




Short- and mid-term morbidity and primary-care burden due to infant respiratory syncytial virus infection: A Spanish 6-year population-based longitudinal study

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Abstract

Background: The morbidity burden of respiratory syncytial virus (RSV) in infants extends beyond hospitalization. Defining the RSV burden before implementing prophylaxis programs is essential for evaluating any potential impact on short- to mid-term morbidity and the utilization of primary healthcare (PHC) and emergency services (ES). We established this reference data using a population-based cohort approach.

Sonia Ares-Gómez and Narmeen Mallah contributed equally to this work.

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Methods: Infants hospitalized for RSV from January 2016 to March 2023 were matched with non-hospitalized ones based on birthdate and sex. We defined the exposure as severe RSV hospitalization. The main study outcomes were as follows: (1) PHC and ES visits for RSV, categorized using the International Classification of Primary Care codes, (2) prescriptions for respiratory airway obstructive disease, and (3) antibacterial prescriptions. Participants were followed up from 30 days before hospitalization for severe RSV until the outcome occurrence or end of the study. Adjusted incidence rate ratios (IRRs) of the outcomes along with their 95% confidence intervals (CI) were estimated using Poisson regression models. Stratified analyses by type of PHC visit (nurse, pediatrician, or pharmacy) and follow-up period were undertaken. We defined mid-term outcomes as those taking place up to 24 months of follow-up period.

Results: The study included 6626 children (3313 RSV-hospitalized; 3313 non-hospitalized) with a median follow-up of 53.7 months (IQR=27.9, 69.4). After a 3-month follow-up, severe RSV was associated with a considerable increase in PHC visits for wheezing/asthma (IRR=4.31, 95% CI: 3.84–4.84), lower respiratory infections (IRR=4.91, 95% CI: 4.34–5.58), and bronchiolitis (IRR=4.68, 95% CI: 2.93–7.65). Severe RSV was also associated with more PHC visits for the pediatrician (IRR=2.00, 95% CI: 1.96–2.05), nurse (IRR=1.89, 95% CI: 1.75–1.92), hospital emergency (IRR=2.39, 95% CI: 2.17–2.63), primary healthcare emergency (IRR: 1.54, 95% CI: 1.31–1.82), as well as with important increase in prescriptions for obstructive airway diseases (IRR=5.98, 95% CI: 5.43–6.60) and antibacterials (IRR=4.02, 95% CI: 3.38–4.81). All findings remained substantial until 2 years of post-infection.

Conclusions: Severe RSV infection in infants significantly increases short- to mid-term respiratory morbidity leading to an escalation in healthcare utilization (PHC/ES attendance) and medication prescriptions for up to 2 years afterward. Our approach could be useful in assessing the impact and cost-effectiveness of RSV prevention programs.

KEYWORDS

asthma, hospitalizations, infants, primary healthcare, respiratory syncytial virus, Spain, viral bronchiolitis

1 | INTRODUCTION

Respiratory Syncytial Virus (RSV) infection stands as the primary pathogen associated with global hospitalizations for lower respiratory tract infections (LRTI) in children.^{1,2} The most significant RSV burden is observed in young infants, with a global estimate of 6.6 million episodes of acute LRTI associated with RSV in infants aged 0–6 months.³ Furthermore, 3.6% of deaths in infants aged 28 days to six months are attributed to RSV.³ In the European Union, from 2006 to 2018, nearly 250,000 annual hospitalizations were linked to RSV infections in children under five, with 75% of these cases occurring in infants under one year.⁴ In Spain, two out of every 100 children under two years of age are hospitalized for RSV, averaging six days stay, and resulting in an estimated annual cost of €49.6 million to the

Key message

We provided an approach for a comprehensive assessment of respiratory syncytial virus (RSV) in infants that extends beyond hospitalization. Through a six-year population-based longitudinal study, we showed that severe RSV infection in infants significantly increases short- and mid-term morbidity leading to an escalation in primary health-care utilization and medication prescriptions for up to two years after hospitalization for severe RSV. Our study could be useful in assessing the impact and cost-effectiveness of RSV prevention programs.

National Health System.^{5,6} Most RSV-related episodes (93.1%) occur in children without any comorbidity, and approximately 27% of the total direct healthcare expenses are unrelated to hospitalizations.⁷

The economic and health impact of RSV extends beyond the acute episode. Children with a history of RSV infections are up to three times more likely to develop recurrent wheezing episodes than those without such a history.⁸ An association between RSV infection in early years and the onset of childhood asthma has also been reported.^{9,10} A double-blind clinical trial investigating the impact of a monoclonal antibody against RSV on the occurrence of wheezing days during the first year of life revealed a 61% reduction in wheezing days, thereby providing compelling evidence for a causal relationship.¹¹

Recently, both a long-acting monoclonal antibody and a maternal vaccine have been approved in Europe for RSV prophylaxis in infants.¹²⁻¹⁴ Galicia, an autonomous community with a 2.7 million population in Northwest Spain, became the world's first region to introduce nirsevimab as part of the 2023 regional immunization program (IP).^{15,16} Recommended actions toward effective RSV immunization policies encompass estimating the RSV burden in specific populations.¹⁷ From 2017 to 2023 (excluding COVID-19 seasons, 2019-2021), the infant RSV hospitalization rate per season in Galicia, Spain, ranged between 3.34 and 5.03 hospital admissions per 100,000 inhabitants.¹⁸

As part of the burden assessment and effort to establish the background burden of RSV in primary care/emergency care utilization and medication use, this retrospective population-based follow-up study was initiated in collaboration with the Galician General Directorate of Public Health. Hereby, we provide a detailed analysis of the association of severe RSV infections acquired during the first year of life with the need for physician consultation, nurse visits, emergency department visits, and medical prescriptions for respiratory symptoms. We also report on the association of severe RSV infections with the subsequent development of clinical episodes of mid-term respiratory morbidity, defined as up to 2 years of follow-up. This approach could prove useful in settings like ours to assess the need for and evaluate the effectiveness of immunization strategies against RSV.

