Respiratory Syncytial Virus-Associated Hospitalizations in Pre-Mature Infants in Lima, Peru

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Abstract. We conducted a prospective cohort study in four hospitals in Lima, Peru in infants with a birth weight $\leq 1{,}500$ g followed from birth hospital discharge up to 1 year of age to determine the incidence of respiratory syncytial virus (RSV) hospitalizations. We enrolled 222 infants from March of 2009 to March of 2010: 48 infants with a birth weight $< 1{,}000$ g and 174 infants with a birth weight of 1,000–1,500 g (birth weight = 1,197 ± 224 g; gestational age = 30.1 ± 2.6 weeks). There were 936 episodes of respiratory infections; the incidence of respiratory infections during the first 1 year of life was 5.7 episodes/child-years. The incidence of RSV respiratory infections that required emergency room management was 103.9 per 1,000 child-years, and the incidence of RSV hospitalizations was 116.2 per 1,000 child-years (244.9 in infants with a birth weight $< 1{,}000$ g and 88.9 in infants 1,000–1,500 g; $P < 0.05$). The incidence of RSV respiratory infections that required emergency management or hospitalization is high among pre-mature infants in Lima.

INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia in infants and young children and the leading cause of respiratory infections that require hospitalization in infants around the world. It is estimated to cause approximately 33 million new episodes of acute lower respiratory infections in children annually and about 53,000–199,000 deaths annually in young children; 96% of episodes and 99% of deaths occur in developing countries.[1,2] In Latin America, there are several studies on the epidemiology of RSV infections in children[2–5]; however, there are limited data on the disease burden of these infections in high-risk groups, such as pre-term infants.[6,7]

Prevention of RSV disease relies on infection control and hygiene measures as well as provision of immunoprophylaxis in select infants. However, the prophylaxis is expensive, and therefore, targeting the recipient population and timing of administration are important for optimal effectiveness and judicious use of limited healthcare resources.[8] Therefore, it is critical to determine the epidemiology and burden of diseases in these resource-limited settings to implement proper guidelines for management and prevention of these infections. We conducted a prospective cohort study to determine the incidence of RSV infections that required hospitalization in premature infants during their first 1 year of life in Lima, Peru.

MATERIALS AND METHODS

We conducted a prospective cohort study in four hospitals in the city of Lima: Hospital Nacional Edgardo Rebagliati Martins (Rebagliati), Instituto de Nacional Marteno Perinatal (Maternidad), Hospital Guillermo Almenara Irigoyen (Almenara), and Hospital Nacional Madre Nino San Bartolome (San Bartolome). We enrolled infants with a birth weight $< 1{,}500$ g and gestational age ≤ 37 weeks born or transferred to one of these hospitals. We excluded infants who could not complete the 1-year follow-up because of social factors (e.g., no home phone or cell phone or infants returning to a hometown outside of the city of Lima). We excluded infants who had received any immunoglobulin preparation, such as cytomegalovirus hyperimmunoglobulin (Cytogam, CSL Behring AG, Bern, Switzerland) or RSV hyperimmunoglobulin (RespiGam, MedImmune, Gaithersburg, MD), before hospital discharge. Because two of four participating hospitals had a program set up to offer prophylaxis with palivizumab (Synagis, MedImmune), the outcome measurements were analyzed excluding the children who received palivizumab. We have also excluded infants with a severe congenital malformation and infants who were older than 6 months of age at hospital discharge.

