Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: http://www.tandfonline.com/loi/icmo20

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To cite this article: Manuel Sanchez-Luna, Francisco J. Elola, Cristina Fernandez-Perez, Jose L. Bernal & Adriana Lopez-Pineda (2016): Trends in respiratory syncytial virus bronchiolitis hospitalizations in children less than 1 year: 2004–2012, Current Medical Research and Opinion, DOI: 10.1185/03007995.2015.1136606

To link to this article: http://dx.doi.org/10.1185/03007995.2015.1136606

Accepted author version posted online: 28 Dec 2015.
Published online: 03 Feb 2016.

CURRENT MEDICAL RESEARCH AND OPINION, 2016
http://dx.doi.org/10.1185/03007995.2015.1136606
Article ST-0395.R2/1136606

Taylor & Francis
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ORIGINAL ARTICLE

Trends in respiratory syncytial virus bronchiolitis hospitalizations in children less than 1 year: 2004–2012

Manuel Sanchez-Luna[a], Francisco J. Elola[b], Cristina Fernandez-Perez[b], Jose L. Bernal[c] and Adriana Lopez-Pineda[b]

[a]Department of Neonatology, Gregorio Marañon Hospital, Madrid, Spain; [b]Institute Foundation for the Improvement of Health Care, Madrid, Spain; [c]Control Management Service, 12 de Octubre Hospital, Madrid, Spain

ABSTRACT

Objective To analyze trends in health outcomes and the influence of risk factors in children under 1 year with acute bronchiolitis due to respiratory syncytial virus (RSV bronchiolitis). A risk-adjustment model for RSV bronchiolitis in-hospital mortality was also developed.

Research design and methods Retrospective study of hospitalizations for RSV bronchiolitis in children aged <1 year from 2004 to 2012. We used nationally representative data from the Spanish National Health Service records.

Results Over the study period, the annual hospital discharges for RSV bronchiolitis ranged between 6390 and 8637. The annual in-hospital mortality rate ranged from 120 (2004) to 69 (2012) per 100,000 hospitalizations and the mean length of stay decreased steadily from 6.5 to 5.2 days ($p < 0.001$); 98.3% of hospitalizations for RSV bronchiolitis were children without risk factors. The in-hospital mortality rate due to RSV bronchiolitis in children with risk factors was 18.8 times higher than non-high-risk children and, in adjusted analyses, the OR of in-hospital mortality due to RSV bronchiolitis was higher than that due to other causes.

Limitations This study is a retrospective analysis, based on administrative data. It does not include data about pre- or in-hospital treatments, and has the limitations inherent in procedures for determining risk-adjusted mortality rates. Socioeconomic and environmental factors have not been considered in this study.

Conclusions RSV bronchiolitis is a leading cause of hospitalizations for infants under 1 year and has not shown incidence reduction over a 9 year period. Risk factors increase the in-hospital mortality risk and it is higher if the hospitalization cause is RSV bronchiolitis than any other reason.

ARTICLE HISTORY
Received 2 September 2015
Revised 20 December 2015
Accepted 23 December 2015
Published online 28 January 2016

KEY WORDS
Bronchiolitis – In-hospital mortality – Readmission – Respiratory syncytial virus

Introduction

Bronchiolitis is the most common respiratory disease in children under 1 year of age and is also a major cause of hospitalization in young children, especially during winter[1]. The majority of hospital admissions because of bronchiolitis take place during the first few months of life[2]. Respiratory syncytial virus (RSV) is the major cause of acute bronchiolitis and the most frequent cause of hospitalization within the pediatric population in industrialized countries[3–5]. Acute bronchiolitis due to RSV (RSV bronchiolitis) has longer hospital stays[6] and a higher risk of admission to the intensive care unit[7] than bronchiolitis due to other causes. The social, economical and health impacts are relevant and go beyond the acute episode phase[8].