2 | METHODS

2.1 | Study design and population

A retrospective population-based cohort study was undertaken in Galicia, Northwest Spain, using registry data of children born between January 1st, 2016, and March 3rd, 2023, inclusive. Galicia, with approximately 2.7 million inhabitants, recorded 14,479 births in 2022, with 5.5 and 5.4 births per 1000 persons in 2021 and 2022, respectively.¹⁹

The population was divided into two groups based on their exposure to RSV infection that required hospitalization within 30 days (hospitalized vs. non-hospitalized). Data on hospitalized children for RSV during infancy were obtained from the Minimum

Basic Data Set (MBDS) hospital registries. Hospitalizations for RSV were considered if any of the following international classification of diseases (ICD-10) codes were present at any position in the discharge diagnosis: J21.0 (Acute bronchiolitis due to respiratory syncytial virus), J20.5 (Acute bronchitis due to respiratory syncytial virus), J12.1 (Respiratory syncytial virus pneumonia), or B97.4 (Respiratory syncytial virus as the cause of diseases classified elsewhere).

Data on non-hospitalized children were obtained from the Galician registry of children with public health assistance (Health Card).

Matching of hospitalized and non-hospitalized infants on a 1:1 ratio was done by the day of birth to control for changes in RSV seasonality, virus epidemiology, and diagnosis. Participants were also matched by sex for biological plausibility. In the case of the multiple matching option, the one with the lowest number on the health card was chosen. To ensure comparability, all participants had approximately 100% compliance in the first year of life in the pediatric control, as per prescheduled visits outlined in the Healthy Child regional program in Galicia (named "Programa do Neno San").²⁰

2.2 | Data

All data required for the analysis were extracted from the Galician Health Care Services (SERGAS) electronic registries, including (MBDS) hospital registries, Galician registry HC card, Primary Health Care (PHC), Emergency services (ES), and Medication Prescriptions (MP). Anonymized data from these registries were obtained for each participant from the day of birth until June 16th, 2023.

2.3 | Outcomes

The main study outcomes encompassed PHC and ES visits, along with medication prescriptions from the initiation of the follow-up period. These outcomes are detailed below:

2.3.1 | Primary health care (PHC)

Visits at demand to the pediatrician, nurse, pharmacy, and social worker

Data from visits to the pediatrician, nurse, and pharmacy were extracted from the PHC records at SERGAS. Examination of visits to the social worker aimed to identify potential disparities in social status between the two groups.

PHC episodes

Episodes related to respiratory sequelae associated with severe RSV infections were categorized using the International Classification of Primary Care (ICPC-2) codes, following the

adapted Spanish version (CIAP-2).²¹ Individual outcomes encompassed various respiratory conditions, including Otitis media/acute myringitis (H71), Respiratory fatigue/dyspnea (R02), Gaspings/wheezing (R03), Other breathing problems (R04), Cough (R05), Sneezing/stuffy nose (R07), Other nasal signs/symptoms (R08), Upper acute respiratory infection (R74), Acute tonsillitis (R76), Acute laryngitis/tracheitis (R77), Acute Bronchitis/bronchiolitis (R78, subdivided into R78.00 for bronchitis and R78.01 for acute bronchiolitis), and Influenza/flu (R80).

Composite outcomes were created to capture broader patterns of RSV morbidity, including Wheezing/Asthma (R02, R03, R04, R05, R78.00, R78.01, R79, R95, R96), LRTI (R02, R03, R04, R78, R78.00, R78.01, R79, R81.00, R81.01, R81.02, R81.03, R82), Acute LRTI (H71, R71, R72, R74, R75, R76, R77, R78, R78.00, R78.01, R80, R81.00, R81.01, R81.02, R81.03, R82, R83), Upper Respiratory Infections (H01, H02, H04, H29, H70, H71, H72, H74, R05, R07, R08, R09, R21, R25, R72, R74, R75, R76, R77), All otitis (H01, H02, H04, H29, H70, H71, H72, and H74), and Otitis media (H71, H72, and H74).

2.3.2 | Emergency Service (ES) visits

ES visits were analyzed by considering each of the total number of ES visits to primary care ES (PCE) and hospital ES (HE), separately.

2.3.3 | Prescription of medications

Prescriptions of medications were extracted from digitalized and centralized medical prescriptions and dispensations. Each prescription is linked to a patient's unique identification number at SERGAS. Prescriptions were analyzed as the number of episodic events with prescription of antibacterials (ATC code J01 comprises antibacterials for systemic use, except antimycobacterials, which are classified in J04) or drugs for obstructive airway diseases (ATC code R03 include: R03A Adrenergics, inhalants, R03B Other drugs for obstructive airway diseases, inhalants, R03C Adrenergics for systemic use, R03D Other systemic drugs for obstructive airway diseases).

2.4 | Follow-up period

All outcomes were examined across five times intervals, with the starting point set up to 30 days before hospitalization for RSV. Given that all the hospitalized participants were matched by birthday to a non-hospitalized child, the time 0 for the initiation of the observation was established as the hospitalization day also for their corresponding match, ensuring an equivalent observation period. Because each hospitalized participant was matched 1:1 to a non-hospitalized child by the exact day of birth, we obtained the same follow-up in both groups. In addition, with this approach, we were able to follow each pair of children the same days before and after the hospitalization

date. The five follow-up intervals were as follows: 30 days before hospitalization until the day before hospital admission (−30 to −1 days), from hospital admission to 89 days after hospitalization (0 to 89 days), from 90 days to 364 days year after hospitalization (90 to 364 days), from 365 to 729 days after hospitalizations (365 to 729 days), and from 730 days after hospitalization till the end of the study, June 16th, 2023 (≥730 days). Cumulative follow-up periods were also considered (30 days before hospitalization until 89 days [−30 to 89 days], from 30 days before hospitalization until 1 year after hospitalization [−30 to 364 days], from 30 days before hospitalization until 2 years after hospitalization [−30 to 729 days], and 30 days before hospitalization till the end of study [−30 days till the end of study]).

