ORIGINAL ARTICLE

Mortality due to Respiratory Syncytial Virus
Burden and Risk Factors

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Abstract

Rationale: Respiratory syncytial virus (RSV) is the most frequent cause of hospitalization and an important cause of death in infants in the developing world. The relative contribution of social, biologic, and clinical risk factors to RSV mortality in low-income regions is unclear.

Objectives: To determine the burden and risk factors for mortality due to RSV in a low-income population of 84,840 infants.

Methods: This was a prospective, population-based, cross-sectional, multicenter study conducted between 2011 and 2013. Hospitalizations and deaths due to severe lower respiratory tract illness (LRTI) were recorded during the RSV season. All-cause hospital deaths and community deaths were monitored. Risk factors for respiratory failure (RF) and mortality due to RSV were assessed using a hierarchical, logistic regression model.

Measurements and Main Results: A total of 2,588 (65.5%) infants with severe LRTI were infected with RSV. A total of 157 infants (148 postneonatal) experienced RF or died with RSV. RSV LRTI accounted for 57% fatal LRTI tested for the virus. A diagnosis of sepsis (odds ratio [OR], 17.03; 95% confidence interval [CI], 13.14–21.16 for RF) (OR, 119.39; 95% CI, 50.98–273.34 for death) and pneumothorax (OR, 17.15; 95% CI, 13.07–21.01 for RF) (OR, 65.49; 95% CI, 28.90–139.17 for death) were the main determinants of poor outcomes.

Conclusions: RSV was the most frequent cause of mortality in low-income postneonatal infants. RF and death due to RSV LRTI, almost exclusively associated with prematurity and cardiopulmonary diseases in industrialized countries, primarily affect term infants in a developing world environment. Poor outcomes at hospitals are frequent and associated with the cooccurrence of bacterial sepsis and clinically significant pneumothoraxes.

Keywords: respiratory syncytial virus; mortality; pneumothorax; bacterial superinfections

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At a Glance Commentary

Scientific Knowledge on the Subject: Respiratory syncytial virus (RSV) lower respiratory tract illness (LRTI) is estimated to cause between 66,000 and 239,000 yearly deaths in children younger than the age of 5. Ninety-nine percent of these fatalities occur in developing countries with limited viral diagnostic capacity. Information about deaths stems from industrialized countries, where RSV mortality associates with chronic comorbidities. The relative contribution of factors characteristic of developing nations, including poor access to health care, biologic handicaps, bacterial infections, and/or gaps in supportive care, is unknown.

What This Study Adds to the Field: RSV LRTI is a leading cause of postneonatal infant mortality. In contrast to data from industrialized countries, RSV death primarily occurred in previously healthy term infants in association with bacterial sepsis and clinically significant pneumothoraxes. The role of age and typical risk factors for severe LRTI was less ostensible. Postneonatal infant community deaths peaked during the RSV season, and their age distribution was similar to that observed in hospitalized infants, suggesting a significant role for RSV in community mortality. Public health efforts should address gaps in hospital care in developing countries, if RSV mortality and that associated with other respiratory viruses is to be tamed.

Lower respiratory tract illness (LRTI) is the foremost preventable cause of childhood death and represented a major obstacle in achieving the United Nations Millennium Development Goal to reduce global mortality in children younger than 5 (1). LRTI due to respiratory syncytial virus (RSV) is the most frequent cause of hospitalization in infants in the world (2), with more than 3 million hospital admissions every year. The disease is estimated to cause between 66,000 and 239,000 yearly deaths in children younger than 5 (2, 3). Ninety-nine percent of these fatalities occur in developing countries, more precisely in low-income regions of middle-income countries (where 60% of deaths in children younger than 5 occur worldwide) (4). RSV remains the only major etiologic agent of LRTI mortality for which no vaccine is available.

Precisely defining the burden of fatal illness due to RSV has been challenging. Most fatalities occur in regions with limited RSV surveillance, which requires molecular diagnostic capabilities (2, 3, 5). In addition, in the absence of specific treatment, physicians may not prioritize obtaining samples for viral identification in critically ill patients. In fact, pediatricians, trying not to overburden grieving families, may also avoid suggesting postmortem cause of death ascertainment (6). Therefore, unless specifically designed to define the role of RSV in fatal infections, studies may underestimate RSV mortality. These limitations preclude a thorough characterization of risk factors associated with death due to RSV, which remain unclear. To date, the relative contribution of factors associated with poor access to health care, biologic handicaps, secondary bacterial infections, and/or gaps in supportive care in medical facilities of the developing world to infant mortality caused by RSV are not known. To add to this complex situation, infants can die at home from RSV LRTI. In the community, verbal autopsies have poor specificity for respiratory causes of death, and obtaining respiratory samples from fatal cases before burial is extremely challenging.

