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ORIGINAL ARTICLE

Clinical and economic impact on the primary care system of respiratory syncytial virus infection in children under 5 years

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Abstract
Introduction and objectives: The burden of disease and costs of respiratory syncytial virus (RSV) infections in children under 5 years in pediatric primary care are not well known.
Patients and methods: Observational, prospective, and analytical study of children with suspected RSV respiratory infection confirmed by molecular testing. Thirty-seven pediatricians in eight autonomous communities recruited patients aged 0–59 months with suspected RSV infection from November 2021 to January 2024. The data were collected on the day of recruitment and at 14 and 30 days. We evaluated direct and indirect health care costs.
Results: Of the 517 recruited children, 206 (39.8%) tested positive for RSV (64.5% for type A; 35.4% for type B; and 2.36% for both A and B). There were significant differences in the proportion of children with dyspnea in the RSV-positive group compared to the RSV-negative group (50.0% vs 31.8%; $P < .001$). In the RSV-positive group, a higher proportion of infants aged less than 12 months, compared to other age groups, visited the emergency department (39.6% versus 22.5%; $P = .010$) and required hospital admission (25.0% versus 9.5%; $P = .004$). Inhaled bronchodilators were administered to 58.4%, inhaled corticosteroids to 9.7%, oral corticosteroids to 11.9%, and antibiotics to 18.3%. In the subset of school-aged children, 69.2% missed at least one

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day of school (median, 8 days; IQR, 5—14). The total cost per episode was €458, with significant differences between infants (€507) and children aged 1 year or older (€419) (mean difference, €88; 95% CI, 76–99; *P* < .001). The only differences between autonomous communities were in the use of bronchodilators and the frequency of emergency department visits.
Conclusions: Infection by RSV in early childhood places a significant clinical, economic and health care resource burden in out-of-hospital settings, which supports the implementation of effective preventive measures.
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PALABRAS CLAVE
Infecciones por virus sincitial respiratorio;
Atención primaria de Salud;
Lactantes;
Preescolares;
Coste de enfermedad

Impacto clínico y económico de la infección por virus respiratorio sincitial en atención primaria en menores de 5 años

Resumen
Introducción y objetivos: la carga de enfermedad y costes de las infecciones por Virus Respiratorio Sincitial (VRS) en pediatría de atención primaria en menores de 5 años no son bien conocidos.
Pacientes y métodos: estudio observacional, prospectivo y analítico de niños con sospecha de infección respiratoria por VRS confirmada mediante prueba molecular. 37 pediatras de 8 Comunidades Autónomas captaron pacientes de 0 a 59 meses sospechosos de infección por VRS de noviembre 2021 a enero 2024. Se recogieron datos el día de captación, a los 14 y 30 días. Se valoraron costes sanitarios directos e indirectos.
Resultados: de 517 menores captados, fueron positivos 206 (39,8%) (64,5% VRS A; 35,4% B; y 2,36% A y B). Hubo significativamente más disnea en el grupo positivo frente al negativo (50,0% y 31,8%, respectivamente, p < 0,001). Entre los positivos, los menores de 12 meses acudieron más a urgencias (39,6% frente a 22,5%; p = 0,010), y requirieron más hospitalizaciones (25,0% frente a 9,5%; p = 0,004). Recibieron broncodilatadores inhalados el 58,4%, 9,7% corticoide inhalado, 11,9% corticoide oral, y 18,3% antibióticos. En escolarizados, el 69,2% faltó al menos un día (mediana días de ausencia 8; RIC 5 a 14). El coste total por episodio fue de 458 €, y difirió entre menores (507€) y mayores de un año (419€) (DM: 88€; IC 95: 76 a 99; p < 0,001). Entre CCAA sólo difirió la utilización de broncodilatadores y la asistencia a servicios de urgencias.
Conclusiones: la infección por VRS en la primera infancia determina una importante carga clínica, económica y de recursos sanitarios fuera del entorno hospitalario y apoya implementar medidas preventivas efectivas.
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Introduction

Infection by respiratory syncytial virus (RSV) is a significant global public health challenge and one of the leading causes of child morbidity and mortality, particularly in children aged less than 5 years.[1,2] This virus is the leading pathogen associated with hospital admissions for lower respiratory tract infection (LRTI) in this age group. It is estimated to be responsible for 33 million cases of acute LRTI annually, and for 3.6% of deaths among infants aged 28 days to six months.[3] In Europe, between 2006 and 2018, there were nearly 250 000 pediatric admissions per year associated with RSV, 75% of which were in infants aged less than one year.[4] In Spain, two out of every 100 children aged less than 2 years are hospitalized due to RSV infection, with a mean length of stay of six days and an estimated annual cost of 49.6 million euros to the public health system.[5,6]

Although risk factors like preterm birth or chronic illnesses increase the risk of serious complications, most cases occur in healthy full-term infants.[6–8]

The burden of disease caused by RSV extends beyond the hospital setting: approximately 90% of bronchiolitis cases in children aged less than 2 years in Valencia are managed at the primary care (PC) level.[5] Despite this, there are limited data on its impact on the primary care system.[7]

The impact of RSV is not limited to acute episodes; in fact, the probability of developing recurrent wheezing and asthma triples following a severe RSV infection.[8,9] This is likely why prophylaxis against RSV with a monoclonal antibody was associated with a 61% reduction in the number of days with wheezing during the first year of life.[10] In recent years, new preventive tools have been approved in Europe to protect infants, such as long-acting monoclonal antibodies (nirsevimab, clesrovimab) and maternal vaccination.[11–14]

