death were respiratory failure ($n=4$) and septic shock ($n=8$).

The results of log-binomial regression analyses showed that the presence of viral co-detection was an independent risk factor for disease severity (Table 2). The presence of shock and the use of inotropes and/or vasopressors were risk factors for death (Table 3).

Table 1
Demographic and clinical characteristics.

Characteristics	All (n=146)	Moderate disease group (n=66)	Severe disease group (n=80)
Age (mo)	7 (0.2–66)	8.5 (0.2–66)	6.5 (0.4–47)
Male gender	92 (63)	40 (60.6)	52 (65)
Respiratory rate at hospital admission (breaths/min)	62 (25–98)	62 (28–95)	63 (25–98)
Heart rate at hospital admission (beats/min)	163 (104–223)	158 (104–219)	168 (105–223)*
O ₂ saturation at hospital admission (%)	90 (32–100)	92 (34–100)	89 (32–99)*
Presence of comorbidity	28 (19.2)	12 (18.2)	16 (20)
Virus type			
Respiratory syncytial virus	103 (70.5)	48 (72.7)	55 (68.7)
Metapneumovirus	24 (16.4)	9 (13.6)	15 (18.7)
Influenza virus A	4 (2.7)	0 (0)	4 (5)
Influenza virus B	13 (8.9)	6 (9.1)	7 (10.6)
Parainfluenza virus 1	1 (0.7)	0 (0)	1 (1.25)
Parainfluenza virus 2	3 (2)	1 (1.5)	2 (2.5)
Parainfluenza virus 3	7 (4.7)	2 (3)	5 (6.3)
Adenovirus	4 (2.7)	2 (3)	2 (2.5)
Viral co-detection	12 (8.2)	2 (3)	10 (12.5)
Duration of mechanical ventilation (d)	0 (0–57)	0 (0–5)	4 (0–57)*
Length of hospital stay (d)	5 (0.1–60)	5 (1–9)	7 (0.1–60)*
Death	12 (8.2)	0 (0)	12 (15)*

Data were expressed as median (range) or n (%).
* P < .05 for comparison between moderate disease versus severe disease groups.

4. Discussion

We found that a viral etiology was confirmed in 146 of 264 (55.3%) young children with ALRI admitted to a general hospital in 2017 to 2018, in Manaus. RSV was the most frequently detected virus (70.5%), followed by metapneumovirus (16.4%). A greater number of cases were observed in the rainiest months, although viral activity was seen all over the year (Figs. 1 and 2). While in regions with temperate climate RSV and influenza peaks occur in the winter months, peak timing is more diverse in tropical areas,^[13] where viral circulation occurs mainly in the rainy season, with residual activity throughout the year,^[3] which agree with our findings. In our study, the highest positivity for influenza and RSV was observed in April and May 2017, and

May and June 2018, respectively (Fig. 2). From 2005 to 2012, the peak of RSV activity in the North of Brazil occurred in April.^[15] In Belem, capital of state of Para, in the North of Brazil, data collected from 1991 to 2007 showed that the peak of influenza activity occurred in March and April.^[14] In our study, we observed that the RSV peak lasted 3 months and influenza peak lasted 2 months. Also, peak influenza activity preceded peak RSV activity by 1 month (Fig. 2). Most regions of the world experience influenza and RSV activity over 3 to 5 months, with peak timing of both viruses differing by 1 to 2.6 months.^[13] We also noted that there were more cases of viral ALRI in Manaus in the first semester of 2017 compared with the same period of the year in 2018, which was temporarily associated with a measles outbreak

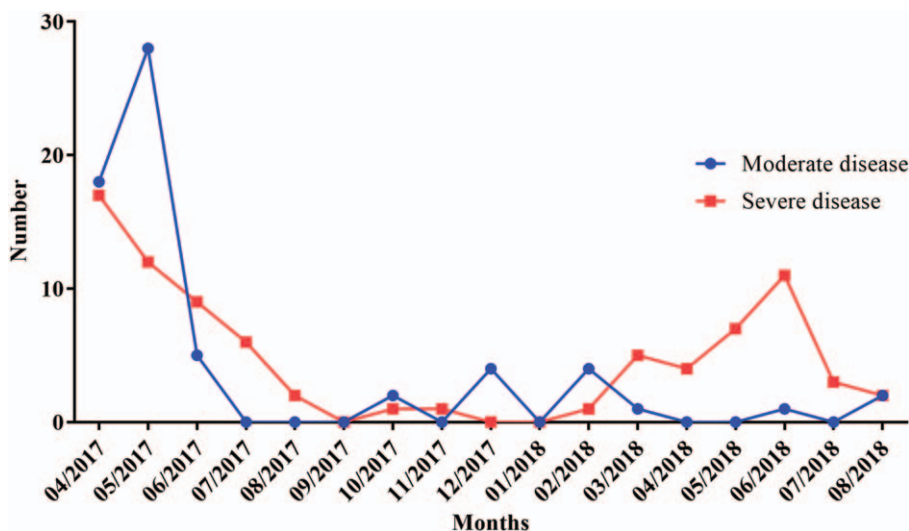


Figure 1. Distribution of severe and moderate cases of acute lower respiratory infection according to the months of the year in Manaus.