To contribute to the understanding of the burden of RSV mortality in low-income regions from developing countries, we conducted a prospective study from 2011 to 2013 in a catchment population of 28,280 infants in a low-resource area of Argentina. In this population, we specifically investigated the mortality burden caused by RSV and used a hierarchical model to determine the social, biologic, and health care risk factors associated with RSV respiratory failure (RF) and mortality in infancy.

Methods

Study Population

A prospective, population-based, cross-sectional, multicenter study aimed to determine the burden and risk factors for mortality due to RSV. The study was conducted between 2011 and 2013 in a catchment population of 28,280 infants younger than 12 months without medical insurance in the southern Region VI of the state of Buenos Aires in Argentina, and was nested in a larger program investigating severe respiratory infections in children younger than 2 years (7). Details of the program are described in previous reports studying the role of macronutrients and alcohol ingestion during pregnancy in childhood respiratory infections (7, 8).

Eligible patients were hospitalized due to severe LRTI in our network of public hospitals (7). Severe LRTI was defined as the sudden onset of cough, tachypnea, wheezing, retractions, and/or crackles with or without fever, and either an oxygen saturation less than 93% at rest when breathing room air or arriving to the emergency room receiving oxygen supplementation due to acute symptoms. Oxygen supplementation in our network was provided by nasal cannula, mask, continuous positive airway pressure, or mechanical ventilation. The institutional review boards at each participating hospital, the state of Buenos Aires, and Vanderbilt University approved the study. Informed consent was obtained from all participating parents or guardians.

Information on socioeconomic and biologic risk factors was collected prospectively from all participants, using questionnaires. Follow-up questionnaires were used daily to collect data on clinical course until discharge or death. In fatal cases at the hospitals, medical records were reviewed to verify and/or obtain specific information. The number of infants dying of all causes at hospitals in the network was obtained through collaboration with the district authorities. Pneumonia and bronchiolitis were defined clinically based on physical examinations performed by the attending pediatrician. Chest radiograph was requested at the discretion of the attending physician.

For community deaths, a state program registered infant home fatalities and trained professionals performed verbal autopsies (30–90 d after death), based on a questionnaire and mortality classification system derived from the International

Statistical Classification of Disease and Related Health Problems, tenth revision from World Health Organization (9). Fatalities were identified at the time families requested death certificates, necessary for the performance of burials.

Viral Detection

Hospital surveillance for RSV LRTI is conducted year round by the state, independently from our program, using a direct fluorescence assay. We obtained nasopharyngeal secretions from infants with severe LRTI on admission to the hospitals during the RSV season (*see* definition below) and tested in duplicate by real-time reverse-transcriptase polymerase chain reaction for RSV as previously described (7, 10). The RSV season started every year on detection of two cases of severe RSV LRTI at 1 of the 12 participating institutions through the hospital's surveillance system. The season ended when no patients were admitted with RSV LRTI to 4 of the 12 participating hospitals during the same week (7). Additional laboratory tests were requested at physicians' discretion.

Statistical Analysis

The estimated census population in the catchment area from 2011 to 2013 was used to calculate RSV incidence rates in infants hospitalized or dying with RSV LRTI. Chi-square and Student's *t* test were used to compare characteristics of infants where appropriate. For each outcome, we fit a three-level, hierarchical, logistic regression model that incorporated socioeconomic variables (level 1), biologic vulnerabilities (level 2), and clinical complications (level 3) (11). The logistic regression models were fitted in R 3.1.1 using the glm() function.

Results

RSV Disease and Death in Hospitalized Infants

A total of 4,045 infants were admitted with severe LRTI during three consecutive RSV seasons between 2011 and 2013; parents/guardians of 3,947 (97.6%) agreed to participate in this study. Of these infants, 2,588 (65.5%) were infected with RSV (Figure 1A). Hospitalizations due to RSV peaked during the second month of life and decreased in frequency thereafter (Figures 1A and 1B). Mean RSV hospitalization rate was 30.08 per 1,000 infants (95% confidence interval [CI], 27.28–32.90 per 1,000). Rates were double those observed in infants with RSV-negative LRTI at 14.59 per 1,000 infants (95% CI, 10.54–18.64 per 1,000).

The case fatality rate for infants due to RSV was 0.90% (95% CI, 0.44–1.35) versus 1.49% (95% CI, 0.51–2.47) for non-RSV LRTI. However, because of its high hospitalization rates, RSV was responsible for four of eight neonatal (0–28 d of life) and 20 of 37 (54%) postneonatal (29–364 d of life) infant deaths that presented with LRTIs and were tested for the virus between 2011 and 2013. An additional two neonate and eight postneonatal infant deaths due to LRTI were not tested for RSV (Figure 1C). Six infants in the latter, older group had a clinical diagnosis of bronchiolitis.

