

Parent's perception of respiratory syncytial virus and subsequent wheezing burden: A multi-country cross-sectional survey

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Abstract

Background: Respiratory Syncytial Virus (RSV) is the leading cause of hospitalization in infants. RSV bronchiolitis is associated with an increased risk of subsequent wheezing. We aimed to document the parents' perception of the link between RSV infection and subsequent wheezing, wheezing-related healthcare and family resources use, and its impact on family daily life.

Methods: This cross-sectional online survey enrolled 1200 parents with at least one child ≤ 6 y living in the United States, United Kingdom, Spain, and Italy. Children diagnosed with RSV bronchiolitis before age of 2 years were included in the RSV group, and those never diagnosed with RSV bronchiolitis in the Reference group.

Results: The odds of wheezing were 4.5-fold (95%CI 3.5–5.9) higher in the RSV than in the Reference group. The odds increased to 7.7-fold (95%CI 5.4–11.1) among children who were hospitalized, and 9-fold (95%CI 5.1–16.6) among those admitted to pediatric intensive care with RSV bronchiolitis. Similar trends were observed across all countries. In total, 57% of parents reported their child's wheezing to have moderate to severe impact on their emotional well-being, and 53% on their daily life activities and/or social life. 64% of parents reported moderate–severe impact of wheezing on child's quality of sleep and 49% and 46% reported a moderate–severe impact on their children's emotional well-being and physical activities.

Conclusions: This survey suggests an association between RSV infection and subsequent wheezing in children across different countries. Wheezing, especially in association with RSV infection, was associated with increased healthcare utilization and costs, and significantly impacted parents' and children daily life.

KEYWORDS

asthma, bronchiolitis, caregivers, cross-sectional survey, infant health, respiratory syncytial virus (RSV), wheezing

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1 | INTRODUCTION

Respiratory syncytial virus (RSV) is a globally distributed, highly contagious seasonal virus and one of the main causes of lower respiratory tract diseases (LRTD) such as bronchiolitis or pneumonia, especially in infants within their first year of life.^{1,2} Elderly (≥ 65 years) and children (< 5 years) are particularly at risk for RSV infection, which is associated with significant morbidity and mortality.³ Almost all children will be exposed to RSV at least once by the age of 3 years.⁴ Symptoms of RSV infection are usually mild and typically resemble the common cold. However, up to 40% of infants develop acute lower respiratory infections (ALRIs) following their primary RSV infection, with cough and wheezing as common symptoms, with severity ranging from mild to moderate to life-threatening respiratory failure.¹

RSV-related hospitalizations in children below age 5 years occur mostly in the first 2 years of life, with infants younger than 1 year accounting for 75% of all hospitalizations.^{5,6} Estimated RSV-LRTD episodes range from 40.3 to 91.2 hospital bed days per 1000 infants annually.⁵ However, it is difficult to predict who will develop a severe RSV infection.

RSV infection is seasonal, with infection peaks during the cold season, sometimes leading to drastic healthcare overload.⁷ In 2019, RSV infections were responsible for 33 million ALRIs, including 3.6 million hospital admissions and 26,300 in-hospital deaths in children under 5 years worldwide.^{8,9} The global cost of medical treatment for RSV infections in infants was estimated at €4.82 billion in 2017, representing a significant economic burden.¹⁰

Many observational studies have suggested an association between RSV-LRTD in early life and subsequent respiratory morbidity, including recurrent wheezing in preschool age and asthma among school-age children.¹¹⁻¹³ Recurrent wheezing and asthma can have a major adverse impact on the quality of life of affected individuals as well as the health, resources, and work life of family caregivers.^{14,15}

Although the association between early childhood RSV infection and recurrent wheezing and asthma has been investigated in several studies, the overall burden on families and the impact on the quality of life of young patients and their caregivers is not fully understood.^{16,17} To enhance the understanding of the impact of RSV-LRTD and subsequent recurrent wheezing on affected children and their parents, we conducted a cross-sectional survey gathering relevant insights from 1200 parents across four countries (Italy, Spain, the United Kingdom, and the United States).

2 | METHODS

The methods are described in detail in Appendix S1.

2.1 | Study design, setting, and participants

We conducted a cross-sectional, self-reported online survey to ascertain information on parents' perception on the potential link

Key message

Despite a lot of literature available related to the respiratory syncytial virus burden, there is a lack of knowledge about the financial and psychological burden of respiratory syncytial virus infection and subsequent wheezing from the perspective of parents. There was a need to generate patient-centered insights to better understand the unmet public health need for respiratory syncytial virus prevention. This study confirmed that protection against respiratory syncytial virus is a necessity for all infants and raised awareness of the disease burden of respiratory syncytial virus.

between RSV infection and wheezing. Methodological approaches of the survey design and questionnaire were validated by an advisory board of five experts from the Netherlands, Italy, Spain, the United Kingdom, and the United States (the advisors' expertise included respiratory and pediatrics, health economics and outcomes research [HEOR], nursing, and parent association groups). The study was approved by an institutional review board (WIRB-Copernicus) in February 2023. All respondents gave their informed online consent before completing the questionnaire.

Using the Carenity online platform,¹⁸ its partners' network and social media campaigns, we enrolled parents having at least one child under age of 6 years living in Italy, Spain, the United Kingdom, and the United States. Parents/carers of children who had been diagnosed with a positive RSV test and/or bronchiolitis (assuming bronchiolitis is most commonly caused by RSV⁸) within the first 2 years of life and in the past 5 years were included in the RSV group (150 per country), and those whose children who had never been diagnosed with RSV infection or bronchiolitis were assigned to the Reference group (150 per country). Infants/children hospitalized for severe RSV infection/bronchiolitis were assigned as "severe RSV group"; this included those admitted to a pediatric intensive care unit (PICU) ("PICU RSV group").