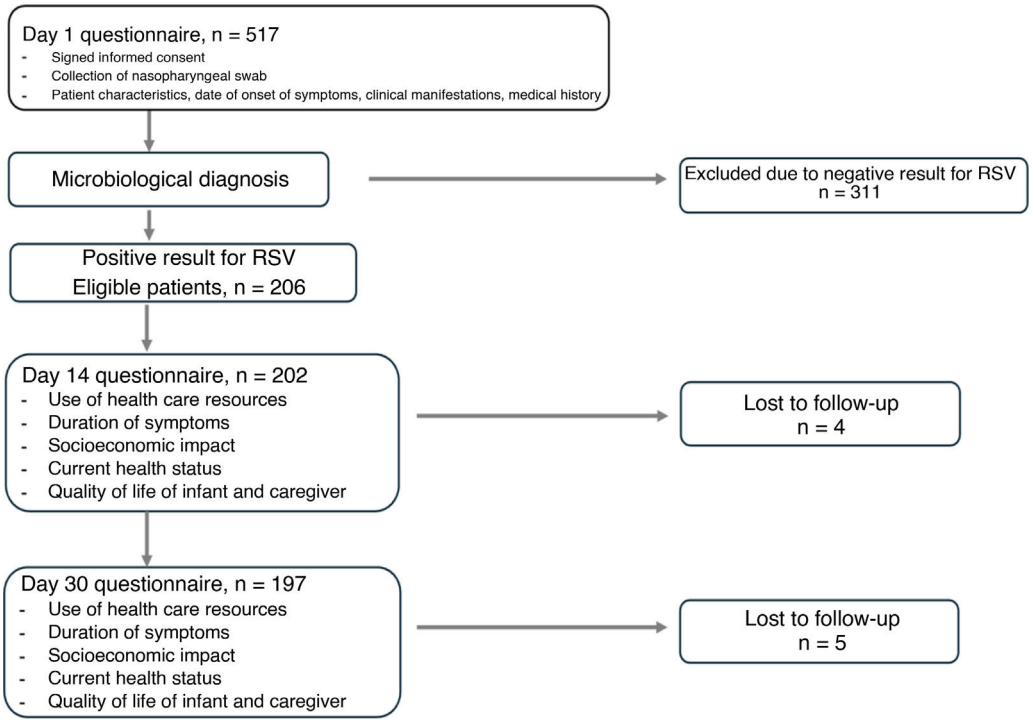

Figure 1 Flow chart of patient recruitment and follow-up.

In 2023, Spain was one of the first countries in the world to introduce nirsevimab as part of its official immunization program.[15,16] The evaluation of its effectiveness requires reliable data on the actual burden of RSV disease, particularly in PC.

The ComNet RSV III multicenter study analyzed the disease burden and societal impact of RSV infections in children aged less than 5 years managed at the PC level in five European countries (Belgium, Italy, Spain, the Netherlands, and the United Kingdom).[17,18]

In the present study, we compiled and analyzed the data on the burden of disease caused by RSV in children younger than five years in Spain at the PC level, a subject that has received little attention to date. This knowledge is essential for optimizing strategies for prevention, management, and treatment.

Patients and methods

We conducted a prospective, observational, descriptive, and analytical study of cases documented by 37 pediatric researchers who were members of the Primary Care Pediatrics Research Network (PAPenRED)[19] in eight of the autonomous communities (ACs) of Spain.

The initial objective was to collect data on 800 cases of suspected RSV infection in children aged less than five years (the estimated minimum sample size, for a 95% level of confidence, a 3% margin of error, a 20% expected prevalence, and accounting for attrition, was 804 Spanish children). The study was interrupted twice by different SARS-CoV-2 epidemic waves. The enrollment period was from November 2021 to January 2024. Fig. 1 shows the study flowchart.

Inclusion criteria: children aged less than 60 months presenting to their primary care pediatrician with respiratory symptoms suggestive of RSV infection. In this study, we applied the WHO definition of acute respiratory tract infection for community-based RSV surveillance (ie, sudden onset of at least one of the following symptoms: dyspnea, cough, sore throat, or coryza).

Exclusion criteria: insufficient understanding of study information by caregivers due to language barriers or intellectual disabilities.

After the legal guardians signed the informed consent form, and following a physical examination and the collection of demographic and clinical data related to the episode, a nasopharyngeal swab was taken from the patient. Swabs were transported in a standard transport medium to a laboratory (one hospital in each autonomous community), where the molecular testing process started within 24 h (polymerase chain reaction, primarily the Allplex Respiratory Full Panel Assay for the detection of 17 different viruses, including RSV A and B).

Each collaborating pediatrician prospectively collected (at 14 and 30 days after enrollment) follow-up clinical and treatment data for patients who tested positive for RSV on the day of enrollment, as well as data regarding the household and caregivers.

We defined a categorical variable: testing positive for RSV A, for RSV B, or for both.

We collected baseline descriptive data in the initial visit when the patient was recruited, including data on presenting symptoms, relevant history, including personal history of chronic conditions, and physical examination findings, in addition to demographic characteristics. In patients who tested positive for RSV, at 14 and 30 days, we collected data on the outcomes of interest: clinical manifestations and lab-

Table 1 Distribution of recruited patients and confirmed cases by autonomous community.