RSV was confirmed in 20 of 122 (16.4%) all-cause postneonatal infant deaths in our region, and was the most frequent cause of hospital mortality in a population with free access to *Haemophilus influenzae* type B and pneumococcal vaccines (12). Conversely, the virus was an infrequent cause of death (0.5%) among 745 dead neonates. Nineteen of all RSV deaths (79.2%) occurred in infants younger than or equal to age 6 months (Figure 1B).

Although our study was conducted in a low-income region, tertiary care facilities are available to the population (7). To estimate the potential impact of RSV on mortality in settings lacking tertiary care hospitals, we reasoned that infants in RF would have died if ventilator support were unavailable. Therefore, we grouped these postneonatal infants with postneonatal fatalities in a category of 148 subjects designated as RF. These patients represented 5.9% of postneonatal infants infected with RSV (Figure 1B). A total of 80.4% were younger than or equal to 6 months of age.

Risk Factors for Hospital RF or Death due to RSV

We next explored risk factors associated with postneonatal infant RF and mortality due to RSV in hospitalized patients. For this purpose, we conducted a hierarchical analysis of socioeconomic variables, biologic vulnerabilities, and clinical complications hypothesized to affect RF (20 RSV-positive deaths plus 128 survivors with mechanical ventilated RSV-positive hospitalized patients) in postneonatal infants with RSV LRTI (2,481 RSV-positive hospitalized children). This analysis informed a second, exploratory analysis focused only on 20 postneonatal infants dying from RSV LRTI.

Socioeconomic Factors in RSV Hospital-based RF

Incomplete immunizations for age, a long distance from home to a tertiary health care facility, and not seeking care before hospitalization during the episode of illness were selected to evaluate access to health care. Rates of incomplete immunizations for age, home distance from a tertiary health care facility, and seeking care during the episode under study did not significantly impact RSV mortality in this population (Table 1).

Adolescent mothers were frequent in our population (9.6%), as was the rate of mothers of late childbearing age (12.3%), and those with an incomplete primary education (13.6%). But none of these indicators of maternal vulnerability significantly increased the risk for RF due to RSV LRTI (Table 1).

Finally, we investigated the effect of living in precarious homes (Table 1). Sixty percent of families lived in homes with no sewage and 25% in homes made of tin or mud and/or lacking running water. In this context, house materials, running water, and crowding did not affect the risk for RSV RF. Conversely, lacking a sewage system and exposure to indoor smoke significantly associated with the endpoint (Table 1).

In summary, few socioeconomic variables significantly affected the odds of experiencing RF due to RSV LRTI in univariable analyses. Modeling these risk factors using logistic regression confirmed lacking a sewage system and exposure to indoor smoke as determinants of RSV RF (Table 2).

Biologic Vulnerability Affects RSV RF

At a second hierarchical level, we investigated biologic vulnerabilities that, potentially conditioned by socioeconomic factors, could lead to RSV RF (Table 1). Seventy percent of patients in the hospitalized population were younger than 6 months of age (Figure 1A), and 12% were born prematurely (Table 1). Both risk factors associated with poor outcomes (Table 1). Similarly, being underweight (11.6% of the infant