2.5 | Statistical analysis

To determine the association of severe RSV with each of the study outcomes, an independent Poisson regression model was employed for each outcome of interest. Count data were analyzed, and to address overdispersion, robust variance through the sandwich method was utilized.²² Incidence rate ratios (IRR) and their 95% confidence intervals (CI) were estimated, adjusting for the number of visits to the Healthy Child regional program to account for possible confounding. All analyses were performed in R version 4.3.1.

3 | RESULTS

3.1 | General study population characteristics

A total of 3313 children hospitalized for RSV during infancy were registered over seven RSV seasons (2016–2017, 2017–2018, 2018–2019, 2019–2020, 2020–2021, 2021–2022, 2022–2023). The median follow-up was 53.7 months (Interquartile range IQR = 27.9, 69.4) with a median age of 75 days (IQR = 40, 106.4) at hospitalization. The annual distribution of hospitalizations was as follows: 2016 ($n=551$), 2017 ($n=451$), 2018 ($n=366$), 2019 ($n=642$), 2020 ($n=247$), 2021 ($n=395$), 2022 ($n=606$), and 2023 ($n=55$). Throughout the study period, the median and range of pediatrician visits, as per the Healthy Child regional program's prescheduled visits, were 20 (IQR: 14–25) for hospitalized infants and 15 (IQR: 2–22) for non-hospitalized ones.

3.2 | RSV severe infection during infancy and primary healthcare (PHC) utilization

3.2.1 | Visits at demand to the pediatrician, nurse, pharmacy, and social worker

The risk of requiring a visit to the pediatrician in infants who had been hospitalized for RSV doubles that of non-hospitalized infants

during the month before hospitalization (−30 to −1 days, IRR=2.15 [95% CI: 2.07–2.23]) as well as in the first 3 months after hospitalization (0 to 89 days, IRR=2.00 [95% CI: 1.96–2.05]). The need for pediatrician visits on demand gradually declines with time after RSV hospitalization, but it remains higher in RSV-hospitalized infants than in non-hospitalized ones until the end of the study (≥ 730 days IRR=1.10 [95% CI: 1.09–1.12]) (Table 1).

Similarly, severe RSV infection during infancy is associated with almost twice the risk of demanding a nurse visit until 3 months after hospitalization (−30 to −1 days, IRR=1.94 [95% CI: 1.81–2.08]; 0 to 89 days, IRR=1.83 [95% CI: 1.75–1.92]). The nurse visits on demand remain higher in RSV-hospitalized infants than in those who were not hospitalized for RSV until the end of the study (≥ 730 days, IRR=1.17 [95% CI: 1.14–1.21]), yet the magnitude of the demanded visits decreased with time (Table 1).

In the 30 days before hospitalization for severe RSV, the risk of visiting the pharmacy is substantially higher in RSV-hospitalized infants than in non-hospitalized ones (−30 to −1 days, IRR=2.67 [95% CI: 1.74–4.21]), yet the association weakens right after hospitalization, reaching borderline until the first year after hospitalization (0 to 89 days, IRR=1.28 [95% CI: 1.01–1.64], 90 to

364 days, IRR=1.29 [95% CI: 1.06–1.58]), then losing its statistical significance after that period (Table 1).

RSV hospitalization was not associated with increased visits to the social worker at any moment after infection (Table 1).

Table S1 summarizes the association of severe RSV with visits at demand to the pediatrician, nurse, pharmacy, and social worker for cumulative follow-up timeframes.

3.2.2 | Primary healthcare (PHC) episodes

Figure 1 and Table S2 represent the association of severe RSV infections during infancy with individual and composite respiratory episodes, characterized based on CIAP-2 codes. Until 2023, bronchiolitis episodes were classified under the CIAP-2 code (R78) which included both bronchitis and bronchiolitis episodes. In 2023, CIAP-2 codification incorporated the R78.01 code which allows for a more precise classification of bronchiolitis. The association of severe RSV with the occurrence of subsequent respiratory episodes was most prominent in the initial 3 months following hospitalization for R78 (0 to 89 days, IRR=5.01 [95% CI: 4.38–5.75])

TABLE 1 Incidence rate ratio (IRR) and 95% confidence interval (CI) of on-demand primary care visits in infants compared to non-RSV-hospitalized children.

