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Economic burden and health-related quality-of-life among infants with respiratory syncytial virus infection: a multi-country prospective cohort study in Europe

Running head: Cost and quality of life of RSV infants

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Abstract

Background

Respiratory syncytial virus (RSV) causes a considerable disease burden in young children globally, but reliable estimates of RSV-related costs and health-related quality-of-life (HRQoL) are scarce. This study aimed to evaluate the RSV-associated costs and HRQoL effects in infants and their caregivers in four European countries.

Methods

Healthy term-born infants were recruited at birth and actively followed up in four European countries. Symptomatic infants were systematically tested for RSV. Caregivers recorded the daily HRQoL of their child and themselves, measured by a modified EQ-5D with Visual Analogue Scale, for 14 consecutive days or until symptoms resolved. At the end of each RSV episode, caregivers reported healthcare resource use and work absenteeism. Direct medical costs per RSV episode were estimated from a healthcare payer's perspective and indirect costs were estimated from a societal perspective. Means and 95% confidence intervals (CI) of direct medical costs, total costs (direct costs + productivity loss) and quality-adjusted life-day (QALD) loss per RSV episode were estimated per RSV episode, as well as per subgroup (medical attendance, country).

Results

Our cohort of 1041 infants experienced 265 RSV episodes with a mean symptom duration of 12.5 days. The mean (95% CI) cost per RSV episode was €399.5 (242.3,

584.2) and €494.3 (317.7, 696.1) from the healthcare payer's and societal perspective, respectively. The mean QALD loss per RSV episode of 1.9 (1.7, 2.1) was independent of medical attendance (in contrast to costs, which also differed by country). Caregiver and infant HRQoL evolved similarly.

Conclusion

This study fills essential gaps for future economic evaluations by prospectively estimating direct and indirect costs and HRQoL effects on healthy term infants and caregivers separately, for both medically attended (MA) and non-MA laboratory-confirmed RSV episodes. We generally observed greater HRQoL losses than in previous studies which used non-community and/or non-prospective designs.

Key words

RSV; cost; productivity loss; health-related quality-of-life; quality-adjusted life-years; infants; outpatients; prospective study; Europe

Background

Respiratory syncytial virus (RSV) is a major cause of acute lower respiratory tract infection (ALRI) among young children. Li et al. estimated globally 33 million RSV-associated ALRI episodes, 3.6 million hospital admissions and 26,300 in-hospital deaths in children below 5 years of age in 2019, with nearly 40% of hospital admissions in infants younger than 6 months [1]. In Europe, RSV infections were found to generate a high disease burden in young children in the community [2, 3].

Substantial efforts have been made to develop preventive measures for RSV illnesses. Several RSV immunisation candidates are currently in late-stage clinical trials and some have shown their efficacy to protect young infants against RSV infection [4, 5]. It is therefore expected that various prophylactic intervention strategies against RSV will become available soon upon successful regulatory authorisation. Subsequently, evaluating the cost-effectiveness of potential infant interventions against RSV is essential for policymakers to optimise their decisions to design immunisation programs in the near future. To inform such an evaluation, reliable estimates of cost and health-related quality-of-life (HRQoL) associated with RSV infection in infants are crucial.

A recent systematic review summarized RSV-associated costs in children younger than five years and found limited published RSV ambulatory cost data for regions outside North America [6]. We found three European studies reporting RSV-associated direct medical cost per RSV outpatient episode, but one only recruited children in emergency departments [7], and one only included pre-term infants [8]. The only community-based

study was not able to identify a sufficient number of non-medically attended RSV infants to calculate the cost burden of this group [9].

The estimates of RSV-related HRQoL loss among infants are also scarce. Previous cost-effectiveness studies of potential infant RSV vaccination were not able to refer to quality-adjusted life years (QALYs) loss estimated specifically for RSV infant episodes [10-12]. Recently, two studies investigated HRQoL loss due to RSV infection in children younger than 5 years old, but both estimates were calculated based on medically attended patients only [13, 14]. The health utility of children with RSV not seeking medical care has no current evidence available, which is a notable research gap.

The primary aim of this study was to estimate the RSV-associated costs and HRQoL effects among infants and their caregivers during an RSV episode with and without seeking professional medical care, using data from a prospective European cohort study. The ultimate aim is to support future cost-effectiveness analyses for emerging RSV immunisation programs.

Methods

This prospective observational multi-country cohort study recruited healthy term-born infants in four European countries (UK, Spain, Finland and the Netherlands) between July 2017 and November 2019 which were actively followed until their first birthday during the RSV seasons of 2017-18, 2018-19 and 2019-20 [15]. A sample size of 1000 infants was estimated for this cohort, which would produce a two-sided 95% Clopper-

Pearson CI with a half-width of 2%, for an assumed incidence of medically attended ARI of 10%, accounting for 10% loss to follow-up [16]. Infants were recruited at birth and a background questionnaire was completed at intake by caregivers (mother, father or other) to record infants' and caregivers' background characteristics (including socio-demographics and potential risk factors). During the RSV season in the first year of life, parents were contacted weekly and if the child had respiratory symptoms, a nasal sample was taken during a home visit and the sample was analysed for RSV (for more details see [15]).