Autonomous Community (no. pediatricians)	Cases (*n*)	% total	RSV+ *n* (%)[a]	Serotype (A, B, A and B, no data)
Aragón (4)	34	6.6	13 (38.2)	8, 0, 0, 6
Asturias (5)	64	12.4	20 (31.2)	8, 6, 0, 6
Castilla La Mancha (4)	80	15.5	23 (28.7)	10, 6, 0, 7
Extremadura (4)	79	15.3	42 (53.2)	25, 15, 0, 2
Canary Islands (4)	23	4.4	9 (39.1)	4, 4, 0, 1
Madrid (6)	85	16.4	27 (31.8)	14, 7, 2, 4
Murcia (7)	106	20.5	52 (49.1)	1, 0, 0, 51
Valencian Community (3)	46	8.9	20 (43.5)	12, 6, 1, 0
Total (37)	517	100.00	206 (39.8)	82, 44, 3, 77

[a] The difference between autonomous communities in the percentage of patients who tested positive for RSV was statistically significant ($P = .012$).

oratory findings, complications, use of medication, duration of illness, school absences, health care visits at any level of care, parental work absence, and current general health of the child on the scale from 0 (worst possible) to 100 (best possible) used in the multicenter study.[17]

Of all the patients included in the study, one received palivizumab, and during the most recent season (October 2023 through January 2024), 32 received nirsevimab for prophylaxis.

For quantitative variables, we calculated measures of central tendency and dispersion and assessed the normality of the distribution (Kolmogorov-Smirnov test); for qualitative variables, we calculated percentages with 95% confidence intervals (CIs). Depending on the type of variable, we used the χ^2 test, Student *t*-test, ANOVA, or, when appropriate, nonparametric tests (Fisher exact test, Mann-Whitney *U* test, Kruskal-Wallis test) in the comparative analysis.

Direct healthcare costs (primary care visits, medications, and emergency department visits) were calculated in euros using official rates adjusted to 2022 prices.[20] Indirect costs were estimated based on parental work absences based on average wages in Spain.

Each participated pediatrician entered the anonymized questionnaire and laboratory data into a custom study database (REDCap tool).

Compared to the European study in which it originated,[17,18] this study included an additional 96 patients (30 RSV-positive) recruited between October 2023 and January 2024.

In Spain, the study was approved by the Ethics Committee of the Principality of Asturias (reference 2021.457 from September 30, 2021).

Results

A total of 517 children aged less than 5 years were recruited and screened, of whom 206 (39.8%) tested positive for RSV. Table 1 shows the distribution of patients in the eight autonomous communities that participated in the study, showing significant differences in the percentage who tested positive for RSV ($P = .012$).

Fifty percent of the RSV + patients were female (95% CI, 43.2–56.7 %).

Table 2 presents the data collected on the day of recruitment, both for the overall sample and for the RSV + and RSV − groups. There were differences between the groups, as the RSV + group had a greater proportion of patients with dyspnea (50.0% vs 31.8%) and wheezing (63.1% vs 53.4%). The probability of testing positive was significantly lower among patients who had received palivizumab or nirsevimab (15.2% vs 41.5%; $P = .004$).

The RSV subtype was established in 127 of the 206 patients who tested positive: 64.5% were positive for RSV A, 35.4% for RSV B, and 2.4% for both. Coinfections were detected in 48.3% of the total sample (95% CI, 44.5%–53.1%). In the RSV + group, coinfections were detected in 35.92% of patients, primarily with rhinovirus, bocavirus, and enterovirus (37, 18, and 9 cases, respectively).

Table 3 shows the changes in study variables between the date of recruitment and the 14- and 30-day follow-ups. Fourteen cases of acute otitis media (7.7%) and eight of pneumonia (4.4%) were diagnosed during the month of follow-up.

Sixty-one patients (31.0%) visited the emergency department; 16.7% of participants required hospitalization, and 1.5% were admitted to the intensive care unit (ICU). There were no deaths. Table 4 compares the characteristics of infants aged less than 12 months and older children.

There were differences in resource utilization among the autonomous communities. The percentage of patients managed in emergency departments differed significantly (47.6% in Extremadura; 28.6% in Aragón; 28% in Murcia; 21.7% in Castilla-La Mancha; 15.8% in the Valencian Community; 15.4% in Madrid; 15% in Asturias; and 12.5% in the Canary Islands; $P = .038$). However, there were no significant differences in the percentage admitted to hospital (23.8% in Extremadura; 21.4% in Aragón; 19.5% in Madrid; 15.8% in the Valencian Community; 15.0% in Asturias; 12.5% in the Canary Islands; 10.0% in Murcia; and 4.34% in Castilla-La Mancha; $P = .504$).

We found no differences in clinical presentation, health care utilization, or duration of illness between patients infected with RSV A versus RSV B.

Table 2 Baseline data at recruitment, total sample and RSV-positive versus RSV-negative patients.