Children with pre-existing morbidities are at an increased risk of hospitalization for acute lower respiratory infection[7,9–11]. RSV causes a more severe form of bronchiolitis in children with risk factors including prematurity, cardiovascular disease and immunodeficiency[12]. However, most children hospitalized for RSV bronchiolitis are previously healthy[10,13]. Despite this, the majority of studies were focused on the association between risk factors and RSV bronchiolitis incidence and mortality[9,10,12].

The objective of this study was to analyze national temporal trends in RSV bronchiolitis hospitalizations, in-hospital mortality and readmissions for children under 1 year in Spain between 2004 and 2012. In addition, we examined the influence of risk factors to health outcomes (hospitalization, in-hospital mortality and hospital readmission) in children less than 1 year of age with RSV bronchiolitis and we developed a risk-adjustment model for RSV bronchiolitis in-hospital mortality.

Patients and methods

Study design and setting

This was a retrospective analysis of pediatric hospitalizations using the Minimum Basic Data Set (MBDS)[14] for the years 2004 through to 2012. MBDS is a compulsory national hospital discharge register by the Spanish National Health

CONTACT Dr. Manuel Sanchez-Luna msluna@salud.madrid.org Neonatology Division, Gregorio Marañon Hospital, O'Donnell 48, 28009 Madrid, Spain

Table 1. Definition of risk groups for RSV bronchiolitis hospitalizations and mortality.

High-risk group	Hospitalized children under 1 year old with one or more of the following risk factors (as principal or secondary diagnosis)*: • Prematurity: – ≤28 weeks (ICD-9 codes 765.21–765.24 or 765.20 and 765.0x) – 29–32 weeks (ICD-9 codes 765.25 or 765.26) – 33–36 weeks (ICD-9 codes 765.27 or 765.28) – If 765.20 or no code for gestation ages, they were grouped by 765.1x: ✓ ≤28 weeks = 765.11–765.13 ✓ 29–32 weeks = 765.14–765.15 ✓ 33–36 weeks = 765.16–765.17 • Congenital Heart Disease: ICD-9 codes 416.8, 425.4, 746.0, 745.x (except 745.5), 746.x (except 746.87, 746.89 and 746.9), 747.0, 747.10, 747.11, 747.21, 747.3, 747.41, 747.49. Hemodynamically significant congenital heart disease was considered if 745.5, 746.87, 746.89 and 746.9 were in relation to 428.x or 416 or 747.83 or 770.83 or 782.5 codes • Chronic Lung Disease (ICD-9 code 770.7) • Down's syndrome (ICD-9 code 758.0) • Velo-cardio-facial syndrome (ICD-9 code 758.32) • Immunodeficiencies (ICD-9 codes 042 or 279) • Heart transplantation (ICD-9 codes 33.6, 37.51 or 996.83) • Neuromuscular disorders (ICD-9 codes 729.1 or 740 or 741 or 742)
Non-high-risk group	Hospitalized children under 1 year old without the risk factors mentioned above, except 765.20 without 765.0x (not included either group)

*Risk factors for severe RSV bronchiolitis.

Service (SNHS). The diagnoses and procedures collected are coded according to the International Disease Classification, Clinical Modification (ICD-9-CM)[15]. The Institutional Review Board did not require human subjects review or approval for this study.

Population

The MBDS includes 1,328,563 discharges for patients aged <1 year old between 2004 and 2012. MBDS does not include discharge records of healthy newborn infants at birth. The analysis focused on patients with RSV bronchiolitis (ICD-9 Diagnostic Code 466.11) as the principal diagnosis.

High-risk group: a relevant number of risk factors for hospitalizations and in-hospital mortality due to RSV bronchiolitis have been identified[9,10,12,16]. We analyzed the risk factors shown in Table 1, based on the recommendation criteria for immunoprophylaxis (with palivizumab) from the Spanish Society of Neonatology[17] and the Spanish Society of Paediatric Cardiology[18]. No other risk factors were considered[9,19–23] in order to have a clear definition of the 'high-risk' population.

