Background: Respiratory syncytial virus is the leading cause of acute lower respiratory infection in children. We aimed to describe the clinical-epidemiologic pattern and risk factors for mortality associated with RSV infection.

Methods: This is a prospective, cross-sectional study of acute lower respiratory infection in children admitted to the Children’s Hospital during 2000 to 2017. Viral diagnosis was made by fluorescent antibody techniques or real-time-polymerase chain reaction. We compared clinical-epidemiologic characteristics of RSV infection in nonfatal versus fatal cases. Multiple logistic regression was used to identify independent predictors of mortality.

Results: Of 15,451 patients with acute lower respiratory infection, 13,033 were tested for respiratory viruses and 5831 (45%) were positive: RSV 81.3% (4738), influenza 7.6% (440), parainfluenza 6.9% (402) and adenovirus 4.3% (251). RSV had a seasonal epidemic pattern coinciding with months of lowest average temperature. RSV cases show a case fatality rate of 1.7% (82/4687). Fatal cases had a higher proportion of prematurity (P < 0.01), perinatal respiratory history (P < 0.01), malnourishment (P < 0.01), congenital heart disease (P < 0.01), chronic neurologic disease (P < 0.01) and pneumonia at clinical presentation (P = 0.014). No significant difference between genders was observed. Most deaths occurred among children who had complications: respiratory distress (80.5%), nosocomial infections (45.7%), sepsis (31.7%) and atelectasis (13.4%). Independent predictors of RSV mortality were moderate-to-severe malnourishment, odds ratio (OR): 3.69 [95% confidence interval (CI): 1.98–6.87; P < 0.0001]; chronic neurologic disease, OR: 4.18 (95% CI: 2.39–7.32; P < 0.0001); and congenital heart disease, OR: 4.14 (95% CI: 2.39–7.32; P < 0.0001); and the age less than 6 months, OR: 1.99 (95% CI: 1.24–3.18; P = 0.004).

Conclusions: RSV showed an epidemic pattern affecting mostly young children. Malnourishment, chronic neurologic disease, congenital heart disease and the age less than 6 months were the independent risk factors for RSV mortality.

Key Words: respiratory syncytial virus, case fatality rate, bronchiolitis, pediatrics, epidemiology

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Acute lower respiratory infection (ALRI) is the most common reason for outpatient visits, school absenteeism and hospitalizations among children.1,2 In Argentina, it is an important cause of mortality as well as hospital admissions during the winter months in all age groups, particularly in children under 5 years of age and adults older than 65 years of age. Most of these infections are viral in origin generating significant morbidity and mortality in individuals with risk factors.3 Respiratory syncytial virus (RSV) is the main cause of bronchiolitis and pneumonia in infants and young children worldwide.4 Primary infection usually occurs in young children 6 weeks to 2 years of age5–9 and is a leading cause of death in infants under 6 months of age. Mortality rates are higher in developing countries than in developed countries, particularly in children less than 5 years of age.10 RSV is spread through direct or indirect contact with nasal and oral secretions of infected individuals. Children are primarily responsible for transmission because they have higher viral loads than adults.11 Reinfections can occur in any stage of life and are usually mild or asymptomatic in adults, but can cause severe disease in the elderly.12 RSV is also an important pathogen in other risk groups such as preterm infants and children with bronchopulmonary dysplasia or hemodynamically unstable congenital heart disease (CHD).13 Worldwide, this virus is responsible for 30 million episodes of ALRI and for more than 50,000 deaths per year in children under 5 years of age.14 A recent publication on global RSV mortality, which included data from our hospital, estimated that the virus causes one-third of all deaths in children less than 1 year of age.15 In Argentina, based on information provided by the National Laboratory-based Surveillance System (SNVS-SIVILA), of 30,949 positive respiratory samples collected in 2017 between epidemiologic weeks 1 and 44, RSV was the main pathogen found in 61.4% (n = 18,738) of samples, followed by influenza viruses (IF) 20.8% (n = 6349).16

Given the global burden of RSV disease in children, the aim of this study was to describe the clinical and epidemiologic characteristics of RSV-ALRI and estimate case fatality risk factors in patients admitted to our hospital.

METHODS

We conducted a prospective, cross-sectional study. Patients with ALRI acquired in the community admitted to the Ricardo Gutierrez Children’s Hospital, Buenos Aires, between 2000 and 2017 were identified through an active surveillance program.