2.2 | Data sources and definition of outcomes

The online self-administered survey (45 questions in total, 4 open-ended questions, Figure S1) was conducted from 10 February 2023 to 28 April 2023. Collected data included parents' and children's sociodemographic profile, children's medical profile, an evaluation of wheezing, perception of healthcare and wheezing burden, parents' awareness about RSV and preventive methods, and parents perceived unmet needs.

Definitions of all clinical outcomes (i.e., RSV infection, RSV hospitalization, history of wheezing) were based on reports by the parents and are provided in Appendix S1.

2.3 | Statistical analysis

Multivariable logistic regression models were used to evaluate the association between RSV infection and wheezing in children. First, a full model was fitted and included all potential confounders associated with both the outcome (presence of wheezing) and RSV exposure at a p -value $< .2$ in univariate logistic regression models. Potential confounders were children's age, parent's age at childbirth, month of birth, children's chronic diseases, mother's chronic diseases, gestational age at birth, sex at birth, breastfeeding duration, pets at home, contact with siblings, smoking household, and collective day-care. The reduced model was then generated using a stepwise selection procedure to retain statistically significant confounding factors while minimizing the Akaike Information Criterion.

Student tests or Wilcoxon's rank sum tests were used to compare quantitative characteristics or outcome between the RSV and Reference groups. Chi-square and Fisher's exact tests were used to compare categorical outcomes between the RSV and Reference groups. A p -value $< .05$ was considered statistically significant. All p -values were corrected using the Benjamini-Hochberg method. Statistical analyses were conducted on R Studio (v4.3.1). Categorical variables were reported by numbers and percentages of respondents. Quantitative variables were reported by their mean and standard deviation, or by their median and interquartile range (IQR).

3 | RESULTS

3.1 | Characteristics of the study population

Participant flow is shown in Figure S2. We enrolled 1200 parents from four countries (300/country), 600 in the RSV group and 600 in the Reference group. Characteristics of the study population are shown in Table 1. Participants in the RSV group were younger (mean age, 2.8 vs. 3.0 years, $p = .05$), significantly more likely to have a maternal history of asthma and allergies, and more likely to be born pre-term and have a personal history of chronic disorders. 73% (435/600) of children in the RSV group tested positive for RSV. Detailed description of participants and RSV infections is provided in Appendix S1.

3.2 | Association between RSV infection and the presence of childhood wheezing

A history of wheezing was reported by parents of 42% (504/1200) of children. Overall, the proportion of children with wheezing was significantly higher in the RSV compared to the Reference group (61 vs. 23%; $p < .01$). The frequency of wheezing increased with RSV severity (61% overall in the RSV group, 75% in the severe-hospitalized and 79% in the PICU RSV group) (Table 2).

Results from multivariable logistic regression models showed that, compared to the Reference group, odds of wheezing were 4.5

TABLE 1 Sociodemographic profile and clinical characteristics.

	RSV group ^a	Reference group ^a
<i>Sociodemographic profile</i>		
Children, <i>n</i> (%)		
Gender		
Male		
Total	613 (51)	
Per group	313 (52)	300 (50)
Female		
Total	584 (49)	
Per group	286 (48)	298 (50)
	$p = .5$	
Country of origin		
Italy	150 (12.5)	150 (12.5)
Spain	150 (12.5)	150 (12.5)
United Kingdom	150 (12.5)	150 (12.5)
United States	150 (12.5)	150 (12.5)
Month of birth		
April to September	285 (48)	302 (50)
October to March	315 (53)	298 (50)
	$p = .4$	
Age (years)		
Mean age, years (95% CI)	2.8 (2.7–2.9)	3.0 (2.9–3.2)
	$p = .05^*$	
<1	81 (14)	95 (16)
[1, 2]	112 (19)	104 (17)
[2, 3]	138 (23)	85 (14)
[3, 4]	108 (18)	107 (18)
[4, 5]	107 (18)	112 (19)
[5, 6]	54 (9)	97 (16)
Environmental exposures		
Pets at home	342 (57)	362 (60)
	$p = .3$	
Contact with siblings	255 (43)	278 (46)
	$p = .2$	
Smoking household	169 (28)	160 (27)
	$p = .6$	
Collective day-care	245 (41)	251 (42)
	$p = .8$	
None	56 (9)	61 (10)
	$p = .7$	
Parents, <i>n</i> (%)		
Age at childbirth (years)		
Mean age, years (95% CI)	32 (31–32)	32 (32–33)
	$p = .1$	
≤25	107 (18)	97 (16)
26–35	319 (53)	324 (54)

(Continues)

TABLE 1 (Continued)