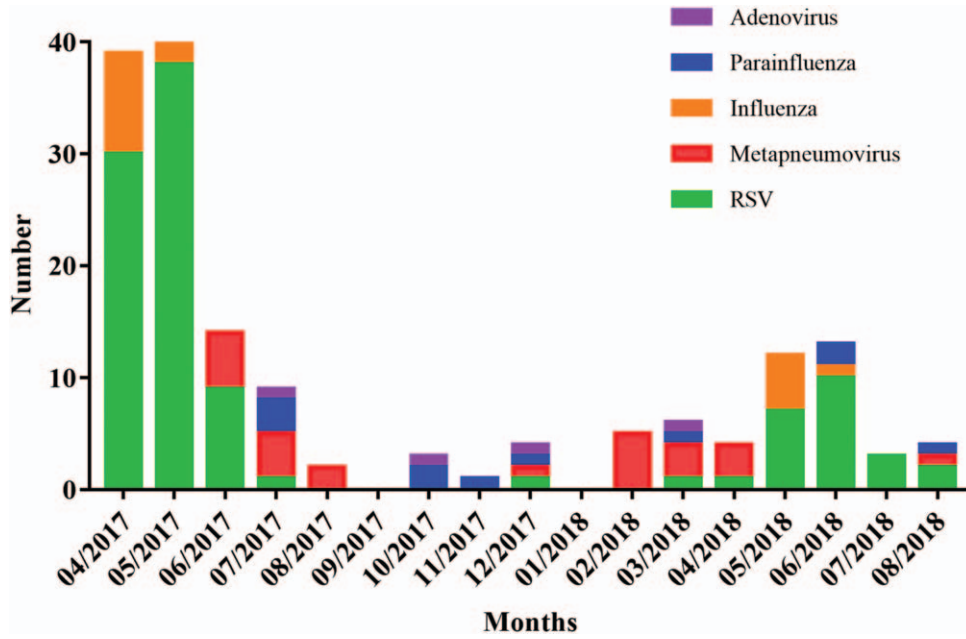


Figure 2. Distribution of virus types according to the months of the year in Manaus.