Population

All children less than 18 years of age hospitalized for ALRI acquired in the community, namely those presenting bronchiolitis or pneumonia, were included. Both definitions met World Health Organization criteria for ALRI.17

Exclusion Criteria

Patients admitted for other causes who developed ALRI during hospitalization were excluded.

Data Collection

Data were collected using a specific case-report form and included date of admission, demographics (age, sex, city of residence), clinical presentation (bronchiolitis, pneumonia), previous
hospitalizations for respiratory diseases, readmission within the same episode, co-morbidities, history of close contact with individuals presenting acute respiratory symptoms of probable viral origin (runny nose, cough and/or fever), perinatal respiratory disorders, complications during hospitalization, treatment, length of stay and outcome (discharged home, transferred to another hospital or died). Comorbidities included chronic or recurrent respiratory disease, moderate-to-severe malnourishment, CHD, genetic or neurologic diseases and immunodeficiency.

Chronic or recurrent respiratory disease was also reported, namely, recurrent obstructive bronchitis or asthma (2 or more episodes of bronchial-obstruction), gastroesophageal reflux disease, cystic fibrosis, bronchopulmonary dysplasia, recurrent laryngitis and pneumonia, as were in-hospital complications such as nosocomial infections, sepsis, persistent atelectasis, pneumothorax, pleural effusion, pulmonary bullae, lung abscesses, ear infections, diarrhea, seizures and meningitis.

Nosocomial infection was defined as exacerbation of respiratory symptoms not present at admission (even if incubation was a possibility), diagnosed in patients hospitalized for ≥48 hours, presenting fever, increased oxygen requirement or changes in radiologic pattern.

Diagnostic Methods
World Health Organization guidelines were used for clinical and radiologic diagnosis of bronchiolitis and pneumonia. Viral diagnosis was performed in all cases by indirect fluorescent antibody testing on nasopharyngeal specimens. After real-time polymerase chain reaction assay became available in 2009, it has been used together with indirect fluorescent antibody test to detect RSV, IF A and B, parainfluenza and adenovirus. Commercially available kits were used in all cases.

Statistical Analysis
Categorical variables were analyzed using the χ2 test with Yates correction. We used the Wilcoxon test for median age comparison. Odds ratio with 95% confidence interval was used for association analysis; a bivariate analysis was performed initially to identify significant associations, and multivariate logistic regression was subsequently carried out to establish independent predictors of case fatality. P values <0.05 were considered statistically significant. STATA/SE version 13 (StatCorp LLC, TX) was used for the analysis.

Multivariate Analysis
A logistic regression model was constructed to identify the predictors of mortality by RSV. The variables with significant association with death in the crude analysis and/or those considered clinically relevant were added one at a time in the multivariate model, and only those significantly associated with the outcome in the multivariable context (Wald test) were retained in the final model. We checked the changes on the coefficients to find confounding variables.

Calibration and Discrimination
The calibration and discrimination of the model were evaluated with the Hosmer–Lemeshow goodness-of-fit test and the area under the receiver operating characteristic curve.

Seasonality
RSV season onset and offset were calculated as described by Panazzo et al in 2007.

Ethical Considerations
Privacy rights of patients were observed in all cases in accordance with the World Medical Association Declaration of Helsinki International Code of Ethics for experiments involving humans. Patient’s informed consent is not applicable in this study because data were obtained from a routine epidemiologic surveillance activity included in the framework of Argentinean Law 15465/60. The study was approved by the Ethics and Research Committees of the Ricardo Gutierrez Children’s Hospital. This study will not affect human rights, nor will it cause damage to the environment, animals and/or future generations.

![FIGURE 1. RSV seasonal pattern, 2000 to 2017.](image-url)
RESULTS

A total of 15,451 patients were admitted for ALRI acquired in the community over a period of 18 years, from them 13,033 (84%) children were tested for respiratory viruses and 5831 (45%) had positive results (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/D397).

RSV predominated throughout the entire study period (4738, 81.3%), followed by IF (440, 7.6%), parainfluenza (402, 6.9%) and adenovirus (251, 4.3%).

RSV had a seasonal epidemic pattern (viral activity onset and offset 18 and 33 epidemiologic weeks, respectively) coinciding with months of lowest median temperature and highest relative humidity (May to July). (Figure 1)

In our study population, there was a slight predominance of boys (56.5%), and the median age was 7 months (interquartile range: 2–12); almost two-thirds were infants less than 12 months and 42% less than 6 months of age.

The distribution of the different clinical and epidemiologic characteristics of patients with RSV disease and their relationship with the outcome (death) is expressed in Table 1, comparing non-fatal and fatal cases.