All other hospitalized children without any of these medical conditions were considered part of the non-high-risk group.

Outcome measures

The outcome measures were: incidences of hospitalization due to RSV bronchiolitis, in-hospital mortality, defined as mortality during RSV-associated hospitalizations among children with a primary diagnosis of RSV bronchiolitis, and readmissions, defined as hospitalizations for any cause (except staged hospitalization) within 30 days after discharge for RSV bronchiolitis.

Statistical analysis

Relative frequencies were used for qualitative variables. Odds ratios (ORs) were estimated to assess the effect of the risk factors on the outcomes (incidences of hospitalization, readmissions and in-hospital mortality due to RSV bronchiolitis), assuming that the non-high-risk group is the reference group. We assessed the association between RSV bronchiolitis risk factors and outcome variables (in-hospital mortality and hospital readmission) by using a chi-square test. Temporal trends were evaluated on an annual time scale (1 year of hospital discharges) using a chi-square test for linear trend proportions and comparing the annual linear change with the first reference. We examined the differences between high-risk and non-high-risk groups by using a multilevel model and taking the center effect into account. The ORs and their 95% confidence intervals (CIs) were evaluated using simple and multilevel logistic regression models and taking the center effect into account. We included in the multilevel analysis only those variables that were statistically significant in the univariate analysis. In order to estimate the impact of the risk population on in-hospital mortality rates and readmissions we calculated the stratified OR (for RSV bronchiolitis hospitalizations and non-RSV bronchiolitis hospitalizations) by introducing the interaction term in the multilevel logistic model. We fit mixed and multilevel logistic regression models to examine hospital discharges. We calculated the intra-hospital correlation coefficient in order to measure the proportion of variance explained by the differences between hospitals and the area under the curve (AUC) of the risk provided by the model to measure the discrimination. In-hospital mortality and readmission outcomes were analyzed by comparing: 1. high-risk group versus non-high-risk group hospitalized for all causes (all cases); 2. high-risk group versus non-high-risk group with RSV bronchiolitis as principal diagnosis; 3. high-risk group versus non-high-risk group hospitalized for any other cause than RSV bronchiolitis as principal diagnosis (due to other causes). All statistical tests were performed considering a significance level of 95% ($p = 0.05$). All analyses used Stata version 13.0.

Results

Over the 9 year study period, MBDS recorded 122,832 discharges (9.2% of all discharges) for acute bronchiolitis as the principal diagnosis among children <1 year old (ICD-9 code 466.1x); with 63,990 (52.1%) of them hospitalized because of RSV bronchiolitis, which was the second most frequent

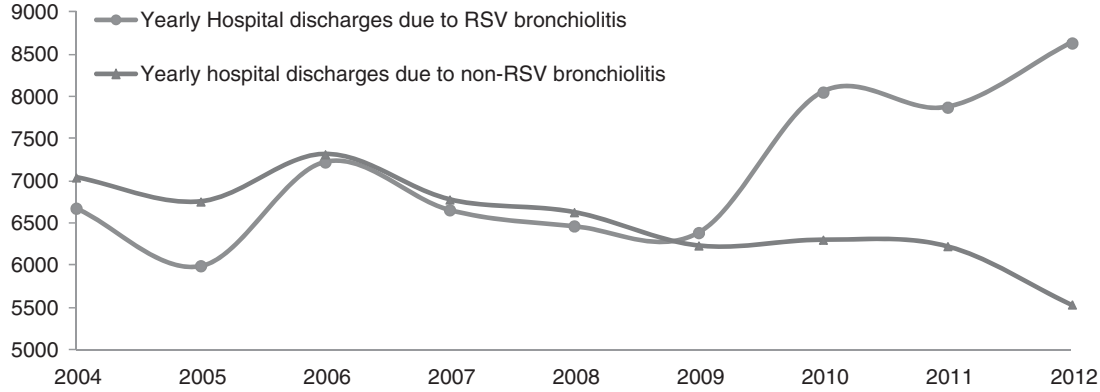

Figure 1. Yearly hospital discharges due to RSV bronchiolitis and non-RSV bronchiolitis.

