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Mortality due to respiratory syncytial virus: burden and risk factors

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F.Martin Ferolla, Fernando Vallone and Fernando P Polack designed the study. Anabella Erviti, Stella M. Zanone, Luciano Alva Grimaldi, Andrea Sancilio, F. Martin Ferolla, Karina Dueñas, Andrea Rodriguez, Gustavo Sastre, Fernando Ferrero, Edgar Barboza, Guadalupe Fernández Gago, Celina Nocito, Edgardo Flamenco, Beatriz Rebec and Alberto Rodriguez Perez and Alejandra Bianchi collected the data. Patricio L. Acosta, Laura B Talarico and Adrian Ferretti analysed samples. Eduardo Bergel, Anabella Erviti, Sarah Geoghegan, Mauricio Caballero, Romina Libster and Fernando P Polack analysed the data. Sarah Geoghegan, Mauricio Caballero, Ruth Karron, Eduardo Bergel and Fernando P Polack wrote the paper.

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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, biological, 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: 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 and mortality due to RSV were assessed using a hierarchical, logistic regression model.

Measurements and Main Results: 2,588(65.5%) infants with severe LRTI were infected with RSV. 157 infants (148 post-neonatal) experienced respiratory failure (RF) or died with RSV. RSV LRTI accounted for 57% fatal LRTI tested for the virus. A diagnosis of sepsis [OR=17.03(95%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.

Conclusion. RSV was the most frequent cause of mortality in low-income

post-neonatal infants. Respiratory failure 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 co-occurrence of bacterial sepsis and clinically significant pneumothoraxes.

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At a Glance Commentary

Scientific Knowledge on the Subject: RSV LRTI is estimated to cause between 66,000 and 239,000 yearly deaths in children under the age of five. 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, biological handicaps, bacterial infections, and/or gaps in supportive is unknown.

What this Study Adds to the Field: RSV LRTI is a leading cause of post-neonatal 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. Post-neonatal 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 under five (U5).[1] LRTI due to respiratory syncytial virus (RSV) is the most frequent cause of hospitalization in infants in the world[2], with over three million hospital admissions every year. The disease is estimated to cause between 66,000 and 239,000 yearly deaths in children U5[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 U5 occur worldwide)[4]. RSV remains the only major etiological 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 post-mortem 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, we do not know the relative

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contribution of factors associated with poor access to health care, biological handicaps, secondary bacterial infections, and/or gaps in supportive care in medical facilities of the developing world to infant mortality caused by RSV. 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, biological 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 under two 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 (SpO2)<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, CPAP 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 biological 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

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authorities. Pneumonia and bronchiolitis were defined clinically based upon physical examinations performed by the attending pediatrician. CXR were 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 days 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 WHO[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 (DFA). 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 RT-PCR for RSV as previously described[7,10]. The RSV season started every year upon detection of two cases of severe RSV LRTI at one of the twelve participating institutions through the hospital's surveillance system. The season ended when no patients were admitted with RSV LRTI to four of the twelve 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(level1), biological vulnerabilities(level2), and clinical complications(level3)[11]**.** The logistic regression models were fitted in R 3.1.1 using the glm() function.

Results

RSV disease and death in hospitalized infants. 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(Fig.1a). Hospitalizations due to RSV peaked during the second month of life and decreased in frequency thereafter(Fig.1a,b). Mean RSV hospitalization rate was 30.08 per 1,000 infants (95%CI, 27.28-32.90/1,000). Rates were double those observed in infants with RSV negative LRTI at 14.59 per 1,000 infants (95%CI, 10.54-18.64/1,000).

The case fatality rate (CFR) for infants due to RSV was 0.90% (95%CI, 0.44-1.35) vs. 1.49%(95%CI 0.51-2.47) for non-RSV LRTI. However, because

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of its high hospitalization rates, RSV was responsible for 4/8 neonatal (0-28 days of life) and 20/37 (54%) post-neonatal (29-364 days of life) infant deaths that presented with LRTIs and were tested for the virus between 2011 and 2013. An additional two neonate and eight post-neonatal infant deaths due to LRTI were not tested for RSV(Fig.1c). Six infants in the latter, older group had a clinical diagnosis of bronchiolitis.