RSV case fatality rate was 1.7% (82/4687).

The annual mortality rate distribution was not stable over the study period with the highest mortality in the year 2002. (Figure 2)

In fatal cases, the most frequent complications were respiratory distress (80.5%), nosocomial infections (45.7%), sepsis (31.7%) and atelectasis (13.4%) (Table 2).

| TABLE 1. Characteristics of Patients With RSV Disease Comparing Nonfatal and Fatal Cases. |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Variables                                        | Total RSV cases, n = 4738                        | Nonfatal RSV cases, n = 4605                     | Fatal RSV cases, n = 82                          |
| Age, n (%) Median (mo); IQR                       | Median (mo); IQR                                 | Median (mo); IQR                                 | Median (mo); IQR                                 |
| <6 mo                                            | 2022 (42.7)                                     | 1961 (42.6)                                     | 62 (51.2)                                       |
| <12 mo                                           | 3505 (74)                                       | 3379 (73.5)                                     | 66 (76.8)                                       |
| Sex (boys), n (%)                                | 2679 (56.5)                                     | 2578 (56.6)                                     | 41 (50)                                         |
| Prematurity, n (%)                               | 655 (13.85)                                     | 629 (13.7)                                      | 20 (24.4)                                       |
| Neonatal respiratory history, n (%)              | 527 (11.15)                                     | 500 (10.9)                                      | 21 (25.6)                                       |
| Immunosuppression, n (%)                         | 87 (1.84)                                       | 83 (1.8)                                        | 4 (4.9)                                         |
| Malnourishment, n (%)                            | 218 (4.82)                                      | 197 (4.3)                                       | 11 (13.5)                                       |
| Readmission for same episode, n (%)              | 1246 (26.4)                                     | 1193 (26)                                       | 53 (65.3)                                       |
| Pneumonia as clinical presentation, n (%)        | 153 (3.24)                                      | 141 (3.1)                                       | 7 (8.5)                                         |
| Comorbidities n (%)                              | 1832 (38.7)                                     | 1772 (38.5)                                     | 56 (68.5)                                       |
| Recurrent obstructive bronchitis                  | 1339 (28.27)                                    | 1306 (28.4)                                     | 33 (40.3)                                       |
| Congenital heart disease                         | 258 (5.4)                                       | 253 (5.7)                                       | 15 (18.3)                                       |
| Chronic neurologic disease                       | 198 (4.18)                                      | 180 (3.9)                                       | 18 (22.0)                                       |

FIGURE 2. Annual RSV cases and mortality rate distribution, 2000 to 2017.
Independent predictors of RSV mortality were moderate-to-severe malnourishment, chronic neurologic disease, CHD and the age less than 6 months (Table 3). The final model achieved good calibration ($P^{2}=0.85$) and discrimination with an area under the receiver operating characteristic curve of 0.712.

**DISCUSSION**

In this study, we evaluated the characteristics and outcome of patients with RSV-ALRI based on active surveillance and systematic data collection over a period of 18 years. Active surveillance of ALRI is crucial for rapid detection of increase in number of cases, identification of high risk groups and to determine the frequency, distribution and characteristics of disease-causing agents.19,20

RSV was the most frequent pathogen found in positive samples from the patients included in our center (81.3%) and that incidence was highest in infants less than 1 year of age (74% of cases). These results are similar to those of other epidemiologic studies carried out in the region.21-23

RSV circulation showed a seasonal epidemic pattern as seen in temperate climate regions. Onset and offset of viral activity were registered during epidemiologic weeks 18 and 33, respectively, coinciding with months of lowest median temperature and highest relative humidity in Argentina (May–July).21 Kamigaki et al found that mean temperature and specific humidity were also positively associated with influenza and RSV at Philippine sites.24 In addition, Meerhoff et al, reported that the combination of both (temperature and humidity) contribute more to RSV activity than each factor independently.25 Furthermore, Walton et al showed that real-time weather forecasts have the potential to predict RSV outbreaks.26 Although we found a similar epidemic seasonal pattern, a proper time-series analysis is needed to draw robust conclusions as mentioned by the authors.

Around the world, 1%-3% of healthy children are hospitalized after RSV respiratory infections during the first year of life.23,27 In our study, although most patients were healthy children younger than 1 year of age, patients with underlying conditions such as prematurity, CHD, malnutrition and chronic neurologic disease showed higher rates of mortality.28,29 In a meta-analysis on incidence and mortality of RSV infections in children, Stein et al concluded that the virus was an important cause of hospitalization and mortality, and that gestational age was a critical determinant of disease severity in the first year of life.30 Unfortunately, as we have not recorded gestational age data in the whole series, we could not include this variable in the analysis.

