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Risk factors for hospitalization due to respiratory syncytial virus infection among infants in the Basque Country, Spain

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SUMMARY

This study analysed the role of several risk factors for hospitalization due to community-acquired, respiratory syncytial virus (RSV) infection. The risk factors detected in infants hospitalized for RSV infection in the first 24 months of life were compared with those in the general infant population in our region. There were 361 episodes of hospitalization in 357 infants. Eighty per cent of the infants did not present underlying conditions for severe RSV infection and only 10 (3%) were candidates for palivizumab prophylaxis. In multivariate analysis, birthweight of <2500 g was independently associated with hospitalization for RSV infection and was the most commonly detected medical risk factor. Other risk factors were maternal age at delivery <25 years, birth in the second half of the year, prematurity, suburban residence and congenital heart disease. In conclusion, together with well-known risk factors, we found that low birthweight was an independent factor for severe RSV infection.

INTRODUCTION

Respiratory syncytial virus (RSV) is the main cause of severe acute respiratory infection (ARI) in infants and young children, especially in the form of bronchiolitis and pneumonia [1, 2]. In developed countries, RSV infection is the main cause of hospitalization in infants [3] and 1–4% of children aged <1 year are hospitalized due to this infection [4–6]. RSV-related morbidity and mortality are higher in infants with certain underlying conditions such as prematurity, chronic bronchopulmonary disease and congenital heart disease [2, 4], while less information is available on the role of other conditions or risk factors. Moreover, the proportion of infants without risk factors within the total number of severe ARIs caused by RSV in the population aged <5 years has been little studied [7].

Prevention of severe infection in high-risk infants is achieved through immunoprophylaxis with specific antibody-containing preparations, especially humanized, murine monoclonal antibody (palivizumab). In the present study we analysed the demographic characteristics and underlying conditions in infants hospitalized for RSV infection, with the aim of identifying the percentage of infants with risk factors, the importance of these factors in hospitalization, and the foreseeable impact of current indications for palivizumab prophylaxis.

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METHODS

General characteristics

This retrospective study included all infants aged <2 years old, born between July 1996 and June 2000, who were hospitalized in the Hospital Donostia (Gipuzkoa, Basque Country, Spain) for virologically confirmed, community-acquired RSV infection. The Hospital Donostia is the public hospital for the capital of the province and surrounding regions and annually attends a population of ≈7000 infants aged <2 years old. This hospital receives more than 97% of paediatric hospitalizations in its catchment area and nasopharyngeal aspirate for virological analysis is routinely performed for 95% of children aged <5 years old admitted for bronchiolitis [6]. The inclusion criteria were: hospitalization for more than 24 h, age <2 years, date of birth in the study period, RSV detection in nasopharyngeal aspirate, and a discharge diagnosis of ARI. Only one positive result was considered in each patient except when positive results were separated by an interval of 2 or more months. Infants with nosocomial RSV infection, those in whom demographic data or data on the causes of hospitalization were lacking ($n=11$), and those born or resident outside the catchment area were excluded. The presence of RSV in nasopharyngeal aspirate was investigated through a commercial enzyme immunoassay (TestPack RSV, Abbott Laboratories, Chicago, IL, USA). We previously published the results of a population-based retrospective study performed in the same geographical area to determine the incidence of hospitalization for virologically confirmed, community-acquired RSV infection in children aged <5 years old, which included most of the infants in the present study. The annual hospitalization rate due to RSV infection between July 1996 and June 2000 was 37/1000 among infants aged <6 months, and was 25/1000 and 15/1000 in infants aged <12 and <24 months respectively [6]. Palivizumab prophylaxis was not used in this region until the autumn of 2000. The study was approved by the Human Research Ethics Committee of the Hospital Donostia.

Patient data

The medical records of infants included in this study were independently reviewed by two pediatricians. Demographic variables (age, sex, month of birth, month of hospitalization, ethnic origin, number of siblings born in the same delivery, the existence of older siblings, maternal age at delivery, and place of residence) and the medical variables of prematurity (gestational age <37 weeks), low birthweight (<2500 g), bronchopulmonary dysplasia, cystic fibrosis, congenital abnormality of the respiratory and/or upper gastrointestinal tract, congenital heart disease, neurological disorders, immunodeficiencies, human immunodeficiency virus (HIV) infection, cancer, diabetes mellitus, and chronic renal disease were recorded.