Table 2. Distribution of risk factors for children under 1 year hospitalized with RSV bronchiolitis/other causes.

Risk factors		Total children <1 year		*p*	Odds ratio[a]	95 CI%	
		RSV bronchiolitis, *n* *N* = 63,990	Total hospital discharges, *n* *N* = 1,328,563			Lower	Upper
Prematurity		54	179,710	<0.001	0.005	0.004	0.007
Type of prematurity	≤28 w	4	14,566	<0.001	0.005	0.002	0.012
	29–32 w	7	35,667	<0.001	0.003	0.002	0.007
	33–36 w	43	129,458	<0.001	0.006	0.004	0.008
Congenital heart disease		670	48,802	<0.001	0.267	0.248	0.289
Chronic lung disease		55	6019	<0.001	0.182	0.139	0.237
Down's syndrome		197	6317	<0.001	0.635	0.551	0.732
Velo-cardio-facial syndrome		4	126	0.393	0.648	0.239	1.754
Inmunodeficiencies		27	1307	<0.001	0.417	0.285	0.61
Heart transplantation		0	21		Undefined		
Neuromuscular disorders		130	12,190	<0.001	0.211	0.178	0.251

[a]Assuming non-high-risk group is the reference group.

diagnosis at the time of discharge after a 'newborn observation suspected infectious condition' diagnosis (ICD-9 V29.0).

Temporal trends in incidence, in-hospital mortality and readmission

The total number of yearly hospital discharges for RSV bronchiolitis (ICD-9 code 466.11) in children under 1 year ranged between 5997 (2005) and 8637 (2012), whereas the total number of discharges for acute bronchiolitis not due to RSV (ICD-9 code 466.19) ranged between 7043 cases in 2004 and 5538 cases in 2012 (Figure 1). The hospitalization rate (discharges per 1000 children under 1 year) for RSV bronchiolitis increased over the period (from 19 to 24.9). The annual in-hospital mortality rate for infants hospitalized with RSV bronchiolitis decreased from 120 incidences per 100,000 hospitalizations in 2004 to 69 per 100,000 hospitalizations in 2012; however, this decrease was not statistically significant when adjusted by complexity. Readmission rates remained unchanged (7.9% in 2004 vs 7.4% in 2012, $p = \text{NS}$). The mean length of stay steadily decreased from 6.5 to 5.4 days ($p < 0.001$).

Risk factors in children hospitalized with RSV bronchiolitis

We analyzed the presence of risk factors that have been associated with RSV bronchiolitis (Table 2). A total of 62,904 (98.4%) children hospitalized for RSV bronchiolitis belonged to the non-high-risk group. The hospitalization rate of the high-risk group was significantly lower than the non-high-risk group, with OR <1 for each risk factor (Table 2). Analysis was performed again excluding children hospitalized at birth, since these infants cannot be hospitalized for bronchiolitis due to community-acquired RSV infection, and we also found that the association between risk factors and a lower hospitalization risk was significant. Table 3 compares in-hospital mortality and readmission rates for RSV bronchiolitis between high-risk and non-high-risk groups. The in-hospital mortality rate due to RSV bronchiolitis in the high-risk group was 18.8 times higher than for the non-high-risk group ($p < 0.001$), whereas the readmissions rate was 3.7 times higher ($p < 0.001$).

Risk adjustment of in-hospital mortality and readmissions due to RSV bronchiolitis

All the selected factors (Table 1) were statistically significant risk factors for in-hospital mortality and readmissions, except velo-cardio-facial syndrome and heart transplantation, for which it was not possible to calculate the ORs due to the low number of cases (Table 4). For prematurity, chronic lung disease and Down's syndrome we obtained the highest ORs. However, the confidence intervals are broad due to the limited number of cases of children with high-risk factors

Table 3. In-hospital mortality and readmission rates for RSV bronchiolitis in high-risk and non-high-risk groups.