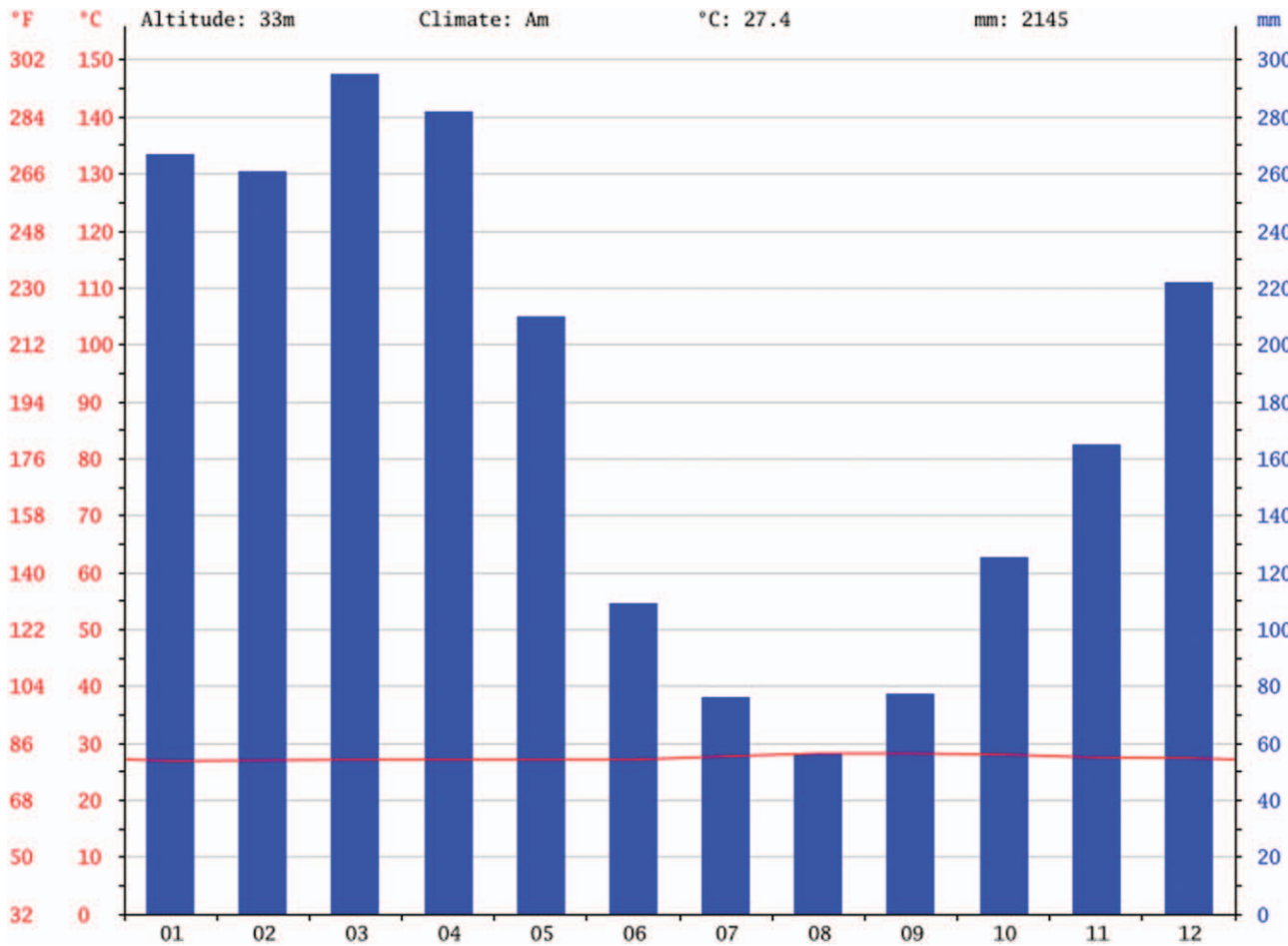


Figure 3. Rainfall index and temperature throughout the year in Manaus. Source: <https://pt.climate-data.org/americas-do-sul/brasil/amazonas/manaus-882/#climate-graph>. [Accessed October 1, 2019].

Table 2**Risk factors for disease severity.**

Variable	Moderate	Severe	Crude RR (95% CI)	Adjusted RR (95% CI)
Age				
≤ 12 mo	25 (39.68)	38 (60.32)	1.19 (0.89; 1.60)	*
> 12 mo	41 (49.40)	42 (50.60)	reference	
Gender				
Male	40 (43.48)	52 (56.52)	1.09 (0.80; 1.49)	*
Female	26 (48.15)	28 (51.85)	reference	
Respiratory syncytial virus				
Yes	48 (46.60)	55 (53.40)	0.92 (0.67; 1.25)	0.80 (0.57; 1.14)
No	18 (41.86)	25 (58.14)	reference	reference
Metapneumovirus				
Yes	9 (37.50)	15 (62.50)	1.17 (0.82; 1.67)	1.37 (0.91; 2.08)
No	57 (46.72)	65 (53.28)	reference	reference
Influenza				
Yes	6 (35.29)	11 (64.71)	1.21 (0.82; 1.78)	1.18 (0.80; 1.77)
No	60 (46.51)	69 (53.49)	reference	reference
Parainfluenza				
Yes	3 (27.27)	8 (72.73)	1.36 (0.91; 2.02)	1.58 (1.02; 2.44)
No	63 (46.67)	72 (53.33)	reference	reference
Adenovirus				
Yes	2 (50.00)	2 (50.00)	0.91 (0.33; 2.45)	0.99 (0.37; 2.72)
No	64 (45.07)	78 (54.93)	reference	reference
Viral co-detection				
Yes	2 (16.67)	10 (83.33)	1.59 (1.18; 2.15)	1.53 (1.10; 2.14)
No	64 (47.76)	70 (52.24)	reference	reference
Comorbidity				
Yes	12 (42.86)	16 (57.14)	1.05 (0.73; 1.51)	1.22 (0.80; 1.87)
No	54 (45.76)	64 (54.24)	reference	reference

Data are expressed as frequency (%). Adjusted relative risk considered age and gender as covariates.

CI = confidence interval, RR = relative risk.

* Adjusted relative risk considered age and gender as covariates.