n (%)	Total	RSV+	RSV−	*P*
	517	206 (39.85%)	311 (60.15%)	–
Baseline descriptive characteristics				
Female sex (%)	244/517 (47.19%)	103/206 (50.00%)	141/311 (45.34%)	.298
Age in months (mean ± SD)	19.31 ± 16.19	17.76 ± 15.17	20.33 ± 16.77	.077
Median (IQR)	14 (6−30)	14 (6−30)	14 (6−30)	–
0−11 months	229/517 (44.29%)	97/206 (47.10%)	132/311 (42.44%)	.298
>11 months	288/517 (55.71%)	109/206 (52.90%)	179/311 (57.56%)	–
Preterm birth	35/516 (6.78%)	12/206 (5.82%)	23/310 (7.42%)	.481
GA (wk) (mean ± SD)	38.93 ± 1.85	38.89 ± 1.8	38.96 ± 1.88	.674
Birth weight (mean ± SD) (g)	3191 ± 548	3176 ± 541	3202 ± 554	.598
Chronic respiratory disease	59/480 (12.29%)	27/190 (14.21%)	32/290 (11.03%)	.300
Previous RSV infection	10/517 (1.93%)	2/206 (0.97%)	8/311 (2.57%)	.196
Previous influenza infection	56/512 (10.94%)	22/203 (10.84%)	34/309 (11.00%)	.953
Palivizumab/nirsevimab	33/503 (6.56%)	5/33 (15.15%)	201/484 (41.53%)	.004
Clinical presentation at recruitment				
Viral coinfection	251/514 (48.83%)	75/204 (36.76%)	188/310 (60.64%)	–
Dyspnea	202/517 (39.07%)	103/206 (50.00%)	99/311 (31.83%)	.000
Wheezing	240/517 (48.36%)	130/206 (63.11%)	110/311 (35.37%)	.000
Productive cough	309/517 (59.77%)	132/206 (64.08%)	177/311 (56.91%)	.104
Unproductive cough	244/517 (47.19%)	99/206 (48.06%)	145/311 (46.62%)	.749
Rhinitis	403/517 (77.95%)	161/206 (78.16%)	242/311 (77.81%)	.927
Fever ≥ 38°	259/517 (50.10%)	99/206 (48.06%)	160/311 (51.45%)	.451
Feeding difficulties	134/517 (25.92%)	62/206 (30.10%)	72/311 (23.15%)	.078

Abbreviations: GA, gestational age; RSV, respiratory syncytial virus.

With regard to medication, 54.3% of children received acetaminophen, 28.3% ibuprofen, 58.4% inhaled bronchodilators, 9.7% inhaled corticosteroids, 11.9% oral corticosteroids, 3.1% cough syrups, and 18.3% antibiotics. Ibuprofen was used significantly less frequently in infants under 12 months compared to older children (7.6% vs 25.7%; $P = .001$), as were inhaled bronchodilators (50.0% vs 64.7%; $P = .036$). Also, the proportion of infants who received antibiotics was 10.9%, compared to 20.0% of older children ($P = .079$). At the autonomous community level, we only found differences in the use of inhaled bronchodilators (64.3% of children in Aragón; 10% in Asturias; 30.4% in Castilla-La Mancha; 66.6% in Extremadura; 62.5% in the Canary Islands; 69.2% in Madrid; 64.0% in Murcia; and 68.4% in the Valencian Community; $P < .001$) and inhaled corticosteroids (Aragón, Asturias, Madrid, Murcia, and Valencia: 0%; Castilla-La Mancha: 4.3%; Canary Islands: 12.5%; and Extremadura: 6.7%; $P = .003$).

Only children included between November 2023 and January 2024 had the option to receive nirsevimab for prophylaxis. Of this total (33 children), only five (15.2%) tested positive, which makes it impossible to draw comparisons with this subgroup.

Among the patients enrolled in school, 69.2% missed at least one day (median days of absence, 8 days; IQR, 5−14). One or both parents missed at least one day of work in 26.7% of cases (median days of absence: 8; IQR, 4−12).

The direct health care costs per RSV episode amounted to a mean of €301 (95% CI, 288−313), primarily due to primary care visits (54%) and emergency department visits (43%). Indirect costs averaged €157 (95% CI, 137−180) per episode (Table 5). Overall, the mean total cost per episode was €458, with significant variations between age groups: €507 for infants aged less than 1 year and €419 for older children (mean difference, €88; 95% CI, 76−99; $P < .001$).

Discussion

This was a study conducted at the national level, integrating data from a multinational study (ComNet RSV III)[17,18] in five European countries (Italy, Spain, Belgium, the Netherlands, and the United Kingdom). Following the COVID-19 pandemic and the restrictive measures imposed on its account, RSV did not circulate during the usual time of the year in the 2020−2021 season, and the RSV season did not return to the prepandemic pattern until 2022.[21–23]

Spain accounted for 23.5% of the RSV + participants in the European study. The positivity rate (39.8%) was similar to the rates reported in other studies conducted during the RSV season.[24–27] Similarly, the positivity rate was higher in infants aged less than 1 year, possibly due to more frequent lower respiratory tract involvement, which may be a source of selection bias. Infants, compared to older children, visited the emergency department more frequently (39.6% vs 22.5%) and a higher proportion were admitted to hospital (25.0% vs. 9.5%), a finding that is consistent with other studies.[5,24,28–30]

In our study, 16.7% of RSV + patients were admitted to hospital. In the ComNet RSV III study,[17] the rate of hospitalization was only higher in Belgium (43.7%) (United Kingdom 5.2%; Italy 4.1%; Netherlands 3.7%). One in four infants

Table 3 Key clinical characteristics and outcomes of RSV + patients.

