

## Hospitalization for respiratory syncytial virus in the paediatric population in Spain

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### SUMMARY

The aim of this population-based retrospective study was to determine the incidence of hospitalization for community-acquired, laboratory-confirmed respiratory syncytial virus (RSV) infection in an unselected paediatric population from southern Europe. The study was performed in an area with 15 700 children aged less than 5 years attended by a single hospital. The presence of RSV in nasopharyngeal aspirates from children with acute respiratory infection treated in the hospital was investigated in four seasons (July 1996–June 2000). A total of 390 episodes of hospitalization for RSV infection were detected and 83·3% of the children were aged less than 1 year old. The annual hospitalization rate was 37/1000 for infants aged less than 6 months and 25/1000 for those aged less than 1 year. During the study period, 2·5% of the infants younger than 1 year and approximately 5% of those younger than 3 months were hospitalized for RSV infection. The mean length of hospital stay was 5·9 days. Seven per cent of the patients required admission to the intensive care unit and more than half of these children were aged less than 1 month. In Spain, community-acquired RSV infection is a highly frequent cause of hospitalization in young children, especially in those aged less than 1 year. Prevention of RSV infection, through the development of vaccines and/or other strategies, should be a public health priority.

### INTRODUCTION

Respiratory syncytial virus (RSV) is the most frequent cause of severe respiratory tract infection in young children and is the primary cause of hospitalization for respiratory disease, especially bronchiolitis, in this population [1]. RSV is also a cause of severe respiratory infection, even of death, in certain groups of adults such as the elderly, individuals with underlying cardiac or pulmonary diseases and the immunocompromised [2]. Significant progress has been made in preventing infections caused by this virus through

the development of prophylactic RSV antibody preparations as well as live attenuated viruses and protein subunit vaccines. Numerous vaccine candidates are currently being tested in early clinical trials [3–5]. Consequently, in future, the health authorities will have to take decisions on the application of these measures in the population. In this context, determination of the impact of RSV in different geographical regions is essential. Studies of hospitalization for RSV in Spain and other southern European countries are scarce and the few that have been published refer to premature or other high-risk infants [6]. However, high-risk infants represent only a proportion

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of children hospitalized with bronchiolitis and thus the burden of this disease is unknown. The aim of the present study was to determine the incidence of hospitalization for community-acquired, laboratory-confirmed RSV infection in an unselected paediatric population from southern Europe.

## METHODS

The study area is situated in the province of Gipuzkoa (northern Spain) and includes the regions of San Sebastián (the capital of the province), Tolosa and Urola-Costa. The population comprises 395 922 inhabitants of which 47 937 are aged less than 14 years and 15 700 are aged less than 5 years [7]. The Hospital Donostia is the public hospital for this geographical area. It attends the paediatric population and is also the referral hospital for the entire province. The hospital has 76 paediatric beds and has an annual mean of approximately 26 500 paediatric emergencies and approximately 3500 deliveries. The hospital belongs to the public health system, which in Gipuzkoa attends more than 97% of paediatric hospitalizations. The study was performed between July 1996 and June 2000. In this period, the presence of RSV in all the nasopharyngeal (NP) aspirates from children attending the hospital's Emergency Pediatric Service for acute respiratory infection was investigated.

### Patients

Cases of RSV infection diagnosed in the Hospital Donostia were gathered from the computerized registries of the Microbiology Service. All children who fulfilled the following four criteria were included in the study: age less than 5 years, RSV detection in NP aspirate, need for hospital admission, and a discharge diagnosis of acute respiratory infection. Because RSV excretion in infants can last for up to 1 month [8], a single positive result per patient was included except when there was an interval of more than 2 months between results. Exclusion criteria consisted of the following: non-residence in the health district in which the study was performed, hospital stay of more than 48 h before the NP aspirate was performed (to exclude nosocomial infections), lack of demographic data on the patient or the reasons for admission and hospital stay for respiratory infection of less than 24 h (Observation Unit). Palivizumab was not used in our region during the study period. In addition, to determine the representativeness of the data obtained, the proportion of hospital admissions for diseases

presumed to be associated with RSV and investigated with virological techniques in our laboratory was determined. To do this, the medical records of all admissions taking place during the study period of children less than 5 years of age with a discharge diagnosis of bronchiolitis or acute bronchiolitis, were obtained from the hospital's Clinical Documentation Service. The diagnosis of bronchiolitis or acute bronchiolitis, the hallmark of RSV infection, correspond with the code 466.1 of the ninth edition of the International Classification of Diseases (Clinical Modification) (ICD-9-CM). We subsequently confirmed whether an NP aspirate had been extracted from these children for virological study during the corresponding episode. Data on hospital activity (number of admissions) were obtained for each quarter, both for the entire Paediatrics Department and for the Admissions Unit. Because RSV infection occurs mainly in cold months, an epidemiological year or study season was defined as the time between 1 July of one year and 30 June of the following year.