	RSV group ^a	Reference group ^a
36–45	153 (26)	164 (27)
>45	21 (4)	15 (3)
<i>Clinical characteristics</i>		
Children, <i>n</i> (%)		
Chronic diseases		
Severe digestive disorder	48 (8)	5 (1)
	$p < .01^*$	
Severe autoimmune disease	31 (5)	4 (1)
	$p < .01^*$	
Epilepsy or neurological disease	16 (3)	6 (1)
	$p = .07$	
Congenital heart disease	20 (3)	0 (0)
	$p < .01^*$	
Obesity	17 (3)	6 (1)
	$p = .05^*$	
Renal disease	8 (1)	3 (1)
	$p = .2$	
Other	12 (2)	14 (2)
	$p = .8$	
None	479 (80)	563 (94)
	$p < .01^*$	
Mother, <i>n</i> (%)		
Chronic diseases		
Asthma	119 (20)	66 (11)
	$p < .01^*$	
Allergies	109 (18)	80 (13)
	$p = .05^*$	
Eczema	58 (10)	43 (7)
	$p = .1$	
Autoimmune disease	51 (9)	34 (6)
	$p = .09$	
Diabetes	59 (10)	41 (7)
	$p = .1$	
Cardiovascular disease	18 (3)	6 (1)
	$p = .03^*$	
Pulmonary disease	7 (1)	4 (1)
	$p = .5$	
Other	14 (2)	7 (1)
	$p = .2$	
None	287 (48)	378 (63)
	$p < .01^*$	
Stage of pregnancy at birth		
At term or post-term (>37 weeks)	449 (75)	492 (82)

TABLE 1 (Continued)

	RSV group ^a	Reference group ^a
Moderate or late preterm (32–37 weeks)	95 (16)	87 (15)
Very preterm (26–36 weeks)	35 (6)	9 (2)
Extremely preterm (<26 weeks)	10 (2)	2 (0)
Unknown/forgotten	11 (2)	10 (2)
	$p < .01^*$	
Description of RSV infections, <i>n</i> (%)		
RSV-induced respiratory infections in the first 2 years of life		
Bronchiolitis	406 (68)	
With positive RSV test	221 (54)	
Without RSV test	185 (46)	
Bronchitis with positive RSV test	189 (32)	
Pneumonia with positive RSV test	122 (20)	
Other infections with positive RSV test	9 (2)	
Age at RSV diagnosis (months)		
Mean age, months (95% CI)	11.2 (10.6–11.8)	
<6	168 (28)	
6–11	148 (25)	
12–17	139 (23)	
18–24	145 (24)	
Number of RSV reinfections in the first 2 years of life		
Mean number (95% CI)	3 (2.6–3.4)	
Month of RSV diagnosis		
April to September	132 (22)	
October to March	468 (78)	
Hospitalization as a result of bronchiolitis or RSV infection		
Number	269 (45)	
Mean length of hospital stay, days (95% CI)	8.3 (7.0–9.7)	
Admission in PICU	112 (42)	
Placement under respiratory support	162 (60)	
Complications after RSV infection		
Shortness of breath	178 (30)	
Respiratory allergy (e.g., pollen, dust, and mold)	75 (13)	
Chest tightness	74 (12)	
Dehydration	66 (11)	
Bronchiolitis obliterans	60 (10)	
Pauses in breathing	55 (9)	

TABLE 1 (Continued)

	RSV group ^a	Reference group ^a
Low oxygen levels	47 (8)	
Blue lips or skin (cyanosis)	35 (6)	
Acute respiratory distress syndrome	18 (3)	
Respiratory failure	17 (3)	
Other	26 (4)	
None	248 (41)	
Number of treatments received for RSV infection		
None	18 (3)	
1	173 (29)	
2	173 (29)	
3	110 (18)	
>3	100 (17)	

Note: RSV, respiratory syncytial virus.

^aPercentages may not equal 100 because of rounding.

*Significant *p*-value (<.05).

times higher in the RSV group (95% CI, 3.5–5.9; *p* < .01), 7.7 times higher in the severe RSV group (95% CI, 5.4–11.1; *p* < .01) and 9.0-time higher in the PICU RSV group (95% CI, 5.1–16.6; *p* < .01). These results were consistent across countries, with the highest odds ratios (OR) observed in the United Kingdom (Figure 1).

Overall, age at the first wheezing episode differed in the RSV and Reference group (*p* < .01), with children in the RSV group starting wheezing earlier (Figure S3). In total, 85% (*n* = 430) of children who have experienced wheezing had one or more wheezing attacks (65% reported one to three attacks since the first one). The proportion of children who experienced more than four wheezing attacks was higher in the RSV group than in the Reference group (24 vs. 12%; *p* = .02) and increased with increasing RSV severity (30% for the severe RSV group and 31% for the PICU RSV group).

3.3 | Use of healthcare resources and costs

Overall, pediatricians were the main healthcare professionals (HCPs) visited for wheezing-related care (visited at least once by 70% of children who experienced wheezing, *n* = 354), followed by general practitioners-GPs (63%, *n* = 265; excluding Italy where GPs were not presented in the survey questionnaire) (Table S1). Moreover, 48% of wheezing children visited a hospital emergency department at least once because of their wheezing. Wheezing-related visits to respiratory specialists were more frequent in Italy (64%, *n* = 55), in Spain (55%, *n* = 64), and in the United States (47%, *n* = 64) compared to the United Kingdom (25%, *n* = 42); GPs were the most frequently visited HCPs in the United Kingdom (72%, *n* = 122). Figure S4 shows treatment received for RSV infection.

Wheezing-related visits to HCPs were more frequent in wheezing children in the RSV than in the Reference group (Figure S5);

among HCPs visited up to 12-times since the child's wheezing onset, pediatricians (75% in the RSV vs. 57% in the Reference group), GPs (66 vs. 54%) and hospital emergency departments (53 vs. 35%) were the most visited ones. This trend was statistically significant for all types of HCPs. In the United States, Spain, and Italy, wheezing-related visits to respiratory specialists were more frequent in wheezing children in the RSV than in the Reference group (Figures S6–S8); in the United Kingdom, wheezing-related visits to pediatricians were more frequent in wheezing children in the RSV than in the Reference group (Figure S9).