Other risk factors such as exposure to tobacco smoke in the family and attendance at a nursery school before the episode of RSV infection requiring hospitalization were studied through a questionnaire sent by post in 2003 to the parents of infants included in this study. Two months after the questionnaire was sent, parents who had not responded were contacted by telephone as a means of obtaining response.

Baseline population, variables studied and statistical analysis

In the cohort of hospitalized infants the distribution of the demographic variables of date of birth, sex, number of siblings born in the same delivery, maternal age and place of residence and the medical variables of prematurity and low birthweight was contrasted with the distribution of the same variables in the general infant population in our region obtained from the Basque Institute of Statistics. To do this, the records of infants living more than 24 h after delivery born between July 1996 and June 2000 in the study area were obtained, together with their corresponding demographic and medical data. Further, the records of infants with congenital heart disease and/or bronchopulmonary dysplasia were obtained from the registries of the Department of Pediatrics of the Hospital Donostia. In the analysis of risk factors, the above-mentioned variables were compared through the χ^2 test or Fisher's exact test (two-tailed), when the number of occurrences in a cell were less than five. Variables with a value of $P<0{\cdot}25$ in these analyses were introduced in a logistic regression model with backward stepwise selection to determine independent associations between hospitalization for RSV infection and the variables analysed. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined. Biologically plausible interactions (i.e. weight and gestational age) were introduced into the model. In all statistical tests, a value of $P<0{\cdot}05$ was considered significant.

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To facilitate comparison of the results obtained with those of other studies, the results for certain risk groups (prematurity and low birthweight) were expressed as the incidence of hospitalization, dividing the number of hospitalizations in each group selected by the total number of infants belonging to that group in the general infant paediatric population. Finally, to calculate the proportion of hospitalized infants suitable for prevention through palivizumab administration, we used the indications for prophylaxis of the American Academy of Pediatrics (AAP) [8].

RESULTS

During the study period there were 361 episodes of hospitalization for virologically confirmed RSV infection in infants aged <2 years, corresponding to 357 infants. Four infants were hospitalized on two occasions (at 3 and 10, 5 and 8, 4 and 16, and 8 and 21 months of age respectively).

Demographic variables

Of the hospitalized infants, 191 (53·5%) were boys, a proportion similar to that found in the reference infant population (51·9%) (Table 1). Most of the episodes causing the first hospitalization occurred in infants aged <1 year (306, 84·8%), being 141 (39·1%) in infants aged <3 months (Fig. 1). Sixteen infants were from gypsy families (4·5%) and one was from Maghreb (0·3%), while the remaining infants were Caucasian. Most of the hospitalizations (323, 90·5%) occurred in cold months (November to March) (Fig. 2), most frequently corresponding to infants born in the second half of the year. Hospitalization for RSV infection was more frequent in infants with young mothers and those living in suburban areas (Table 1).

Medical risk factors for hospitalization

Prematurity and birthweight

The percentage of RSV-associated hospitalizations was greater in premature infants and in those with low birthweight. When these data are expressed as the incidence of hospitalization, in the first year of life the incidence was 44·2 cases/1000 infants (5/113) for those born with a gestational age of <33 weeks, and was 78·1 cases/1000 infants (26/333), 29·4 cases/1000 infants (40/1362), and 19·1 cases/1000 infants (233/12 178), for those born with a gestational age of 33–35 weeks, 36–37 weeks and ⩾38 weeks respectively. The incidence according to birthweight was: 58·4 cases/1000 infants (52/891) for those with a birthweight of <2500 g *vs.* 19·3 cases/1000 infants (253/13 095) for those with the birthweight of ⩾2500 g. Combining gestational age and birthweight, the incidence of hospitalization for RSV among infants aged <1 year was: 80·9 (28/346), 48·8 (14/287) and 34·9 (9/258) cases/1000 infants for those with birthweight <2500 g and a gestational age of ⩽35, 36–37 and ⩾38 weeks respectively *vs.* 30·0 (3/100), 24·2 (26/1075) and 18·8 (224/11 920) cases/1000 infants for the same gestational age but with a birthweight of ⩾2500 g. In the second year of life, the incidence of hospitalization was low, being <14 cases/1000 infants in the six subgroups. When the data for both variables were stratified in six subgroups (of the cases accumulated in the 2 years), the incidence of hospitalization was greater in infants with a birthweight of <2500 g than in those with higher birthweight and the same gestational age (Mantel–Haenszel summary $\chi^2 = 12{\cdot}94$, $P < 0{\cdot}001$, OR 2·18, 95% CI 1·39–3·14).