Follow-up time (days)	Outcome	Hospitalized (N = 3313)		Not hospitalized (N = 3313)		IRR (95% CI)
		% (N)	Mean (SD)	% (N)	Mean (SD)	
−30 to −1	Pediatrician	71.1% (2356)	3.1 (3.2)	34.0% (1126)	1.2 (2.2)	2.15 (2.07–2.23)
	Nurse	30.5% (1012)	0.9 (1.6)	14.4% (477)	0.4 (1.1)	1.94 (1.81–2.08)
	Pharmacy	0.9% (30)	0.0 (0.3)	0.4% (12)	0.0 (0.2)	2.67 (1.74–4.21)
	Social worker	0.4% (14)	0.0 (0.1)	0.5% (16)	0.0 (0.2)	0.67 (0.41–1.10)
0 to 89	Pediatrician	91.8% (3040)	9.1 (7.2)	57.3% (1899)	3.8 (5.1)	2.00 (1.96–2.05)
	Nurse	49.5% (1640)	1.8 (2.6)	27.5% (911)	0.9 (1.8)	1.83 (1.75–1.92)
	Pharmacy	1.9% (63)	0.1 (0.4)	1.0% (33)	0.0 (0.4)	1.28 (1.01–1.64)
	Social worker	1.0% (32)	0.0 (0.3)	0.7% (23)	0.0 (0.2)	1.29 (0.92–1.83)
90 to 364	Pediatrician	92.4% (3062)	16.0 (13.6)	67.0% (2220)	9.0 (11.3)	1.42 (1.40–1.44)
	Nurse	62.8% (2081)	3.3 (4.1)	41.7% (1380)	1.9 (3.2)	1.42 (1.37–1.46)
	Pharmacy	2.1% (71)	0.1 (0.7)	1.5% (49)	0.0 (0.5)	1.29 (1.06–1.58)
	Social worker	1.2% (41)	0.0 (0.6)	0.9% (31)	0.0 (0.6)	1.01 (0.80–1.28)
365 to 729	Pediatrician	74.2% (2459)	13.9 (14.9)	53.3% (1767)	8.7 (13.1)	1.20 (1.18–1.22)
	Nurse	46.8% (1550)	2.2 (3.4)	30.2% (1000)	1.3 (2.7)	1.28 (1.23–1.33)
	Pharmacy	0.6% (21)	0.0 (0.3)	0.6% (20)	0.0 (0.3)	0.75 (0.53–1.07)
	Social worker	0.9% (29)	0.0 (0.5)	1.0% (32)	0.0 (0.5)	0.91 (0.70–1.18)
≥ 730	Pediatrician	65.0% (2153)	24.8 (30.5)	50.8% (1684)	16.8 (27.1)	1.10 (1.09–1.12)
	Nurse	49.2% (1629)	3.2 (5.1)	34.7% (1148)	2.0 (4.2)	1.17 (1.14–1.21)
	Pharmacy	0.6% (19)	0.0 (0.3)	0.4% (14)	0.0 (0.2)	1.41 (0.92–2.20)
	Social worker	2.2% (72)	0.1 (1.0)	2.7% (90)	0.2 (1.3)	0.70 (0.62–0.80)

Note: Data are presented by type of primary care specialist visit and stratified by follow-up period since severe RSV infection. N: total number of infants with at least one visit for pediatrician, nurse, pharmacist, or social worker. The same infant could visit the pediatrician, nurse, pharmacist, and/or social worker, hence, the total of these visits may not be equal to that of infants (3133 per exposure strata); %: percentage of children with at least one visit for pediatrician, nurse, pharmacist, or social worker.

Abbreviation: SD, standard deviation.