Among the 506 children who experienced wheezing, prescribed routine medication (72% in RSV vs. 60% in the Reference group), over-the-counter medication or alternative medication (70 vs. 57%) and prescribed medication for wheezing (69 vs. 55%) were the most frequently reported sources of wheezing-related healthcare costs (Figure S10). Prescribed and over-the-counter medications were the main sources of wheezing-related healthcare expenses for parents in all countries. However, those expenses were lower in the United Kingdom (Table S2).

3.4 | Impact of wheezing on daily life

In total, 57% (*n* = 288/504) of parents reported their child's wheezing to have moderate to severe impact on their emotional well-being, and 53% (*n* = 268) stated a moderate to severe impact on their daily life activities and/or social life. Burden was slightly higher in Italy and Spain than in the United Kingdom and the United States (Figure S11). All aspects of parents' and children's lives were significantly more impacted by wheezing in the RSV than in the Reference group (Figure 2), but this was not the case in all countries. In the United Kingdom and Italy, there were no significant differences between the two groups. In Spain, only professional life was different, and in the United States, all aspects were, except activities of daily living.

Worry (75%, *n* = 380) and stress (66%, *n* = 332) were the two main feelings reported by parents since the onset of their child's wheezing and were ranked as the most prevalent feelings by 53% and 26%, respectively. Other feelings were anxiety about the future (55%, *n* = 279), sadness (52%, *n* = 262), mental fatigue (51%, *n* = 257) and physical fatigue (47%, *n* = 238). Psychosocial burden aspects had a similar importance in both groups. Parent's psychosocial perceptions and quality of life were not significantly different according to the child's age at the time of RSV infection.

With regards to impact on children's life, the parameter most impacted by wheezing was quality of sleep (moderate to severe impact reported by 64% of parents, *n* = 325). In addition, 49% (*n* = 248) and 46% (*n* = 235) reported a moderate to severe impact of wheezing on their children's emotional well-being and physical activities. A higher impact on quality of sleep was observed in Italy (73%) and Spain (66%) compared to the United Kingdom (62%) and the United States (60%) (Figure S12). Overall, all aspects of children's lives assessed in the survey were significantly more impacted by wheezing in the RSV than in the Reference

	RSV group	Severe RSV group	PICU group	Reference group
Global	N=600	N=269	N=112	N=600
Wheezing	365 (61)	201 (75)	89 (79)	141 (23)
Not wheezing	235 (39)	68 (25)	23 (21)	459 (77)
	<i>p</i> < .01*	<i>p</i> < .01*	<i>p</i> < .01*	
Italy	N=150	N=53	N=17	N=150
Wheezing	65 (43)	31 (58)	12 (71)	21 (14)
Not wheezing	85 (57)	22 (42)	5 (29)	129 (86)
	<i>p</i> < .01*	<i>p</i> < .01*	<i>p</i> < .01*	
Spain	N=150	N=53	N=20	N=150
Wheezing	85 (57)	41 (77)	16 (80)	31 (21)
Not wheezing	65 (43)	12 (23)	4 (20)	119 (79)
	<i>p</i> < .01*	<i>p</i> < .01*	<i>p</i> < .01*	
United Kingdom	N=150	N=82	N=31	N=150
Wheezing	120 (80)	71 (87)	28 (90)	49 (33)
Not wheezing	30 (20)	11 (13)	3 (10)	101 (67)
	<i>p</i> < .01*	<i>p</i> < .01*	<i>p</i> < .01*	
United States	N=150	N=81	N=44	N=150
Wheezing	95 (63)	58 (72)	33 (75)	40 (27)
Not wheezing	55 (37)	23 (28)	11 (25)	110 (73)
	<i>p</i> < .01*	<i>p</i> < .01*	<i>p</i> < .01*	

Abbreviations: PICU, pediatric intensive care unit; RSV, respiratory syncytial virus.

*Significant *p*-value compared to the reference group (<.05).

group (Figure 3), but this was not the case in all countries. In the United Kingdom and Italy, there were no significant differences between the two groups. In Spain, only family relationships were different, and in the United States, all aspects were except family relationships.

Among parents of wheezing children, 70% (*n* = 355) had to take at least once a day off work because of their child's wheezing (38% 1–5 days, 17% 6–10 days, and 16% >10 days). Overall, wheezing had a higher impact on parents' professional life in the RSV than in the Reference group (≥ 1 day off, 78 vs. 50%); this trend was observed in all countries except Spain (Table S3). The proportion of parents who missed 6 or more workdays because of their child's wheezing was higher in the RSV than in the Reference group (38 vs. 17%; Table S4).

In total, 69% (*n* = 351) of wheezing children had to miss at least 1 day of day-care or school because of their wheezing (25% 1–5 days, 20% 6–10 days and 25% >10 days). Overall, wheezing had a higher impact on children's life in the RSV than in the Reference group (≥ 1 day missed, 74 vs. 57%). The proportion of children who missed at least 6 days of day-care due to wheezing was higher in the RSV group than in the Reference group (50 vs. 33%).

Parents of wheezing children reported that wheezing-related costs had a mild (22%, *n* = 111), moderate (20%, *n* = 100), or strong (17%, *n* = 86) impact on their way of living. Particularly, 50% of parents living in the United Kingdom and 71% of those in Italy reported being impacted by their child's wheezing-related costs. Those in the

TABLE 2 Presence of wheezing regarding RSV status overall and by country.

RSV group more frequently reported a moderate to strong impact of wheezing-related costs on their way of living compared to the Reference group (45 vs. 16%).