	Non-high-risk		High-risk		Total	
	n	%	*n*	%	*n*	%
Mortality	32	0.1	10	0.9	42	0.1
Total	62,936		1054		63,990	
OR (95 CI%)	1		18.83 (9.23–38.40)*			
Readmissions	4535	7.2	231	22.1	4766	7.5
Total	62,904		1044		63,948	
OR (95 CI%)	1		3.68 (3.15–4.25)*			

*$p < .001$.

Table 4. Influence of the risk factors on in-hospital mortality and readmission rates for RSV bronchiolitis.

Mortality		*N*	%	*p*	OR	95% CI	
Prematurity		1	1.85	0.001	29.4	3.97	217.69
Gestational age	≤28 w	0	0.00		Undefined		
	29–32 w	0	0.00		Undefined		
	33–36 w	1	2.33	0.001	37.11	4.99	276
Congenital heart disease		6	0.90	<0.001	15.88	6.67	37.83
Chronic lung disease		1	1.82	0.001	28.86	3.90	213.58
Down's syndrome		3	1.52	<0.001	25.28	7.75	82.49
Velo-cardio-facial syndrome		0	0.00		Undefined		
Heart transplant		0	0.00		Undefined		
Neuromuscular disorders		1	0.77	0.014	12.07	1.65	88.38
Inmunodeficiency		0	0.00		Undefined		
Number of risk factors	1	8	0.82	<0.001	16.28	7.48	35.42
	≥2	2	2.50	<0.001	50.4	11.87	213.96
Readmission		*N*	%	*p*	OR	CI (95%)	
Prematurity		21	39.62	<0.001	3.66	3.15	4.27
Gestational age	≤28 w	2	50.00	0.012	12.47	1.76	88.51
	29–32 w	2	28.57	0.055	4.99	0.97	25.71
	33–36 w	17	40.48	<0.001	8.48	4.57	15.71
Congenital heart disease		129	19.43	<0.001	3.05	2.51	3.71
Chronic lung disease		19	35.19	<0.001	6.76	3.87	11.83
Down's syndrome		34	17.53	<0.001	2.65	1.83	3.84
Velo-cardio-facial syndrome		2	50.00	0.012	12.42	1.75	88.21
Heart transplant		0	0.00		Undefined		
Neuromuscular disorders		39	30.23	<0.001	5.42	3.72	7.89
Inmunodeficiency				<0.001	4.35	1.84	10.3
Number of risk factors	1	213	22.05	<0.001	3.64	3.12	4.25
	≥2	18	23.08	<0.001	3.86	2.28	6.54

hospitalized for RSV bronchiolitis. Premature children born between 33 and 36 weeks of gestation were associated with a 37 times higher risk of in-hospital mortality due to RSV bronchiolitis compared to non-high-risk children (Table 4). This analysis was performed excluding children with other comorbidities besides prematurity and we obtained the same result.

In adjusted analyses, the ORs of in-hospital mortality and readmissions for the high-risk group versus the non-high-risk group were compared in Table 5. Risk factors were weighted for predictive capability using the ORs (Table 4) in in-hospital mortality and readmission models. The multilevel logistical regression model for in-hospital mortality showed good adjustment, AUC = 0.84, with a high variability among hospitals (median OR: 2.3). When comparing in-hospital mortality rate due to RSV bronchiolitis against in-hospital mortality for other causes the OR for the high-risk group was higher (17.27 vs 7.23; *p* interaction: 0.046) (Table 5). The same result was found for readmissions (3.63 vs 0.54; *p* interaction: 0.001) (Table 5).