Caregivers were provided with a diary in the local language of the country, to record the daily symptoms for 14 consecutive days. This enabled us to obtain the mean length of symptom duration per RSV episode. They were also asked to record HRQoL of their children as well as their own HRQoL from symptom onset for 14 days or until symptom-free (see below). After completing the 14-day diary, caregivers were also asked to record healthcare resource use and work absenteeism 14 days after the onset of each symptomatic period (hereafter termed "the end-of-diary"). Additionally, all caregivers were followed up to complete a questionnaire about their own HRQoL when their child reached approximately one year of age. Follow up is continuing until 3 years of age but falls beyond the scope of the current paper.

Cost

Number of days off from work and healthcare resource use, including consultations of general practitioners (GPs), out-of-hours services, emergency departments and

specialists as well as medication use were extracted from the end-of-diary record. Hospital admission and duration were obtained from patients' hospitalisation records. Country-specific national unit costs for healthcare visits, hospitalisation and medication were obtained from corresponding databases: NHS reference cost (UK) [17], 'Kostenhandleiding' (the Netherlands) [18], 'Terveyden ja sosiaalihuollon yksikkökustannukset Suomessa vuonna 2017' (Finland) [19] and 'Diario Oficial de Galicia' (Spain) [20]. Productivity loss per day was estimated following the human capital approach, using the gross average work-day salary, based on the number of days off work reported by caregivers. Costs were inflated and converted to Euro (€) year 2021. See Supplementary Methods (S. Method 1, S. Method 2, and Table S.1) for more details.

Direct costs per episode were calculated by multiplying the quantity of healthcare resource use with the corresponding unit cost. Indirect costs per episode were obtained by multiplying off-work days with the average gross salary per day (Table S.1).

We calculated costs from (1) a healthcare payer's perspective (i.e., direct cost per RSV episode) and (2) a societal perspective (i.e., total cost per RSV episode = direct cost + indirect cost).

HRQoL

Caregivers (one caregiver in each household) were asked to rate their and their children's HRQoL during the RSV episode based on the EQ-5D instrument. Each day, caregivers were asked to answer the "Usual Activities" (UA) and "Anxiety/Depression"

(AD) dimensions from the EQ-5D-5L [21] and the EQ-5D-VAS (visual analogue scale) for themselves, and to complete the "Pain/Discomfort" and "Sad" dimension from EQ-5D-3L-Y [21] and the EQ-5D-VAS for their infants. An additional question, phrased and structured in the same manner as the 5-dimension questions on the EQ-5D-5L was presented immediately after the caregivers' own VAS evaluation. This question is referred to as "worried about my child" (See S. Method 3). These five questions to determine HRQoL were selected based on available literature and extensive deliberation between senior health economists and clinicians, adapted according to the designs and aims of this prospective cohort study (further addressed in the Discussion). Because not all dimensions of the EQ-5D were measured, instead of calculating health utility scores, we calculated the differences in disutility of the two available health dimensions between baseline and on each diary day and assumed the other three health dimensions did not change due to RSV infection. For example, if a caregiver had no problem [level 1] in UA and AD at baseline and reported level 3 problems in these two dimensions on diary Day 1, the utility loss on Day 1 would be: $(1-UA_3-AD_3) - (1-UA_1-AD_1) = UA_1-UA_3+AD_1-AD_3$. UA_n and AD_n are the coefficients in EQ-5D's valuation regression models for calculating the utility values, representing the estimated disutility of having problems on dimension UA or AD at level n. The utility loss can be understood as quality-adjusted life-day (QALD) loss in this study. We obtained the total QALD loss for each episode. We used caregivers' HRQoL collected around the infants' first birthday as the baseline HRQoL for caregivers. Caregivers' HRQoL on Day 14 or

at birth was not used as baseline, because more than half of the episodes still reported symptoms on Day 14 and caregivers reported poorer HRQoL at birth than during the RSV symptom period. Because no HRQoL was collected for infants at age one year and there are no population norms for infants of this age in most countries, we assumed their baseline HRQoL to be in full health (no problem in Sad and Pain dimension). For caregivers' QALD loss, the corresponding country's EQ-5D-5L valuation models were used [22-24]. Since only Finland does not have an EQ-5D-5L valuation model, we used the only available Nordic European country's valuation model (Denmark) for that country [25]. For infant QALD loss, the only published Western European EQ-5D-Y valuation model was used, which was for Spain [26].