	Day 0 ($n = 206$)	Day 14 ($n = 202$)	Day 30 ($n = 197$)
Clinical manifestations (n/N, %)			
Dyspnea	103/206 (50.0%)	2/186 (1.1%)	3/183 (1.6%)
Wheezing	130/206 (63.1%)	Not available	Not available
Productive cough	132/206 (64.1%)	29/186 (15.6%)	22/182 (12.1%)
Unproductive cough	99/206 (48.1%)	34/186 (18.3%)	21/183 (11.5%)
Rhinitis	161/206 (78.2%)	56/186 (30.1%)	50/183 (27.3%)
Fever > 38 °C	99/206 (48.1%)	0/183 (0%)	2/183 (1.1%)
Feeding difficulties	62/206 (30.1%)	7/186 (3.8%)	6/183 (3.3%)
Complications (n/N, %)			Total follow-up
Acute otitis media			14/183 (7.7%)
Pneumonia			8/183 (4.4%)
Health care visits			Total follow-up
At least l after recruitment visit	159/202 (78.7%)	78/197 (39.6%)	170/194 (87.6%)
Number of visits, median (IQR)	2 (1−3)	0 (0−1)	2 (1−2.75)
Number of visits, mean ± SD	2.01 ± 1.09	0.42 ± 0.72	1.97 ± 1.09
Children who visited ED	54/202 (26.7%)	7/198 (3.5%)	61/197 (31.0%)
Children admitted to hospital	31/202 (15.4%)	2/198 (1.0%)	33/197 (16.7%)
LOS in days, median (IQR)			4 (3−7)
LOS in days, mean ± SD			5.15 ± 3.01
Children admitted to PICU			3/197 (1.5%)
Duration of illness (days)			Total follow-up
Median (IQR)			10 (7−13)
Mean ± SD			10.03 ± 4.46
Missed school/day care in enrolled children			Total follow-up
At least one day			(72/104; 69.23%)
Median (IQR) (days)			8 (5−14)
Mean ± SD (days)			8.81 ± 5.18
HS scale (0 worst possible to 100, best possible)			Day 30
Mean ± SD		88.24 ± 13.58	91.53 ± 13.61
Parental work absence (days)			Total follow-up
Work absence in one or both parents		21/86 (24.4%)	23/86 (26.7%)
Median (IQR) (days)		4 (3−7)	5 (4−12)
Mean ± SD (days)		5.38 ± 4.26	8.36 ± 6.52

Abbreviations: ED, emergency department; HS, health status; LOS, length of stay; PICU, pediatric intensive care unit.

required admission, compared to one in ten children aged more than 12 months. Differences in health care systems alone cannot fully explain these discrepancies, and potential selection biases could explain the observed variation among the autonomous communities (with hospitalization rates ranging from 23.8% in Extremadura to 4.34% in Castilla-La Mancha).

There were no differences based on the RSV subtype (some studies found greater severity associated with RSV A, a few found greater severity with RSV B, and others found no differences).[31]

In our study, viral coinfection was detected in 36.8% of RSV + patients and 60.6% of RSV − patients, in agreement with previous studies,[27,28,32] although the reported prevalence of coinfection varies widely, from 6% in the study by Hall et al.[27] to 51% in the study by Sankatsing et al. in Italy.[32] Variation in study methodology, the age of included patients[33] and the sensitivity of the test used for detection of RSV can explain these differences. A recent meta-analysis found no differences between RSV monoinfection and RSV coinfection with other viruses, except for a higher rate of ICU admission associated with metapneumovirus, although this subject is still under debate.[34]

Only wheezing and dyspnea were significantly more prevalent among RSV + patients. Furthermore, data on disease duration, impact on the frequency of office visits, emergency department visits, and hospital admission confirm, as in other studies, that this infection is more severe than other viral respiratory tract infections.[7,23–28,31,32,35]

Despite the limited evidence in support of its effectiveness, the excessive use of medication stands out as a clear area for improvement. Antibiotic use in Spain was similar to that in neighboring countries like the Netherlands or the United Kingdom and lower compared to Italy[32] and previous studies in Spain.[25] The use of bronchodilators, however, was very high (over 50%). In Spain, medication was prescribed more frequently to children aged more than 12 months, possibly on account of a higher frequency of fever and a

Table 4 Comparison of infants vs children aged 12 to 59 months.

	Total RSV+	RSV + infants	RSV+ > 11 months	*P*
Frequency	206	97 (47.1%)	109 (52.9%)	
Baseline descriptive variables				
Female (%)	103/206 (50.00%)	48/97 (49.48%)	55/109 (50.46%)	.889
Age in months, mean ± SD	17.76 ± 15.17	5.88 ± 3.06	28.34 ± 13.73	–
Median (IQR)	14 (6–30)	6 (4–8)	25 (16–37.5)	–
GA (weeks), mean ± SD	38.89 ± 1.8	38.66 ± 2.13	39.10 ± 1.42	.087
Birth weight (g), mean ± SD	3176 ± 541	3215 ± 595	3141 ± 489	.334
Vaccinated against flu	22/203 (10.84%)	5/94 (5.32%)	17/109 (15.60%)	
Palivizumab/nirsevimab	5/202 (2.47%)	5/97 (2.47%)	0/105 (0.00%)	
Initial clinical presentation				
Viral coinfection	75/204 (36.76%)	30/96 (31.25%)	45/108 (41.67%)	.124
Dyspnea	103/206 (50.00%)	56/97 (57.73%)	47/109 (43.12%)	.036
Wheezing	130/206 (63.11%)	64/97 (65.98%)	66/109 (60.55%)	.420
Productive cough	132/206 (64.08%)	59/97 (57.23%)	73/109 (66.97%)	.359
Unproductive cough	99/206 (48.06%)	46/97 (47.42%)	53/109 (48.62%)	.863
Rhinitis	161/206 (78.16%)	70/97 (72.17%)	91/109 (83.49%)	.050
Fever ≥ 38°	99/206 (48.06%)	31/97 (31.96%)	68/109 (62.38%)	.000
Feeding difficulties	62/206 (30.10%)	38/97 (39.17%)	24/109 (22.01%)	.007
Outcome variables				
Days of illness, mean ± SD	10.03 ± 4.46	10.36 ± 3.85	9.43 ± 4.11	.109
Median (IQR)	10 (7–13)	10 (7–14)	8 (7–13)	–
Visited ED	61/197 (31.0%)	36/91 (39.56%)	24/106 (22.54%)	.010
No. of visits, mean ± SD	1.37 ± 0.64	1.33 ± 0.63	1.71 ± 1.49	.248
Median (IQR)	1 (1–2)	1 (1–1.75)	1 (1–2)	
Hospital admission	33/197 (16.75%)	23/92 (25.00%)	10/105 (9.52%)	.004
LOS in days, mean ± SD	5.15 ± 3.01	5.13 ± 2.62	5.2 ± 3.94	.943
Median (IQR)	4 (3–7)	4 (3–7)	3.5 (2–8.5)	
Complications				
Acute otitis media	14/183 (7.7%)	5/86 (5.82%)	9/97 (9.28%)	.548
Pneumonia	8/183 (4.4%)	3/86 (3.49%)	5/97 (5.15%)	.851
HS scale, mean ± SD	88.24 ± 13.58	87.53 ± 14.80	89.04 ± 12.11	.490