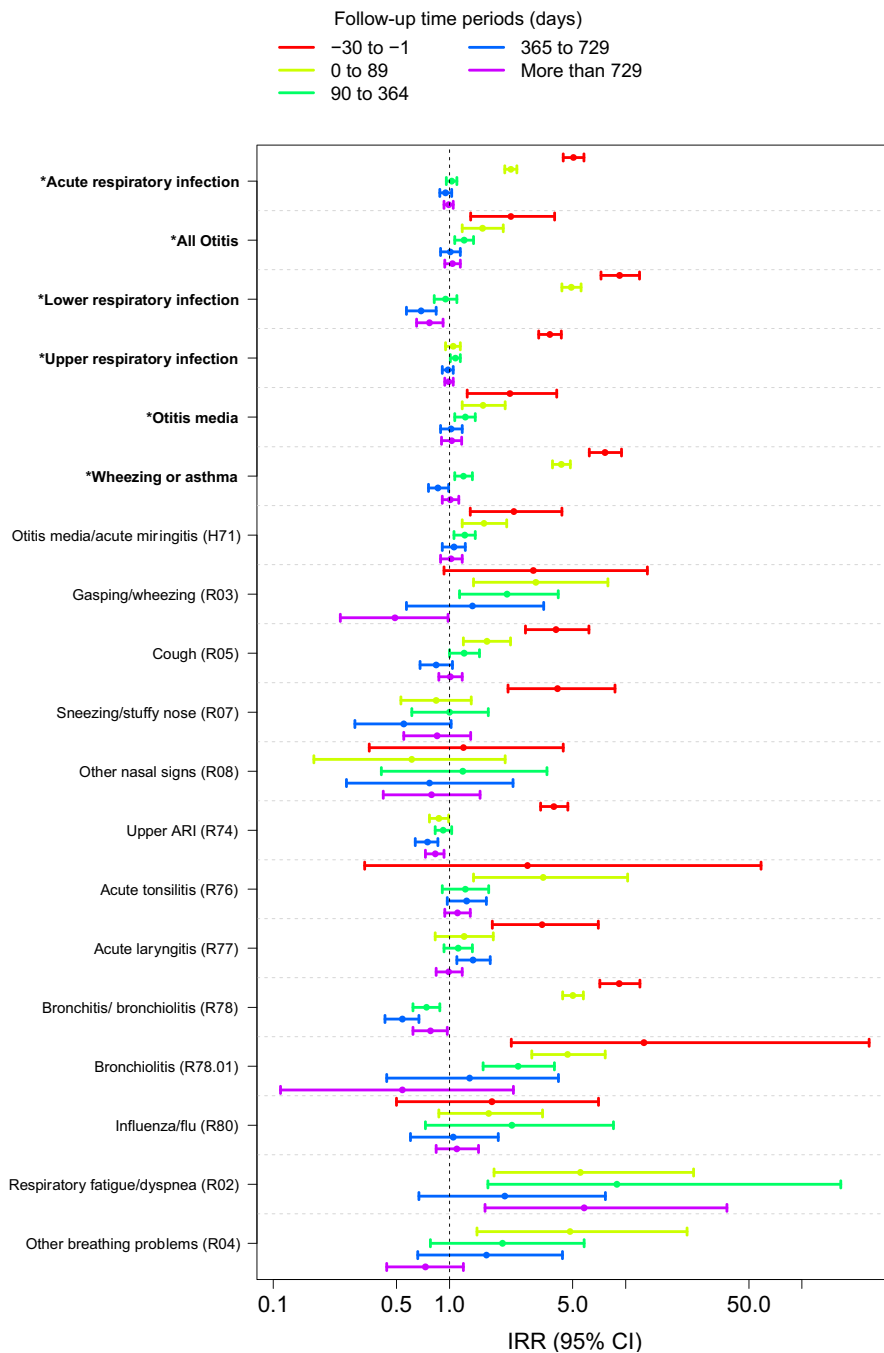


FIGURE 1 Incidence rate ratios for primary care diagnostic codes (CIAP-2 codes) in children attending primary care after RSV hospitalization compared to not-hospitalized children, reported by different length follow-up periods since hospitalization day. Each follow-up period is represented by a specific color. CIAP 2 codes included in the composite endpoints: Acute respiratory infection: H71, R71, R72, R74, R75, R76, R77, R78, R78.00, R78.01, R80, R81.00, R81.01, R81.02, R81.03, R82, R83; All otitis: H01, H02, H04, H29, H70, H71, H72, H74; Lower respiratory infections: R02, R03, R04, R78, R78.00, R78.01, R79, R81.00, R81.01, R81.02, R81.03, R82; Upper respiratory infections: H01, H02, H04, H29, H70, H71, H72, H74, R05, R07, R08, R09, R21, R25, R72, R74, R75, R76, R77; Otitis media: H71, H72, H74; Wheezing/Asthma; R02, R03, R04, R05, R78.00, R78.01, R79, R95, R96.

and R78.01 (0 to 89 days, IRR=4.68 [95% CI: 2.93–7.65]) coded diagnosis. The risk of bronchiolitis, as a specific diagnosis (R78.01), in infants who had been hospitalized for severe RSV remained significantly higher than that in the non-hospitalized infants up to one year after hospitalization [90 to 364 days, IRR=2.45 (95% CI: 1.55–3.94)] (Table S2).

Beyond 90 days of hospitalization for severe RSV, the risk of needing PHC for bronchitis (R78) was 26% lower in hospitalized than in non-hospitalized infants (90 to 364 days, IRR=0.74 [95% CI: 0.62–0.88]). Of the bronchitis episodes observed in the severe RSV infection cases, 70% occurred within the first 4 months of follow-up coinciding with the period around hospitalization; meanwhile,

among non-hospitalized infants, only 30% of the bronchitis episodes took place during this follow-up period.

PHC visits for respiratory fatigue/dyspnea were infrequent, with only three episodes reported during the 0 to 89 days of follow-up period in non-hospitalized infants compared with 17 episodes in hospitalized ones (IRR=5.53 [95% CI: 1.79–24.29]) (Figure 1, Table S2).

No significant association was observed between severe RSV infections and PHC visits for influenza at any follow-up period. The cumulative number of influenza-related PHC visits at the end of the study (June 16th, 2023) was 200 in participants who had severe RSV during infancy and 124 in those who were not hospitalized for RSV (IRR=1.20 [95% CI: 0.93–1.54]) (Table S3).

3.2.3 | Composite outcomes: wheezing/asthma and others

The examination of the composite outcomes of respiratory morbidity following severe RSV infections revealed that during the first 3 months of follow-up, severe RSV infection during infancy is associated with a more than fourfold higher risk of PHC visits for wheezing/ asthma (IRR=4.31 [95% CI: 3.84–4.84]) and LRTI (IRR=4.91 [95% CI: 4.34–5.58]) (Figure 1, Table S2). Additionally, during that same follow-up period (0–89 days), infants who had been hospitalized for severe RSV have more than twofold higher risk of acute respiratory infections (IRR=2.23 [95% CI: 2.06–2.41]), a 54% higher risk of all otitis (IRR=1.54 [95% CI: 1.18–2.02]) and 57% higher risk of otitis media/acute miringitis (IRR=1.57 [95% CI: 1.18–2.11]) compared with non-hospitalized infants (Figure 1, Table S2).

3.3 | RSV severe infection during infancy and emergency services visits: Primary care emergency (PCE) and hospital emergency (HE)

A total number of 55,294 ES visits were recorded during the study period: 17,492 visits took place in primary care emergency (PCE) settings, 35,123 visits were in hospital emergency departments (HE), and 2679 visits were transferred from PCE to HE. Compared with non-hospitalized children, patients who had been hospitalized for severe RSV have more than twice the risk of visiting HE (0–89 days, IRR: 2.39 [95% CI: 2.17–2.63]); and 54% higher risk of requiring PCE (0 to 89 days, IRR: 1.54 [95% CI: 1.31–1.82]) during the first three months after hospitalization (Table 2). A higher risk of requiring HE or PCE was observed until the end of the study, yet with a lower

magnitude of association. Beyond two years of follow-up, the risk of visiting HE and PCE after severe RSV infection was 24% (≥ 730 days, IRR=1.24 [95% CI: 1.20–1.29]), and 13% (≥ 730 days, IRR=1.13 [95% CI: 1.08–1.17]), respectively (Table 2).

Table S4 represents the association of severe RSV with the risk of requiring HE or PCE by cumulative follow-up timeframes.