Summary statistics

We calculated summary statistics for RSV-related direct and total costs. For HRQoL, we calculated the percentage of respondents reporting problems on each available EQ-5D dimension. In addition, summary statistics of VAS scores on each day as well as that of total EQ-5D QALD loss for caregivers and infants during an RSV episode were obtained. Because we did not observe a relationship between respondent's missing data and the episode's characteristics, including age, gender and types of healthcare resource use, we assumed our missing data were missing completely at random (assuming that the missing data followed the same patterns as the non-missing data) and only included those records without missing values to calculate the mean symptom duration and QALD loss (see S. Result 3 and Table S.9). We did not account formally for right-

censored data (i.e. infants showing symptoms at Day 14), because QALD loss for Day 14 was negligible (see results). Costs, VAS scores, and QALD loss were also evaluated in subgroups, stratified by type of healthcare resource use (no professional medical care [non-MA], ambulatory care [AMB] or hospitalisation). We also calculated 95% confidence intervals (95% CI) of the mean length of symptom duration, mean QALD loss and mean costs using bootstrap (number of samples =1000). Different caregivers, including mother, father, and other family members, may have completed the diary to assess their infant's HRQoL during the RSV episode. Mean QALD loss was obtained separately for RSV episodes for which HRQoL questions were answered only by the father, and for episodes for which HRQoL questions were answered only by the mother of the child with RSV.

All analyses were conducted in R (version 3.6.2) [27].

Results

We recruited 1041 infants at birth and identified 265 RSV episodes in 252 children in total (Figure 1). No RSV-related deaths occurred. Nine episodes did not have healthcare resource use data and 34 episodes did not have a returned symptom and HRQoL diary record. Among those who had diary data, 184 episodes had a full 14-day diary record of their symptom status. The RSV episodes' baseline characteristics are reported in Table 1.

Costs

As shown in Table 2, the mean (95% CI) direct cost per RSV episode was €399.5 (242.3, 584.2) from a healthcare payer's perspective and the mean total cost was €494.3 (317.7, 696.1) from a societal perspective.

Eighteen RSV episodes required hospitalisation with a mean direct cost of €4587.9 (3085, 6229) per episode (healthcare payer's perspective). Hospitalised cases reported a mean total cost of €5094.9 (3507, 6894) per admission from the societal perspective. AMB patients (n=116) reported a mean direct cost of €167.8 (129.9, 202.9) per episode. The incurred productivity loss was lower for AMB than for hospitalised RSV cases, resulting in a mean total cost of €254.7 (197.9, 318.2) per AMB episode from the societal perspective. Non-MA episodes (n=120) reported a mean direct cost of €1.8 (1.4, 2.3) (medication cost) with less than half of the non-MA episodes (47.5%) reporting medication use. Patients not seeking professional medical care reported a mean total cost of €44.2 (17.1, 81) from a societal perspective. We further categorised the AMB patients into those who only received primary care, who only received secondary care and who received both primary and secondary care. The estimates for these subgroups can be found in Table S.5.

Mean costs varied across the four different countries (see Figure S.1 and Figure S.2). Spanish RSV episodes yielded the highest mean costs from both perspectives, while RSV episodes in the UK yielded the lowest mean costs. The cross-country discrepancy was mostly due to different unit costs and different proportions of RSV episodes

requiring hospital and non-hospital medical attendance (Table S.2, Table S.3 and Table S.4). For further cross-country comparisons, we obtained mean costs based on the purchasing power parity and the results are available in Table S.6.

HRQoL

In total, 231 episodes of patients returned HRQoL data for at least one day and were included in the HRQoL analysis. Figure 2 shows a peak in percentage of patients and caregivers reporting any health problems around Days 3 and 4 after symptom onset (percentages in Table S.7). The percentage of children reporting "pain" and "sadness" were largely similar to the percentage of caregivers reporting "worry about my child" (Figure 2). Any "sadness", "pain" and "worry" were more frequently reported than problems with "usual activities" and "anxiety/depression". For instance, at Day 4 about 65-70% of the respondents reported any "sadness", "pain" and "worry", whereas 42% of respondents reported problems with "usual activities" and 27% reported any "anxiety/depression" (Figure 2).

Figure 3 shows that VAS for infants during an RSV episode showed a similar trend as the EQ-5D dimensions, with the lowest VAS score (95% CI) on Day 4 [65.2 (62.8, 67.5)]. The VAS scores of caregivers exhibited a similar but lagged and less pronounced trend. They dropped from 83.9 (82.1, 85.6) to 80.1 (78, 82.2) on Day 5, then went up to 84.4 (82.1, 86.5) on Day 14. Hospitalised patients reported lower VAS scores than those who received ambulatory care, whereas AMB patients had poorer VAS scores on most symptom days compared to those who did not seek professional medical care. In

contrast, differences in VAS scores of caregivers caring for a hospitalised, AMB or non-MA child with RSV were less noticeable. The boxplots for subgroup results by healthcare resource use can be found in Figure S.3 and Figure S.4.

For 184 RSV episodes, the occurrence of symptoms (yes/no) was reported on each day for 14 consecutive days. Types of recorded symptoms included cough, nasal congestion, wheeze, shortness of breath and apnea. The lowest QALD losses were found for patients with only cough and runny nose and the largest for patients with shortness of breath (for further details see Table S.8). Among the RSV episodes, 22 episodes had fluctuating symptoms, i.e., symptoms stopped then recurred with a mean length (95% CI) of symptom duration (between the first and last symptom day) of 12.5 (11.6, 13.1) days. Episodes without fluctuation in symptom reporting had the same mean length of 12.5 (12.1, 12.9) days. Non-MA patients (n=77) had a mean length of 12.4 (11.8, 12.9) symptom days; AMB patients (n=77) reported a mean of 12.6 (12.1, 13.0) symptom days; hospitalised patients (n=6) had the longest mean symptom duration of 13.3 (12.0, 14.0) days. Two episodes did not have healthcare resource use status: they had symptoms for 10 days and for 14 days, respectively.

