RESEARCH

Impact of RSV hospitalization on healthcare costs, caregivers' productivity loss, and quality of life in children ≤ 2 years old in five European countries

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Abstract

Respiratory syncytial virus (RSV) is a leading cause of hospitalizations in young children globally. We evaluated direct medical costs, caregiver work loss, and child quality of life (QoL) impairment associated with RSV hospitalization. Children ≤ 2 years with laboratory-confirmed RSV infection were prospectively identified between October 2020 and May 2023 at ten hospitals in Germany, Spain, Italy, France, and England. Direct costs were calculated based on country-specific unit costs per hospital day. Productivity loss and QoL impairment were ascertained by two validated, caregiver-administered instruments: 1) Work Productivity and Activity Impairment Questionnaire: Child's Hospitalization for Respiratory Illness (WPAI:CHRI), administered before discharge and 2) TNO AZL Child Quality of Life (TAPQOL), administered at baseline (shortly after admission) and before discharge. Among 382 hospitalized children, 261 (69%) were < 6 months and 306 (80%) were previously healthy. Median length of stay was 6 days (Interquartile Range (IQR) 4–8) and 50 (13%) were admitted to Paediatric Intensive Care Unit (PICU). Median hospital costs/admission were €4,266 (IQR 2,438–8,442), substantially varying by country (range €2,377-€8,541). Productivity loss was substantial with 129/211 (61%) employed caregivers reporting lost work-hours (mean 30.5 ± 18/admission). Child QoL was significantly reduced during RSV hospitalization in most domains, with the highest QoL impairment observed in the lung domain (mean difference 34.2 out of 100 [95% CI 30–38.4]. Conclusion: RSV hospitalization in children ≤ 2 years was associated with significant costs and QoL impairment in five European countries, emphasizing the importance of preventing severe RSV disease.

What is known:
- *RSV is a major cause of hospitalization in young children under 5 years of age globally.*
- *Most hospitalized children with RSV are previously healthy.*

What is new:
- *RSV hospitalization in children ≤2 years was associated with significant costs in Europe, with median hospital costs per admission at €4,266, substantial varying by country (range: €2,377 - €8,541).*
- *Caregivers of children ≤2 years hospitalized with RSV reported substantial productivity loss and a reduction in the quality of life of their child during hospitalization, as measured using validated instruments (WPAI-CHRI and TAPQOL).*

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Introduction

Respiratory syncytial virus (RSV) infections in young children are among the main causes of hospital admission for acute respiratory tract infections (ARTI) worldwide. It was estimated that in 2019, around 3.6 million RSV-associated acute lower respiratory infection hospital admissions and around 100,000 RSV-attributable overall deaths occurred in children under 5 years of age globally with more than 95% of RSV associated acute lower respiratory tract infections and more than 97% of RSV-attributable deaths occurring in low- and middle-income countries [1]. Hospitalization rates in infants in Europe were estimated to vary between 0.9% and 5.6%, depending on country, season, and methods used [2–8]. Risk of RSV hospitalization is higher in infants with comorbidities such as hemodynamically significant congenital heart disease, bronchopulmonary dysplasia, and Down syndrome. However, the majority of hospitalizations occur in healthy, full-term infants [9, 10].

Treatment options are limited to supportive care, which includes Paediatric Intensive Care Unit (PICU) admission in 4–20% of admitted infants [11–13]. While high-risk infants had access to the short-acting RSV monoclonal antibody Palivizumab (Synagis®) for decades, recent advancements have expanded immunization strategies to include all infants. Since 2023, prevention of RSV disease for all infants has been available through long-acting monoclonal antibodies and maternal RSV vaccination, both of which have been approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). The long-acting monoclonal antibody Nirsevimab (BEYFORTUS™, AstraZeneca AB, Södertälje, Sweden) is indicated for preventing RSV lower respiratory tract infections (LRTI) in neonates and infants entering their first season, as well as for children up to 24 months at high risk for severe RSV disease [14, 15]. The maternal RSV vaccine ABRYSVO™ (Pfizer, Inc., NY, USA) is indicated for preventing RSV-associated LRTI in infants from birth to six months [16, 17]. Furthermore, another long-acting monoclonal antibody Clesrovimab (ENFLONSIA™, Merck & Co., Inc., Rahway, NJ, US) was recently approved by the FDA [18, 19].

Despite numerous studies focusing on the incidence of RSV hospitalization in young children, there is currently a lack of information about the impact of these hospitalizations on both direct and indirect healthcare costs, as well as children's quality of life (QoL). A recent systematic review and meta-analysis attempted to bridge this knowledge gap and estimated the global healthcare costs for RSV-associated hospitalizations in children under 5 years to be approximately 2.65 billion euros (95% CI 2.26–3.28) [20]. However, most studies reported costs for a single country, and comparisons across countries were challenging due to a lack of standardized costing methodologies. Furthermore, there is a significant lack of data regarding QoL in young children hospitalized with RSV. A comprehensive European birth cohort study evaluated QoL of healthy term-born infants with symptomatic RSV infection, revealing that RSV infections resulted in a mean quality-adjusted life-day (QALD) loss of 1.9 (95% CI 1.7–2.1) [21]. This loss was notably higher in hospitalized infants, with a mean loss of 3.7 (3.3, 4.3) QALD per hospitalization. However, the number of hospitalized children in this study was limited, emphasizing the need to fully understand the multifaceted impact of RSV hospitalizations on both healthcare costs and QoL in affected infants and children, to serve as baseline for evaluation of the impact of new immunization strategies.