For consecutive infants who met the inclusion and exclusion criteria, parents were approached by a neonatologist in each participating hospital before the infants were discharged from the intensive or intermediate care unit. After getting written informed consent, the neonatologist collected data on sociodemographics, past medical history, prior and current illnesses, and complications as well as risk factors for RSV infection. Patient follow-up consisted of clinic visits or phone calls to the parents every 2 weeks by a research nurse to collect data on the infant's overall health and document respiratory infections in the previous 2 weeks. Parents were asked to call the research nurse if their child required a visit to the emergency room or hospitalization because of a respiratory infection clinically defined by the attending physicians at each hospital. The research nurse then performed a site visit to the hospital to collect data on the diagnosis and complications of the respiratory infection and collect a sample for analysis. Samples were taken from the nasopharynx using a sterile Dacron swab. The samples were placed on a transport media (tryptose phosphate broth) and sent to a reference laboratory (Virustec, Lima, Peru) to determine the presence of respiratory viruses (RSV, influenza A and B, parainfluenza-1, –2, and –3, and adenovirus) using a commercial immunoassay (Bartels VRK; Trinity Biotech PLC, Ireland). Infants had a complete medical evaluation by the neonatologist at enrollment and 6 and 12 months of age, at which time the infants completed their follow-up and participation in the study.

Data analysis was performed using STATA 11 (StataCorp.). Differences in proportions between the two birth weight

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groups were calculated using Fisher exact test. Student *t* test was used for the group comparison of means. Infants who received palivizumab during the follow-up period were excluded from the analyses of outcome measurements. To evaluate potential risk factors for having a respiratory infection that required hospitalization or emergency room evaluation, we used random-effects logistic regressions. Because it was a cohort and observations are correlated, the random effects model was used for both the univariate analysis and the multivariate analysis. Inclusion criterion used to include potential risk factors in the multivariate analysis was a *P* value < 0.25. Results of regression are reported as odds ratios (ORs). The incidence rate difference between the two birth weight groups and the associated Poisson 95% confidence interval and *P* value were calculated using MEDCALC statistical packages. *P* values ≤ 0.05 were judged statistically significant.

The study was reviewed and approved by the Institutional Ethics Review Boards of Universidad Peruana Cayetano Heredia and each of the participating hospitals.

RESULTS

Infants were enrolled from March of 2009 to March of 2010. During this period, 335 infants with a birth weight < 1,500 g were assess for eligibility in the four participating hospitals; 21 parents did not consent to participate (6.3%), and 57 parents could not complete the 1-year follow up (17%) because of social factors. No infants had received some immunoglobulin preparation other than palivizumab, 35 infants had some other exclusion criteria (4 infants had congenital malformation, 11 infants were transferred to another hospital before home discharge, 1 infant was older than 6 months of age at hospital discharge, 15 infants were excluded with other reasons (10.4%), and 222 infants were enrolled in the study (66.3%): 87 infants from Rebagliati, 55 infants from Maternidad, 49 infants from Almenara, and 31 infants from San Bartolome. There were 48 infants enrolled with a birth weight < 1,000 g and 174 infants enrolled with a birth weight between 1,000 and 1,500 g. The infants had a median birth weight of 1,250 g (interquartile range [IQR] = 1,020–1,390 g) and a median gestational age of 30.0 weeks (IQR = 29–32 weeks). The sociodemographic and clinical characteristics of the enrolled infants and their mothers are presented in Table 1; 211 (95.1%) mothers had complications during preg-

nancy. The main complications were pre-eclampsia (39.1%), premature rupture of membranes (26.7%), urinary tract infection (4.8%), and third trimester hemorrhage (4.3%); there was no significant difference in complications between the two birth weight groups. Neonatal jaundice was diagnosed during the initial hospitalization in 89.6% of infants with a birth weight of < 1,000 g versus 90.2% of infants with a birth weight of 1,000–1,500 g (*P* = 0.157), anemia was diagnosed in 97.9% versus 60.9% (*P* < 0.001), neonatal sepsis was diagnosed in 66.7% versus 51.2% (*P* = 0.002), respiratory distress syndrome of the newborn was diagnosed in 77.1% versus 46.0% (*P* < 0.001), chronic lung disease was diagnosed in 66.7% versus 13.8% (*P* < 0.001), and pneumonia was diagnosed in 25.0% versus 14.4% (*P* = 0.080). The mean duration of hospitalization was 44.5 days (IQR = 33–59 days). As expected, there were significant differences in the requirement of respiratory support and length of hospitalization in relation to birth age group, with higher use of respiratory support and length of hospitalization in the infants with lower birth weight (Table 2).