Table 3 shows the QALD loss of infants and caregivers per RSV episode. One hundred and eighty episodes (78%) had full EQ-5D health information for infants and the mean (95% CI) total QALD loss for each infant with RSV infection was 1.9 (1.7, 2.1). It is worth noting that 106 episodes still reported symptoms on Day 14, although 73% of

these reported no QALD loss. As for caregivers, 164 of them (71%) reported full health information and the total QALD loss was 0.1 (0, 0.2) per RSV episode.

Mean QALD loss was observed to be higher for AMB patients and their caregivers compared to non-MA patients and their caregivers (see Table 3). Hospitalised episodes yielded the most QALD loss. We observed that the largest and smallest QALD losses were reported for Spain and the Netherlands, respectively. We also found mother (caregiver) respondents (n=146) to report smaller QALD losses compared to father respondents (n=8) for their infants.

Discussion

Our study is the first prospective multi-country study that measured costs and HRQoL of RSV in healthy term babies and their caregivers during the first RSV season in a community setting. We found a mean cost of €4587.9 (95%CI: 3085, 6229) per hospitalised RSV episode from a healthcare payer perspective, which was more than 20-fold higher than the cost of AMB patients; the direct medical cost per non-MA RSV episodes can be argued to be negligible. The mean QALD loss for an AMB RSV episode was 2.3 (2.6, 2.0), which was almost twice as much as that of a non-MA episode. This study observed a mean symptom duration of 12.5 (11.6, 13.1) days for RSV in children under one year of age. This was twice as long as the previous study by Hodgson and colleagues who reported a median of five symptom days in children under five years, but they only focused on the coughing symptom and they obtained a poor response rate for reporting the duration of symptoms (the response rate of their

questionnaires was 16%; the response rate of the symptom duration question was 67%) [14]. Our results are supported by two recent studies in Finland, which reported a mean duration of RSV illness to be 12 days (standard deviation [SD], 5.7) in infants under 1 year of age [3] and a mean duration of 13 days (SD, 7.8) in children under 3 years [28] . One recent study reported the median direct cost per Spanish RSV infant patient (both inpatients and outpatients) to be €598.8 (IQR: 359.6–2425.9), which was higher than the median costs of the Spanish episodes in our study [the median cost of all Spanish episodes: €75.1 (IQR: 1.8-466.3); of MA episodes: €458.2 (139.3-639.1)] [13]. This may be because Díez-Gandía's study recruited a higher proportion of hospitalised cases (40%) and the unit cost for inpatient service was considerably higher than that of outpatient service. In addition, their study included premature infants or infants with comorbidities, which can be risk factors for higher RSV-associated costs [6].

We estimated the mean direct medical cost to be €167.8 (95%CI: 129.9, 202.9) per RSV ambulatory episode, which is slightly lower than what was estimated for two included European studies (one in Germany, i.e. €200 [9] and the other in Spain, i.e. €292 [7]), which were included in Zhang et al's systematic review and meta-analysis [6]. This is likely due to differences in healthcare systems and associated costs. Differences in between-country costs per case in our study were mostly driven by different unit costs and different proportions of RSV episodes seeking medical attendance. Clearly, more country- or region-specific estimates of costs are most appropriate to inform future country- or region-specific economic evaluations.

This is the first multi-country study measuring indirect costs due to RSV in a community setting in Europe. Our study assessed indirect costs representing productivity loss associated with RSV infection to be approximately 20% of the societal costs per episode. This ratio is comparable to previous studies which reported productivity loss to be 5.8%–31.6% of the total cost [6].

Since no other study reported HRQoL impact on caregivers in the context of RSV, we can only make limited comparisons with previous studies. The negative signs of QALD loss in non-MA caregivers and in Finnish caregivers indicate that the average health utility of these caregivers was reported to be slightly higher during the RSV episode as compared to their average health utility around the infants' first birthday, but note that the QALD gain is very small. Although not common, a few studies also reported that caregivers received a positive benefit during the illness of their ill family member, which may be due to feelings of altruism and fulfillment of obligations [29]. For non-MA caregivers in our study, parents may need to go to work again at the infants' first birthday, which can cause more negative impacts than when their child suffered from (mild) RSV during their parental leave. As for Finland, Finnish parents have the longest government-mandated parental paid leave [30], and it was found that mothers' better mental health was generally associated with more generous parental leave policies [31].