We aimed to describe the direct and indirect healthcare costs and QoL associated with children ≤ 2 years in five European countries as part of the larger 'Burden of RSV Infection in Young Children in European countries' (BRICE) study.

Methods

Study design

The BRICE study is a prospective multicenter, multicountry cohort study that included children ≤ 24 months hospitalized with laboratory-confirmed RSV infection. A total of 10 study sites from 5 European countries participated in this study: Spain (Hospital Clínico Universitario de Santiago, Santiago de Compostela and Hospital La Paz, Madrid), France (Hospital Intercommunal de Créteil, Créteil and Centre Hospitalier Universitaire de Caen Côte de Nacre, Caen), Italy (Pediatric Hospital Meyer, Florence and Bambino Gesù Hospital, Rome), Germany (University Hospital Würzburg, Childrens Hospital and University Hospital Schleswig Holstein—Campus Lübeck, Lübeck) and England (King's College Hospital, London and St George's University Hospital NHS Foundation Trust, London).

From October 1, 2020, to May 31, 2023, all children ≤ 24 months with laboratory-confirmed RSV infection were prospectively identified in participating hospitals. RSV testing was standard of care for children ≤ 2 years old who were admitted with respiratory symptoms at all study hospitals throughout the entire study period. In this substudy, we recruited caregivers, defined as parents or legal guardians of the child, from a sequential sample of children during hospitalization for RSV during the 3 prospective seasons. Recruitment for the substudy continued until we reached the target of 100 participants per country or by May 31, 2023.

This target was established based on a margin of error calculation, which anticipated a 9.8% probability that our sample results would differ from the true population average. The survey assessed risk factors for RSV hospitalization, including age at admission and underlying medical conditions, as well as impact on infants' quality of life and caregivers' productivity loss.

Direct medical costs

The average direct medical cost per RSV hospitalization was calculated based on publicly available, country-specific unit costs per hospitalization day in a paediatric general ward and PICU. Country-specific unit costs associated with admission to a general ward, high dependency unit (HDU) and PICU were identified from the literature (Table 1) and adjusted to 2023 Euros. Unit costs for general paediatric ward were significantly higher for Italy compared with other countries. If separate unit costs were unavailable for HDU, we used PICU unit costs for the days admitted to HDU. If children were transferred to or from another hospital, the number of days they were admitted to that hospital was included, if this information was available.

Caregiver's productivity loss

To evaluate loss of productivity among caregivers resulting from their child's hospitalization for RSV, we utilized the Work Productivity and Activity Impairment Questionnaire: Child's Hospitalization for Respiratory Illness (WPAI:CHRI). This validated questionnaire has been specifically designed for caregivers of children hospitalized with respiratory illness. It evaluates the impact on productivity in parents due to their infant's hospitalization for LRTI by measuring absenteeism, presenteeism, overall work impairment, and activity impairment [25]. Work absenteeism is defined as hours of work missed, presenteeism is defined as impaired productivity while at work, and daily activity impairment is defined as impairment in activities performed outside of work. Outcomes are expressed on a scale of 1–10, with higher numbers indicating greater impairment and less productivity. Caregivers were asked to fill out the WPAI:CHRI questionnaire once before discharge.

Children's quality of life

The TNO AZL Child Quality of Life (TAPQOL) questionnaire was utilized to assess changes in children's quality of life (QoL) during RSV hospitalization. The TAPQOL questionnaire has been designed to measure caregivers' perceptions of health-related quality of life (HRQoL) in preschool children (1 to 5 years old) and has also been validated for infants (0–1 years old) [26]. It comprises 43 questions and evaluates 12 domains: stomach, skin, and lung problems, sleeping, appetite, motor functioning, social functioning, problem behaviour, communication, anxiety, positive mood and liveliness. The items related to motor functioning, social functioning, and problem behaviour are only asked for children > 18 months old. The items are scored 0 to 4, and total scores are Linearly converted to a 0 to 100 scale, with higher scores indicating better QoL [27].

The TAPQOL was administered twice: 1) shortly after admission to measure baseline QoL, during which caregivers were asked to recall the child's QoL three months before the onset of RSV illness, and 2) at discharge, where caregivers reported the child's QoL affected by RSV hospitalization.

Statistical analysis

The mean, standard deviation (SD), median, and interquartile range (IQR) of direct medical costs, as well as productivity loss, were calculated. Additionally, for QoL, the mean change in scores for each domain, along with their 95% confidence intervals, was calculated.