Abbreviations: ED, emergency department; HS, health status (assessment of patient health at 30 days on a scale from 0 [worst possible] to 100 [best possible]); LOS, length of stay.

Table 5 Health care outcomes: health care costs and societal impact of the 206 RSV-positive cases.

Cost category	Mean cost (€)	95% CI	Proportion of total costs
Direct health care costs	301	288–313	66%
Primary care visits	163	155–170	54%
Emergency department visits	129	120–137	43%
Medication	9	7–11	3%
Indirect costs (missed work)	157	137–180	34%
Total cost/episode	458	430–487	100%

significantly greater use of bronchodilators overall. Furthermore, the differences between autonomous communities in the use of inhaled bronchodilators (beta-2-adrenergics and corticosteroids) do not seem justified.

However, the use of antibiotics (in 18.3% of patients) appeared reasonable given the complications, such as acute otitis media or pneumonia, with 6.2% of the total prescriptions without a clear justification. Compared to other studies,[7,23,25,32] we ought to highlight the infrequent use of antibiotics in infants aged less than 1 year (10.9% in infants, and less than 20% in older children). Bacterial superinfection is considered rare in these patients; therefore, guidelines do not support routine antibiotherapy.[36,37] In our study, 7.7% of the children received a diagnosis of otitis, a proportion that was lower compared to other studies (which have reported rates of up to 23% and 30%, particularly in infants).[26,34,38,39] This difference could be explained, at least in part, by the difficulty of making an accurate diagnosis with conventional otoscopy, which is the customary practice in Spain. The prevalence of bacterial pneumonia associated with RSV

infection (3.7% in the ComNet RSV III study and 4.4% in our study) was not clearly defined in primary care, as most studies were conducted in the hospital setting.[36]

The cost per patient hospitalized for RSV ranges from €3500 to €4500 in Spain and neighboring countries,[30,31,40] although the burden of care is highest at the PC level (90% of cases).[5] The mean number of PC visits was 1.97, although higher numbers have been reported in Spain.[25] Similarly, the frequency of visits to emergency departments was high (31.0%), comparable to that in Belgium, but much higher than in Italy, the United Kingdom, and the Netherlands.[17,18,32] In Spain, percentages as high as 61.6% have also been reported.[25] The differences between autonomous communities is striking, ranging from 12.5% in the Canary Islands to 47.6% in Extremadura. These figures are most likely related to the accessibility of both resources in Spain and to inadequate health education, given that there are no substantial differences in epidemiological trends.

The total cost per episode (€458) was significantly higher for infants aged less than 1 year, as is the case in most studies.[5,18,26,28,32] The mean direct health care costs in Spain (€301) chiefly stemmed from PC visits (54%) and emergency department visits (43%). In the ComNet III study, 26.7% of Spanish parents missed work hours to care for their children, the lowest percentage among the participating countries, which ranged from 35% in the United Kingdom to 71% in Italy.[18] In our study, direct costs were higher than indirect costs (the opposite of what has been reported elsewhere). This distribution appears to be closely related to the characteristics of the different health care systems, parental leave policies, and available family support.

Finally, as observed in other studies, the infection rate was significantly lower among those immunized with nirsevimab.[41,42]

Our study has several limitations. A number of factors may have introduced selection bias: patients were selected by pediatricians motivated by research and by addressing common diseases like this one; some patients were recruited after presenting to emergency departments with lower respiratory tract symptoms and even after hospitalization (which would explain the high use of these resources observed in the study); conversely, the number of severe cases may have been underestimated because severely ill patients may go directly to the emergency department and not visit a PC center; patients with mild symptoms who did not seek medical care were not included, nor were those with language barriers or comprehension difficulties, those using private health care services, or even those with serious economic disadvantage. In addition, pediatricians participated on a voluntary basis and were likely to be highly motivated, which also constitutes a positive selection bias that may have led to underestimation of resource utilization and drug prescribing.

It is important to note that the sample was not large enough to draw conclusions about at-risk populations. Finally, we calculated costs based on official rates, which do not necessarily reflect actual costs, vary by autonomous community, and do not account for the variation between health care organizations.

Since this project was conducted in the framework of a larger prospective study in several European countries with standardized methodology, and included 8 autonomous communities with different geographical characteristics, we can extrapolate the findings to all of Spain and make comparisons with other studies. In addition, the completion rate was substantial, with high response rates in all questionnaires through day 30 of follow-up. All of this strengthens our findings and their relevance.

It is reasonable to conclude that RSV infection places a considerable economic burden on the primary care system in Spain, chiefly on account of direct health care costs due to high utilization. The high hospitalization rate and the prolonged lengths of stay are also significant. Furthermore, we identified a frequent use of medications considered ineffective for RSV infection. These findings highlight the importance of considering the economic burden beyond the hospital setting and contribute data toward the evaluation (in terms of cost-effectiveness) of effective preventive measures, such as monoclonal antibodies and the recently introduced maternal vaccination program, implemented to mitigate the impact of RSV. In Spain, there is a clear opportunity to improve the management of RSV infection, primarily in terms of health care utilization and the rational use of medications.

