Substantial burden of non-medically attended RSV infection in healthy term infants – an international prospective birth cohort study

The Journal of Infectious Diseases

PROMISE SUPPLEMENT

Substantial burden of non-medically attended RSV infection in healthy term infants – an international prospective birth cohort study

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Background: During the first year of life, one in four infants develops a symptomatic respiratory syncytial virus (RSV) infection, yet only half seek medical attention. The current focus on medically attended RSV, therefore, underrepresents the true societal burden of RSV. We

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DOI: 10.1093/infdis/jiad477

assessed the burden of non-medically attended RSV infections and compared them with medically attended RSV.

Methods: We performed active RSV surveillance until the age of one year in a cohort (n=993) nested within RESCEU, a prospective birth cohort study enrolling healthy term-born infants in five European countries. Parent-reported daily symptoms, medication use, wheezing and impact on family life were analyzed.

Results: For 97 of 120 (80.1%) non-medically attended RSV episodes sufficient data were available for analysis. In 50.5% (49/97), symptoms lasted ≥15 days. Parents reported impairment in usual daily activities in 59.8% (58/97), worries in 75.3% (73/97), anxiety in 34.0% (33/97), and work absenteeism in 10.8% (10/93) of episodes. Compared with medically attended RSV (n=102, 9 hospital admissions), ReSViNET severity scores were lower (3.5 vs. 4.6, p<0.001), whereas durations of respiratory symptoms and impairment of usual activities were comparable.

Conclusion: Even when medical attendance is not required, RSV infection poses a substantial burden to infants, families and society at large. These findings are important for policymakers when considering the implementation of RSV immunization in national programs.

Clinical Trials Registration: NCT03627572

Keywords RSV; respiratory syncytial virus; burden of disease; non-medically attended; acute respiratory infections.

BACKGROUND

Respiratory syncytial virus (RSV) is a leading cause of childhood respiratory tract infections with around 1 in 4 European infants developing a symptomatic RSV infection during their first year of life[1]. Although RSV can cause severe acute respiratory distress necessitating hospitalization and intensive care unit admission, nearly half of these symptomatic RSV infections are managed by caregivers at home without medical help[1,2]. Data about symptom severity and duration of these non-medically attended RSV infections as well as their impact on general wellbeing, family life and society at large through parental absenteeism from work are scarce.

Previous studies mainly focused on RSV-infected infants who were hospitalized or received outpatient care, demonstrating a substantial clinical and socioeconomic disease burden in these settings[3–8]. However, this approach likely underestimates the true burden of RSV on society since non-medically attended RSV infections may also affect infants' and parents' wellbeing[3,9,10], and incur substantial costs[11].

With preventive options against RSV, such as long-acting monoclonal antibodies and maternal vaccination, coming within reach[12], it is key to capture the total burden of RSV disease on

society. This information will allow policymakers to carefully balance the benefits and costs of nationwide implementation of such preventative measures. We therefore assessed the clinical and societal burden of non-medically attended RSV infections in otherwise healthy term-born infants during their first year of life, and compared this with medically attended RSV, as part of the REspiratory Syncytial virus Consortium in Europe (RESCEU) birth cohort study.

METHODS

Study population

In this study, we performed active RSV surveillance during the first year of life in a cohort (n=993) nested within the RESCEU prospective observational birth cohort study (ClinicalTrials.gov identifier: NCT03756766), which methods have been described elsewhere[13]. In short, healthy term-born infants were enrolled at birth between July 2017 and December 2019 in five European countries (Finland, England, Scotland, Spain and the Netherlands). Infants were considered healthy term-born when born after at least 37 weeks of gestation, and without evidence of significant cardiovascular, respiratory, renal, gastrointestinal, hematological, neurological, endocrine, immunological, musculoskeletal, oncological, or congenital disorders. Written or electronic informed consent was obtained from the parents or guardians of all participating infants.

Study procedures

During the RSV season (between 1 October and 1 May, or longer if RSV was still circulating) parents were instructed and weekly reminded to report symptoms of acute respiratory infections (ARI) of their infant to the study team. An ARI episode was defined as the onset or worsening of any of the following symptoms for at least one day: runny or blocked nose, coughing, wheezing or dyspnea. The onset of symptoms after an ARI symptom-free interval of at least 48 hours was considered a new ARI episode.