Ethical approval was obtained from all study sites prior to initiation of the research.

Table 1 Unit costs of RSV hospitalization per country

Country	Unit cost general paediatric ward (€ per day)	Unit cost paediatric intensive care unit (€ per day)	Unit cost high dependency unit (€ per day)	Source
Germany	475.48	1304.25	-	Ehlken et al. 2005 [22]
France	518.90	1576.43	-	Butel et al. 2021 [23]
Spain	609.39	1316.21	-	Mao et al. 2023 [21]
Italy	1423.42	1689.22	-	Bozzola et al. 2020 [12]
England	760.41	2434.74	1802.85	NHS [24]*

Unit costs were calculated according to information from source and corrected for inflation to 2023 Euros (conversion rate £ to €: 1.19)

*Unit costs used for PICU "Paediatric Critical Care, Basic Critical Care"; for HDU "Enhanced Care"; for General ward "Paediatric Acute Bronchiolitis with cc score 0"

Results

Between October 2020 and September 2023, 3,931 children were hospitalized with RSV and caregivers of 382 (9.7%) children participated in the survey. Baseline characteristics were similar between children whose caregivers participated in the survey substudy, and the total number of children hospitalized with RSV during the study period (Table 2). Most RSV hospitalizations (68–70%) occurred in infants younger than 6 months old, and 80–82% did not have known underlying medical conditions. The mean length of stay (LOS) was

Table 2 Characteristics of substudy population compared with all RSV hospitalizations

		Substudy population*	All RSV hospitalizations	P-value[#]
Total N		382	3931	
Country (%)	Germany	101 (26.4%)	420 (10.7%)	<0.0001
	France	49 (12.8%)	1288 (32.8%)	
	Spain	105 (27.5%)	613 (15.6%)	
	Italy	101 (26.4%)	1085 (27.6%)	
	England	26 (6.8%)	525 (13.4%)	
Season[1] (%)	2020–2021	54 (14.1%)	610 (15.5%)	<0.0001
	2021–2022	178 (46.6%)	1410 (35.9%)	
	2022–2023	150 (39.2%)	1911 (48.6%)	
Age at admission (%)	0–2 months	192 (50.1%)	2118 (53.9%)	0.39
	3–5 months	69 (18%)	686 (17.5%)	
	6–12 months	69 (18%)	612 (15.6%)	
	13–24 months	53 (13.8%)	515 (13.1%)	
Sex[2] (%)	Male	196 (51.3%)	2098/3754 (55.9%)	0.06
	Female	186 (48.7%)	1656/3754 (44.1%)	
	Unknown	0	177	
Underlying medical condition[2] (%)	No underlying medical condition	306 (80%)	2508/3067 (81.8%)	0.37
	Prematurity[6]	42/355 (11.8%)	231 (7.5%)	<0.01
	Congenital heart disease	13 (3.4%)	120 (3.9%)	
	Chronic lung disease	5 (1.3%)	67 (2.2%)	
	Syndrome/Genetic disorder	4 (1.0%)	23 (0.8%)	
	Other	7 (1.8%)	223 (7.3%)	
	Unknown		864	
Length of stay (days, mean ± SD)	Overall	6.9 (±6.6)	n/a[3]	n/a[3]
	2020–2021	7.1 (±3.3)	5.5 (±3.7)	
	2021–2022	7.3 (±7.6)	5.7 (±4.2)	
	2022–2023	6.4 (±6.1)	5.8 (±6.0)	
	Median (IQR)	6 (4–8)	Not collected[3]	
Critical care support (%)	PICU admission (%)	50 (13.1%)	886 (22.5%)	<0.00001
	HDU admission (%)	18 (4.7%)[5]	Not collected[4]	

*Subset of children hospitalized for RSV whose caregivers consented to participate in the survey. Proportion relative to the total number in the column

[#]P-value calculated based on differences between substudy population and all RSV associated hospitalizations

[1]The seasons were defined as: October 1, 2020, to September 30, 2021 (2020–2021); October 1, 2021, to September 30, 2022 (2021–2022); and October 1, 2022, to May 31, 2023 (2022–2023)

[2]The proportion was calculated among those with a known sex and those with a known underlying medical condition, respectively

[3]For the total cohort only the mean and standard deviation of the length of stay of all admissions per season were calculated because only aggregated data were collected (mean and standard deviation per month per site)

[4]For the total cohort, only PICU admission status was collected

[5]Six children were admitted to both PICU and HDU

[6]Prematurity was defined as GA < 36 weeks

PICU pediatric intensive care unit, *HDU* High dependency unit

6.9 days among the children whose caregivers participated in the survey substudy, compared with 5.5–5.8 days in all children hospitalized with RSV.

The proportion of PICU admissions among the survey participants was significantly lower compared with the total cohort (13% versus 23%, $p < 0.0001$). The proportion and number of included RSV hospitalizations were lower in England (5%, 26/525 participants) and France (3.8%, 49/1288 participants) compared with other countries (Germany 24%, 101/1085 participants; Spain 17%, 105/613 participants; Italy 9.3%, 101/1085 participants). The proportion of included RSV hospitalizations was higher in the 2021–2022 season (12.6%, 178/1410) compared with the 2020–2021 (8.9%, 54/610) and the 2022–2023 (7.8%, 150/1911) season.