Infants were followed from hospital discharge until 12 months of age; 198 children completed the study, 14 children were lost during follow-up, and 10 children died (only one death was associated to RSV infection). During the study period, 11 infants received palivizumab. Three infants received one dose, two infants received two doses, four infants received three doses, and two infants received four or more doses. Excluding those infants from the analysis, there were 66,839 child-days of observation. During this follow-up period, there were 936 episodes of respiratory (both upper and lower) infections reported, including 519 outpatient visits, 155 emergency visits, and 48 hospitalizations for respiratory diseases. From those reported episodes, we were able to document 68 emergency visits (43.9%) and 40 hospitalizations (83.3%). The mean duration of hospitalization was 7.6 ± 4.3 days (range = 2–52 days). The incidence of respiratory infections during the first 1 year of life after hospital discharge was 5.7 episodes/child-years (Table 3).

After excluding patients who received palivizumab, there were 36 documented RSV infections in infants that required an emergency room visit or hospitalization (outpatient visits not included) because of a respiratory infection as well as 2 documented influenza and 2 documented parainfluenza infections of 99 samples evaluated. We found one RSV-positive sample in the group that received palivizumab. Between September of 2009 and May of 2010 (spring of 2009 and fall of 2010 in Peru), a larger number of nasopharyngeal samples was collected, with an average percentage of RSV-positive samples of 36% and rates from 17% to 50% in individual seasons (Figure 1). The incidence of RSV respiratory infections that required emergency management or hospitalization was 202.0 per 1,000 child-years in infants < 2 months, 234.5 per 1,000 child-years in infants from 2 to 5 months, 343.3 per 1,000 child-years in infants from 6 to 9 months, and 93.8 per 1,000 child-years in infants from 9 to 12 months. Using the corrected age, the incidences are 250.0 per 1,000 child-years before 40 weeks of post-menstrual age, 132.0 per 1,000 child-years in infants < 2 months, 337.1 per 1,000 child-years in infants from 2 to 5 months, 177.8 per 1,000 child-years in infants from 6 to 9 months, and 50.0 per 1,000 child-years in infants from 9 to 12 months. The mean duration of hospitalization of RSV respiratory infections was 8.2 ± 9.3 days (range = 2–44 days). During hospitalization of RSV respiratory infections,

Table 1
Sociodemographic and clinical characteristics of the enrolled infants and their mothers by birth weight group

	Birth weight group		
	< 1,000 g (N = 48)	1,000–1,500 g (N = 174)	All infants (N = 222)
Maternal age, mean (SD)	30.7 (6.3)	29.8 (7.4)	30.0 (7.1)
Number of pregnancies, mean (SD)	2.3 (1.4)	2.2 (1.3)	2.2 (1.3)
Human immunodeficiency virus-positive, %	0.0	0.7	0.6
Twin pregnancy, %	22.9	18.4	19.4
Cesarean delivery, %	72.9	89.1	85.6
Gestational age, mean (SD)	27.3 (1.9)	30.9 (2.2)	30.1 (2.6)
Birth weight (kg), mean (SD)	0.8 (0.1)	1.3 (0.1)	1.2 (0.2)
Small for gestational age, %	29.2	38.5	36.5
Male sex, %	41.7	45.4	44.6
Apgar at 1 minute, mean (SD)	5.7 (2.5)	6.9 (1.8)	6.6 (2.0)
Apgar at 5 minutes, mean (SD)	7.7 (1.6)	8.3 (1.2)	8.2 (1.3)

TABLE 2
Characteristics of initial hospitalization

	Birth weight group (%)			
	< 1,000 g (N = 48)	1,000–1,500 g (N = 174)	All infants (%; N = 222)	P value*
Days in intensive care unit, mean (SD)	57.3 (24.9)	21.8 (15.7)	29.4 (23.1)	< 0.001
Days in intermediate care, mean (SD)	21.7 (14.8)	18.5 (8.8)	19.2 (10.4)	0.490
Required CPAP	85.4	62.1	67.1	0.001
Days on CPAP, mean (SD)	10.8 (7.7)	4.8 (6.0)	6.4 (7.0)	< 0.001
Required mechanical ventilation	77.1	37.9	46.4	< 0.001
Days on mechanical ventilation, mean (SD)	15.7 (14.0)	6.1 (7.8)	9.4 (11.3)	< 0.001
Duration of hospitalization (days), mean (SD)	82.1 (32.2)	42.7 (19.9)	51.2 (28.2)	< 0.001
Weight at hospital discharge (kg), mean (SD)	2.1 (0.5)	2.0 (0.4)	2.0 (0.4)	0.482