Cardiac malformations

Eight infants (2·2%) had congenital cardiac malformations. Three of these had required surgical treatment in the previous months: one with atrioventricular septal defect in the context of Down syndrome, another with Di George syndrome and complex congenital heart disease and another with tetralogy of Fallot. A fourth child was under medical treatment for atrioventricular septal defect, pending clinical course and possible surgical correction. The four remaining infants had no haemodynamic compromise (atrial septal defect or patent ductus arteriosus). In the same period 108 (0·8%) infants with congenital heart defects were diagnosed in the reference infant population (Fisher's exact test $P = 0{\cdot}008$), of which 22 (0·2%) had haemodynamic compromise (Fisher's exact test $P = 0{\cdot}004$).

Underlying pulmonary diseases and other diseases

None of the infants had bronchopulmonary dysplasia while in the same period eight infants in the reference population were diagnosed with this underlying condition. One child had a congenital bronchial

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Table 1. *Distribution of 357 infants born between July 1996 and June 2000 hospitalized for respiratory syncytial virus (RSV) infection according to various demographic variables and the clinical variables of gestational age and birthweight. Comparison with the general infant population composed of infants living more than 24 h after delivery in the same period and geographical area*

	Infants hospitalized for RSV infection		General infant population		Statistical test		
Study variable	*n*	(%)	*n*	(%)	Test	*P* value	OR (95% CI)
Sex							
Male	191	(53·5)	7255	(51·9)	$\chi^2=0{\cdot}37$	0·543	1·07 (0·86–1·32)
Female	166	(46·5)	6731	(48·1)			
Month of birth							
Jan.–Mar.	62	(17·4)	3528	(25·2)	$\chi^2=11{\cdot}46$	<0·001	0·62 (0·47–0·83)
Apr.–June	56	(15·7)	3557	(25·4)	$\chi^2=17{\cdot}55$	<0·001	0·55 (0·40–0·73)
July–Sept.	105	(29·4)	3531	(25·3)	$\chi^2=3{\cdot}19$	0·074	1·23 (0·97–1·56)
Oct.–Dec.	134	(37·5)	3370	(24·1)	$\chi^2=34{\cdot}06$	<0·001	1·89 (1·51–2·37)
Twin siblings in the same delivery							
⩾1*	16	(4·5)	449	(3·2)	$\chi^2=1{\cdot}79$	0·180	1·41 (0·82–2·41)
01	341	(95·5)	13 537	(96·8)			
Maternal age (years)†							
<25 years	38	(11·0)	703	(5·0)	$\chi^2=24{\cdot}24$	<0·001	2·32 (1·62–3·32)
25–34·9 years	240	(69·1)	10 294	(73·6)	$\chi^2=3{\cdot}42$	0·064	0·80 (0·63–1·02)
>35 years	69	(19·9)	2989	(21·4)	$\chi^2=0{\cdot}45$	0·504	0·91 (0·69–1·20)
Rural-suburban/urban residence†							
Rural-suburban	224	(64·6)	8088	(57·8)	$\chi^2=6{\cdot}28$	0·012	1·33 (1·06–1·67)
Urban	123	(35·4)	5898	(42·2)			
Gestational age (weeks)†							
<33	7	(2·0)	113	(0·8)	Fisher's	0·029	n.a.
33–35	26	(7·3)	333	(2·4)	$\chi^2=34{\cdot}66$	<0·001	3·24 (2·09–4·98)
36–37	47	(13·2)	1362	(9·7)	$\chi^2=4{\cdot}79$	0·029	1·41 (1·02–1·95)
⩾38	275	(77·5)	12 178	(87·1)	$\chi^2=27{\cdot}96$	<0·001	0·51 (0·39–0·66)
Birthweight (g)†							
<2000	16	(4·5)	247	(1·8)	$\chi^2=14{\cdot}36$	<0·001	2·62 (1·50–4·49)
2000–2499	43	(12·1)	644	(4·6)	$\chi^2=42{\cdot}52$	<0·001	2·85 (2·02–4·01)
2500–2999	60	(16·9)	2787	(19·9)	$\chi^2=2{\cdot}06$	0·151	0·81 (0·61–1·09)
⩾3000	237	(66·5)	10 308	(73·7)	$\chi^2=9{\cdot}06$	0·002	0·71 (0·57–0·89)
Heart disease							
Heart disease (all)	8	(2·2)	108	(0·8)	Fisher's	0·008	n.a.
Unstable heart disease	4	(1·1)	22	(0·2)	Fisher's	0·004	n.a.
No heart disease	349	(97·7)	13 878	(99·2)			
Total	357		13 986				