Direct medical costs

The median and mean hospitalization costs were respectively €4,266 (IQR 2,438–8,442) and €6,295 (± 7,711) per admission across all countries. Costs differed significantly between countries ($p < 0.05$), with Italy and England having the highest costs (median (IQR) respectively €8,541 (5,694–11,387) and €5,323 (2,852–10,999), Table 3). In England, a significant factor contributing to hospitalization costs was the high percentage of children admitted to PICU and HDU, which accounts for 35% of admissions, as well as high unit cost of PICU and HDU. The median cost of hospitalizations for children not admitted to PICU or HDU was €3,802 (IQR 2,281–5,323). This figure is comparable to costs in other countries, with the exception of Italy, where the median hospitalization cost for RSV in general wards was notably higher at €7,829 (IQR 5,694–10,320 (Table 3). This higher cost in Italy is primarily due to elevated unit costs for general ward admissions (Table 1).

The overall mean LOS was longer for patients admitted to the HDU or PICU (13.5 days ± 13.4) compared to those without such admissions (5.6 days ± 2.5). Mean LOS for patients with HDU and/or PICU admissions by country was: Germany 17.6 days (± 20.0), Spain 10 days (± 3.1), France 10.4 days (± 3.9), Italy 14.6 days (± 9.1), and England 15.4 days (± 20.7). For patients without HDU or PICU admissions, the mean LOS was much lower: Germany 5.4 days (± 2.5), Spain 5.9 days (± 2.5), France 5.4 days (± 2.0), Italy 5.8 days (± 2.6), and England 4.8 days (± 2.2).

Caregivers' productivity loss

Out of 382 survey participants, 374 completed the WPAI:CHRI (98%). Of those, 211 caregivers (56%) were employed. Sixty-one percent (129/209) reported missed hours from work with a mean of 30.5 (± 14.8) hours (median 30 (IQR 18–40). Productivity loss was substantial with a mean productivity loss score of 7.9 (± 2.9), with

10 indicating the worst impairment (Table 4). Both non-employed caregivers and employed caregivers reported significant impairment in daily activities, with a mean of 8.6 (± 2.3) and 8.5 (± 2.5), respectively. There were no statistically significant differences between countries (Fig. 1, suppl Table 1).

Scores are displayed as mean ± SD. The y-axis labels correspond to those on the x-axis beneath the groups of plots.

Children's quality of life

A total of 372 out of 382 survey participants completed the TAPQOL survey. During RSV hospitalization, a significant impairment in QoL was observed in 11 out of 12 domains of TAPQOL (Table 5). The domains that were most affected included lung problems (mean difference 34.3 out of 100 [95% CI 30.2–38.5]), liveliness (23.2 [19.8–26.7]), and positive mood (22.6 [19.3–25.9]). Across countries, the TAPQOL domain with the highest mean reduction compared with baseline was consistently lung problems (Suppl Fig. 1).

Discussion

To our knowledge, this study represents the first comprehensive evaluation of the economic and humanistic burden associated with RSV hospitalizations in children under two years of age across five European countries. Building on our previous findings [13], which indicated a high incidence rate of RSV hospitalizations at 14–19 per 1,000 child-years during the 2021–2022 and 2022–2023-RSV seasons, we extend the evaluation by incorporating a societal perspective into our burden assessment. Our results reveal high median and mean direct hospitalization costs, averaging €4,266 and €6,295 respectively per hospitalization, and ranging from median costs of €2,377 in Germany to €8,541 in Italy. In addition, we found that 60% of employed caregivers faced work disruptions during their child's hospitalization, resulting in a mean loss of 30 hours and a substantial productivity loss score of 9 out of 10, even while present at work. Furthermore, the assessment of child QoL revealed a significant decline in 10 out of 12 domains of the TAPQoL, underscoring the extensive deterioration in children's well-being during RSV hospitalizations.

Despite the relatively limited number of studies assessing costs of RSV hospitalizations in European countries, our findings closely align with the existing literature. A recent birth cohort study conducted across England, Scotland, Spain, the Netherlands and Finland estimated mean costs of €4,587.90 (95% CI 3,085–6,229, as of 2021€) per RSV hospitalization for healthy term infants, although this estimate was derived from only 18 hospitalizations [21]. Additionally,