3.5 | Awareness about RSV and perceived unmet needs

A higher proportion of parents in the RSV group considered that they had no knowledge of RSV prior to their child's infection compared to parents in the Reference group (52 vs. 42%). On a country level, most respondents in the RSV group declared not having this knowledge (Spain, 71%; Italy, 59%; United Kingdom, 48%), except in the United States (28%). Overall, only 12% (*n* = 70) of parents in the RSV group considered they had a rather good knowledge of RSV prior to their child's infection versus 21% (*n* = 123) in the Reference group.

Most parents of wheezing children reported that they did not receive advice on how to handle feeding (43%, *n* = 218) or prevent exacerbations (46%, *n* = 235), on the risk for asthma (43%, *n* = 215), or psychological support (60%, *n* = 304). The latter support was considered as particularly useful by 68% (*n* = 208). This trend was observed for all analyzed parameters (Figure 4). For optimal management of their child's wheezing, parents expressed the need for better access to information, psychological/organizational/financial support, and support on child's care. In the United Kingdom, Spain and Italy, there were no significant differences between the RSV and the Reference

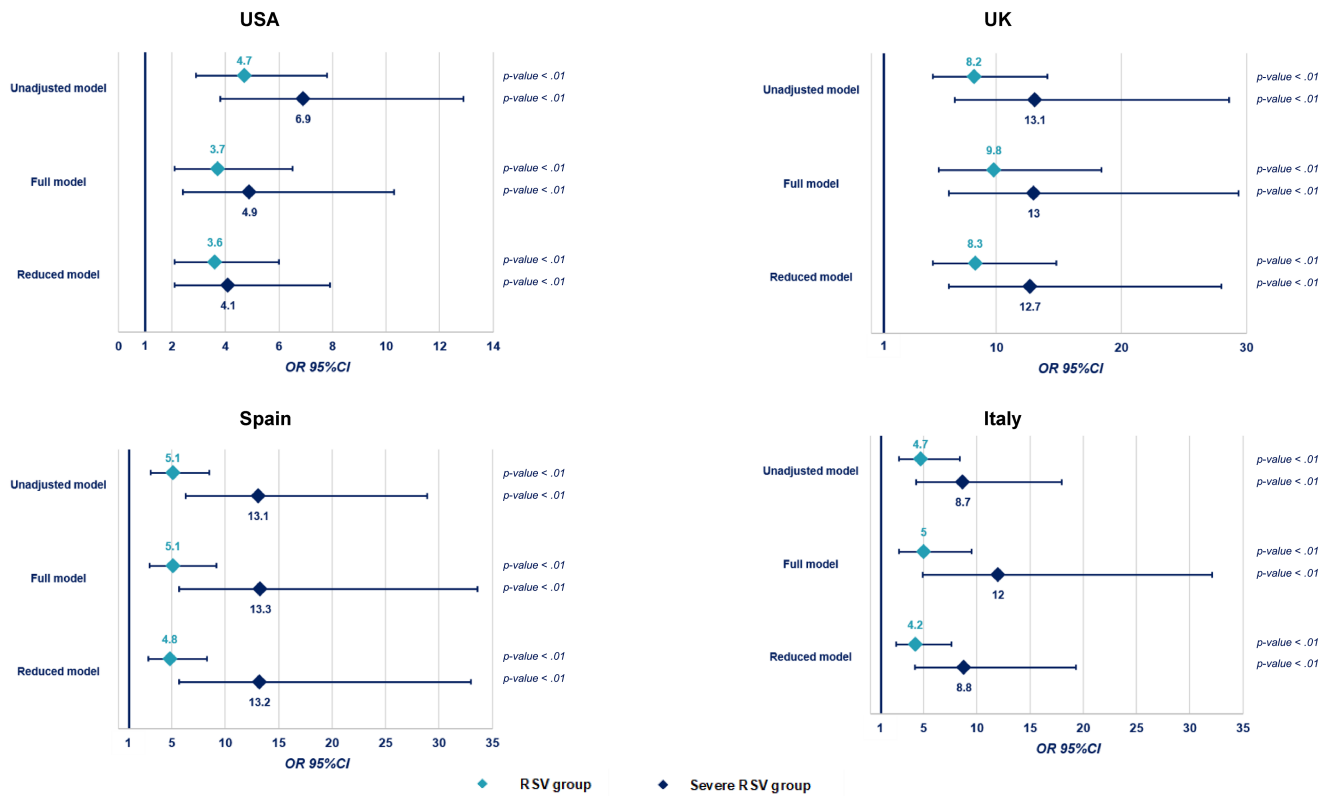


FIGURE 1 Associations between RSV infection and the presence of wheezing in children younger than 6 years in the RSV group and the severe RSV group per country after logistic regression with adjustment variables[‡]. CI, confidence interval; OR, odds ratio; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus. [†]Statistical power was not sufficient to conduct this analysis on the PICU RSV group; [‡]adjustment variables were children's age, parent's age at childbirth, month of birth, children's chronic diseases, mother's chronic diseases, gestational age at birth, sex at birth, breastfeeding duration, pets at home, contact with siblings, smoking household, and collective day-care; *significant p-value (<.05).

group. In the United States, all the parameters were different, with the exception of information about when to go to the hospital.

In total, 31% ($n=367$) of all respondents reported being aware of preventive options against RSV infections, with a higher proportion in the RSV group than in the Reference group (35 vs. 26%). The proportion of parents willing to use preventive options against RSV infections was similar in both RSV and Reference groups (79 vs. 69%).

4 | DISCUSSION

This cross-sectional survey among 1200 parents across four countries gives insights into the experiences of parents of infants and young children with an RSV infection and/or bronchiolitis compared to a reference group.