CPAP = continuous positive airway pressure.
* P value is for the comparison of the two birth weight groups.

two infants required mechanical ventilation, and one patient died. The percentage of RSV respiratory infections in patients who required an emergency room evaluation was 27.4%, and the percentage of RSV respiratory infections that required hospitalization for respiratory infections among infants was 45.9%. The main diagnoses of respiratory infections that required emergency management at the emergency room (N = 68) were bronchial obstruction (48.5%), bronchiolitis (33.8%), laryngotracheobronchitis (7.4%), and pneumonia (2.9%). The main diagnoses in hospitalized patients with respiratory infections (N = 40) were bronchial obstructive syndrome (40.0%), bronchiolitis (37.5%), and pneumonia (20.0%).

The main risk factors associated with hospitalization caused by RSV infections were previous use of mechanical ventilation (OR = 3.1; 95% confidence interval [95% CI] = 1.1–8.8; $P = 0.036$) and chronic lung disease (OR = 2.5; 95% CI = 1.0–6.6; $P = 0.055$). There were only 24 children with at least one smoker in the house. Five people was the median number of people living in the same house as the infant (IQR = 4–7 people). Neither of these factors (smoking and crowding)

was a significant risk in our model. Additional multivariate analysis resulted in previous mechanical ventilation (OR = 2.72; 95% CI = 0.59–12.68, $P = 0.202$) and having contact with a child who attends daycare (OR = 2.10; 95% CI = 0.53–8.34; $P = 2.60$) being risk factors for hospitalization because of RSV infections, but neither achieved statistical significance (Table 4).

DISCUSSION

This study is the first epidemiological study evaluating the incidence of RSV respiratory infections in pre-term infants in Lima, Peru. We found an incidence of RSV hospitalizations of 116.2 per 1,000 child-years and an incidence of RSV respiratory infections that required emergency management (without hospitalization) of 103.9 per 1,000 child-years.

Estimates of RSV-associated severe acute lower respiratory infections are highly variable within studies and range from 10 to 200 per 1,000 child-years in children < 1 year of age. These studies included all children (not only pre-mature children) and were performed in different regions.[2] The

TABLE 3
Incidence of respiratory infections and follow-up data from discharge until 12 months of age

	Birth weight group		
	< 1,000 g (N = 41)	1,000–1,500 g (N = 170)	All infants (N = 211)
Child/days of observation	11,717	55,122	66,839
Number of phone or clinic visits two times a month	820	3,756	4,576
Total reported respiratory infections	148	788	936
Without medical evaluation	25	189	214
With an outpatient visit	71	448	519
With an ER evaluation	37	118	155
Required hospitalization	15	33	48
Total duration of respiratory infections, days	1,279	5,812	7,091
Total incidence of respiratory infections, episodes per child per year	5.2	5.8	5.7
Without medical evaluation	0.9	1.4*	1.3
With an outpatient visit	2.5	3.3*	3.2
With an ER evaluation	1.3	0.9*	0.9
Required hospitalization	0.5	0.2†	0.3
Documented respiratory infections that required an ER visit (nasal swabs performed)	11(6)	57(56)	68(62)
Documented respiratory infections that required hospitalization (nasal swabs performed)	11(10)	29(27)	40(37)
Incidence of RSV-associated respiratory infections, 1,000 children-years			
Required ER evaluation	69.9	111.1	103.9
Required hospitalization	244.9	88.9*	116.2
Prevalence of RSV infections, %			
Among infants that required ER evaluation for respiratory infections	33.3	26.8	27.4
Among infants that required hospitalization for respiratory infections	70.0	44.4	45.9