Table 3 Direct medical costs overall and by country

Country	Number of hospitalized children	Length of stay, days		Critical care			Overall cost, €		Cost without PICU/HDU admissions, €#		Cost with PICU/HDU admissions, €$	
		Mean (±SD)	Median (IQR)	N (%) PICU and/or HDU admission*	N (%) PICU admission	N (%) HDU admission	Mean (±SD)	Median (IQR)	Mean (±SD)	Median (IQR)	Mean (±SD)	Median (IQR)
Germany	101	7.4 (±9.2)	5 (4–9)	16 (16%)	14 (14%)	5 (5%)	4,548 (±6,718)	2,377 (1,902–4,279)	2,584 (±1,186)	2,377 (1902–3328)	14,981 (±12451)	10,556 (9,493–11,255)
Spain	105	6.7 (±3.1)	6 (4.5–8)	20 (19%)	20 (19%)	0	4,643 (±2,897)	3,656 (2,438–5,485)	3,570 (±1534)	3,656 (2,438–4,570)	9204 (±2911)	8,921 (6947–11,255)
France	49	6.1 (±2.9)	5 (4–8)	7 (14%)	0	7 (14%)	3,771 (±3,014)	3,113 (2,076–4,151)	2,792 (±1,063)	2,595 (2,076–3,113)	9642 (±4247)	9,419 (7,304–10,996)
Italy	101	6.8 (±4.7)	6 (4–8)	11 (11%)	7 (7%)	4 (4%)	9,907 (±7,567)	8,541 (5,694–11,387)	8,303 (±3,679)	7,829 (5,694–10,320)	23024 (±15481)	17,346 (10,495.5–38,852)
England	26	8.5 (±12.9)	5 (3.8–7)	9 (35%)	9 (35%)	3 (12%)	10,475 (±18,360)	5,323 (2,852–10,999)	3,623 (±1,647)	3,802 (2,281–5,323)	23416 (±12174)	12,174 (10,249–25,767)
Total	382	6.9 (±6.6)	6 (4–8)	63 (17%)	50 (13%)	19 (5%)	6,295 (±7,711)	4,266 (2,438–8,442)	4,543 (±3,285)	3,656 (2,377–5,694)	15163 (±14639)	10,496 (8,824–14,469)

N number of admissions, *PICU* Paediatric Intensive Care Unit, *HDU* High Dependency Unit, *SD* Standard Deviation, *IQR* Inter Quartile Range

*Children could be admitted to PICU and HDU during the same hospitalization episode

#Cost calculated among all children not admitted to HDU/PICU (N = 319)

$Cost calculated among all children admitted to HDU/PICU, including cost for admission to general ward during same episode (N = 63)

Table 4 Caregiver's productivity and daily activity impairment due to child's RSV hospitalization: pooled analysis across countries

	Employed caregivers (n=211)	Non-employed caregivers (n=163)
Caregivers who reported missed hours from work		Not applicable
N (%)	129/209* (61%)	
Number of missed hours from work (n=129)[1]		
Mean ± SD	30.5 ± 14.8	
Median (IQR)	30 (18–40)	
Work productivity loss score (0–10)[2] (n=71)		
Mean ± SD	7.9 ± 2.9	
Median (IQR)	9 (7—10)	
Daily activity impairment score (0–10)[3] (n=202)		(n=157)
Mean ± SD	8.5 ± 2.5	8.6 ± 2.3
Median (IQR)	9.5 (8—10)	10 (8—10)

IQR Inter Quartile Range

*number of caregivers who responded to this section of the questionnaire

[1]Number of missed hours among caregivers who reported missed hours. Only hours missed due to their child's illness are reported

[2]Only completed by caregivers who indicated that they worked during the child's hospitalization with n=number of caregivers who completed this part of the questionnaire. Loss of productivity related to the child's hospitalization is measured on a scale from 0 to 10, where 0 indicates that the child's hospitalization had no effect on their work, and 10 indicates that the child's hospitalization completely prevented them from working