### Laboratory analysis

In all NP aspirates, RSV antigen detection was performed with a commercial enzyme-linked immunosorbent assay method (TestPack RSV, Abbott Laboratories, North Chicago, IL, USA) following the manufacturer's instructions. This method was chosen because it is more convenient for large scale testing than direct immunofluorescence and faster than viral culture, and its sensitivity and specificity are >90% [9]. In all cases, the test was performed less than 3 h after the sample was taken. Specimens in which RSV was detected were frozen at  $-80^{\circ}\text{C}$  for subsequent identification of the circulating RSV group. To do this, multiplex reverse transcriptase-polymerase chain reaction was performed with the RSV primers under the conditions described by Stockton et al. [10], randomly selecting six positive NP aspirates for each month in which viral activity was detected. In total, 131 samples from positive aspirates were investigated to identify the circulating RSV group corresponding to 35, 26, 34 and 36 isolates for each study season, respectively. Negative and positive controls were included in each run.

## RESULTS

During the study period, the presence of RSV in NP aspirates obtained in the course of 1604 episodes of

Table 1. Children hospitalized for RSV infection according to age and study season. Number of cases and incidence rate  $\times$  1000 inhabitants

Age	1996–1997		1997–1998		1998–1999		1999–2000		Total	
	No. cases	Rate $\times$ 1000	No. cases	Rate $\times$ 1000	No. cases	Rate $\times$ 1000	No. cases	Rate $\times$ 1000	No. cases	Rate $\times$ 1000
< 1 month	11	41.4	2	7.5	6	22.6	14	52.6	33	31.0
< 3 months	44	55.1	20	25.1	40	50.1	45	56.4	149	46.7
< 6 months	66	41.4	27	16.9	62	38.8	80	50.1	235	36.8
< 12 months	95	29.8	40	12.5	78	24.4	112	35.1	325	25.5
< 2 years	106	16.8	48	7.6	83	13.2	133	21.1	370	14.7
< 3 years	111	11.8	49	5.2	87	9.2	140	14.9	387	10.3
< 5 years	112	7.1	49	3.1	87	5.5	142	9.0	390	6.2

Table 2. Number of hospitalizations for bronchiolitis in children aged less than 5 years, number of bronchiolitis hospitalizations in which nasopharyngeal aspirate was performed to investigate RSV infection and number of RSV-positive bronchiolitis hospitalizations

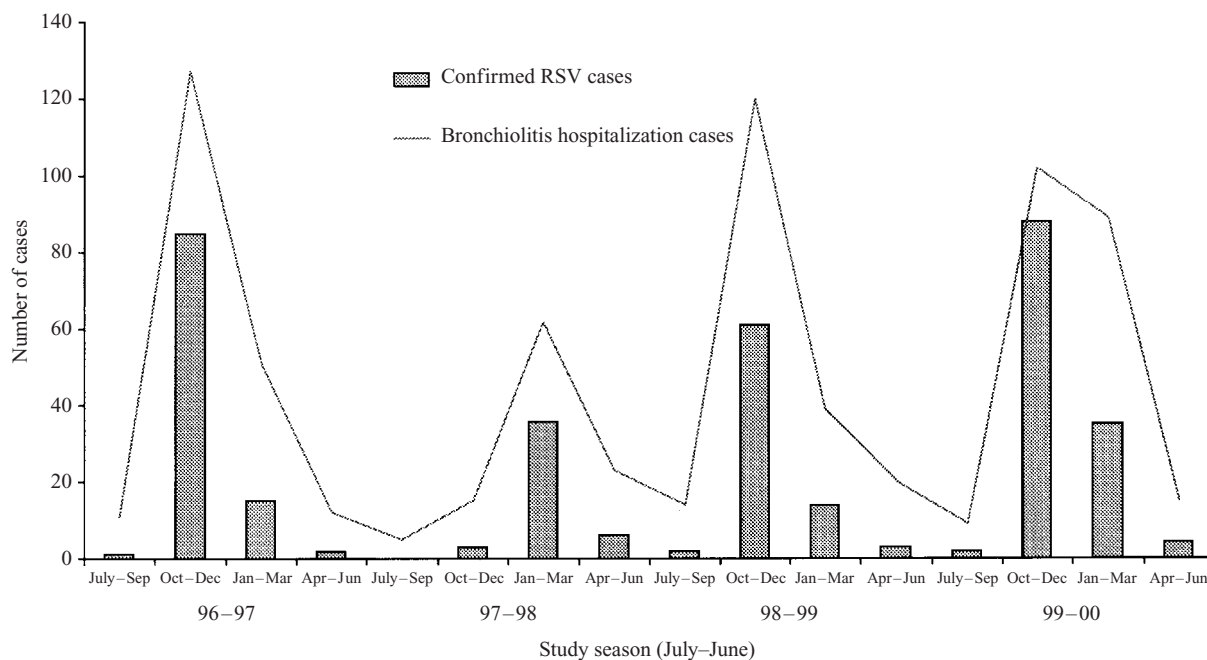
Year	1996–1997	1997–1998	1998–1999	1999–2000	Total
Number of bronchiolitis hospitalizations	170	94	176	195	635
Number of virologically-investigated bronchiolitis hospitalizations (% of total)	159 (93.5%)	88 (93.6%)	170 (96.6%)	187 (95.9%)	604 (95.1%)
Number of RSV-positive hospitalizations for bronchiolitis (% out of virologically tested)	103 (64.8%)	44 (50%)	81 (47.6%)	129 (69%)	357 (59.1%)
Circulating RSV group	A	A + B	B	A	—