ER = emergency room.
* P < 0.05 for the comparison of the two birth weight groups.
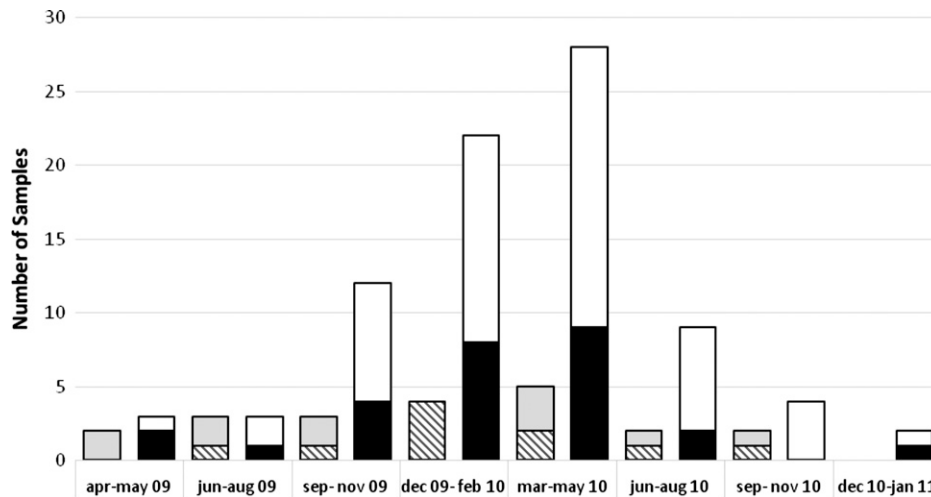† P < 0.01 for the comparison of the two birth weight groups.

FIGURE 1.　Seasonal distribution of nasopharyngeal samples among 211 pre-term infants who required emergency room visit or hospitalization because of a respiratory infection during their first 1 year of life after hospital discharge. Black, RSV-positive samples in infants > 1,000 g; white, RSV-negative samples in infants > 1,000 g; hatched, RSV-positive samples in infants < 1,000 g; gray, RSV-negative samples in infants < 1,000 g.

incidence of RSV hospitalizations in children with conditions like pre-maturity, chronic lung disease, congenital heart disease, and immunosuppression, considered high-risk groups, is also variable and ranges from 60 to 90 per 1,000 child-years.[8] The rates of outpatient emergency room treatment of confirmed RSV infections in children under 1 year of age, both pre-term and term, in the United States range from 40 to 60 per 1,000 child-years.[9] Although it is difficult to determine how much of this variation is caused by methodological differences and how much is because of variations in RSV epidemiology between study populations, when comparing our data with other studies, the incidence of RSV infections in pre-mature infants in Lima seems to be high. As a comparison at a regional level, in a prospective cohort study of 207 very low-birth weight (birth weight < 1,500 g) pre-mature infants followed until 1 year of age in Buenos Aires, Argentina, the incidence of RSV-associated hospitalizations was approximately 90 per 1,000 child-years of follow-up.[6,7]

Children with underlying conditions, such as pre-maturity, chronic lung disease, congenital heart disease, and immunosuppression, are at high risk for severe RSV disease.[8] Pre-maturity, a major risk factor for RSV hospitalization, goes along with small, immature, and vulnerable airways, an imma-ture immune system, an incomplete transfer of maternal anti-bodies, and an inadequate cellular immunity.[10] All of these factors, despite the absence of clinically defined chronic lung disease, are thought to contribute to the increase risk of severe disease. Other risk factors for RSV acquisition are birth before or during the RSV season, daycare attendance or older sibling in school or daycare, and breastfeeding for < 2 months.[10] Risk factors for RSV infection in developing countries are not well-defined, although crowding, indoor smoke pollution, and malnutrition may play a part in the development of more severe disease.[11] In this study, the only potential risk factors for RSV hospitalizations were previous mechanical ventilation requirement and chronic lung diseases, although these factors were not significant after adjusting for other factors in the multivariate analysis. Environmental factors, such as crowding and living with children who attended daycare or school, were not found to be significant in this setting; however, the study may not have been adequately powered to detect these additional risk factors.