OR, Odds ratio; CI, confidence interval; n.a., not applicable.

* Fourteen twins and two triplets.

† Two, one, 10 and 10 observations lost in the series of hospitalized infants in the variables: gestational age, birthweight, maternal age and suburban/urban residence respectively.

cyst requiring lobectomy and another child had laryngotracheomalacia. Finally, one infant had severe neuromuscular disease due to mitochondrial myopathy and another infant had a thoracic neuroblastoma which was diagnosed during the RSV-related hospitalization. No children had diabetes mellitus or chronic renal disease.

Number of patients with risk factors for hospitalization for RSV infection

In total, 72 (20·2%) infants had at least one risk factor for hospitalization due to RSV infection when the following conditions were considered as risk factors: birthweight <2500 g ($n=59$), gestational age

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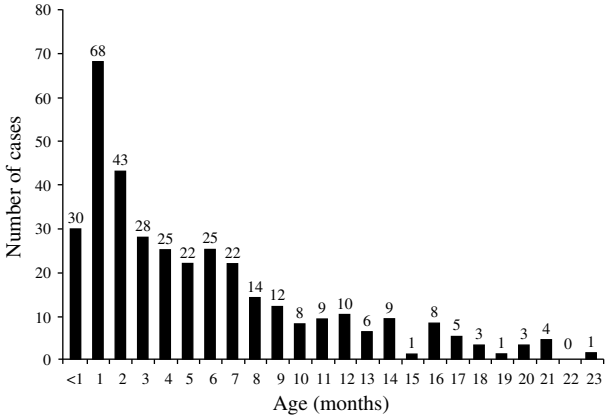

Fig. 1. Distribution by age of infants born between July 1996 and June 2000 hospitalized for virologically confirmed respiratory syncytial virus infection in the first 2 years of life.

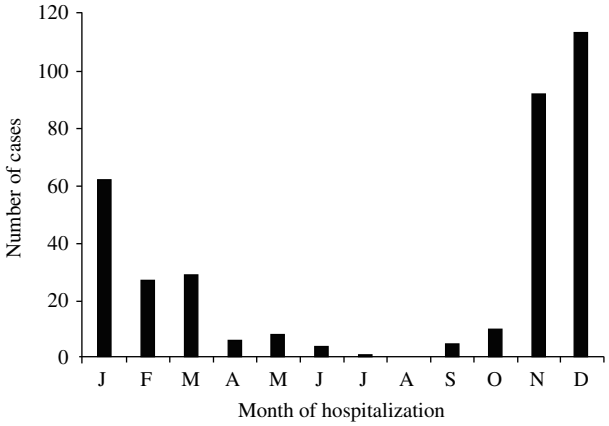

Fig. 2. Monthly distribution of children hospitalized due to severe respiratory syncytial virus infection.

<37 weeks ($n=44$), congenital heart disease with haemodynamic compromise requiring medical or surgical treatment ($n=4$), bronchial cyst ($n=1$), laryngotracheomalacia ($n=1$), muscle disease ($n=1$) and cancer ($n=1$). When low birthweight was not considered, 41 of the 44 premature infants (93·2%) presented no other risk factors.

Admission to the paediatric intensive care unit (*PICU*)

Twenty-three infants were admitted to the PICU (6·4%). Of these, 19 (82·6%) were aged <3 months old ($\chi^2=18{\cdot}90$, $P<0{\cdot}001$). Of these later 19 infants, six weighed <2500 g at birth (two of them born at a gestational age <37 weeks and one with bronchial cyst), one had a congenital heart disease with haemodynamic compromise, and the remaining 12 had no known risk factors.