Although being a boy was found to be a risk factor in some studies,31 we did not observe significant gender differences in our population. Regarding CHD, a 20-year systematic review was undertaken across studies reporting data for hospital visits/admissions for RSV infection among children with CHD, concluding that young children with CHD have a significant risk for RSV mortality.32 This risk is specially for severe disease and hospitalization and, in some instances, may require admission to the intensive care unit, supplemental oxygen therapy and prolonged mechanical ventilation.33,34

In a study based on national data sets, Byington et al also found children with complex chronic conditions accounted for most RSV-associated deaths.35 Scheltema et al also found that more than half of all children included in the RSV Gold RSV-associated study had a weight for age of less than –2 standard deviations.36 Garcia et al describe several factors that independently correlated with the severity of illness as trisomy 21, lower weights on admission, neuromuscular disorders.28

Death from RSV infection was more common in patients requiring mechanical ventilation, longer hospital length of stay, presenting sepsis and atelectasis, in line with other regional studies.36,37 Most deaths were associated with complex chronic conditions or acute disorders such as sepsis or respiratory failure. Moreover, many children have more than 1 complication during hospitalization.

Case fatality rate was 1.7% (82/4687) similar to values reported by Nair et al who found rates of 0.3% and 2.1% in children under 5 years and 0.7% and 2.1% in infants (<1 year of age) for industrialized and developing countries, respectively.38

One of the strengths of this study lies in its methodologic design, a prospective active surveillance based on robust epidemiologic data, a sample large enough that allows statistical robust conclusions and individual data of each patient. The model showed good calibration and discriminative capacity in the studied population.

In addition, indirect immunofluorescence test is recommended for rapid detection and diagnosis of respiratory viruses. This method is widely used because it is a simple, quick, low-cost test with high specificity and sensitivity detecting viruses that usually cause ALRI, namely RSV, IF, parainfluenza and adenovirus.39-41

As a limitation, this study was conducted in a single tertiary hospital, so the complexity of our patients makes it difficult to extrapolate results to the general population. The high proportion of comorbidities in our patients perhaps overestimates the more

**TABLE 2. Complications in Patients With RSV-ALRI**

| Complications                  | Total RSV cases, n = 4687 | Nonfatal cases, n = 4605 | Fatal cases, n = 82 | P    |
|-------------------------------|---------------------------|-------------------------|---------------------|------|
| Total, n (%)                  | 5121*                     | 981 (21.3)              | 77 (93.9)           | <0.01|
| Respiratory distress          | 300 (6.8)                 | 66 (80.5)               | 11 (13.4)           | <0.01|
| Atlectasia                    | 168 (3.6)                 | 37 (45.7)               | 26 (31.7)           | <0.01|
| Sepsis                        | 149 (3.18)                | 251 (5.6)               | 26 (31.7)           | <0.01|
| Nosocomial infection          | 288 (6.3)                 | 7 (5–10)                | 17 (8–31)           | <0.01|
| Length of hospital stay       |                           |                         |                     |      |
| median (days); IQR            |                           |                         |                     |      |

IQR indicates interquartile range.

*Many children have more than 1 complication during hospitalization.

**TABLE 3. Results of the Final Model of Multiple Logistic Regression: Independent Predictors for RSV Mortality**

| Variables                    | OR  | 95% CI          | P    |
|------------------------------|-----|-----------------|------|
| Malnourishment               | 3.69| 1.98–6.67       | <0.0001|
| Chronic neurologic disease   | 4.14| 2.12–8.08       | <0.0001|
| Congenital heart disease     | 4.18| 2.39–7.32       | <0.0001|
| Age less than 6 mo           | 1.99| 1.24–3.18       | 0.004 |

OR indicates odds ratio; CI, confidence interval.
severe RSV symptoms when we analyzed complications. Moreo-
ver, hospital case-fatality ratios cannot be translated to population-
based mortality.

Around 60 different strategies to prevent RSV infection are
being developed involving candidate vaccines and human mono-
clonal antibodies, of which 16 are currently undergoing phase
I–III studies.42 The data afforded by this epidemiologic study and
other similar investigations will be crucial to assess the effective-
ness and impact of new RSV vaccines, as well as for establishing
age-specific immunization strategies and harmonizing health care
policies.43

In conclusion, multiple independent characteristics have
been identified, which significantly increase the risk of death in the
population studied.

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