RSV was confirmed in 20/122 (16.4%) all cause post-neonatal infant deaths in our region, and was the most frequent cause of hospital mortality in a population with free access to *H.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 or equal to age six months (Fig.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 respiratory failure would have died if ventilator support were unavailable. Therefore, we grouped these post-neonatal infants with post-neonatal fatalities in a category of 148 subjects designated as RF. These patients represented 5.9% of post-neonatal infants infected with RSV (Fig.1b). 80.4% were younger or equal to six months of age.

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

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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).

Biological vulnerability affects RSV RF. At a second hierarchical level, we investigated biological vulnerabilities that, potentially conditioned by socioeconomic factors, could lead to RSV RF (Table 1).

Seventy percent of patients in the hospitalized population were under six months of age (Fig.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 population) influenced RSV RF in univariable analyses (Table 1).

Comorbidities, including congenital heart disease (CHD), neurological illness and Down's syndrome, have been associated with severe RSV LRTI and

mortality in industrialized countries[13,14]. In our population, 4/148 (3.4%) cases of RF due to RSV LRTI had CHD, two of whom had Down's syndrome (DS). Conversely, 27 (1.2%) infants among the remaining hospitalized patients had CHD and 7 (0.3%) DS. Both these comorbidities and neurological 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), while 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 biological vulnerability affected the odds for RSV RF. In a second multivariable analysis, age ≤6 months, being underweight, requiring mechanical ventilation at birth, and preexistent neurological 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). 11/148 (7.4%) patients in the RF group had a positive blood culture. Isolates included two methicillin resistant *S. aureus*, one methicillin sensitive *S. aureus,* and one *S.*

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pneumoniae causing fatal disease, and two *H. influenzae* type b, three *K. pneumoniae,* one *P. aeruginosa* and one *S. marscesens* in ventilated survivors. Only 7/2,333 (0.3%) of surviving hospitalized infants with RSV LRTI had bacteria recovered from the bloodstream.(Suppl Table 1)

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 of 23.02± 20.16 days (12.73 ±10.27 days in death patients) vs. 6.77±4.16 days in surviving, hospitalized non-intubated 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 biological 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 Down's syndrome) exhibited an

association among biological factors (Table 1). Interestingly, confirming our previous observations, clinical complications had strong associations with death. A diagnosis of pneumonia [7/20(35%)], a positive blood culture [4/20(20%)], sepsis [13/20(65%)], and pneumothorax [8/20(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, 2/20 RSV deaths did not have sepsis and/or a pneumothorax; one of these two had CHD and Down´s syndrome.

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 [3/17(18%)]. In fact, an exploratory analysis of risk factors for developing a clinically significant pneumothorax identified RSV infection [OR 5.93, 95%CI 1.52-40.2; p=0.026] and mechanical ventilation [OR 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 14/17 (82%) deaths with non-RSV LRTI.

Community deaths. In an attempt to account for all deaths attributable to RSV in our population, we explored community deaths during the study period

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(Fig.1d). Sixty-two neonates and 342 post-neonatal infants were reported dead by the state public health system in the community between 2011 and 2013 (Fig.1d). Interestingly, while neonatal deaths at home exhibited no specific seasonal distribution, peaks and valleys in the number of post neonatal infant deaths in the community paralleled post-neonatal deaths at the hospitals (Fig.1c,d). In fact, community deaths peaked during the respiratory season and their age distribution was similar to that observed in hospitalized infants (Fig.1a,e).

Among hospitalized infants, RSV was responsible for 16.4% all-cause post neonatal and 0.5% neonatal deaths (Fig 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 post-neonatal and 3 neonatal deaths(Fig 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 post-mortem ICD10 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 post-neonatal 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].

While our data suggests that RSV is not particularly aggressive compared to 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 respiratory failure 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

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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, since between 0.8 to 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-control-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 for four fatal cases. The remaining blood isolates in the RF group were Gram-negative rods, characteristic of ill patients with prolonged hospitalizations[26]. In fact, while 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/leading to prolonged

hospitalizations may explain this sequential occurrence of RSV season and death.