In case of an ARI, a study visit was performed, during which a nasal swab was obtained for RSV testing by a trained member of the study team. RSV diagnosis was confirmed by point-of-care testing on the Alere i RSV assay (Abbott) and/or a polymerase chain reaction (PCR) test. In case of point-of-care testing, parents were informed of the test result. During the home visit, the study team member also recorded the Respiratory Syncytial Virus Network (ReSViNET) score to determine disease severity[14].

Symptom diary and questionnaires

During every ARI episode parents completed a daily diary from symptom onset to day 14, either digitally (the Netherlands, England and Scotland) or on paper (Spain, Finland). Respiratory and illness-related symptoms were collected using an adapted version of the parental ReSViNET

score[14]. Parents were asked to score symptom severity for coughing, dyspnea, wheezing, rhinitis, vomiting and feeding difficulties. The severity scores for individual symptoms were summed to calculate a daily symptom severity score, with a maximum of 23 points (Supplementary Table 1). In addition, parental and infant's health-related quality of life (HRQoL) were captured daily using an adapted version of the EQ-5D instrument (EuroQoL)[15]. For their infant, parents completed two dimensions of the EQ-5D-Y: 'Pain/Discomfort' and 'Sad'. For themselves, parents completed three dimensions: 'Anxiety/Depression' and 'Usual Activities' from the EQ-5D-5L, plus an additional dimension referred to as 'Worried about my child'. For both their infant and themselves, parents daily recorded the EQ-5D-VAS (visual analogue scale). On day 15, parents completed a final questionnaire on any remaining symptoms, medication use, healthcare consumption and work absenteeism during the ARI episode. At the first birthday of their child, parents completed an additional questionnaire on presence of wheezing during the past year.

Definitions and outcomes of interest

We defined the following main outcomes of interest:

1. Clinical course of disease, expressed as duration of illness, moderate-severe respiratory symptoms and individual symptoms, and daily symptom severity score;
2. HRQoL impact;
3. Parental absenteeism from work;
4. Medication use;
5. Parent-reported wheezing during first year of life

A non-medically attended RSV episode was defined as an RSV episode for which no healthcare visit (general practitioner, outpatient clinic, or emergency department visits) or hospitalization was recorded. If no RSV test result or no healthcare visit status was available, the ARI episode was excluded. RSV-positive episodes within 6 weeks of a previous RSV episode in the same infant were also excluded if the same RSV subtype (RSV A or B) was detected. Duration of an RSV episode was defined as time to resolution of all respiratory symptoms. Duration of moderate-severe respiratory symptoms was defined as the sum of days with at least moderate cough, dyspnea, rhinitis or wheezing ('moderate': score ≥2 out of 3 for any of these symptoms), or presence of apnea. Wheezing during the first year of life was defined as at least one wheezing episode reported by parents in the 1-year questionnaire.

Statistical analysis

Baseline demographics and clinical parameters were presented descriptively using frequency and percentage for categorical variables and mean (with standard deviations (SD)) or median (with

interquartile range (IQR)) for continuous variables. Categorical variables were compared between groups using χ^2 tests or Fisher's exact tests. Continuous normally distributed variables were compared using Student's t-test, whereas Mann-Whitney U tests were used to compare non-normally distributed continuous variables.

Survival analysis was used to calculate median duration of RSV ARIs. When respiratory symptoms resolution was not reported, data were censored on the last known symptomatic day. If any symptoms were still reported on day 15, data was censored on that day. A log-rank test was performed to compare illness duration between non-medically attended and medically attended RSV ARIs. When comparing non-medically to medically attended RSV ARIs, we performed sensitivity analyses excluding infants hospitalized with RSV, to assess the relative impact of these hospitalized cases on the outcome variables.

Multiple imputation was considered for imputing missing diary data, but we assumed that these data were not missing at random, as parents were probably less likely to complete a symptom diary when symptoms were mild or had resolved. Therefore, we developed a pre-defined algorithm to partially impute missing data for the variable related to the presence of any respiratory symptoms, in which we considered absence of respiratory symptoms for a specific day if there were no symptoms reported the day before or after the day with missing symptoms (Supplementary Table 2). Symptom diaries were excluded if parents had recorded information on respiratory symptoms for fewer than two consecutive days, or if parents skipped recording for two or more consecutive days. We refrained from imputing missing data on individual symptoms, symptom severity, and infant's and parents' HRQoL since we were not able to make reasonable clinical assumptions

Statistical analyses were performed in IBM SPSS Statistics 27 software (IBM, Armonk, New York). A two-sided p-value < .05 was considered statistically significant.