Multivariate analysis of risk factors associated with hospitalization

An association was found between hospitalization for RSV and birthweight ($P<0{\cdot}001$), gestational age ($P=0{\cdot}022$), maternal age ($P<0{\cdot}001$), suburban residence ($P=0{\cdot}017$), birth in the second half of the year ($P<0{\cdot}001$) (in both trimesters), and haemodynamically unstable heart disease ($P<0{\cdot}001$) (Table 2). No association was found with multiple births or congenital heart disease, considered as one group. The incidence of hospitalization in infants without the risk factors identified in multivariate analysis was 12·5/1000 (8·5–17·6 cases/1000 infants) (32/2566) *vs.* 100/1000 (65·8–144·1/1000 infants) (25/250) for premature infants with low birthweight born in the second half of the year.

Epidemiologically relevant variables obtained through survey

In total, 271 families responded to the postal survey (75·9%). The mothers of 30·3% (82/271) of the infants regularly smoked during pregnancy and 56·8% (154/271) of the infants were exposed to tobacco smoke after birth because one or both parents regularly smoked in the home. These figures could be expected from the prevalence of smoking in Spain, given that 44% of women and 50% of men aged from 25 to 34 years smoked during the study period [9], even though 42% of women smokers quit during pregnancy [10]. Finally, 49 infants (18%) were attending nursery school when the first episode of hospitalization for RSV infection occurred and this percentage was 34·8% (8/23) in infants aged >12 months. These figures are higher than those for the general infant population, ~10% of which attended nursery school in the second year of life.

Hospitalization for RSV infection and AAP indication for palivizumab

Ten infants (2·8%) had risk factors that made them suitable candidates for palivizumab prophylaxis according to the indications of the AAP [8]: one because he was a neonate with a gestational age of <32 weeks and was aged <6 months old at the beginning of the RSV season; four because they had haemodynamically unstable congenital heart disease and were aged <24 months at the beginning of the RSV season; four because they were born at 32 to ⩽35 weeks of gestation, were aged <6 months at the beginning of the RSV season, were exposed to environmental air pollutants (including tobacco

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Table 2. *Summary of multivariate analysis (logistic regression) of risk factors for hospitalization among infants born in Gipuzkoa (Basque Country, Spain) between July 1996 and June 2000 hospitalized for respiratory syncytial virus (RSV) infection in the first 2 years of life (α constant of the model −4·467). The table shows the variables accepted by the model, which excluded two variables initially submitted for study: multiple births and heart disease considered as a whole (including all infants with heart disease in the same group whether haemodynamically stable or not)*

Variable	Coefficient	χ^2	*P*	OR (95% CI)
Haemodynamically unstable heart disease	2·547	17·64	<0·001	12·77 (3·89–41·89)
Maternal age (<25 years)*	0·822	21·19	<0·001	2·28 (1·60–3·23)
Birthweight (<2500 g)†	0·807	17·32	<0·001	2·24 (1·53–3·28)
Period of birth‡	0·735	40·22	<0·001	2·09 (1·66–2·62)
Gestational age (<37 weeks)§	0·477	5·28	0·022	1·61 (1·07–2·42)
Suburban residence‖	0·274	5·72	0·017	1·32 (1·05–1·65)

OR, Odds ratio; CI, confidence interval.
* Maternal age classified as <25 years and ⩾25 years (reference ⩾25 years).
† Birthweight classified as <2500 g and ⩾2500 g (reference ⩾2500 g).
‡ Period of birth classified into two periods: during the first or second half of the year (reference birth in the first 6 months of the year); when date of birth by trimester was included, the third and fourth trimesters were statistically significant ($\chi^2 = 11{\cdot}96$, $P = 0{\cdot}001$ and $\chi^2 = 30{\cdot}70$, $P < 0{\cdot}001$ respectively).
§ Gestational age <37 weeks or ⩾37 weeks (reference ⩾37 weeks).
‖ Urban or suburban residence (adjacent satellite towns) (reference urban setting).

smoke at home) and had school-aged siblings; and one born at 33 weeks of gestation, aged <6 months at the beginning of the RSV season with congenital abnormalities of the airways and school-aged siblings.

DISCUSSION

Numerous studies have analysed the association between severe RSV infection and distinct risk factors but, unlike the present study, few have been performed in non-selected hospitalized patients with virologically confirmed infection and few have taken into account the incidence of these risk factors in the general infant population in which the study was performed.