acute respiratory infection was investigated. RSV was detected in 570 episodes, of which 513 occurred in children admitted to hospital. A total of 123 children were excluded (79 lived outside the study health district, 32 stayed in the hospital < 24 h, 11 lacked data on the reason for admission and one was admitted for reasons unrelated to the study). Finally, 447 episodes and 390 admissions (87.2%) were included. Although the number of admissions differed from one season to another, the percentage of confirmed RSV infections requiring hospitalization hardly varied: 89.6, 89.1, 83.6 and 83% for each season, respectively. In total, 211 admissions occurred in boys (54.1%) and 179 in girls (45.9%). Most of the hospitalized children were aged less than 1 year, accounting for 83.3% of the total. Infants aged less than 3 months accounted for 38.2% of all hospitalized children. Only three children aged more than 3 years were hospitalized (0.8%). Table 1 shows the annual hospitalization rate according to age groups.

The mean length of hospital stay was 5.9 days (range: 2–34 days) and was 6.9 days in infants aged less than 6 months and 5.2 days in children aged

more than 6 months ( $P=0.02$ , ANOVA:  $F=1.874$ ). Because of the severity of the episode, 28 children (7% of the episodes) required admission to the Intensive Care Unit (ICU), and of these, 23 children (82%) were aged less than 3 months and 15 (53%) were aged less than 1 month. Almost one out of every two hospitalized neonates (15/33) aged less than 1 month required admission to the ICU. The discharge diagnosis was bronchiolitis in 357 patients (91.5%) and pneumonia in 14 (3.6%), while in the remaining 19 patients (4.9%) admission was due to acute respiratory problems (bronchitis, apnoea crisis, atelectasia and respiratory distress). The number of admissions due to bronchiolitis showed marked variations in the different seasons (Table 2).

From the 131 RSV samples selected to identify the circulating viral group, RSV group A was detected in 90 samples and RSV group B was found in 41. Circulation of both group A and B strains of RSV infection was detected in the 1997–1998 season only. None of the NP aspirates showed the simultaneous presence of both RSV groups. Only two children experienced more than one episode of RSV-positive



**Fig. 1.** Quarterly distribution of hospitalized children less than 5 years old with a discharge diagnosis of bronchiolitis and of children aged less than 5 years hospitalized with community-acquired laboratory-confirmed RSV infection.

hospitalization. These episodes occurred at 5 and 25 months of life in one patient and at 8 and 20 months of life in the other. In both patients the first episode was caused by RSV group B and the second by group A.

The search for episodes of possible RSV infection in the hospital's computerized registries identified 635 children who were admitted with a diagnosis of bronchiolitis during the study period. One-by-one comparison of these patients with those included in the Microbiology Service registries showed that NP aspirates had been taken for laboratory study from 604 children (95.1%). RSV was detected in 357 (59.1%) of these samples and its quarterly distribution for each season is shown in Figure 1. Most admissions for RSV (82.6%: 322/390) occurred between November and February.

In the 4 years of the study, community-acquired RSV infection was responsible for 6.4% (387/6047) of nonsurgical admissions in children younger than 3 years and 15.7% (293/1865) of admissions in the trimesters when circulation of the virus was most intense.