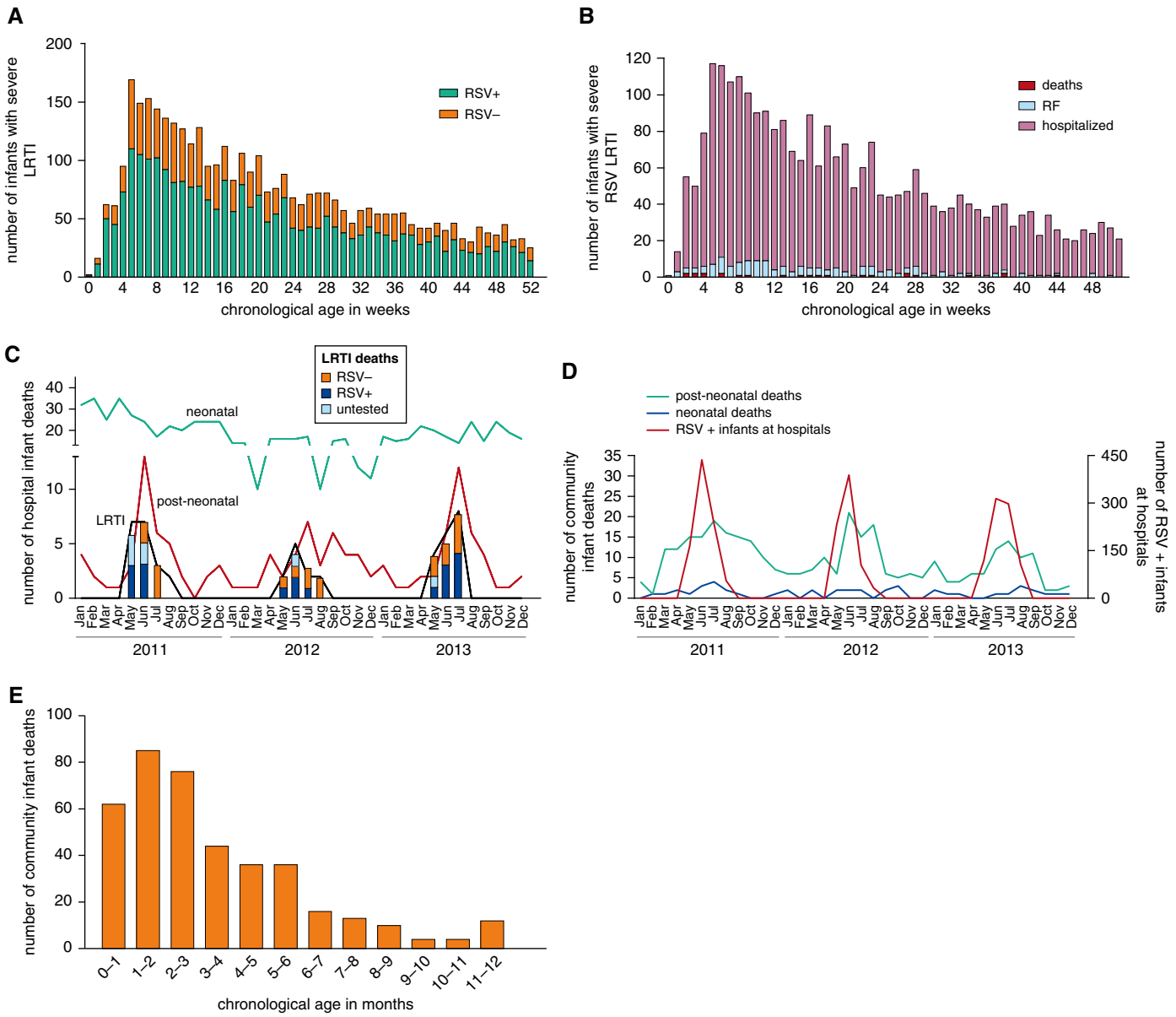

Figure 1. Burden of illness and mortality due to respiratory syncytial virus (RSV) in infants. (*A*) Number of infants with severe lower respiratory tract illness (LRTI) infected with RSV (*green*) or not-infected with RSV (*orange*) by week of chronologic age. (*B*) Number of infants hospitalized not requiring ventilation or dying (*purple*), in respiratory failure (*blue*), or dead (*red*) due to RSV LRTI by week of chronologic age. (*C*) Infant deaths at the hospital by month from 2011 to 2013. All-cause neonatal deaths (*green line*), all-cause postneonatal deaths (*red line*), fatal postneonatal LRTI during the RSV season (*black line*), RSV-negative LRTI (*orange bars*; n = 17), RSV-positive LRTI (*blue bars*; n = 20), and untested LRTI (*turquoise bars*; n = 8). (*D*) Infant deaths in the community by month from 2011 to 2013. All-cause neonatal deaths (*blue line*) and all-cause postneonatal deaths (*green line*). The *red line* represents RSV detections by reverse-transcriptase polymerase chain reaction in hospitalized infants with severe LRTI. (*E*) Number of infant deaths in the community by month of chronologic age. RF = respiratory failure.

population) influenced RSV RF in univariable analyses (Table 1).

Comorbidities, including congenital heart disease (CHD), neurologic illness, and Down syndrome (DS), have been associated with severe RSV LRTI and mortality in industrialized countries (13, 14). In our population, 4 of 148 (3.4%) cases of RF due to RSV LRTI had CHD, two of whom had DS. Conversely, 27 (1.2%) infants among the remaining hospitalized patients had CHD and 7 (0.3%) had DS. Both these comorbidities and neurologic disease (5 [3.3%] vs. 12 [0.4%]) associated with poor outcomes (Table 1).

Next, we explored a range of factors associated with vulnerable lungs in infancy. Ventilation at birth, male sex, and lack of breastfeeding increased the odds for RF (Table 1), whereas factors linked to risk for asthma (a parental history of asthma and recurrent wheezing) did not (Table 1).

In summary, numerous risk factors associated individually with biologic vulnerability affected the odds for RSV RF.