Like previous studies, we observed a greater risk of hospitalization among younger infants, as well as among those who were born near the beginning of the RSV season [4, 11–14]. A total of 39% of hospitalized infants and 83% of those treated in the PICU were aged <3 months, showing the greater severity of RSV infection in younger infants. The risk of hospitalization was higher in infants with younger mothers and in those who lived in the suburbs. Both factors are associated with low socio-economic status, a factor that we have not been able to investigate, but which has been related to a greater risk of severe RSV infections [1, 2]. Recently, young maternal age has been independently associated with a higher risk of bronchiolitis-associated deaths in the United States [15]. Interestingly, 5% of the infants hospitalized in that study belonged to the gypsy ethnic group, a proportion higher than that in our population, which, lacking official statistics, we estimate is lower than 1% [16]. This finding is probably related to the lower socio-economic status of these families and presents similarities with the situation found in some minority ethnic groups, among which the incidence rates of hospitalization due to RSV infections or bronchiolitis were higher than those among the general paediatric population [17, 18].

Prematurity is an underlying condition that is frequently identified in children with severe RSV infection [1–4]. The incidence of hospitalization for RSV infection in premature infants in the present series was two or three times higher than that in term infants, a finding that is in agreement with those of other studies [5, 19]. It is noteworthy that most of the premature infants in the present series had no underlying diseases, providing evidence that premature infants without underlying conditions are at increased risk of developing severe RSV infection. The hospitalization rates observed in the first year of life in the present study were within the range obtained by Boyce et al. in a large study that used the Medicaid database in the United States [4] (65·9/1000

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and 57·2/1000 for children with a gestational age of 29 to <33 weeks and 33 to <36 weeks respectively *vs.* 44·2/1000 and 78·1/1000 in the present study). The risk of hospitalization for RSV infection was drastically reduced in the second year of life.

Stratification of gestational age according to birthweight suggested that the latter was a risk factor for severe RSV infection independently of gestational age, a finding that was confirmed in the multivariate analysis. The incidence of hospitalization in the first year of life in low birthweight infants with a gestational age of ⩽35, 36–37 and ⩾38 weeks was approximately twice that of infants with the same gestational age but who had a birthweight of ⩾2500 g. Moreover, most of the infants with a gestational age of ⩾36 weeks and low birthweight (25/28) did not present other risk factors. Few studies that have investigated the role of risk factors in severe RSV infection have considered the variable of low birthweight [4, 5, 7, 19]. Furthermore, many studies included a large number of premature infants, a condition that is closely related with low birthweight, thus hampering independent evaluation of this factor. Some recent studies have found that low birthweight independently increases the risk of hospitalization due to RSV infection [11, 20, 21] and the risk of RSV-associated death [3, 15]. Our results reinforce the observation that low birthweight should be considered as an underlying condition that increases the severity of RSV-related illness.

Infants with congenital heart disease had an increased risk of hospitalization for RSV infection, which was observed only in children with heart disease with haemodynamic compromise. Other authors have reported that haemodynamically significant congenital heart disease is a risk factor for more severe RSV infection, with more frequent and more prolonged hospitalization, a greater number of complications and admissions to the ICU and greater mortality [4, 22, 23].

In the present study only 2·8% of the infants fulfilled the criteria of the AAP for palivizumab prophylaxis. Among infants admitted to the ICU, this percentage was 13·0% (3/23). This finding underscores the observations made by Prais et al. who recently reported similar results in Israel, observing that 84% of the infants admitted to 11 PICUs for severe bronchiolitis were not candidates for RSV prophylaxis according to AAP criteria [24]. If future studies report low birthweight to be an independent risk factor for RSV-related hospitalization, a placebo-controlled trial ought to be implemented to demonstrate the effectiveness of palivizumab in this situation, as a previous step to be considered in the guidelines for indications for palivizumab prophylaxis. Nevertheless, most of the infants hospitalized in the present study did not present risk factors (78·8%) and were previously healthy. This result is in agreement with those of several studies performed in the last few years in developed countries, reporting that low-risk infants account for between 75 and 98% of RSV-related hospitalizations [5, 7, 19, 25]. Due to its high cost, palivizumab should not be used in the absence of risk factors. Therefore, to reduce significantly the incidence of hospitalization due to severe RSV infection, the development of effective vaccines against RSV should be a priority.

DECLARATION OF INTEREST

None.

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