Our study has caveats. First, fatalities in post-neonatal 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 respiratory failure or death, data on socioeconomic risk factors is 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. While we cannot exclude the possibility of underestimating the impact of certain socioeconomic factors in hospital-based respiratory failure 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, biological 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 post-mortem diagnoses, which are often imprecise[31]. Yet, similarities in temporal distribution between hospital and home post-neonatal

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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. This said, 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 post-neonatal infant respiratory failure 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.

Figure Legend

Figure 1. Burden of illness and mortality due to RSV in infants. (A) Number of infants with severe LRTI infected with RSV (green) or not-infected with RSV (orange) by week of chronological 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 chronological age. (C) Infant deaths at the hospital by month from 2011 to 2013. All-cause neonatal deaths (green line), all-cause post-neonatal deaths (red line), fatal post-neonatal LRTI during the RSV season (black line), RSV negative LRTI (orange bars; n=17), RSV positive LRTI (blue bars; n=20), 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 post-neonatal deaths (green line). The red line represents RSV detections by RT-PCR in hospitalized infants with severe LRTI. (E) Number of infant deaths in the community by month of chronological age.

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Table 1. Univariable analysis: Risk factors for death or RF due to RSV in post-neonatal infants

	Death n=20			Respiratory failure n=148		
	n/N (%)	n/N (%)	OR (CI 95%)	n/N (%)	n/N (%)	OR (CI 95%)
SOCIOECONOMIC	Yes	No		Yes	No	
Access to Health Care						
Incomplete Vaccination	6/945 (0.64)	9/1364 (0.66)	0.96 (0.36-2.56)	50/945 (5.29)	74/1364 (5.43)	0.98 (0.69-1.38)
Distance to the hospital (>30min)	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	10/1040(0.96)	6/517 (1.16)	1.21 (0.46-3.17)	73/1040 (7.02)	39/517 (7.54)	1.07 (0.74-1.56)
Vulnerable Mother						
Adolescent mother (<18yr)	2/225 (0.89)	11/2115 (0.52)	1.71 (0.43-6.79)	17/225 (7.56)	109/2115(5.31)	1.47 (0.9-2.37)
Late Childbearing (>35yr)	3/288 (1.04)	10/2052 (0.64)	2.14 (0.64-7.13)	17/288 (5.9)	109/2052(5.31)	1.11 (0.68-1.8)
Incomplete primary education	3/328 (0.92)	9/2074 (0.43)	2.11 (0.62-7.14)	18/328 (5.49)	110/2074 (5.3)	1.03 (0.64-1.66)
Precarious Home						
No running water	6/621 (0.97)	8/1808 (0.44)	2.18 (0.79-5.99)	31/621 (4.99)	103/1808 (5.7)	0.88 (0.59-1.29)
No sewage system	9/1507 (0.60)	3/900 (0.33)	1.79 (0.53-6.11)	95/1507 (6.3)	34/900 (3.78)	**1.67 (1.14-2.44)***
Tin or Mud house	8/643 (1.24)	12/1838 (0.65)	1.91 (0.8-4.51)	47/643 (7.31)	101/1838 (5.5)	1.33 (0.95-1.85)
Tobacco smoking at home	5/1080 (0.46)	8/1322 (0.60)	0.76 (0.26-2.21)	70/1080 (6.48)	61/1322 (4.61)	**1.4 (1.01-1.96)***
Crowding ǂ	3/595 (0.50)	10/1616 (0.62)	0.82 (0.24-2.73)	28/595 (4.71)	88/1616 (5.44)	0.86 (0.57-1.3)
BIOLOGICAL						
Young and light						
Age ≤6m	15/1726(0.87)	4/741 (0.54)	1.61 (0.56-4.61)	119/1726(6.89)	27/741 (3.64)	**1.89 (1.26-2.85)***
Prematurity	5/301 (1.66)	14/2111 (0.66)	2.5 (0.94-6.61)	30/301 (9.97)	111/2111(5.26)	**1.9 (1.29-2.77)***
Low birth weight	2/309 (0.65)	17/2130 (0.80)	0.81 (0.21-3.12)	25/309 (8.09)	114/2130(5.35)	**1.51 (1.00-2.27)***
Underweight**	3/277 (1.08)	13/2098 (0.62)	1.75 (0.54-5.65)	31/277 (11.19)	96/2098 (4.18)	**2.45 (1.66-3.57)***