3.4 | RSV severe infection during infancy and prescription of medications

The number of episodic events with prescription of antibacterials, obstructive airway disease drugs, or any of both was substantially higher in RSV-related hospitalized children than in non-RSV hospitalized children. The most pronounced association was found for the prescription of obstructive airway disease drugs during the month before hospitalization for severe RSV infection (–30 to –1 days, IRR=7.41 [95% CI: 6.04–9.18]) and 3 months after admission (0 to 89 days, IRR=5.98 [95% CI: 5.43–6.60]) (Table 3). In the first 3 months after admission, the risk of requiring a prescription of any of the two drugs was 5.50 times higher in hospitalized infants than in non-hospitalized ones (0–89 days, IRR=5.50 [95% CI: 5.05–5.99]) (Table 3). Hospitalized infants for severe RSV were also at fourfold higher risk of receiving antibacterials prescription during the first 3 months after admission than the non-hospitalized ones (0 to 89 days, IRR=4.02 [95% CI: 3.38–4.81]) (Table 3). Significant associations between severe RSV infection during infancy and the prescription of antibacterials and/or obstructive airway disease drugs were sustained throughout all follow-up periods (Table 3). Findings on the prescription of those drugs during cumulative follow-up periods are summarized in Table S5.

TABLE 2 Incidence rate ratio (IRR) of primary care emergency (PCE) visits and hospital emergencies (HE) along with their 95% confidence intervals (CI) in RSV hospitalized children compared to those not hospitalized children.

Follow-up time (days)	Outcome	Hospitalized (N=3313)		Not Hospitalized (N=3313)		IRR (95% CI)
		Mean (SD)	% (N)	Mean (SD)	% (N)	
–30 to –1	PCE	0.2 (0.5)	14.9% (495)	0.0 (0.2)	3.2% (105)	4.89 (4.03–5.99)
	HE	0.9 (1)	58.4% (1936)	0.1 (0.4)	9.9% (328)	6.52 (5.88–7.25)
0 to 89	PCE	0.1 (0.5)	9.9% (327)	0.1 (0.3)	5.6% (185)	1.54 (1.31–1.82)
	HE	0.5 (0.9)	30.4% (1006)	0.2 (0.5)	12.5% (413)	2.39 (2.17–2.63)
90 to 364	PCE	0.7 (1.5)	30.7% (1017)	0.4 (1.0)	22.8% (755)	1.29 (1.21–1.39)
	HE	1.6 (2.2)	58.4% (1934)	0.8 (1.4)	35.9% (1190)	1.69 (1.61–1.77)
365 to 729	PCE	0.8 (1.6)	31.8% (1055)	0.5 (1.2)	22.6% (749)	1.25 (1.17–1.33)
	HE	1.4 (2.3)	49.5% (1641)	0.7 (1.6)	30.9% (1023)	1.45 (1.38–1.52)
≥ 730	PCE	1.7 (3.2)	41.1% (1362)	1.2 (2.6)	32.9% (1090)	1.13 (1.08–1.17)
	HE	2.1 (3.4)	50.6% (1676)	1.3 (2.6)	36.1% (1197)	1.24 (1.20–1.29)

Note: N: total number of children who attended at least once to primary care or hospital emergency. %, percentage of children who attended at least once to primary care or hospital emergency.

Abbreviation: SD, standard deviation.

TABLE 3 Incidence rate ratio (IRR) and 95% confidence intervals (CI) of antibacterials, obstructive airway disease drug prescription in children who were RSV hospitalized during infancy compared to those who were not RSV-hospitalized children.

Follow-up time (days)	Outcome	Hospitalized (N = 3313)		Not hospitalized (N = 3313)		IRR (95% CI)
		Mean (SD)	% (N)	Mean (SD)	% (N)	
-30 to -1	Antibacterials	0 (0.2)	2.2% (73)	0 (0.1)	0.5% (15)	4.38 (2.73-7.39)
	Obstructive airway disease drugs	0.3 (1.1)	14.2% (469)	0 (0.3)	1.8% (59)	7.41 (6.04-9.18)
	Antibacterials or obstructive airway disease drugs	0.3 (1.1)	15% (498)	0 (0.4)	2.1% (68)	6.91 (5.72-8.41)
0 to 89	Antibacterials	0.2 (1.8)	10.3% (340)	0 (0.5)	3% (98)	4.02 (3.38-4.81)
	Obstructive airway disease drugs	1 (2.5)	31% (1028)	0.1 (0.7)	7.9% (261)	5.98 (5.43-6.6)
	Antibacterials or obstructive airway disease drugs	1.2 (3.3)	34.8% (1153)	0.2 (1)	9.4% (313)	5.50 (5.05-5.99)
90 to 364	Antibacterials	0.4 (1.7)	18.7% (621)	0.2 (0.8)	10.2% (339)	1.94 (1.76-2.14)
	Obstructive airway disease drugs	1.7 (4.1)	40.2% (1332)	0.4 (2.1)	14.3% (473)	3.43 (3.23-3.65)
	Antibacterials or obstructive airway disease drugs	2.1 (4.7)	46.5% (1540)	0.6 (2.4)	19.9% (660)	2.97 (2.82-3.13)
365 to 729	Antibacterials	0.7 (2.8)	27.1% (898)	0.3 (0.9)	16.2% (537)	1.76 (1.63-1.9)
	Obstructive airway disease drugs	1.4 (3.8)	36.1% (1196)	0.5 (1.7)	17.1% (566)	2.40 (2.27-2.55)
	Antibacterials or obstructive airway disease drugs	2.1 (5.1)	46.8% (1549)	0.8 (2.2)	25.7% (850)	2.15 (2.05-2.26)
≥730	Antibacterials	1.1 (3.4)	36.6% (1211)	0.6 (1.6)	24.6% (815)	1.35 (1.28-1.43)
	Obstructive airway disease drugs	2.2 (5.6)	38.1% (1262)	0.9 (3.5)	21.4% (710)	1.83 (1.75-1.91)
	Antibacterials or obstructive airway disease drugs	3.3 (7.3)	49.9% (1653)	1.5 (4.4)	32.5% (1076)	1.64 (1.58-1.70)

Note: N, total number of children with at least one episodic event with a prescription of obstructive airway disease drug or antibacterials; %, percentage of children with at least one episodic event with a prescription of obstructive airway disease drug or antibacterials. Abbreviation: SD, standard deviation.