[3]Caregiver's score indicating how much the child's hospitalization affected their ability to perform regular daily activities—other than work—on a scale from 0 to 10, where 0 means that the child's hospitalization had no effect on their regular daily activities, and 10 means that the child's hospitalization completely prevented them from performing their daily activities. n=number of caregivers who completed this part of the questionnaire
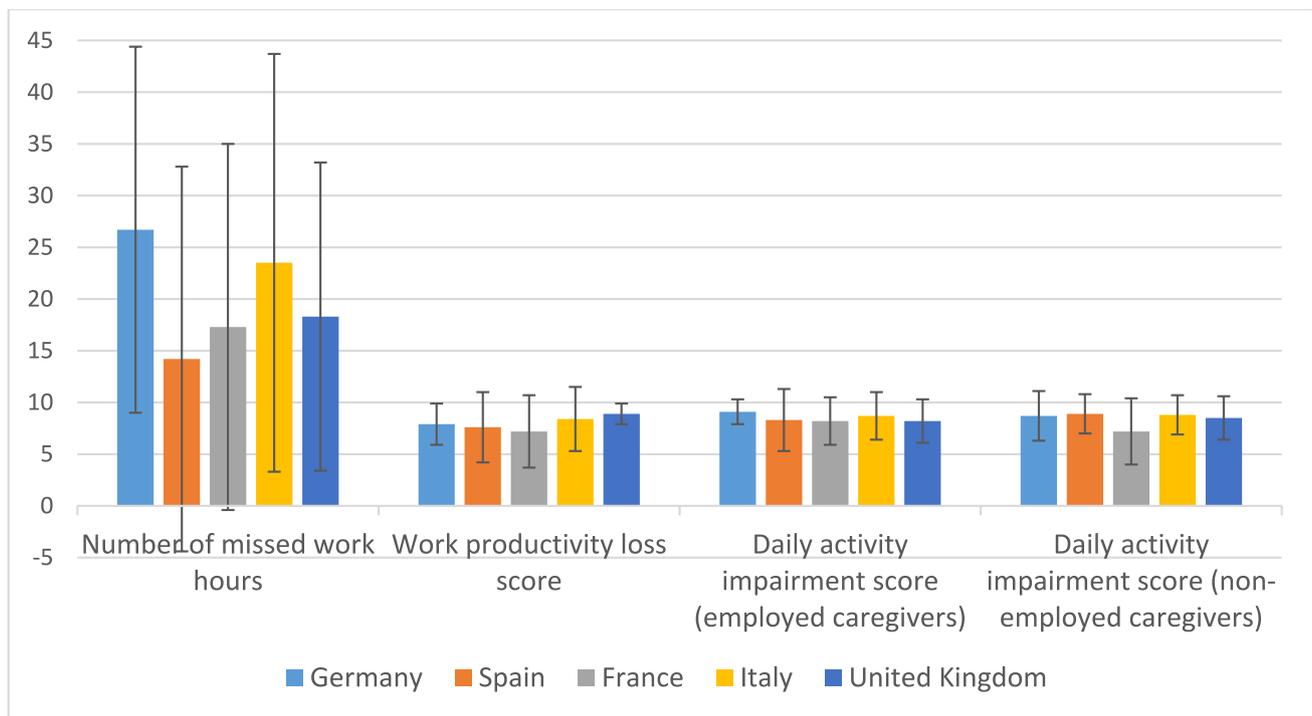
Fig. 1 Caregiver's productivity and daily activity impairment due to child's RSV hospitalization per country

Table 5 QoL impairment due to RSV hospitalization, pooled across countries

Domain	TAPQOL score at baseline Mean ± SD (N)	TAPQOL score at discharge Mean ± SD (N)	Mean difference between TAPQOL at baseline and at discharge [95% CI] (N)
1. Stomach problems	82.9 ± 19.0 ($n=370$)	80.4 ± 22.2 ($n=353$)	−2.7 [−5.0, −0.5] ($n=350$)
2. Skin problems	94.3 ± 10.2 ($n=370$)	94.2 ± 12.0 ($n=355$)	−0.4 [−1.4, 0.6] ($n=351$)
3. Lung problems	82.5 ± 27.2 ($n=371$)	47.8 ± 33.9 ($n=352$)	−34.3 [−38.5, −30.2] ($n=350$)
4. Sleeping	75.5 ± 18.5 ($n=370$)	60.6 ± 26.8 ($n=355$)	−14.8 [−17.8, −11.9] ($n=351$)
5. Appetite	83.3 ± 24.0 ($n=372$)	63.1 ± 33.0 ($n=355$)	−20.0 [−23.9, −16.2] ($n=353$)
6. Liveliness	88.1 ± 21.2 ($n=353$)	64.2 ± 32.1 ($n=340$)	−23.2 [−26.7, −19.8] ($n=332$)
7. Positive mood	93.9 ± 16.1 ($n=355$)	71.0 ± 29.0 ($n=339$)	−22.6 [−25.9, −19.3] ($n=331$)
8. Problem behaviour	83.8 ± 17.5 ($n=364$)	78.1 ± 21.4 ($n=346$)	−5.9 [−7.8, −3.9] ($n=341$)
9. Anxiety	79.7 ± 21.5 ($n=350$)	63.3 ± 29.6 ($n=330$)	−16.6 [−20.0, −13.2] ($n=326$)
10. Social functioning[1]	89.6 ± 12.8 ($n=24$)	65.8 ± 34.4 ($n=20$)	−23.3 [−42.0, −4.7] ($n=20$)
11. Motor functioning[1]	92.7 ± 9.9 ($n=24$)	69.8 ± 31.9 ($n=23$)	−22.8 [−37.0, −8.6] ($n=23$)
12. Communication[1]	86.7 ± 13.2 ($n=23$)	75.3 ± 24.2 ($n=22$)	−11.9 [−23.4, −0.5] ($n=22$)

[1]Only applicable to children ≥ 18 months of age

a meta-analysis that included ten studies from Germany, the Netherlands, Norway, Spain, and England reported a wide range of hospitalization costs for RSV, from €781 to €6,156 (as of 2017€), for children under five [20]. Furthermore, a recent study from Germany found mean costs of €6,356.71 for PICU admissions and €3,781.44 (as of 2015€) for general ward admissions in children under five [28], which aligns with our mean hospitalization cost of €4,548 for Germany, encompassing both general ward and PICU stays.