To explore whether a higher readmission rate was related mainly to the patients' underlying comorbidity rather than RSV alone, we have contrasted the likelihood of readmission within the high-risk group comparing RSV bronchiolitis versus other diagnoses. The OR for adjusted readmission risk for the high-risk group with RSV bronchiolitis was 3.5 times higher than for other causes ($p < 0.001$).

Discussion

RSV bronchiolitis is a leading cause of hospitalizations for children younger than the age of 1 year in the SNHS. RSV bronchiolitis increased slightly over the period between 2004 and 2012 whereas in-hospital mortality rates for RSV bronchiolitis in the high-risk and non-high-risk groups declined significantly over the study period. When high-risk children are hospitalized for RSV bronchiolitis there are higher numbers of in-hospital mortality instances and readmission cases compared to the non-high-risk group (Table 3) and, most importantly, children from the high-risk group have a higher risk of in-hospital mortality and readmission when they are hospitalized for RSV bronchiolitis rather than for a different reason. Chronic respiratory disease, prematurity, Down's syndrome, neuromuscular disease and congenital heart disease are strong predictors of in-hospital mortality due to RSV bronchiolitis, and this result seems to be consistent with other studies[9,10,12,23–26].

As described[3,24,25,27,28], RSV was the principal etiological agent of bronchiolitis among infants under 12 months old. The increase in the hospitalization rate for RSV bronchiolitis over the study period contrasts with a flatter curve of hospitalization rates for acute bronchiolitis, and this finding may be explained by higher diagnostic accuracy (increase in RSV tests in emergency departments when RSV bronchiolitis is suspected). We found reductions in in-hospital mortality (NS when adjusted by complexity) with a significant decrease in the length of stay, whereas the readmission rates remained unchanged during the study period. Previous studies that examined temporal trends in bronchiolitis due to RSV infections have reported a decline and no change in mortality rates[10,13,29]. The in-hospital mortality rate associated with RSV bronchiolitis in infants from the SNHS is similar (90 incidents per 100,000 discharges) to those reported in the USA[29]. A temporal trend towards improved RSV-bronchiolitis-associated in-hospital survival over time in Spain may be attributed to improvement in the quality of in-hospital management of the disease and perhaps to better control before an admission to hospital in the primary healthcare system. We cannot rule out that the trend to decreased in-hospital mortality and length of stay was due to milder forms of disease, but the trend to an increase in RSV bronchiolitis hospitalizations does not support this hypothesis and we haven't found any significant change during the analyzed period in the complexity mix of RSV bronchiolitis episodes. We cannot dismiss that improved socioeconomic or other environmental conditions may also have played a role[11].

As expected, infants hospitalized because of RSV bronchiolitis are generally previously healthy prior and under

Table 5. Multilevel effects logistic regression model. High-risk group versus non-high-risk group for RSV bronchiolitis.

	OR[a]	95 CI%		p	Interaction p	AUC[a]	95 CI%		ICC[b]	Median Odds Ratio
In-hospital mortality										
All cases	7.63	7.33	7.93	<0.001		0.835	0.831	0.837	0.331	3.374
Due to RSV bronchiolitis	17.27	8.36	35.66	<0.001	0.046	0.836	0.835	0.841	0.189	2.303
Due to other causes*	7.23	6.95	7.52	<0.001		0.769	0.766	0.775	0.331	3.381
Readmission										
All cases	0.56	0.54	0.57	<0.001		0.611	0.603	0.619	0.074	1.633
Due to RSV bronchiolitis	3.63	3.12	4.21	<0.001	0.001	0.481	0.480	0.48	0.024	1.309
Due to other causes*	0.54	0.53	0.56	<0.001		0.612	0.609	0.613	0.077	1.646

[a]Area under curve.
[b]Intraclass correlation coefficient.
*In-hospital mortality and readmissions due to any cause other than RSV bronchiolitis.