4 | DISCUSSION

Our study delineates the considerable short- to mid-term burden resulting from infant RSV. We demonstrate an elevated utilization of PHC services during childhood following severe RSV infections in infancy. This highlights a substantial increase in both PHC and ES visits, indicating a heightened risk of developing mid-term respiratory morbidities. These findings significantly contribute to understanding the broader health-related and socioeconomic impact of severe RSV infections beyond their acute phase. These aspects should be considered in evaluating the cost-effectiveness of prevention programs.

We observed that severe RSV infection during infancy is associated with a twofold increased risk of needing a pediatric or nurse consultation and more than fivefold the risk of ES visits during the first 3 months after infection. This underscores the heavy burden that severe RSV infections may impose on PHC/ES. Research on RSV burden in PHC is limited, with most studies focusing on hospitalizations, leaving PHC understudied. Global estimates of acute lower respiratory infections due to RSV in 2019 did not specifically report the burden of RSV-associated acute lower respiratory tract infections in primary care, such as general practice and outpatient settings.³ A study conducted in the United States between 2008 and 2014, reported that over two-thirds of healthcare consultations for RSV-attributable conditions in infants occurred in outpatient

settings, constituting about 40% of total medical costs related to RSV. Only 13% occurred in emergencies, and 10% resulted in hospitalizations.²³ Our research extends these findings by offering detailed insights into morbidity patterns in primary care settings, as indicated by CIAP-2.

The use of composite endpoints in our study, including related codes under broader categories, aimed for more robust end points that may be less dependent on codification practice differences across primary care professionals. Concretely, bronchitis/bronchiolitis, lower and upper respiratory episodes, and wheezing/asthma up to 1 year after infection, were the most frequent causes of increased need of primary care attendance. Consistent with our findings, a systematic review of the economic and health impact of RSV affirmed that the most frequent complication of severe RSV infection is acute bronchiolitis.⁸ In Spain, nearly 90% of bronchiolitis cases are managed in primary care offices, revealing the burden imposed by this disease on PHC.²⁴ A six-year follow-up study of American children who had RSV bronchiolitis during infancy reported that around half of these children develop asthma during the first 6 years of life.¹⁰ Similarly, in Australia, a population-based cohort study indicated that hospitalization for severe RSV disease in the first 2 years of life was associated with almost four times the risk of subsequent hospitalization for the first episode of asthma.²⁵ Furthermore, the same research group reported that, despite RSV

burden being highest in children younger than 6 months, the risk of hospitalization for subsequent asthma was higher in children who develop RSV disease at an age older than 6 months, with an IRR of subsequent asthma of 2.0 (95% CI, 1.4–2.7) and 1.7 (95% CI, 1.0–2.5) for children hospitalized for RSV at an age of 6 to <12 and 12–24 months, respectively.²⁶ In line with these findings, Szabo et al. estimated, through a meta-analysis, that after RSV hospitalization during infancy, the attributable risk of asthma due to RSV ranges from 13% to 22% among children younger than five, from 11% to 27% among those aged 5 to 11 years and was 32% among children 12 years and older.²⁷ The biological explanation of the association between RSV and asthma is related to an immune-response cluster characterized by lower non-interferon-gamma and higher type-2 and type-17 cytokines.²⁸

We also found that severe RSV is associated with a considerable increase in the risk of requiring obstructive airway disease and antibacterial treatments for more than 2 years after hospitalization. The increase in the risk of antibacterial use and that of acute tonsillitis after severe RSV may suggest that the host is more vulnerable to secondary bacterial infections after a severe RSV infection. Several previous studies reported that respiratory viral infections like RSV often increase the host predisposition to secondary respiratory bacterial infections caused by pathogens, such as *Streptococcus pneumoniae* and *Staphylococcus aureus*, which may lead to life-threatening sequelae.^{11,29,30} In the case of co-pathogenesis, RSV and secondary bacterial infections, RSV infections were suggested to facilitate bacterial adhesion in epithelial cells and increment the bacterial capacity to colonize the airway. Clinical studies also observed that the upper airway microbiota of RSV-infected children is significantly enriched with *Haemophilus influenzae* and *Streptococcus pneumoniae*.^{31,32} The host response to RSV infection is characterized by the recruitment of innate immune cells and the release of inflammatory cytokines, such as IL-17A and other soluble mediators.^{33,34} Proteomics and metagenomics analysis showed an association between RSV infection and the neutrophil influx into the airway and degranulation which is marked by overexpression of proteins with known antibacterial activity.³⁵ In this sense, the airway secretions of RSV-infected children have significantly greater antibacterial activity compared to RSV-negative children.³⁵ In addition, the RSV-associated, neutrophil-mediated antibacterial response in the airway was suggested to act as a regulatory mechanism that modulates bacterial growth in the airways of RSV-infected children.³⁵ In their randomized control trial, Lewnard and colleagues, also found that RSV infections significantly contribute to substantial antimicrobial use among young infants.³⁶ Our findings underscore the heavy burden of RSV on PHC, justifying the need for estimating PHC utilization when assessing RSV burden on public health and evaluating the cost-effectiveness of prevention programs.³⁷

The main strength of our study lies in its population-based nature, minimizing the risk of population-selection bias. Matching the exposed (severe RSV-infected infants) and unexposed participants by birthday helped control for changes in RSV seasonality, virus

epidemiology, and diagnosis. The inclusion of healthcare needs related to RSV and the use of proxies for disease episodes potentially related to RSV allowed for a comprehensive evaluation of PHC expenses. The prolonged study period covering six RSV seasons and the extended follow-up duration provide robust estimates of PHC associated with severe RSV. However, due to the observational nature of this study, our findings establish associations rather than causality.