Average hospitalization costs for Italy in our study are significantly higher compared with other countries. A retrospective administrative database based study of RSV hospitalizations in children < 5 years in Italy between 2014–2018 reported mean direct annual healthcare costs (from hospitalization until 1 year after) of €3,346 for children aged 0–1 year and €3,979 for those aged 1–2 years [29]. They used Diagnosis Related Groups (DRG) tariffs, which represent the reimbursement levels by the Italian National Health System (INHS) to healthcare providers. These figures were significantly lower than our estimates, which were derived from Bozzola et al. [12], who calculated direct bronchiolitis hospitalization costs based on laboratory and imaging exams, specialist evaluations, therapy, and hospital accommodation instead of using DRG tariffs. They found that their calculated mean costs were significantly higher than the Lazio Region DRG tariffs (€5,572 versus €2,338). Since their study, like our study, was done in a tertiary hospital, this may (partly) explain the higher actual costs they found [12]. This difference underscores the potential variability in cost assessments, even within countries, and highlights the need for caution when interpreting these costs.

Research on work absenteeism associated with RSV hospitalizations is limited. One study conducted in Germany, which focused on LRTI episodes—including pneumonia, bronchitis, bronchiolitis, croup, and apnea in infants under six months—reported that 8.3% of parents of hospitalized children experienced work absenteeism, with an average of 1.5 days (± 3.0) per episode [22]. While this figure is lower than what we observed in our cohort, it should be noted that their study included children with a range of viral infections, not solely RSV, and encompassed older children up to 36 months of age.

Additionally, changes in QoL during RSV hospitalizations among young children are seldom evaluated due to the lack of validated QoL questionnaires tailored for infants. We employed the TAPQOL, which is validated for infants and young children [26]; however, other studies have measured QoL in young children with RSV infections using different methods, such as adapted EQ-5D questionnaires. The EQ-5D assesses QoL across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by means of self-reporting, and is therefore not suitable to measure quality of life in young children without adaptation. The TAPQOL is specifically designed for young children as it measures a caregiver's perception of their young child's QoL by means of 43 questions. This variation in measurement techniques makes it difficult to compare results across these studies. Nonetheless, consistent with our findings, they reported a significant decline in QoL due to RSV hospitalization and medically attended RSV infections [21, 30].

Considering emerging preventive options for severe RSV disease in young infants, governments in the USA and Europe are currently implementing RSV prevention into national immunization programs. It is vital to thoroughly consider the full impact of RSV hospitalization, including direct medical costs, caregivers' productivity loss, and the effects on children's QoL, when evaluating cost-effectiveness of such programs.

Our study has several strengths. Participating hospitals conducted active surveillance of children ≤ 2 years old who were hospitalized for ARTI, which included routine testing for RSV. This approach allowed for standardized case identification. Furthermore, the inclusion of five different European countries during multiple RSV seasons provides a reliable estimate of the impact of RSV-associated hospitalizations in early life, facilitating comparisons across participating countries. Finally, prospective recruitment and data collection offered a unique opportunity to evaluate both direct and indirect costs, as well as QoL impairment.

Our study also has several limitations. First, the study period coincided with the COVID-19 pandemic, which significantly disrupted RSV seasonality and hospitalization rates as described in our previous study. There was a distinct decrease in the incidence of RSV hospitalizations during the 2020–2021 season, followed by an unusual increase in late summer 2021, and varying rebound trends across countries during the 2021–2022 and 2022–2023 seasons [13, 31–33]. Nevertheless, our previous research and other studies have indicated that the age distribution, severity of illness, and duration of RSV hospitalizations were comparable with pre-pandemic periods [13, 34–38]. Second, due to the inability to directly extract costs from participating hospitals, we extrapolated country-specific healthcare costs to estimate RSV hospitalization costs. Calculation of unit costs was based on the cost per hospital day for each country, obtained from publicly available sources. When only older cost data were available, adjustments were made to account for inflation. This may have impacted the precision of our cost estimations. Also, each country utilizes its own healthcare cost calculation system, necessitating careful interpretation of our results. Third, the convenience sampling method employed in our substudy may not adequately represent the broader spectrum of severity among infants and children hospitalized. For example, the mean length of stay of the survey substudy population seems longer compared with that for all hospitalizations associated with RSV. Similarly, since our study focused on tertiary hospitals with a relatively high proportion of PICU admissions, the findings could have overestimated RSV associated hospitalization costs and may not be applicable to the entire country. Lastly, self-reporting by caregivers may introduce biases, including social desirability, inaccurate recall, or deliberate misreporting. Specifically, baseline measurements of the TAPQOL, which were intended to capture the three-month period prior to the child's RSV illness, may have been influenced by the timing of the survey, which was conducted during hospitalization, potentially underestimating the extent of QoL impairment.

Conclusion

There is a significant economic and health-related quality of life burden associated with the hospitalization of children ≤ 2 years old due to RSV. Most hospitalized children with RSV were previously healthy and under 6 months of age. The implementation of RSV prevention strategies has the potential to reduce the significant socio-economic and quality of life burden of RSV hospitalization in infants.