Our data from parents' insights showed that an RSV infection before the age of 2 years may be linked with wheezing. Moreover, the higher the RSV infection severity, the stronger the link. Our parent-reported data on the link between RSV infection and wheezing is in line with previously published data from the structured research context.¹⁹⁻²³ A retrospective study on >68,000

children reported a higher risk of wheezing/asthma in RSV hospitalized infants compared to controls.¹³ Wang et al. reported more frequent hospitalizations for wheezing in the 2 years following RSV hospitalization.²⁴ Several studies support persistence of wheezing during childhood²⁵ and a decreased lung function that may persist into adulthood²⁶ after RSV infection. Higher risk of developing asthma²⁷ has been reported in children with a history of RSV-LRTIs, and the onset of asthma and wheezing may be influenced by the severity of the initial RSV infection.^{16,27} Whether the association between RSV and asthma is a causal relationship or a correlation with a shared predisposition has not yet been clearly established and was discussed in detail in a WHO report in 2020.¹¹ There is, however, accumulating evidence from multiple observational studies, animal and in vitro models, and one randomized controlled trial of RSV monoclonal antibodies that provide multi-level support for a causal association between infant RSV infection and childhood asthma.²⁸

We found that wheezing leads to increased use of healthcare resources and represents a financial, emotional, and social burden for the families. This involves repeated healthcare visits, increased long-term healthcare utilization, and contributes to a significant psychological, clinical, and economic burden.^{16,17,29} A large burden of

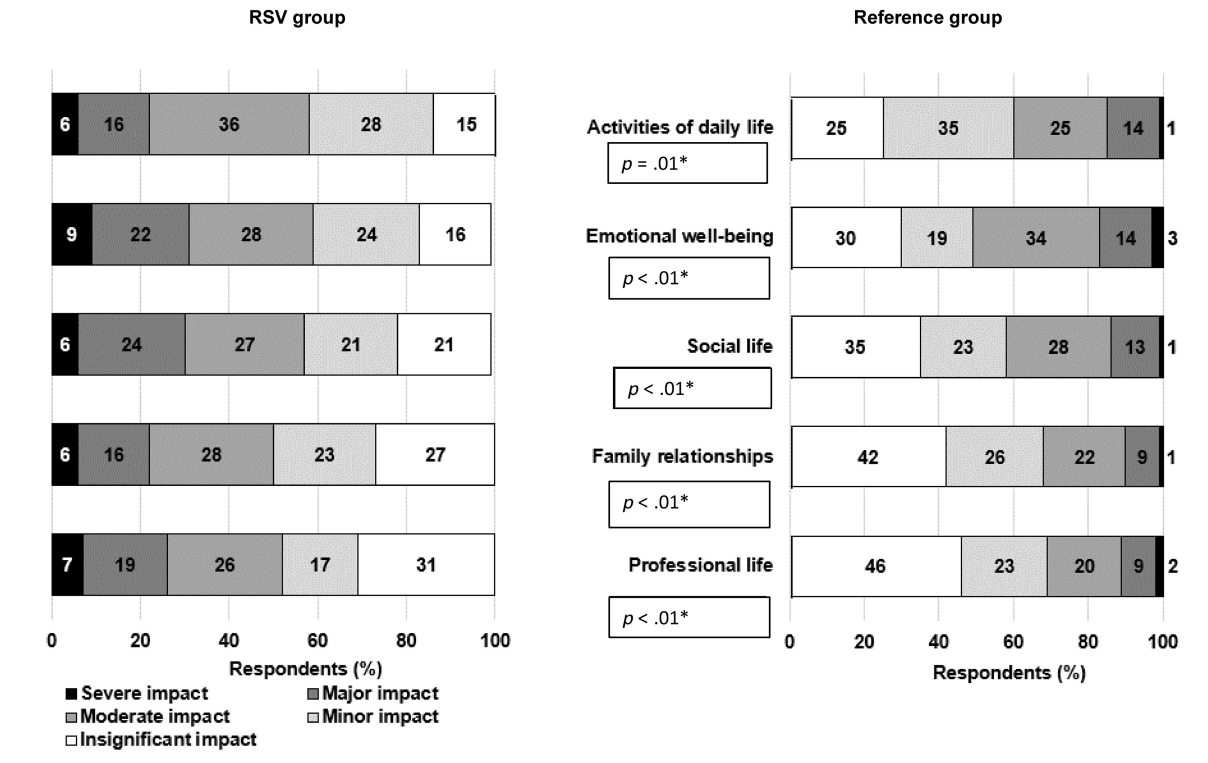


FIGURE 2 Perceived impact of wheezing on parents' life in the RSV group (n=365) and the Reference group (n=141). RSV, respiratory syncytial virus; *significant p-value (<.05).