The use of PHC indicators, encompassing visits to pediatrician, nurses, pharmacies, social workers, and emergency department, along with individual and composite outcomes of respiratory-disease-related episodes and treatment, makes a valuable contribution to comprehensively understanding the economic and health impact of RSV infections in infants. Consequently, it could prove useful for conducting cost-effectiveness analyses on preventive measures against RSV infections. Furthermore, this approach may assist in establishing reference background data to objectively evaluate the effectiveness and impact of the newly available preventive tools on this expanded burden of RSV infection.

While our study is registry-based, potential limitations related to data registry errors were addressed by conducting independent replication for data cleaning and analysis. Data from private care were not included, but this limitation is mitigated by universal public health coverage in Galicia. We focused on severe RSV leading to hospitalization, and outpatient RSV-LRTI cases were not included in our study due to a lack of specific RSV codification in emergency registries. The study's observational nature necessitates acknowledging these associations, emphasizing the need for further research to establish causality.

The impact of severe RSV infection on PHC events may commence before patient admission, justifying the inclusion of the 30 days preceding hospitalization in the follow-up period. A sensitivity analysis, starting from hospital discharge to 90 days later, confirmed our findings, reinforcing that the impact of severe RSV infection on PHC/ES use begins even before hospital admission. Additionally, we have performed 3 more sensitivity analyses with chunks of the follow-up period (90–365 days, >365–730 days, >730 days till the end of the study). The sensitivity analysis results are presented in detail as supplementary material annexed to this report (Tables S2–S5). These findings reinforce the notion that the impact of severe RSV infection on PHC/ES use starts even before hospital admission, and this should be considered in the disease burden quantification.

5 | CONCLUSIONS

Severe RSV infections in infants have notable short and mid-term consequences for healthcare utilization, manifesting in an increased number of visits to pediatricians for respiratory-related consultations, mainly bronchitis/bronchiolitis, lower and upper respiratory episodes, and asthma/wheezing diagnosis. Prescriptions of antibacterials or obstructive airway disease drugs, and visits to primary care

and emergency departments are also significantly augmented. These consequences may persist for up to 2 years after RSV hospitalization. Our findings confirm the impact of RSV beyond the acute infection phase and provide crucial insights and practical tools for evaluating the cost-effectiveness of RSV prevention programs in infants.

6 | IMPACT STATEMENT

This study shows that severe RSV infections during infancy significantly increase primary healthcare resources use for more than 2 years after infection. It also shows that individuals who had severe RSV infections as infants are at substantial risk of developing respiratory morbidity in the short and mid term. They are also at higher risk of receiving prescriptions for obstructive airway diseases and antibiotics. All these findings corroborate that RSV burden beyond hospitalization is significant and should be considered in any assessment of costs derived from RSV. Our methodological approach may be useful in the assessment of the efficiency and the mid-term impact of RSV prevention programs.

AUTHOR CONTRIBUTIONS

Sonia Ares-Gómez: Methodology; investigation; supervision; writing – review and editing; writing – original draft; formal analysis; resources. **Narmeen Mallah:** Writing – original draft; methodology; writing – review and editing; investigation; formal analysis; resources; supervision. **Jacobo Pardo-Seco:** Formal analysis; writing – review and editing; data curation; methodology. **Alberto Malvar-Pintos:** Methodology; writing – review and editing; formal analysis. **Olaia Pérez-Martínez:** Investigation; writing – review and editing; data curation. **María-Teresa Otero-Barrós:** Data curation; investigation; writing – review and editing. **Nuria Suárez-Gaiche:** Data curation; investigation; writing – review and editing. **María-Isolina Santiago-Pérez:** Investigation; writing – review and editing; data curation. **Juan-Manuel González-Pérez:** Investigation; writing – review and editing; resources. **Luis-Ricardo López-Pérez:** Resources; investigation; writing – review and editing; data curation. **Benigno Rosón:** Writing – review and editing; resources; data curation. **Rosa-María Álvarez-Gil:** Data curation; writing – review and editing; resources. **Olga-María Ces-Ozores:** Writing – review and editing; resources; data curation. **Victoria Nartallo-Penas:** Investigation; writing – review and editing; resources; project administration. **Susana Mirás-Carballal:** Investigation; project administration; resources; writing – review and editing. **Carmen Rodríguez-Tenreiro:** Project administration; resources; writing – review and editing. **Irene Rivero-Calle:** Writing – review and editing; resources; investigation. **Antonio Salas:** Investigation; writing – review and editing; resources; project administration. **Carmen Durán-Parrondo:** Writing – review and editing; project administration; resources; conceptualization; investigation; visualization. **Federico Martínón-Torres:** Conceptualization; investigation; funding acquisition; writing – review and editing; supervision; resources; project administration; visualization; validation; methodology.

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CONFLICT OF INTEREST STATEMENT

FM-T has acted as principal investigator in randomized controlled trials of Ablynx, Abbot, Seqirus, Sanofi Pasteur MSD, Sanofi Pasteur, Cubist, Wyeth, Merck, Pfizer, Roche, Regeneron, Jansen, Medimmune, Novavax, Novartis, and GSK, with honoraria paid to his institution. FM-T reports a relationship with GSK Vaccines SRL Sanofi Pasteur, Pfizer, Janssen Pharmaceuticals, Moderna, Novavax, Merck, and Seqirus that includes consulting or advisory. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/pai.14131>.

DATA AVAILABILITY STATEMENT

Data used in this study are made available upon reasonable request from the corresponding author (F.M-T).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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