Variation in the timing and intensity of RSV outbreaks among communities and difference across years may be caused by several factors that affect the likelihood of transmission, such as meteorological conditions, levels of population

TABLE 4
Risk factors for RSV-associated infections and hospitalizations in pre-term infants

	Bivariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Birth weight, kg	0.2 (0.0–1.2)	0.079	0.16 (0.01–3.74)	0.254
Gestational age, years	0.9 (0.7–1.1)	0.193	1.14 (0.86–1.52)	0.360
Maternal age, years	0.9 (0.9–1.0)	0.120	0.94 (0.87–1.01)	0.088
Lives with a child who attends daycare	2.3 (0.6–9.5)	0.236	2.10 (0.53–8.34)	0.290
Respiratory distress syndrome of the newborn	2.3 (0.8–6.7)	0.114	0.91 (0.19–4.34)	0.906
Chronic lung disease	2.5 (1.0–6.6)	0.055	1.67 (0.41–6.75)	0.472
Required mechanical ventilation	3.1 (1.1–8.8)	0.036	2.72 (0.59–12.68)	0.202
Pneumonia	1.8 (0.6–5.8)	0.293		
Sex	1.6 (0.6–4.1)	0.337		
Pulmonary hypertension	1.5 (0.3–7.6)	0.602		
Retinopathy of pre-maturity	1.4 (0.5–4.0)	0.546		
Persistent ductus arteriosus	1.2 (0.5–3.3)	0.698		
Family members with allergies	1.2 (0.5–3.3)	0.659		

immunity, and household crowding and population density conditions.[12,13] In temperate climates, such as in the United States, annual RSV outbreaks generally occur during the late fall, winter, and early spring months.[8,14] In South America, especially in the southern part of the continent (i.e., Chile and Argentina), some studies have shown a clear seasonality, with a peak around the fall and winter months (May to August).[5,7] However, in equatorial regions that lack dramatic seasonal temperature variations (i.e., Fortaleza, Brazil), RSV infection may have a peak in the rainy season (January to August).[15] In this study, we were not able to define a clear-cut RSV seasonality. However, we found a large proportion of RSV-positive samples during spring and summer (October to April) (Figure 1). We documented RSV infections and hospitalizations all year long in Lima (not just in winter).

This study has several limitations. First, during 2009, we had the influenza A(H1N1)pdm2009 virus pandemic; the effect of this outbreak on RSV infections is uncertain. However, some studies have shown that the H1N1v2009 strain had a modest impact on the epidemiology of other respiratory viruses.[16] Nevertheless, future studies are needed to confirm the current RSV incidence estimates in Lima. Second, we were not able to collect nasal samples on all respiratory infections that required an emergency room evaluation or hospitalization. Samples were collected in 40% (62 of 155) of emergency room visits and 77% (37 of 48) of hospitalizations for respiratory infections, because mothers were responsible for calling the research nurse during an emergency room evaluation or hospitalization. It is possible that this introduced some bias. For example, if samples were taken from the most severe infants with a higher likelihood of RSV infection, we are overestimating the true incidence rates of RSV. However, if samples were taken more frequently from infants with milder conditions (i.e., from infants from more responsible mothers with a higher likelihood of seeking medical evaluation with more mild cases) and thus, less likely to have RSV infections, it is possible that we are underestimating the true rates. Nevertheless, this study contributes to the clinical and epidemiological understanding of RSV infection in this population and similar populations.

CONCLUSIONS

In summary, the incidence of RSV-associated respiratory infections and hospitalizations in pre-mature infants in Lima was high; RSV-associated hospitalizations and emergency room evaluations occurred all year long, and infants with previous mechanical ventilation and chronic lung disease were at a somewhat higher risk for 1 rehospitalization with RSV during their first year of life. This study will help the development of proper guidelines for the management and prevention of RSV infection in resource-limited settings, like Peru and other countries in the region.

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