Table 1. Univariable Analysis: Risk Factors for Death or RF due to RSV in Postneonatal Infants

	Death (*n* = *20*)			RF (*n* = *148*)		
	Yes [*n/N (%)*]	No [*n/N (%)*]	OR (95% CI)	Yes [*n/N (%)*]	No [*n/N (%)*]	OR (95% CI)
Socioeconomic						
Access to health care						
Incomplete vaccination	6/945 (0.64)	9/1,364 (0.66)	0.96 (0.36–2.56)	50/945 (5.29)	74/1,364 (5.43)	0.98 (0.69–1.38)
Distance to the hospital (>30 min)	6/886 (0.68)	3/676 (0.44)	1.53 (0.42–5.55)	65/886 (7.34)	41/676 (6.07)	1.21 (0.83–1.76)
Previous visits in this episode	10/1,040 (0.96)	6/517 (1.16)	1.21 (0.46–3.17)	73/1,040 (7.02)	39/517 (7.54)	1.07 (0.74–1.56)
Vulnerable mother						
Adolescent mother (<18 yr)	2/225 (0.89)	11/2,115 (0.52)	1.71 (0.43–6.79)	17/225 (7.56)	109/2,115 (5.31)	1.47 (0.9–2.37)
Late childbearing (>35 yr)	3/288 (1.04)	10/2,052 (0.64)	2.14 (0.64–7.13)	17/288 (5.9)	109/2,052 (5.31)	1.11 (0.68–1.8)
Incomplete primary education	3/328 (0.92)	9/2,074 (0.43)	2.11 (0.62–7.14)	18/328 (5.49)	110/2,074 (5.3)	1.03 (0.64–1.66)
Precarious home						
No running water	6/621 (0.97)	8/1,808 (0.44)	2.18 (0.79–5.99)	31/621 (4.99)	103/1,808 (5.7)	0.88 (0.59–1.29)
No sewage system	9/1,507 (0.60)	3/900 (0.33)	1.79 (0.53–6.11)	95/1,507 (6.3)	34/900 (3.78)	**1.67 (1.14–2.44)**
Tin or mud house	8/643 (1.24)	12/1,838 (0.65)	1.91 (0.8–4.51)	47/643 (7.31)	101/1,838 (5.5)	1.33 (0.95–1.85)
Tobacco smoking at home	5/1,080 (0.46)	8/1,322 (0.60)	0.76 (0.26–2.21)	70/1,080 (6.48)	61/1,322 (4.61)	**1.4 (1.01–1.96)**
Crowding*	3/595 (0.50)	10/1,616 (0.62)	0.82 (0.24–2.73)	28/595 (4.71)	88/1,616 (5.44)	0.86 (0.57–1.3)
Biologic						
Young and light						
Age ⩽6 mo	15/1,726 (0.87)	4/741 (0.54)	1.61 (0.56–4.61)	119/1,726 (6.89)	27/741 (3.64)	**1.89 (1.26–2.85)**
Prematurity	5/301 (1.66)	14/2,111 (0.66)	2.5 (0.94–6.61)	30/301 (9.97)	111/2,111 (5.26)	**1.9 (1.29–2.77)**
Low birth weight	2/309 (0.65)	17/2,130 (0.80)	0.81 (0.21–3.12)	25/309 (8.09)	114/2,130 (5.35)	**1.51 (1.00–2.27)**
Underweight†	3/277 (1.08)	13/2,098 (0.62)	1.75 (0.54–5.65)	31/277 (11.19)	96/2,098 (4.18)	**2.45 (1.66–3.57)**
Comorbidities						
Cardiac disease	2/32 (6.25)	18/2,449 (0.74)	**8.5 (2.22–29.96)**	5/32 (15.62)	143/2,449 (5.84)	**2.68 (1.16–5.55)**
Neurologic disease	0	0	0	5/17 (29.41)	143/2,464 (5.8)	**5.07 (2.26–9.41)**
Down syndrome	1/10 (10)	19/2,471 (0.77)	**13.01 (2.24–57.98)**	3/10 (30)	145/2,471 (5.87)	**5.11 (1.82–10.56)**
Vulnerable lungs						
Parent with asthma	2/202 (0.99)	10/2,133 (0.47)	2.11 (0.52–8.46)	13/202 (6.44)	113/2,133 (5.3)	1.22 (0.7–2.08)
Recurrent wheeze	4/292 (1.37)	8/2,106 (0.38)	**3.61 (1.16–11.15)**	17/292 (5.82)	107/2,106 (5.08)	1.15 (0.7–1.86)
Male sex	11/1,410 (0.78)	9/1,064 (0.85)	0.92 (0.39–2.16)	95/1,410 (6.74)	51/1,064 (4.79)	**1.41 (1.01–1.96)**
Not breastfed	1/223 (0.45)	13/2,195 (0.59)	0.76 (0.13–4.46)	20/223 (8.97)	113/2,195 (5.15)	**1.74 (1.10–2.71)**
Ventilated at birth	1/95 (1.05)	19/2,386 (0.8)	1.32 (0.22–7.51)	17/95 (17.89)	131/2,386 (5.49)	**3.26 (2.03–5.05)**
Clinical complications						
Apnea	0	0	0	3/24 (12.5)	145/2,457 (5.9)	2.12 (0.73–5.34)
Pneumonia	7/185 (3.78)	13/2,296 (0.57)	**6.68 (2.76–15.99)**	45/185 (24.32)	103/2,296 (4.49)	**5.52 (3.93–7.39)**
Sepsis	13/38 (34.21)	7/2,443 (0.29)	**119.39 (50.98–273.34)**	31/38 (81.58)	117/2,443 (4.79)	**17.03 (13.14–21.16)**
Positive blood culture	4/22 (18.18)	16/2,459 (0.65)	**11.25 (4.71–25.00)**	11/22 (50)	103/2,459 (4.49)	**6.03 (3.74–8.95)**
Pneumothorax	8/25 (32)	12/2,456 (0.49)	**65.49 (28.90–139.17)**	22/25 (88)	126/2,456 (5.13)	**17.15 (13.07–21.01)**
Bronchiolitis	19/1,982 (0.96)	1/499 (0.20)	4.78 (0.82–28.08)	113/1,982 (5.7)	35/499 (7.01)	0.81 (0.57–1.17)