Comorbidities						
Cardiac Disease	2/32 (6.25)	18/2449 (0.74)	**8.5 (2.22-29.96)***	5/32 (15.62)	143/2449(5.84)	**2.68 (1.16-5.55)***
Neurological Disease	0	0	0	5/17 (29.41)	143/2464 (5.8)	**5.07 (2.26-9.41)***
Down's Syndrome	1/10 (10)	19/2471 (0.77)	**13.01 (2.24-57.98)***	3/10 (30)	145/2471(5.87)	**5.11 (1.82-10.56)***
Vulnerable lungs						
Parent with asthma	2/202 (0.99)	10/2133 (0.47)	2.11 (0.52-8.46)	13/202 (6.44)	113/2133 (5.3)	1.22 (0.7-2.08)
Recurrent Wheeze	4/292 (1.37)	8/2106 (0.38)	**3.61 (1.16-11.15)***	17/292 (5.82)	107/2106(5.08)	1.15 (0.7-1.86)
Male Sex	11/1410(0.78)	9/1064 (0.85)	0.92 (0.39-2.16)	95/1410 (6.74)	51/1064 (4.79)	**1.41 (1.01-1.96)***
Not Breastfed	1/223 (0.45)	13/2195 (0.59)	0.76 (0.13-4.46)	20/223 (8.97)	113/2195(5.15)	**1.74 (1.10-2.71)***
Ventilated at birth	1/95 (1.05)	19/2386 (0.8)	1.32 (0.22-7.51)	17/95 (17.89)	131/2386(5.49)	**3.26 (2.03-5.05)***
CLINICAL COMPLICATIONS						
Apnea	0	0	0	3/24 (12.5)	145/2457 (5.9)	2.12 (0.73-5.34)
Pneumonia	7/185 (3.78)	13/2296 (0.57)	**6.68 (2.76-15.99)***	45/185 (24.32)	103/2296(4.49)	**5.52 (3.93-7.39)***
Sepsis	13/38 (34.21)	7/2443 (0.29)	**119.39 (50.98-273.34)***	31/38 (81.58)	117/2443(4.79)	**17.03 (13.14-21.16)***
Positive Blood Culture	4/22 (18.18)	16/2459 (0.65)	**11,25 (4.71-25.00)***	11/22 (50)	103/2459(4.49)	**6.03 (3.74-8,95)***
Pneumothorax	8/25 (32)	12/2456 (0.49)	**65.49 (28.90-139.17)***	22/25 (88)	126/2456(5.13)	**17.15 (13.07-21.01)***
Bronchiolitis	19/1982(0.96)	1/499 (0.20)	4.78 (0.82-28.08)	113/1982 (5.7)	35/499 (7.01)	0.81 (0.57-1.17)

*P=<0.05. ǂ ≥7 household members ** weight for age Z-score ≤-2SD
"n" represents the number of infants who died (1st and 2nd column)or suffered respiratory failure (4th and 5th column) and experienced a specific risk factor (Yes, 1nd and 4th column) or did not (No, 2nd and 5th column)
"N" represents the Number of control infants who had severe RSV LRTI and experienced a specific risk factor (Yes, 1st and 4th column) or did not (No, 2nd and 5th column).

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Table 2. Multivariable analysis: Risk factors for respiratory failure due to RSV in post-neonatal infants

	OR (CI 95%)	*p*	OR (CI 95%)	*p*	OR (CI 95%)	*p*
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 (<18yr)	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 ≤6m			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
Neurological disease			7.37 (1.87 – 25.81)	**0.002**	9.92 (2.24 – 38.32)	**0.001**
Down's syndrome			4.03 (0.57 – 18.71)	0.1	7.93 (1.10 – 37.72)	**0.016**
Pneumothorax					261.3 (56.13 – 1926.10)	**<.001**
Sepsis					57.9 (20.63 – 189.51)	**<.001**
Pneumonia					6.42 (3.64 – 11.04)	**<.001**

Table 3. Multivariable analysis: Risk factors for death due to RSV in post-neonatal infants

	OR (CI 95%)	*p*	OR (CI 95%)	*p*	OR (CI 95%)	*p*
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 ≤6m			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)	**<.001**
Pneumothorax					77.4 (14.69 – 381.74)	**<.001**