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Data availability Due to commercial restrictions supporting data is not available.

Declarations

Ethics approval The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from all study sites prior to the initiation of the research; Ethikkommission der Universität zu Lübeck (no. 20–345) and Ethik-Kommission der Universität Würzburg (no. 1/20_z) in Germany, Comité de Ética de la Investigación de Santiago y Lugo (no. 2020/452) and Comité de Ética de la Investigación Hospital Universitario La Paz (no. 22/2020) in Spain; Comitato Etico Regione Toscana—Pediatricoc/o Azienda Ospedaliero Universitaria Meyer (no. 247/2020) and Comitato Etico Ospedale Pediatrico Bambino Gesù IRCCS (no. 2275/2020) in Italy; London—Brighton & Sussex Research Ethics Committee (no. 21/LO/0578) in England; Comité de protection des personnes Sud Ouest et Outre Mer IV Cabanis Haut – Centre Cabanis Haut (no. 20.10.09.60811/CPP2020-11-094b) in France. Written informed consent was obtained from the parents/legally authorized representatives.

Conflict of interests Yoonyoung Choi and Madelyn Ruggieri are employees at Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. FM-T has acted as principal investigator in randomized controlled trials of Ablynx, Abbot, Seqirus, Sanofi Pasteur, MSD, Pfizer, Roche, Regeneron, Jansen, Medimmune, Novavax, Novartis and GSK, with honoraria paid to his institution. FM-T reports a relationship with GSK Vaccines SRL that includes consulting or advisory. FM-T reports a relationship with Pfizer Inc that includes consulting or advisory. FM-T reports a relationship with Sanofi Pasteur Inc that includes consulting or advisory. FM-T reports a relationship with Janssen Pharmaceuticals Inc that includes consulting or advisory. FM-T reports a relationship with MSD that includes consulting or advisory. FM-T reports a relationship with Seqirus Pty Ltd that includes consulting or advisory. SBD has previously received honoraria from Sanofi for taking part in RSV advisory boards and has provided consultancy and/or investigator roles in relation to product development for Janssen, AstraZeneca, Pfizer, Moderna, Valneva, MSD, iLiAD and Sanofi with fees paid to my institution. SBD is a member of the UK Department of Health and Social Care's (DHSC) Joint Committee on Vaccination and Immunisation (JCVI) RSV subcommittee and Medicines and Healthcare products Regulatory Agency's (MHRA) Paediatric Medicine Expert Advisory Group (PMEAG), but the reviews expressed herein do not necessarily represent those of DHSC, JCVI, MHRA or PMEAG. JGW has been an investigator for clinical trials sponsored by pharmaceutical companies including AstraZeneca, MSD, Pfizer, Sanofi, and Janssen and an investigator for clinical trials funded by IMI/Horizon2020 and ZonMw. All funds have been paid to UMCU. JGW participated in advisory boards of Janssen and Sanofi and was a speaker at a Sanofi sponsored symposium with honoraria paid to UMCU. LB has regular interaction with pharmaceutical and other industrial partners. He has not received personal fees or other personal benefits. UMCU has received major funding (> €100,000 per industrial partner) for investigator initiated studies from AstraZeneca, Sanofi, Janssen, Pfizer, MSD and MeMed Diagnostics. UMCU has received major funding from the Bill and Melinda Gates Foundation. UMCU has received major funding as part of the public private partnership IMI-funded RESCEU and PROMISE projects with partners GSK, Novavax, Janssen, AstraZeneca, Pfizer and Sanofi. UMCU has received major funding by Julius Clinical for participating in clinical studies sponsored by AstraZeneca, Merck and Pfizer. UMCU received minor funding (€1000–25,000 per industrial partner) for consultation, DSMB membership or invited lectures by Ablynx, Bavaria Nordic, GSK, Novavax, Pfizer, Moderna, Astrazeneca, MSD, Sanofi, Janssen. LB is the founding chairman of the ReSViNET Foundation. EH has received speaking fees and travel support from Pfizer, MSD, Sanofi, Abbvie/AstraZeneca and Chiesi. RE has previously received honoraria for lectures, expertise or educational events. RE has previously received honoraria from AstraZeneca and Sanofi for taking part in RSV advisory boards and also from AstraZeneca, GSK Pfizer, and Sanofi for lectures, expertise or educational events. RE has acted as principal investigator in randomized controlled trials of AstraZeneca, Sanofi, GSK, with honoraria paid to his institution. JB has previously received honoraria from MSD and ALK for taking part in advisory boards and from AstraZeneca, MSD, and Sanofi for lectures, expertise or educational events. JL has been an investigator for clinical trials sponsored by pharmaceutical companies including AstraZeneca, GSK, MSD, Pfizer and Sanofi and received consulting or lecture fees from Enanta, Engelhard Pharma, Gilead Sciences, MSD, Pfizer, Sanofi and Siemens Health Care. CA has received fees for meetings or consulting or advisory boards from Astra Zeneca, GSK, MSD, Moderna, Novavax, Pfizer, Sanofi.

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