Table 3**Risk factors for death.**

Variable	Survival	Death	Crude RR (95% CI)	Adjusted RR (95% CI)
Age				
≤ 12 mo	86 (89.58)	10 (10.42)	1.84 (0.61; 5.54)	*
> 12 mo	48 (96.00)	2 (4.00)	reference	
Gender				
Male	87 (94.57)	5 (5.43)	0.41 (0.14; 1.26)	*
Female	47 (87.04)	7 (12.96)	reference	
respiratory syncytial virus				
Yes	93 (90.29)	10 (9.71)	2.08 (0.48; 9.13)	1.83 (0.38; 8.78)
No	41 (95.35)	2 (4.65)	reference	reference
Metapneumovirus				
Yes	23 (95.83)	1 (4.17)	0.46 (0.06; 3.41)	0.51 (0.07; 3.80)
No	111 (90.98)	11 (9.02)	reference	reference
Influenza virus				
Yes	16 (94.12)	1 (5.88)	0.68 (0.09; 5.01)	0.76 (0.10; 5.47)
No	118 (91.47)	11 (8.53)	reference	reference
Parainfluenza				
Yes	10 (90.91)	1 (9.09)	1.11 (0.15; 7.86)	1.18 (0.17; 8.24)
No	124 (91.85)	11 (8.15)	reference	reference
Adenovirus				
Yes	4 (100)	0 (0)	†	†
No	130 (91.55)	12 (8.45)		
Presence of comorbidity				
Yes	24 (85.71)	4 (14.29)	2.11 (0.68; 6.51)	4.75 (0.86; 26.20)
No	110 (93.22)	8 (6.78)	reference	reference
Presence of shock				
Yes	37 (78.72)	10 (21.28)	10.53 (2.40; 46.17)	10.09 (2.31; 43.90)
No	97 (97.98)	2 (2.02)	reference	reference
Use of vasoactive drugs				
Yes	36 (78.26)	10 (21.74)	10.86 (2.48; 47.63)	10.63 (2.44; 46.31)
No	98 (98.00)	2 (2.00)	reference	reference

Data are expressed as number (%). Adjusted relative risk considered age and gender as covariates.

* Adjusted relative risk considered age and gender as covariates.

† Not possible to calculate because n=0.

in the city in 2018. Biennial cycles of RSV activity have also been reported in the Northern Hemisphere.^[13]

In the present study, ~55% of children with ALRI had severe disease (severity scores 5–7). We found that viral co-detection was an independent risk factor for disease severity. Also, we observed that parainfluenza virus became a risk factor for disease severity only after adjustment for age and gender, which may indicate interaction among the variables. The presence of comorbidities was not associated with disease severity, in our study. In contrast, a previous study from Southeast Brazil showed that viral co-detection was not a risk factor for disease severity defined as need for pediatric intensive care unit admission.^[15] In addition, a systematic review and meta-analysis showed that respiratory viral coinfection was not associated with need of hospitalization, need of admission to the intensive care unit, mechanical ventilation, or death.^[16] However, a recent study showed that a respiratory coinfection with RSV and the presence of a chronic respiratory disease, including asthma, were independent risk factors for severe disease in children aged less than or equal to 2 years.^[17]

In our study, 8.2% of the patients died. This mortality rate is much higher than the rate observed in Southeast Brazil (3.4%)^[15] and those reported from developed countries (<1%).^[18] Although co-detection was associated with disease severity in our study population, 11 of 12 children who died had a single virus detected; only 1 had a viral co-detection (RSV + influenza A). In addition, we found that the main cause of death was septic shock, and the risk factors for death identified in our study were the presence of shock and the requirement for inotropes and/or vasopressors. Indeed, a study performed in Argentina found that sepsis was a risk factor for death in infants with RSV ALRI.^[19] Also, sepsis was the main cause of death in children with RSV infection hospitalized in the United States.^[18] Most children (83.3%) who died in our study were less than or equal to 12 months old. Accordingly, the majority of deaths associated with RSV infection have been reported in infants aged less than or equal to 12 months.^[18] We observed that comorbidities were present in one-third of our patients who died. However, more than two-thirds of RSV-associated deaths occurred in children with chronic complex conditions in a developed world environment.^[18]

The strength of this study is that we present original data on the epidemiology, seasonality, clinical characteristics, and outcome of pediatric ALRI of viral etiology from the largest city of the Brazilian Amazon region. The limitations of our study include its retrospective nature, with possible loss of information. Also, as this is a single-center study, generalizability of our data may be limited. However, we showed data from a unit that is sentinel for respiratory viruses, which can be extrapolated to other centers in the region.

In conclusion, a greater number of patients with viral ALRI were observed in the rainiest months in Manaus. RSV was the most frequently detected virus. The presence of viral coinfection was an independent risk factor for disease severity. Mortality rate was high (8.2%). The presence of shock and the requirement for inotropes and/or vasopressors were risk factors for death.

Author contributions

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