## DISCUSSION

Numerous investigations have been performed on the impact of RSV infection but few have been population-based studies and, in the absence of

virological data, many have been based on estimations. The present study provides a good approximation in our environment to the real situation of admissions for community-acquired RSV infection for the following reasons. Most of the children in our health district, independently of their socioeconomic status, are treated by the public health system (approximately 97%), in 95.1% of the children admitted for bronchiolitis, the aetiological role of RSV was investigated and in infants, the sensitivity and specificity of the diagnostic method used is >90% [9]. Moreover, the study was conducted over 4 years to compensate for annual variations in the intensity of epidemics. A potential limitation of the study could be that, due to the lack of clinical suspicion, the role of RSV in clinical pictures other than bronchiolitis was insufficiently investigated; thus the burden of the disease could be even greater.

The annual hospitalization rate obtained for the health district of San Sebastián and surrounding areas (37/1000 for infants aged less than 6 months and 25/1000 for infants aged less than 1 year) confirms the considerable burden of RSV infection in our paediatric population. Two other population-based studies performed in 1995 in Europe, which were also based on confirmed cases, obtained different results: In Denmark, Kristensen et al. [11] reported an incidence of RSV-positive hospitalizations among infants

aged less than 6 months of 34/1000/season, similar to that obtained in our study; however, in Germany the incidence of RSV-positive hospitalizations obtained over 3 years was much lower, with an annual rate of 12/1000 for infants aged less than 1 year [12]. Despite these differences, overall the data obtained indicate the significant impact of RSV infection in the health of the paediatric population across Europe. During the study period, 2.5% of the infants younger than 1 year and 4.7% of those younger than 3 months were hospitalized for RSV infection. On reaching the age of 3 years, 1 out of every 32 children has been admitted to hospital for RSV infection. Other infectious agents with marked impact among young children such as rotavirus, do not cause such a high number of admissions in our environment (between 1993 and 1996 the mean annual incidence of hospitalization for rotavirus was 3.1/1000 children aged 1 month to 5 years) [13].

The incidence rates obtained from confirmed cases in our study are similar to those obtained from estimations based on the number of patients hospitalized with a clinical diagnosis of bronchiolitis and other lower respiratory illnesses in other countries [14–16]. In the national estimates performed in the USA by Shay et al. [14] the annual hospitalization rate for bronchiolitis in 1996 was 31.2/1000 in infants younger than 1 year. This figure is similar to that of 29.5/1000 obtained by Boyce et al. for RSV hospitalizations in infants aged less than 1 year without underlining medical conditions who were enrolled in the Medicaid programme [15]. In England the annual incidence of hospital admissions attributable to RSV was 28.3/1000 children younger than 1 year [16]. In the present study, only two children suffered from more than one episode of RSV-positive hospitalization, representing a reinfection rate of 0.5% of the total number of admissions. These data indicate that, although reinfections are common [17], they lead only exceptionally to hospitalization in the general paediatric population.

The temporal evolution of hospitalizations for bronchiolitis and RSV-positive hospitalizations showed great similarity (Fig. 1), confirming that, year after year, RSV is the main cause of the annual epidemic wave of bronchiolitis. The high number of admissions observed among confirmed cases could be thought to be due to an RSV-positive result in the NP aspirate being interpreted by paediatricians as a criterion for admission. However, this result did not influence the decision to admit patients since RSV-positive and RSV-negative patients with a diagnosis

of bronchiolitis were admitted with the same frequency (82 and 80% hospitalizations, respectively). Both the intensity and the duration of the epidemic varied each season and were influenced by factors that are poorly understood such as climate, the activity of other respiratory viruses and variations in the circulating RSV strain [18–20].

Although both RSV group A and B strains can circulate in the same season, group A usually predominates [18, 21], a phenomenon that also occurred in the present study. In the most intense seasons (1996–1997 and 1999–2000) we detected circulation of group A strains exclusively. By contrast, in the seasons with lower activity, group B strains predominated while both groups circulated in the 1997–1998 season. However, even in the seasons with lower incidence, the impact of RSV infection in the paediatric population was considerable.

The World Health Organization has recommended the introduction of systems of local surveillance of RSV infection, which could help local health authorities to plan future immunization programmes [22]. In the present population-based study performed in a southern European country, the impact of community-acquired RSV infection in the health of the paediatric population was observed to be as important as that found in other industrialized countries. In view of the high incidence of hospitalization observed, prevention of RSV infection in infants through the development of vaccines and/or other strategies should be a public health priority.

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