We reported a larger mean QALY loss per RSV episode under age of one year (MA: 2.4/365 days=6.58×10^{-3}; non-MA: 3.62×10^{-3}) compared to Hodgson's study for children under age of five years [14]: (MA: 3.823×10^{-3}, non-MA: 3.024×10^{-3}). We

note the following differences between our studies. First, the QALY loss estimate by Hodgson et al was predicted using the EQ-5D of suspected RSV among children who experienced RSV-like symptoms, while we directly assessed health status information of confirmed RSV in children under one year old. RSV-confirmed cases may experience larger health decline than the suspected cases and the choice of respondents can affect the valuation of health states [32]. As was found in our study, even the gender of the caregivers (mother vs father) can influence the interpretation and scoring of HRQoL for caregivers themselves and their children. Second, QALY loss in the Hodgson study was calculated based on a shorter symptom duration (median 5 days) than the reported symptom duration in our study. Third, Hodgson and colleagues used the full EQ-5D health profile, and the UK value set of EQ-5D-3L to calculate QALY for very young children but questions such as “mobility”, “looking after myself” and “usual activities” were less appropriate for use in valuing the health of an infant less than one year. Fourth, we assumed the baseline HRQoL of infants to be in full health which can overestimate QALY loss. Lastly, because RSV disease severity is higher in infants under one year old and decreases with age [1], QALY loss can be greater for children younger than one than those under five years. Diez-Gandia and colleagues [13] calculated the HRQoL loss to be 37.5% and 31.5% on days 0 and 7 since the diagnosis of the disease, respectively, which was comparable to our results. We observed a mean HRQoL loss of 29% and 46% for AMB and hospitalised infant patients on the worst day, respectively. The slight discrepancy may be due to the different questionnaires

used and because Diez-Gandia and colleagues did not differentiate between caregivers and children for calculating HRQoL loss (they combined children's symptoms, children's behaviours, parents' concerns, parents' emotions and the impact of the infection on family activities). Another study [33] estimated the disutility of children due to RSV infection to be between 0.14 and 0.57, which was comparable to our results (the mean utility loss per day for infants was between 7% to 23%), but their estimate was obtained from a proxy perspective: participants imagined hypothetical scenarios in a time trade-off experiment to give their preferences.

Despite not being an aim of this study, it was found that the evolution of the VAS scores of caregivers seemed to be driven by the persistence of a lower VAS score in the infant. This is consistent with previous studies showing evident correlation between children's and caregivers' HRQoL, especially in children and caregivers affected by acute illnesses [34, 35].

Strengths and Limitations

One strength of this prospective cohort study is that it actively followed healthy infants and identified those with RSV infection in a community setting. While previous studies were mainly conducted in an inpatient setting and did not have detailed costs and HRQoL data for RSV infant patients, especially for those who did not seek medical care, we were able to fill this research gap. We confirmed that costs of non-MA patients seem negligible compared to costs of patients seeking professional medical care, but the HRQoL loss of non-MA seems not negligible.

We aimed to reflect the reality of the cost and health burden of RSV by obtaining the quantities of healthcare resource use, productivity loss as well as detailed changes of HRQoL directly from patients and their caregivers that were experiencing RSV infection. We collected daily health data to ensure HRQoL changes were monitored throughout the whole RSV infection period and were with minimal recall biases, compared to the previous studies that only obtained one (worst health) [14] or two time points (on day 7 and day 14 after symptom onset) during an RSV episode [13].

Our study has the following limitations. First, in this descriptive paper, we opted to apply a practical, conservative but less efficient approach to deal with missing data. To the best of our knowledge, no conclusive guideline has been proposed on how to handle missing cost and HRQoL data [36], and an exploration of methods for this should be the subject of future work. A second minor limitation is associated with the possibility of underestimating productivity losses, as we did not count productivity losses of caregivers other than fathers or mothers (although non-parental caregivers were given the option to complete the diaries; n=24, 9.4%). A more fundamental limitation is related to the absence of standard methods for utility-yielding HRQoL elicitation for young children. The choice of questions to collect health status information was based on considering the available literature and options at the start of the study and extensive deliberation between senior health economists and clinicians on the REspiratory Syncytial virus Consortium in EUrope (RESCEU) project. The considerations towards which these deliberations converged can be briefly summarised as follows. First,

quality of life measurement was not the primary aim of this cohort study (see also Wildenbeest et al. [15]), and the questionnaire should not be too demanding on respondents in order not to jeopardise the primary aims of the study. Second, the most widely used and in many European country-specific guidelines for economic evaluation recommended standard instrument, the EQ-5D, or a modified version thereof, has not been validated for the HRQoL impact in children under the age of 4 years. Third, changes on the health dimensions of "mobility", "looking after myself" and "doing usual activities" as standard in the EQ-5D can be considered irrelevant for infants and could lead to irritation when repeatedly presented to respondents on a daily basis. Fourth, the circumstances of recent parenthood, the associated emotional experience and practical considerations would make a full parental EQ-5D assessment shortly after they had a new baby difficult to interpret, vis-à-vis an age-adjusted population norm (which may or may not contain an unknown prevalence of recent parents). Hence it would be better to present the full EQ-5D-5L to caregivers one year after birth, despite the health state can be affected by the long term sequelae of RSV. Fifth, the EQ-5D-VAS is an intuitively attractive and rapid way to evaluate the evolving health status of young children and their parents alike. Considering all these arguments, we only included part of the EQ-5D questions to follow-up the infants' health experience. In the meantime, development and wider validation of a few promising preference-based HRQoL instruments specifically for use in infants continues. Currently, the Infant Quality of Life instrument (IQI) [37], which was validated for infants 1 month to 11