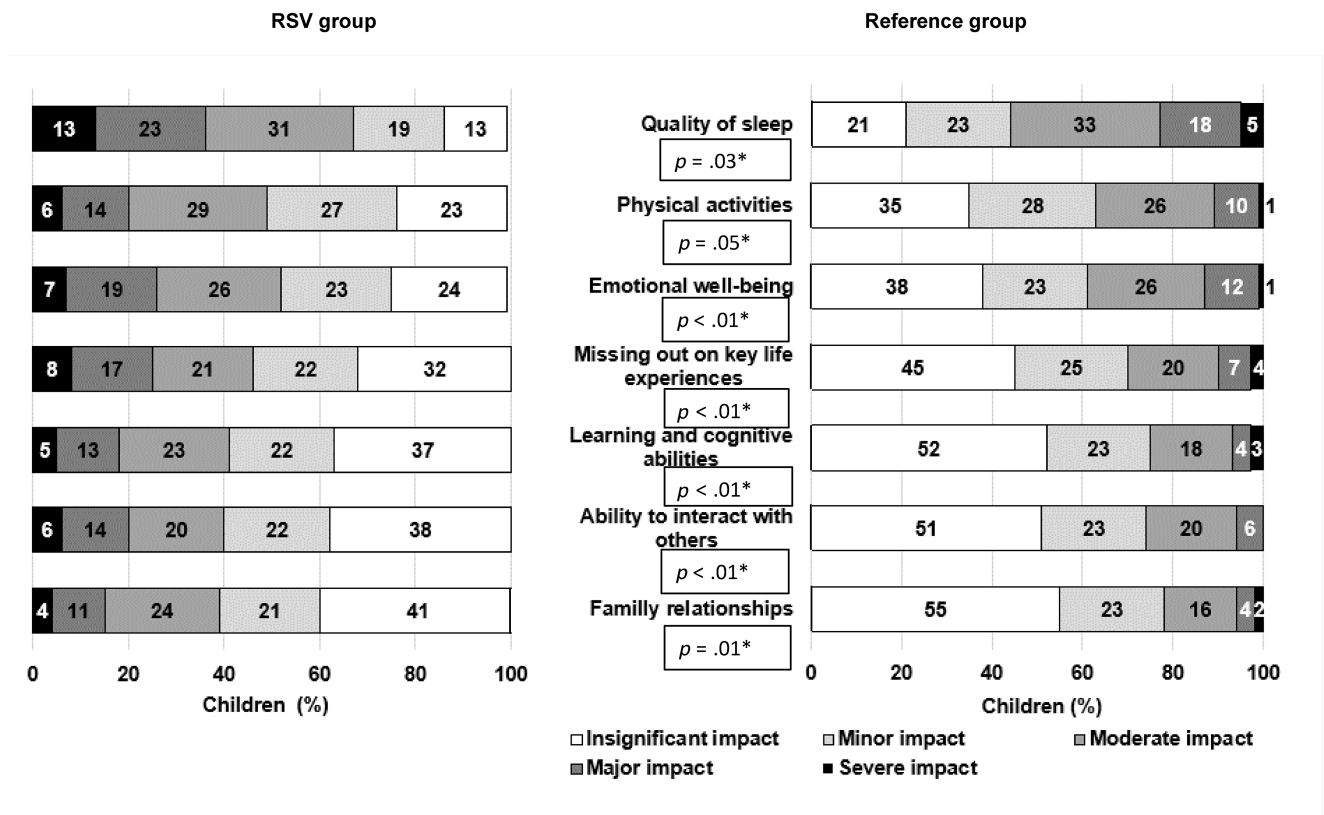


FIGURE 3 Psychosocial burden of wheezing on children's life in the RSV group (n=365) and the Reference group (n=141). RSV, respiratory syncytial virus; *significant p-value (<.05).