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Declaration of competing interest

In addition to the funding received by all authors and collaborators for the work conducted for this project from Nivel (with funds contributed by Sanofi/AstraZeneca), MCM is the coordinator of PAPenRed and has received funds from Leti, MSD and Cinfa to register in courses beyond the scope of the study. MGS is a member of the Committee on Vaccines of the Asociación Española de Pediatría and has received fees from GSK companies and Pfizer, Sanofi and MSD for acting as a consultant in advisory boards and expert panels and as a speaker in conferences unrelated to the study through August 2024.

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References

1. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet. 2010;375:1545–55.
2. Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global epidemiology of respiratory syncytial virus-associated acute lower respiratory infection in young children: a systematic review and meta-analysis. Lancet. 2017;390:946–58.
3. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med. 2005;352:1749–59.
4. Bont L, Checchia PA, Fauroux B, Figueras-Aloy J, Manzoni P, Paes B, et al. REGAL SERIES defining the epidemiology and burden of severe respiratory syncytial virus infection among infants and children in western countries. Infect Dis Ther. 2016;5:271–98.
5. Muñoz-Quiles C, López-Lacort M, Úbeda-Sansano I, Alemán-Sánchez S, Pérez-Vilar S, Puig-Barberà J, et al. Population-based analysis of bronchiolitis epidemiology in Valencia. Spain. Pediatr Infect Dis J. 2016;35:75–80.
6. Martinón-Torres F, Carmo M, Platero L, Drago G, López-Belmonte JL, Bangert M, et al. Clinical and economic burden of RSV infections in Spanish children: the BARI study. BMC Infect Dis. 2022;22:759.
7. Ares-Gómez S, Mallah N, Pardo-Seco J, Malvar-Pintos A, Pérez-Martínez O, Otero-Barrós MT, et al. Short- and medium-term morbidity associated with RSV: a longitudinal study in Spain. Pediatr Allergy Immunol. 2024;35:e14131.
8. Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in infancy. Thorax. 2010;65:1045–52.
9. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, et al; Dutch RSV Neonatal Network. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med. 2013;368:1791.
10. Scheltema NM, Nibbelke EE, Pouw J, Blanken MO, Rovers MM, Naaktgeboren CA, et al. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. Lancet Respir Med. 2018;6:257–64.
11. Rodríguez-Fernández R, Mejías A, Ramilo O. Monoclonal antibodies for prevention of respiratory syncytial virus infection. Pediatr Infect Dis J. 2021;40(5S):S35–9.
12. Hodgson D, Wilkins N, van Leeuwen E, Watson CH, Crofts J, Flasche S, et al. Protecting infants against RSV disease: an impact and cost-effectiveness comparison of long-acting monoclonal antibodies and maternal vaccination. Lancet Reg Health Eur. 2024;38:100829.
13. Anderson LJ, Walsh EE. The challenge of respiratory syncytial virus human challenge studies. N Engl J Med. 2022;386:696–7.
14. Mazur NI, Terstappen J, Baral R, Bardaji A, Beutels P, Buchholz UJ, et al. Respiratory syncytial virus prevention within reach: the vaccine and monoclonal antibody landscape. Lancet Infect Dis. 2023;23:E2–21.
15. Manzanares A, Pardo-Seco J, Rivero-Calle I, Dacosta-Urbieta A, Mallah N, Santiago-Pérez MI, et al. Respiratory syncytial virus-related lower respiratory tract infection hospitalizations in infants receiving nirsevimab in Galicia (Spain): the NIRSE-GAL study. Eur J Pediatr. 2025;184:321.
16. García-Basteiro AL, et al. RSV seasonality and healthcare burden in Spain: a multicenter analysis. J Infect Dis. 2022;36:56–62.
17. Hak SF, Sankatsing VDV, Wildenbeest JG, Venekamp RP, Casini B, Rizzo C, et al. Burden of RSV infections among young children in primary care: a prospective cohort study in five European countries (2021-23). Lancet Respir Med. 2025;13:153–65.
18. Sankatsing VD, Hak SF, Wildenbeest JG, Venekamp RP, Pistello M, Rizzo C, et al. Economic impact of RSV infections in young children attending primary care: a prospective cohort study in five European countries, 2021 to 2023. Euro Surveill. 2025;30:2400797.
19. Red de Investigación en Pediatría de Atención Primaria (PAPen-RED) de la Asociación Española de Pediatría de AtenciónPrimaria, 2026. [Accessed 1 January 2026]. Available from: https://aepap.org/001-pagina-de-grupo-4/.
20. Decreto 56/2014, del 30 de abril, por el que se establecen las tarifas de los servicios sanitarios prestados en centros dependientes del SERGAS. [Accessed 1 December 2023]. Available from: https://www.xunta.gal/dog/Publicados/2014/20140521/AnuncioC3K1-140514-0001_es.html.
21. Puma-Olguin TC, Mazagatos C, Galindo-Carretero S, Vega-Piris L, Lozano-Álvarez M, Pérez-Gimeno G, et al. Epidemiología y carga de enfermedad por VRS en España. SiVIRA, temporadas 2021-22 y 2022-23. Boletín Epidemiológico Semanal. 2024;32:21–35.
22. European Centre for Disease Prevention and Control. In: Intensified circulation of respiratory syncytial virus (RSV) and associated hospital burden in the EU/EEA – 12 December 2022. Stockholm: ECDC; 2022.
23. Scarpaci M, Bracaloni S, Esposito E, De Angelis L, Baglivo F, Casini B, et al. RSV disease burden in primary care in Italy: a multi-region pediatric study, winter season 2022-2023. Influenza Other Respir Viruses. 2024;18:e13282.
24. Heemskerk S, van Heuvel L, Asey T, Bangert M, Kramer R, Paget J, et al. Disease burden of RSV infections and bronchiolitis in young children (< 5 Years) in primary care and emergency departments: a systematic literature review. Influenza Other Respir Viruses. 2024;18:e13344.
25. Díez-Gandía E, Gómez-Álvarez C, López-Lacort M, Muñoz-Quiles C, Úbeda-Sansano I, Díez-Domingo J, et al. The impact of childhood RSV infection on children's and parents' quality of life: a prospective multicenter study in Spain. BMC Infect Dis. 2021;21:924.
26. Rybak A, Cohen R, Bangert M, Kramer R, Delobbe JF, Deberdt P, et al. Assessing the burden of respiratory syncytial virus-related bronchiolitis in primary care and at 15-day and 6-month follow-up before prophylaxis in France: a test-negative study. Pediatr Infect Dis J. 2024;43:657–62.
27. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360(6):588–98,