3 months of age. Risk factors increase the risk of in-hospital mortality and readmission for RSV bronchiolitis in the child's first year of life (Table 4) and, more importantly, the risk is higher when a high-risk group is hospitalized for RSV bronchiolitis than for any other reason (Table 5). In addition, the younger the infant the higher the in-hospital mortality rate for those in the non-high-risk group because of RSV bronchiolitis. These findings are in accordance with previous studies[9,10,12,13,23,29] which showed that mortality from RSV bronchiolitis was low among children from the non-high-risk group. Though we are not able to conclude any recommendation due to the wide confidence intervals of the association between late prematurity and higher in-hospital mortality due to RSV bronchiolitis (Table 4), the high rate of RSV bronchiolitis in the group not receiving immunoprophylaxis[30] suggests a careful reconsideration of the cost–benefit ratio of policies aimed at withdrawing RSV bronchiolitis immunoprophylaxis for this group[31]. The rates of in-hospital mortality for RSV bronchiolitis were higher in children with multiple risk factors than in children with isolated underlying diseases (Table 4). The multilevel logistic regression model developed in this study for RSV bronchiolitis in-hospital mortality (Table 5) shows reasonably predictive accuracy. The striking variability in adjusted in-hospital mortality between hospitals (mean OR = 2.3, Table 5) may be caused by variation in the quality of pediatric care in hospitals, disparities in local preventive strategies against RSV, social inequalities or a mix of all these factors. A relevant finding is the higher adjusted in-hospital mortality and readmissions risks for the high-risk group with RSV bronchiolitis versus any cause of discharge other than RSV bronchiolitis in the same high-risk group.

Limitations

This study is a retrospective analysis, based on administrative data, and has the limitations inherent in procedures for determining risk-adjusted mortality rates. However, the use of administrative records to estimate outcomes in health services has been validated by comparing them with data from medical records[32] and has been applied to research on health service outcomes[32–35]. The data from the MBDS, which are subjected to quality auditing, provide valid information. MBDS does not provide data about RSV laboratory findings; however, all the discharges coded with 466.11 (RSV bronchiolitis diagnosis code) must have a positive identification of RSV infection. Other RSV diagnoses, e.g. RSV pneumonia or RSV infection, have not been included in this analysis because this study was focused on RSV bronchiolitis and the number of hospitalizations for these causes was very low (in 2013, the number of cases were 20 and 16, respectively). Nevertheless, we cannot rule out that other hospitalizations with a diagnosis of 'bronchitis' might be mild cases of RSV bronchiolitis that were not tested, even if this possibility seems quite unlikely.

Socioeconomic and environmental factors, which have been described as influential in RSV bronchiolitis hospitalizations and outcomes[10,11], have not been considered in this study.

Conclusions

RSV bronchiolitis is a leading cause of hospitalization for infants under the age of 1 year in the SNHS and has not shown incidence reduction over a 9 year period. When high-risk infants are hospitalized for RSV bronchiolitis they have an in-hospital mortality and readmission risk that is higher than for those children that are part of the non-high-risk group, and this risk is higher than when they are hospitalized for any other reason. The in-hospital mortality rates and the mean length of stay declined over the period between 2004 and 2012, suggesting an improvement in the quality of in-hospital management of the disease. However, there are marked differences in RSV bronchiolitis adjusted in-hospital mortality rates among hospitals suggesting variations in the quality of healthcare management and/or socioeconomic conditions. Prematurity, chronic respiratory diseases, Down's syndrome, neuromuscular diseases and congenital heart diseases are strong predictors of in-hospital mortality due to RSV bronchiolitis.

Transparency

Declaration of funding

This study was supported by an unconditional grant from AbbVie.

Declaration of financial/other relationships

M.S.-L., F.J.E., C.F.-P., J.L.B., and A.L.-P. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgments

The authors thank the Spanish Ministry of Health, Social Services, and Equality for the facilities it has made available for the development of this study, with special gratitude to the General Directorate of Public Health, Quality, and Innovation and the Spanish Health Information Institute.

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