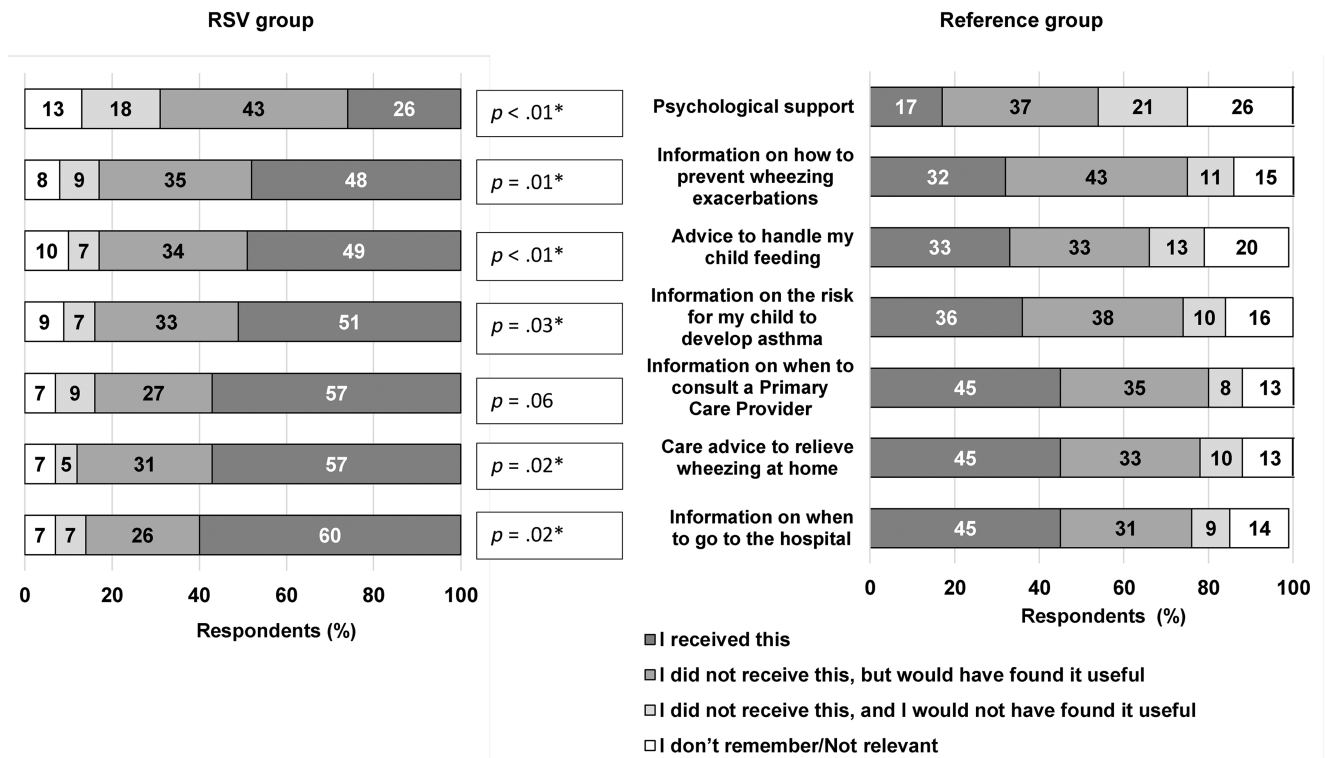


FIGURE 4 Parents' unmet support for wheezing management in the RSV group ($n=365$) and the Reference group ($n=141$). RSV, respiratory syncytial virus; *significant p -value ($<.05$).

morbidity has been reported among children suffering from wheezing and/or asthma.³⁰

In our survey, all aspects of parents' lives and children's lives assessed, including daily life, professional life, and emotional well-being, were more impacted by children's wheezing in the RSV group than in the Reference group. Previous studies highlighted parents' and caregivers' uncertainty and fear,³¹ higher levels of stress, greater anxiety, poorer health, and poorer family health³² linked to asthma, wheezing, and hospital admissions for RSV, as well as a subsequent decline in health-related quality of life in adulthood.³³

This survey has several limitations, mostly inherent to its design: selection bias (online access, IT and literacy bias, overrepresentation of respondents looking for healthcare information and members of Carenity communities), self-reported perceptions and symptoms, and recall bias. The social desirability bias was however limited as patients answered themselves the questionnaire in the absence of their physician. As 67% of parents responded to the survey at least 1 year after their child's RSV episode, this might have induced a recall bias. The question on co-infection was not evaluated, but the presence of another concomitant infection could have been included as a confounding factor. In the survey, 45% of children were reported to have been hospitalized for their RSV infection, which reflects a higher-than-expected rate of severe RSV cases in our sample; this selection bias in favor of more severe cases may be explained by the self-enrollment. As no information on the respondents' financial status was asked, this could have impacted the answers related to the financial burden. Moreover, for 28% ($n=103$) of children with wheezing in the RSV group, wheezing episodes occurred before

their RSV diagnosis. This could be explained by early symptoms before diagnosis, by wheezing due to causes other than RSV (e.g. smoking, pollution), or by a pre-disposition to wheezing that could have been exacerbated by RSV infection. A sensitivity analysis, in which this subgroup has been excluded, resulted in similar OR and p -values (the odds of wheezing were 3.2 times higher in the RSV group, 5.3 times higher in the severe RSV group and 5.3 times higher in the RSV PICU group compared with the reference group, $p < .01$ in all cases, detailed results available upon request).

There are several strengths to our study. Our surveyed population included a large sample of respondents from several countries sharing their perceptions on their quality of life and the healthcare pathway of their children. Additionally, this survey was validated by experts in the RSV field, health economics and outcome research specialists, as well as nurses, to ensure that the questionnaire was adapted to the target population. Moreover, our population was well-balanced and representative in terms of sociodemographic and clinical characteristics.

Half of parents in the RSV group and more than a third of parents in the Reference group also perceived a lack of knowledge about RSV. The survey highlighted a lack of knowledge about RSV prevention and insufficient support for parents. As such, stronger communication targeting parents, with joint efforts from policymakers, healthcare professionals, and industry stakeholders, needs to be in place to raise knowledge about RSV disease and complement parents' strong willingness to use preventive solutions.

Indeed, considerable advances in RSV disease prevention have been made in recent years. The monoclonal antibody palivizumab is

available as prophylaxis to prevent severe RSV infections in high-risk children.³⁴ Furthermore, a new long-acting monoclonal antibody, nirsevimab, has been approved in EU and the United Kingdom in 2022 and the United States, for prevention of RSV in all infants during their first RSV season.^{35–37} Lastly, since 2023, two RSV vaccines have been approved for the use in adults aged 60 and above^{38,39}; one of them is also approved for passive immunization of infants after administration of the vaccine to the mother during pregnancy.⁴⁰ With the arrival of new RSV immunization solutions for all infants, it is important to consider the full impact of RSV disease and related complications when evaluating the public health and socio-economic benefits of RSV immunization programs for this large infant population.

AUTHOR CONTRIBUTIONS

Adnan Custovic: Validation; writing – review and editing. **Jorge Mestre-Ferrandiz:** Validation; writing – review and editing. **Leyla Kragten-Tabatabaie:** Validation; writing – review and editing. **Julie Laurent:** Formal analysis; investigation; methodology; project administration; resources; supervision; visualization; writing – original draft. **Laury Sellem:** Formal analysis; investigation; resources; methodology; writing – original draft; visualization. **Mary Koslap-Petraco:** Validation; writing – review and editing. **Chiara Cadeddu:** Validation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

AC declares the payments received from Sanofi for the support provided throughout the study and reports personal fees from Novartis, personal fees from Sanofi, personal fees from Stallergenes Greer, personal fees from AstraZeneca, personal fees from Worg Pharmaceuticals, from GSK, outside the submitted work. JMF declares the payments received for the support provided throughout the study and reports consulting honoraria from Sanofi in other related work to RSV. LKT, MKP, LS, and JL declare no conflict of interests. CC declares having received expert consultant fees from Sanofi for the support provided throughout the study, expert consultant fees from GSK, and expert consultant fees from MSD.

ETHICS STATEMENT

The study was approved by an institutional review board (WIRB-Copernicus) in February 2023.

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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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