Definition of abbreviations: CI = confidence interval; OR = odds ratio; RF = respiratory failure; RSV = respiratory syncytial virus.
"n" represents the number of infants who died (second and third columns) or suffered respiratory failure (fifth and sixth columns) and experienced a specific risk factor (Yes, second and fifth columns) or did not (No, third and sixth columns). "N" represents the number of control infants who had severe RSV lower respiratory tract illness and experienced a specific risk factor (Yes, second and fifth columns) or did not (No, third and sixth columns). Bold indicates $P \leqslant 0.05$.
*Seven or more household members.
†Weight-for-age *Z*-score ⩽ −2 SD.

In a second multivariable analysis, age less than or equal to 6 months, being underweight, requiring mechanical ventilation at birth, and preexistent neurologic disease remained significantly associated with the study endpoint (Table 2).

Medical Complications Are Important Determinants of RSV RF

Finally, we determined the role of clinical complications affecting the course of illness at the hospital. There, a diagnosis of pneumonia, a positive blood culture, and sepsis strongly associated with RF in univariable analyses (Table 1). A total of 11 of 148 (7.4%) patients in the RF group had a positive blood culture. Isolates included two methicillin-resistant *Staphylococcus aureus*, one methicillin-sensitive *S. aureus*, and one *Streptococcus pneumoniae* causing fatal disease, and two *H. influenzae* type b, three *Klebsiella pneumoniae*, one *Pseudomonas aeruginosa*, and one *Serratia marscesens* in ventilated survivors. Only 7 of 2,333 (0.3%) of surviving hospitalized infants with RSV LRTI had bacteria recovered from the bloodstream (*see* Table E1 in the online supplement)

In addition, developing a clinically significant pneumothorax was frequent in infants with poor outcomes. Pneumothorax was strongly associated with RF due to RSV (22 [14.9%]) (Table 1). The rate of pneumothorax in the rest of surviving RSV-infected patients was 0.6%. RF subjects typically suffered prolonged hospitalizations, with a mean hospital stay

Table 2. Multivariable Analysis: Risk Factors for Respiratory Failure due to RSV in Postneonatal Infants

	Level 1		Level 2		Level 3	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
No sewage system	*1.72 (1.15–2.65)*	***0.011***	1.79 (1.15–2.84)	0.011	1.91 (1.16–3.23)	**0.013**
Adolescent mother (<18 yr)	*1.64 (0.91–2.76)*	*0.078*	1.84 (1.00–3.18)	**0.038**	2.01 (1.04–3.68)	**0.03**
Tobacco smoking at home	*1.5 (1.03–2.18)*	***0.034***	1.51 (1.01–2.26)	**0.047**	1.52 (0.96–2.41)	0.075
Age ⩽6 mo			*2.13 (1.28–3.77)*	***0.006***	1.86 (1.06–3.45)	**0.039**
Ventilated at birth			*2.22 (1.01–4.52)*	***0.037***	2.37 (0.97–5.29)	**0.045**
Male sex			*1.47 (0.97–2.27)*	*0.073*	2.08 (1.28–3.50)	**0.004**
Underweight*			*1.93 (1.13–3.19)*	***0.013***	1.52 (0.79–2.77)	0.188
Neurologic disease			*7.37 (1.87–25.81)*	***0.002***	9.92 (2.24–38.32)	**0.001**
Down syndrome			*4.03 (0.57–18.71)*	*0.1*	7.93 (1.10–37.72)	**0.016**
Pneumothorax					*261.3 (56.13–1,926.10)*	***<0.001***
Sepsis					*57.9 (20.63–189.51)*	***<0.001***
Pneumonia					*6.42 (3.64–11.04)*	***<0.001***

Definition of abbreviations: CI = confidence interval; OR = odds ratio; RSV = respiratory syncytial virus.
In levels 2 and 3 of the hierarchical analysis, the variables used in the previous levels were used only to adjust the new ones (italicized). Bold indicates $P < 0.05$.
*Weight-for-age *Z*-score ⩽ −2SD.

of 23.02 ± 20.16 days (12.73 ± 10.27 d in death patients) versus 6.77 ± 4.16 days in surviving, hospitalized nonintubated infants ($P < 0.001$ vs. RF).