months of age, and the Toddler and Infant (TANDI) instrument [38], which was validated for 1- to 36-month-old children seem good candidates for future utility estimation. Another limitation was that the participants in this cohort might not be representative of the respective country population. The labour force participation rate of the caregivers in our sample (women/men, 89%/97%) was higher compared to that in the respective countries (women/men, age group 35-39: 83%/94%, 83%/94%, 85%/94%, 81%/94% in Finland, the Netherlands, Spain, and the UK, respectively) in 2019 [39]. In addition, 70% of mothers in our cohort reported university education, while the tertiary education attainment rates were 51%, 50.9%, 46.7%, 44.4% from 35 to 44 years in Finland, the UK, the Netherlands and Spain, respectively [40]. This could have resulted in an underestimation of the cost burden and QALY loss, because socioeconomic status was found to be associated with severe, early-life RSV-related illness [41]. Finally, the advent of the SARS-CoV-2 pandemic after data collection was finalised may have impacts we could not measure in our study.

Conclusion

This multi-country study is the first to prospectively collect RSV-associated costs and HRQoL in RSV-infected healthy term infants and their families in a community setting. It helps understand the current economic and health burden of RSV in infants younger than one year of age, who are most likely to be affected by severe RSV infection. Our estimates can be used to inform future decision-making regarding RSV-related intervention programs for young children.

Given differences in healthcare systems and healthcare seeking behaviour, obtaining country-specific RSV costs may be required. Efforts should continue to develop standard tools to measure HRQoL in young children.

RESCEU investigators

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Ethics approval

The study was approved by the Institutional Review Board (IRB) of the University Medical Center Utrecht (Ref 17/069), NHS National Research Ethics Service Oxfordshire Committee A (Ref 17/SC/0335) and South East Scotland Research Ethics Committee (Ref 17/SS/0086), the Ethics Committee of the Hospital District of Southwest Finland (Ref 17201), and Hospital Clínico Universitario de Santiago de Compostela (Ref 2017/175).

Author contribution

The study was conceived and supervised by PB and LB, questionnaire-based data collection was conceptualized by PB and JW in consultation with LB, BD and MP. Cohort set up and implementation were done by LB, MNB, JW, KK, FMT, TH, SC, MDS, HR, AJP. Unit cost data were collected by XL, ZM, AD and TH, statistical analyses were conducted by ZM, in consultation with XL, JB, NH and PB. The first draft of the manuscript was written by ZM. All authors critically reviewed the manuscript and provided final approval of the manuscript.

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Commission is not responsible for any use that may be made of the information it contains.

Conflict of interest

PB reported consulting fees from Pfizer, GSK on 2 occasions for discussions on economic evaluation, for a total of <€3000 combined, paid 100% directly to the University of Antwerp. NH reported grants from Janssen Vaccines & Prevention BV (R-11873) for collection of social contact data relevant for the spread of respiratory pathogens including SARS-CoV-2, RSV, influenza. NH reports consulting fees from Janssen Global Services for participation in advisory board related to RSV disease transmission modelling; payments made to Hasselt University. LJB 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 AbbVie, MedImmune, Janssen, the Bill and Melinda Gates Foundation, Nutricia (Danone) and MeMed Diagnostics. UMCU has received major cash or in kind funding as part of the public private partnership IMI-funded RESCEU project from GSK, Novavax, Janssen, AstraZeneca, Pfizer and Sanofi. UMCU has received major funding by Julius Clinical for participating in the INFORM study sponsored by MedImmune. UMCU has received minor funding for participation in trials by Regeneron and Janssen from 2015-2017 (total annual estimate less than €20,000). UMCU received minor funding for consultation and invited lectures by AbbVie, MedImmune, Ablynx, Bavaria Nordic,

MabXience, Novavax, Pfizer, Janssen (total annual estimate less than €20,000). Dr. Bont is the founding chairman of the ReSViNET Foundation. SC reported IMI – RESCEU grant funding (as detailed in manuscript), with fees paid to the University of Edinburgh. FM-T has received honoraria from GSK group of companies, Pfizer Inc, Sanofi Pasteur, MSD, Seqirus, Biofabri and Janssen for taking part in advisory boards and expert meetings and for acting as a speaker in congresses outside the scope of the submitted work. FM-T has also acted as principal investigator in randomized controlled trials of the above-mentioned companies as well as Ablynx, Gilead, Regeneron, Roche, Abbott, Novavax, and MedImmune, with honoraria paid to his institution. SBD had received honoraria from MSD and Sanofi Pasteur for taking part in advisory boards and has provided consultancy and/or investigator roles in relation to product development for Janssen, AstraZeneca, Pfizer, Valneva, MSD and Sanofi Pasteur with fees paid to St George's University of London. TH has received honoraria for lectures and/or participation in advisory boards or data monitoring committees from Janssen, Sanofi Pasteur, Enanta and MSD. MDS acted until September 2022 on behalf of the University of Oxford as an Investigator on research studies funded or supported by the vaccine manufacturers GlaxoSmithKline, Janssen, AstraZeneca, Novavax, MCM vaccines and Pfizer. He received no direct personal benefit for this work. From September 2022 he has been an employee at Moderna Biotech UK and holds stock options in this company. AJP is a member of AMS and Senior Investigator of NIHR. KK has received fees for interview for expert opinion considering the burden of RSV in older adults with IQVIA