http://dx.doi.org/10.1056/NEJMoa0804877. PMID: 19196675; PMCID: PMC4829966.
28. Wildenbeest JG, Billard MN, Zuurbier RP, Korsten K, Langedijk AC, van de Ven PM, et al. The burden of respiratory syncytial virus in healthy term-born infants in Europe: a prospective birth cohort study. Lancet Respir Med. 2023;11:341–53.
29. Gil-Prieto R, González-Escalada A, Marín-García P, Gallardo-Pino C, Gil-de-Miguel A. Respiratory syncytial virus bronchiolitis in children up to 5 years of age in Spain: epidemiology and comorbidities: an observational study. Medicine (Baltimore). 2015;94:e831.
30. Lade C, Bayer L, Huebbe B, Riedel J, Melnik S, Brestrich G, et al. Clinical and economic inpatient burden of respiratory syncytial virus (RSV) infections in children < 2 years of age in Germany, 2014-2019: a retrospective health claims analysis. Infection. 2025;53:393–404.
31. Nuttens C, Moyersoen J, Curcio D, Aponte-Torres Z, Baay M, Vroling H, et al. Differences between RSV A and RSV B subgroups and implications for pharmaceutical preventive measures. Infect Dis Ther. 2024;13:1725–42.
32. Sankatsing VDV, van Summeren J, Abreha FM, Pandolfi E, Chironna M, Loconsole D, et al. Economic impact of respiratory syncytial virus infections in children under 5 years of age attending primary care in Italy: a prospective cohort study in two regions. Influenza Other Respir Viruses. 2025;19:e70074.
33. Nickbakhsh S, Thorburn F, Von Wissmann B, McMenamin J, Gunson RN, Murcia PR. Extensive multiplex PCR diagnostics reveal new insights into the epidemiology of viral respiratory infections. Epidemiol Infect. 2016;144:2064–76.
34. Li Y, Pillai P, Miyake F, Nair H. The role of viral co-infections in the severity of acute respiratory infections among children infected with respiratory syncytial virus (RSV): a systematic review and meta-analysis. J Glob Health. 2020;10:010426.
35. Toivonen L, Karppinen S, Schuez-Havupalo L, Teros-Jaakkola T, Mertsola J, Waris M, et al. Respiratory syncytial virus infections in children 0-24 months of age in the community. J Infect. 2020;80:69–75.
36. Hall CB, Powell KR, Schnabel KC, Gala CL, Pincus PH. Risk of secondary bacterial infection in infants hospitalized with respiratory syncytial viral infection. J Pediatr. 1988;113:266–71.
37. Diaz-Diaz A, García-Maurino C, Jordán-Villegas A, Naples J, Ramilo O, Mejías A. Viral bacterial interactions in children: impact on clinical outcomes. Pediatr Infect Dis J. 2019;38 6S Suppl 1:S14–9.
38. Phillips M, Finelli L, Saiman L, Wang C, Choi Y, Patel J. Respiratory syncytial virus-associated acute otitis media in infants and children. J Pediatric Infect Dis Soc. 2020;9:544–50.
39. Abreo A, Wu P, Donovan BM, Ding T, Gebretsadik T, Huang X, et al. Infant respiratory syncytial virus bronchiolitis and subsequent risk of pneumonia, otitis media, and antibiotic utilization. Clin Infect Dis. 2020;71:211–4.
40. Zhang S, Akmar LZ, Bailey F, Rath BA, Alchikh M, Schweiger B, et al. Cost of respiratory syncytial virus-associated acute lower respiratory infection management in young children at the regional and global level: a systematic review and meta-analysis. J Infect Dis. 2020;222 Suppl 7:S680–7.
41. López-Lacort M, Muñoz-Quiles C, Mira-Iglesias A, Xavier López-Labrador F, Garcés-Sánchez M, Escribano-López B, et al. Nirsevimab effectiveness against severe respiratory syncytial virus infection in the primary care setting. Pediatrics. 2025;155:e2024066393.
42. Mallah N, Pardo-Seco J, Pérez-Martínez O, Durán-Parrondo C, Martinón-Torres F, NIRSE-GAL study group. Full 2023-24 season results of universal prophylaxis with nirsevimab in Galicia, Spain: the NIRSE-GAL study. Lancet Infect Dis. 2025;25:e62–3.