The overall multivariable analysis of risk factors examined the role of clinical variables in the context of socioeconomic and biologic vulnerabilities (Table 2). Sepsis, pneumonia, and a clinically significant pneumothorax strongly associated with RF in RSV-infected infants (Table 2).

Pneumothorax and Sepsis as Risk Factors for Mortality in RSV LRTI

We next restricted our analysis to explore risk factors in infants dying from RSV LRTI. In this analysis, no socioeconomic variable associated with mortality, and only significant comorbidities (CHD and DS) exhibited an association among biologic factors (Table 1). Interestingly, confirming our previous observations, clinical complications had strong associations with death. A diagnosis of pneumonia (7 of 20 [35%]), a positive blood culture (4 of 20 [20%]), sepsis (13 of 20 [65%]), and pneumothorax (8 of 20 [40%]) increased the odds for RSV mortality (Table 1). Multivariable analysis confirmed a clinically significant pneumothorax and sepsis as the critical factors associated with fatal outcomes (Table 3). Only 2 of 20 RSV deaths did not have sepsis and/or a pneumothorax; one of these two had CHD and DS.

RSV Increases Risk of Pneumothorax

Given the 40% rate of clinically significant pneumothorax observed in infants dying from RSV LRTI, we explored whether this complication was frequent in infants dying from other respiratory infections (3 of 17 [18%]). In fact, an exploratory analysis of risk factors for developing a clinically significant pneumothorax identified RSV infection (odds ratio, 5.93; 95% CI, 1.52–40.2; $P = 0.026$) and mechanical ventilation (odds ratio, 106.2; 95% CI, 34.6–408.8; $P < 0.001$) as the sole determinants of significant air leaks. Conversely, sepsis was not specifically associated with fatal infections due to RSV, and was diagnosed in 14 of 17 (82%) deaths with non-RSV LRTI.

Community Deaths

To account for all deaths attributable to RSV in our population, we explored community deaths during the study period (Figure 1D). Sixty-two neonates and 342 postneonatal infants were reported dead by the state public health system in the community between 2011 and 2013 (Figure 1D). Interestingly, although neonatal deaths at home exhibited no specific seasonal distribution, peaks and valleys in the number of postneonatal infant deaths in the community paralleled postneonatal deaths

Table 3. Multivariable Analysis: Risk Factors for Death due to RSV in Postneonatal Infants

	Level 1		Level 2		Level 3	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Tin or mud house	*1.92 (0.75–4.66)*	*0.156*	1.51 (0.52–3.92)	0.412	2 (0.57–6.77)	0.263
Prematurity			*2.01 (0.56–5.73)*	*0.227*	0.27 (0.03–1.60)	0.205
Age ⩽6 mo			*2.25 (0.74–9.79)*	*0.202*	1.19 (0.29–6.62)	0.82
Cardiac disease			*4.27 (0.23–22.84)*	*0.171*	8.26 (0.30–84.85)	0.127
Sepsis					*151.9 (44.78–580.52)*	***<0.001***
Pneumothorax					*77.4 (14.69–381.74)*	***<0.001***

Definition of abbreviations: CI = confidence interval; OR = odds ratio; RSV = respiratory syncytial virus.
In levels 2 and 3 of the hierarchical analysis, the variables used in the previous levels were used only to adjust the new ones (italicized). Bold indicates $P < 0.05$.

at the hospitals (Figures 1C and 1D). In fact, community deaths peaked during the respiratory season and their age distribution was similar to that observed in hospitalized infants (Figures 1A and 1E).

Among hospitalized infants, RSV was responsible for 16.4% all-cause postneonatal and 0.5% neonatal deaths (Figure 1C). If we extrapolate hospital results to the community, the overall death toll attributable to RSV in our community during the same period would approximate 56 postneonatal and three neonatal deaths (Figure 1D). These calculations yield an overall (hospital + home) infant mortality rate attributable to RSV of 0.94 per 1,000 (95% CI, 0.55–1.33) live births. Alternatively, if we base our estimates on postmortem International Statistical Classification of Disease and Related Health Problems, tenth revision coding of pneumonia during the RSV season (n = 100) and adjust this estimate by the rate of RSV LRTIs (65.5%), the overall attributable rate would be 0.86 per 1,000 (0.57–1.15) live births.