(part of Janssen) as well as interview for expert opinion considering the burden of RSV in older adults with Deallus. AD has participated as sub-investigator in clinical trials and observational studies for Novavax, MedImmune, Janssen GSK, Pfizer, Merk, Sharp Donme, ReViral, Enanta Pharmaceuticals. All payments were made to the institution and no direct payment was received. MJP is a member of JCVI and reports stock or stock options for HealthEcore (25% of shares) and PAG BV (100% of shares). All other authors report no potential conflicts of interest.

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Tables:

Table 1: Baseline characteristics of RSV episodes (N=265)

	RSV episodes (N=265)
Study site	
Spain	62 (23.4%)
Finland	21 (7.9%)
The UK	95 (35.9%)
The Netherlands	87 (32.8%)
Season	
2017-18	18 (6.8%)
2018-19	81 (30.6%)
2019-20	166 (62.6%)
Gender of infants	
Female	124 (46.8%)
Male	140 (52.8%)
Missing	1 (0.4%)
Mother Education	
Primary	3 (1.1%)
Secondary	16 (6.0%)
Vocational	57 (21.5%)
Applied University	82 (30.9%)
Science University	107 (40.4%)
Father Education	
Primary	7 (2.6%)
Secondary	30 (11.3%)
Vocational	70 (26.4%)
University of applied sciences*	66 (24.9%)
University of sciences	90 (34.0%)
Missing	2 (0.8%)
Mother work status (before the birth of the newborn)	
Full-time	152 (57.4%)
Part-time	83 (31.3%)
Full-time caring for the children	6 (2.3%)
No	15 (5.7%)
Other	9 (3.4%)
Mother work status (resume working after the maternity leave)	
Yes, full-time	82 (30.9%)
Yes, part-time	125 (47.2%)
No	11 (4.2%)
Unknown	47 (17.7%)
Father work status (before the birth of the newborn)	
Full-time	236 (89.1%)
Part-time	20 (7.5%)
Full-time caring for the children	0 (0)
No	5 (1.9%)
Other	4 (1.5%)
Father work status (resume working after the paternity leave)	
Yes, full-time	221 (83.4%)
Yes, part-time	31 (11.7%)
No	1 (0.4%)
Unknown	12 (4.5%)
Other characteristics	
ARTI age (in months): Mean [median] (IQR)	6.0 [5.8] (3.7-8.5)
Mother age: Mean [median] (IQR)	33.8 [34] (31-36)
Father age: Mean [median] (IQR)	36.0 [36] (33-39)

% Maternal influenza vaccination	108 (40.8%)
% Maternal pertussis	150 (56.6%)
% Smoke during pregnancy	11 (4.2%)
% Smoke in the household	32 (12.1%)

1 * Universities of applied sciences are mostly practical and profession-orientated; universities of science are academical orientated.

2

1 Table 2: Average costs per RSV episode

	Healthcare payer		Societal		
	Mean (95% CI) *	Median (Q1-Q3)	Mean (95% CI)	Median (Q1-Q3)	Number
Pooled	399.5 (242.3, 584.2)	26.9 (0-85)	494.3 (317.7, 696.1)	40.6 (1.3-290.2)	256
AMB vs Hospital vs Non-MA					
AMB	167.8 (129.9, 202.9)	73 (41.2-222)	254.7 (197.9, 318.2)	87.2 (44.2-383.3)	116
Hospital	4587.9 (3085, 6229)	3479.7 (2591.8-5548.2)	5094.9 (3507, 6894)	3785.8 (2655.5-6636.7)	18
Non-MA	1.8 (1.4, 2.3)	0 (0-2.5)	44.2 (17.13, 80.98)	0.9 (0-4.3)	120
Different countries					
Finland	317.7 (103.1, 692.7)	89.3 (2.1-301.7)	395.1 (145.5, 777.6)	182.9 (2.12-303.8)	21
Netherlands	335.4 (116.8, 660.3)	7.9 (0-44.4)	445.5 (197.7, 801.6)	40.6 (0-211.3)	86
Spain	803.7 (322.2, 1460.4)	75.1 (1.8-466.3)	912.9 (383.4, 1588.1)	75.1 (1.75-471.3)	61
UK	201.4 (66.7, 383.1)	7.4 (2.5-46.2)	275.6 (115.3, 482.3)	11.4 (2.5-48.3)	88

2 * Confidence intervals were calculated by using bootstrapping (1000 bootstrap samples). Abbreviations: AMB, ambulatory care;