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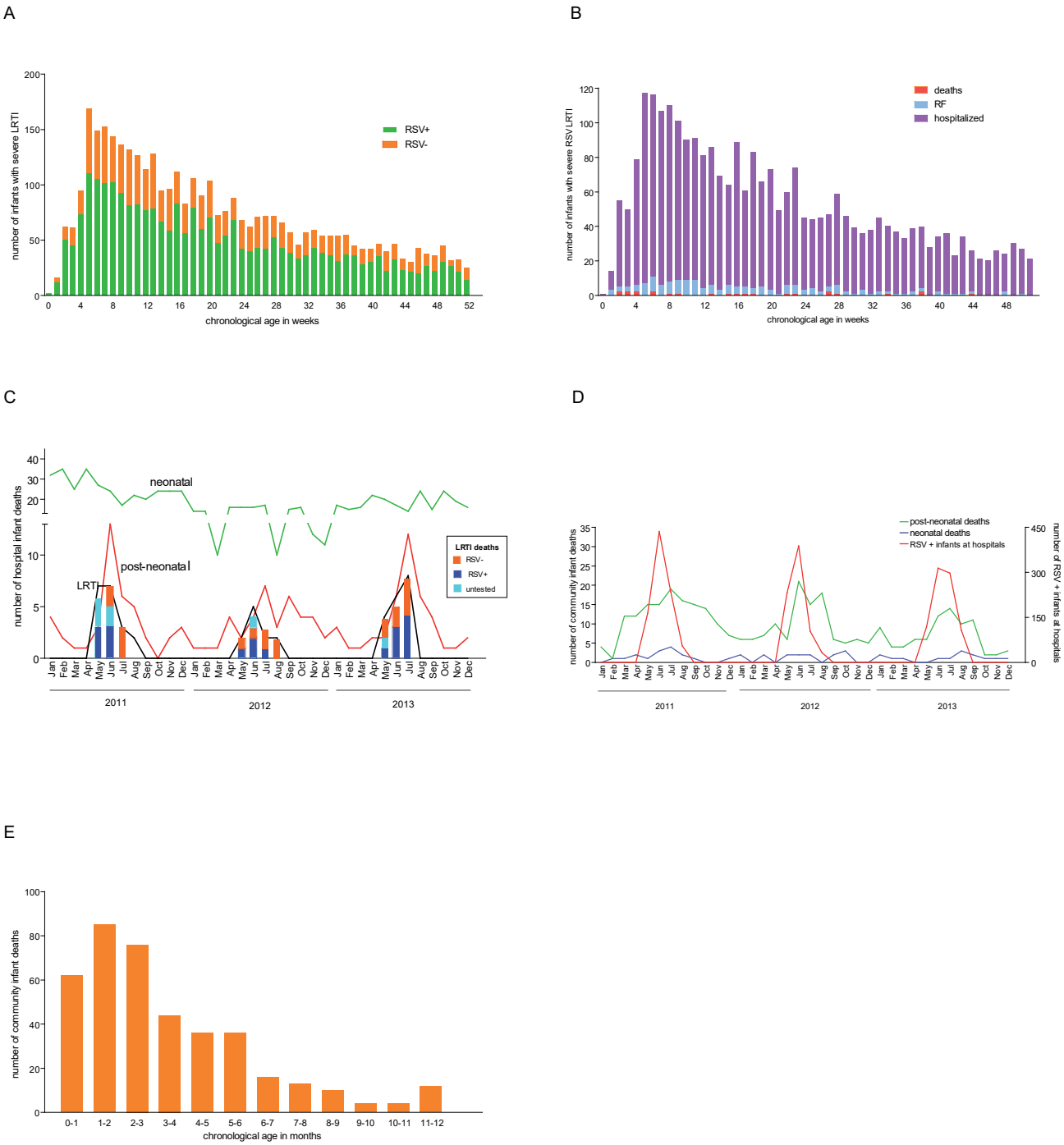
Figure 1



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Supplementary Table 1.

Blood culture isolates in RSV positive non ventilated survivors. (7/2333 0.3%)	
Klebsiella oxitoca	n=1
Staphylococcus aureus	n=2
Escherichia coli	n=1
Streptococcus pneumoniae	n=1
Haemophilus influenzae b	n=1