Discussion

In this study, we prospectively examined RSV mortality in a low-income region from a developing country. RSV was the main cause of postneonatal infant death in our population, affecting two different groups of infants: one at medical institutions, often experiencing a clinically significant pneumothorax and/or sepsis; and a second group dying in the community presumably due to RSV in association with poor access to health care (15).

Although our data suggest that RSV is not particularly aggressive compared with other agents (16), the virus exceeded in frequency all other pathogens combined as a cause of severe LRTI every year. Hence, its importance as a cause of RF and/or death in our population seems to reside on the number of RSV-infected patients, rather than on its specific lethality. The frequency of pneumothorax in hospitalized infants with fatal RSV LRTI is of concern. In fact, rates of pneumothorax in intensive care units in industrialized countries are typically lower (17). Spontaneous pneumothoraxes have been rarely reported with RSV, and were low in our population at 0.6%. But mechanical ventilation in RSV-infected patients can induce or aggravate pulmonary inflammation (18). In addition, segmental atelectasis and lung hyperinflation during RSV disease may result in ventilation using high volumes to overcome hypercapnia, increasing risk of air leaks (19). As infants from low-income countries progressively access these lifesaving technologies, expert training of health care personnel will be critical to prevent excess mortality.

Blood-borne infections were frequent and severe bacterial infections played a pivotal role in RSV-related mortality. A Dutch study reported bacterial isolates in 3.7% blood cultures from ventilated RSV-infected patients, half the rate observed in our study (20). Given that RSV causes functional changes in respiratory epithelial cells facilitating adherence and invasion of bacteria (21), excess invasive disease may associate with higher nasopharyngeal carriage rates in infants from developing countries (22, 23). Even then, because between 0.8 and 17.4% bacterial pneumonia yield positive blood cultures (24), we may be underestimating bacterial burden in RSV mortality.

Lower hospitalization rates due to RSV pneumonia following administration of pneumococcal vaccine in a randomized-controlled trial in South Africa support the association between the virus and *S. pneumoniae* (25). *S. pneumoniae* and *S. aureus* were identified in the bloodstream in four fatal cases. The remaining blood isolates in the RF group were gram-negative rods, characteristic of ill patients with prolonged hospitalizations (26). Although a temporal overlap between infant mortality and RSV outbreaks has been previously noted (27–29), infant deaths in other studies followed the peak of the RSV season (30). Secondary infections associated with or leading to prolonged hospitalizations may explain this sequential occurrence of RSV season and death.

Our study has caveats. First, fatalities in postneonatal infants are infrequent, prompting us to use a surrogate outcome defined as RF. Therefore, our analysis of risk factors specifically affecting deaths is exploratory. Second, collecting samples and obtaining information from families at a time of extreme stress is challenging (6). As a consequence, we were unable to test 20% LRTI deaths during the season for RSV. Third, in some patients, particularly within the group of infants with RF or death, data on socioeconomic risk factors are incomplete. This limitation is probably explained by the challenge of interviewing frail parents facing a situation of extraordinary stress (i.e., the probable death of their child). Although we cannot exclude the possibility of underestimating the impact of certain socioeconomic factors in hospital-based RF or mortality, we believe that the magnitude of effects observed in the study for the main associations (pneumothorax and sepsis) is such that they are unlikely to be significantly altered by the missing information. In fact, biologic characteristics in infants missing data for different socioeconomic variables and those for whom that information was available were similar.

Fourth, community disease-specific mortality estimates relied on physician postmortem diagnoses, which are often imprecise (31). Yet, similarities in temporal distribution between hospital and home postneonatal mortality frequencies were striking, suggesting causes of death probably overlap. Fifth, our study was designed to monitor respiratory deaths during the RSV season, while number of all-cause deaths was obtained from collaborations with a program ran by district authorities, explaining small discrepancies in specific numbers. Finally, differences in living standards and quality of health care may alter the relative importance of risk factors in other regions of the world. However, our hierarchical analysis permits sequentially gauging the evidence at different levels to better translate risks in different settings (11).

In summary, RSV LRTI is the main cause of postneonatal infant RF and mortality at the hospital in our population. These outcomes frequently associate with at least one other determinant, bacterial sepsis and/or a pneumothorax. The temporal overlap and similar age distribution between hospital and home deaths suggests that

RSV LRTI also causes significant community mortality. To achieve the Sustainable Development Goal of ending preventable child death in coming years, interventions addressing the socioeconomic and public health problems associated with LRTI outcomes will be necessary. Meanwhile, protecting young infants by development of RSV vaccines or specific antibodies is the most immediate strategy to decrease RSV mortality. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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