3 Non-MA: non-medical attendance; CI, confidence interval.

4

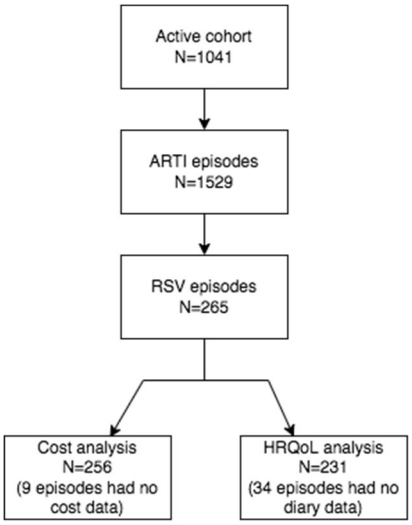
Table 3: Average QALD loss of infants and caregivers per RSV episode

		QALD loss		
		Mean (95% CI)	Median (Q1-Q3)	Number
Infant	Infant pooled	1.9 (1.7, 2.1)	1.7 (0.8 – 2.7)	180
By healthcare resource use*	AMB	2.3 (2.0, 2.6)	2.1 (1.4 – 2.9)	81
	Non-MA	1.3 (1.1, 1.6)	1.1 (0.5 – 1.9)	90
	Hospitalised	3.7 (3.3, 4.3)	3.6 (3.3 – 4.1)	7
By country	Spain	2.3 (1.9, 2.7)	2.3 (1.4 – 3.1)	36
	Finland	2.0 (1.5, 2.6)	1.7 (1.4 – 2.6)	14
	UK	1.8 (1.5, 2.1)	1.7 (0.9 – 2.5)	76
	Netherlands	1.6 (1.2, 2.0)	1.1 (0.5 – 2.6)	54
By caregiver	All-mother	1.9 (1.6, 2.1)	1.7 (0.8 – 2.7)	146
	All-father	2.0 (1.4, 2.6)	2.3 (1.1 – 2.7)	8
Caregivers	Caregivers pooled	0.1 (0, 0.2)	0.1 (0 – 0.4)	164
By healthcare resource use	AMB	0.2 (0, 0.4)	0.2 (0 – 0.5)	75
	Non-MA	-0.1 (-0.3, 0.1)	0 (-0.1 - 0.2)	81
	Hospitalised	1.2 (0.8, 1.7)	0.9 (0.9 – 1.6)	6
By country	Spain	0.2 (0, 0.3)	0 (0 – 0.3)	33
	Finland	-0.5 (-1.2, 0.1)	0 (-0.7 – 0.1)	14
	UK	0.2 (0.1, 0.4)	0.1 (-0.1 – 0.5)	69
	Netherlands	0 (-0.2, 0.2)	0 (0 – 0.3)	48
By caregiver	All-mother	0.1 (-0.1, 0.2)	0 (0 – 0.4)	133
	All-father	0.1 (-0.2, 0.4)	0 (0 – 0.2)	8

* Two episodes did not have healthcare resource use status. Abbreviations: QALD, quality-adjusted life-day; AMB, ambulatory care; non-MA, non-medical attendance; CI, confidence interval; Q1, first interquartile; Q3: third interquartile.

Figures

Figure 1: Patient flowchart for cost and health-related quality-of-life analysis



Abbreviations: ARTI, acute respiratory tract infection; RSV, respiratory syncytial virus; HRQoL, health-related quality of life.

Figure 2: Proportions of participants having any problem in 5 health dimensions (2 for children and 3 for caregivers)

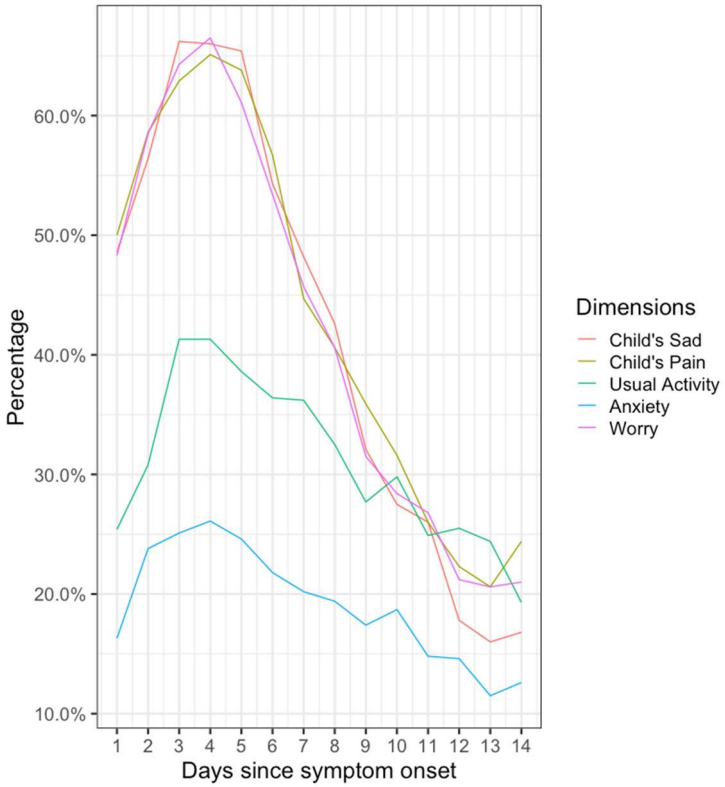


Figure 3: Boxplots of EQ-Visual Analogue Scale (VAS) scores for infants with RSV and caregivers