RESULTS

Study population

In total, 1520 ARIs were reported in 683 infants. Of the 1419 ARIs tested for RSV, 262 (18.5%) were RSV-positive. We excluded 9 RSV ARI due to missing medical attendance information, 12 because they occurred within 6 weeks of a prior RSV ARI, and an additional 42 due to insufficient or missing diary data (**Figure 1**). This resulted in 199 (75.9%) RSV ARI that were included in our analysis, of which 97 non-medically attended and 102 medically attended RSV ARIs, respectively. Complete diary data on respiratory symptoms were available for 84 (86.6%) non-medically attended and 86 (84.3%) medically attended RSV ARIs.

Baseline characteristics are shown in **Table 1**. Most infants were from the Netherlands (33.3%) and Scotland (24.8%). Nine out of the 102 (8.8%) medically attended RSV episodes concerned

hospitalized infants. Mean age at onset of RSV ARI did not differ between those with a non-medically and medically attended RSV episode (6.3 vs. 5.8 months, p=0.30), whereas among infants with a medically attended RSV episode, those requiring hospitalization were younger than those who did not (3.6 months vs. 6.1 months, p=0.03). RSV-A was the most detected subtype in both non-medically attended and medically attended RSV episodes. Infants with a non-medically attended RSV ARI more often had siblings (62.9% vs. 49.0%, p=0.049).

Disease characteristics of non-medically attended RSV aris

In 50.5% (49/97) of episodes, parents still reported respiratory symptoms on day 15 (**Figure 2**). Parents reported moderate-severe respiratory symptoms in 92.9% of episodes, lasting a median duration of 6 days (IQR: 5.0-9.0) (**Table 2**). Rhinitis (99.0%), cough (96.9%), and wheezing (66.0%) were the most commonly reported respiratory symptoms, while feeding difficulty (71.1%) was the most frequently reported non-respiratory symptom. Rhinitis (12 days; IQR: 9.0-14.0) and cough (11 days; IQR: 8.0-14.0) lasted longest. Symptom severity peaked at the fourth day of illness (**Figure 3**). Country-specific outcomes are shown in **Supplementary Table 3**.

Health-related quality of life (HRQoL)

Problems in each of the five HRQoL dimensions were most common during days 2-5 (**Figure 4**). Overall, more than three-quarters of parents reported their infant having pain (76.3%) and being sad (82.5%) (**Supplementary Figure 3**). The majority of parents were worried (75.3%), with a median duration of 5 days (IQR: 3.0-8.0) (**Supplementary Table 4**). Parents reported any impairment of usual activities in 59.8% episodes, with a median duration of 5.5 days (IQR: 2.0-10.0).

Parental work absenteeism

Most infants (62.5%; 55/88) had parents who were both employed. However, 40.0% (22/55) of working mothers and 16.7% (9/54) of working fathers were still on maternity/paternity leave during the non-medically attended RSV ARI episode (**Table 1**). In 25.8% (24/93) of episodes any caretaker had to stay home to take care of the infant, of which in 41.7% (10/24) one or both parents had to miss ≥1 day of work. In the remainder of episodes (58.3%; 14/24) another family member took care of the infant. In the case of parental work absenteeism, the median duration was 1 day (IQR: 1.0-4.25) per household (**Table 3**).

Use of medication

Parents reported use of medication in 52.6% of episodes (**Table 3**). This mostly consisted of over-the-counter medication use; painkillers/antipyretics and nasal spray were used in 37.9% and 20.0% of episodes, respectively.

Parent-reported wheezing during and after non-medically attended RSV infection

Wheezing during the course of the infection was reported in 66.0% (64/97). Any wheezing episodes during the infant's first year of life was reported at least once in 38.9% in the 1-year questionnaire, whereas multiple wheezing episodes were reported in 12.2% of infants (**Supplementary Table 5**).

Comparison of non-medically attended vs. Medically attended RSV ARI

The median duration of any respiratory symptoms and moderate-severe respiratory symptoms did not significantly differ between non-medically and medically attended RSV ARIs (15 vs. 15 days; p=0.94, and 6 vs. 7 days; p=0.52, respectively) (**Figure 2**). Shortness of breath and feeding difficulties were more common and lasted longer in medically attended RSV ARI (**Table 2**). The maximum symptom severity score reported by parents was higher in medically attended RSV ARIs (9.7 vs. 7.4; p<0.001), as well as the total ReSViNET score reported by the study team (4.6 vs. 3.5; p=0.001). Daily infant and parental VAS-scores did not significantly differ (**Supplementary Figure 1** & **2**).

Parental worries and anxiety were more common in medically attended RSV ARIs, as well as parents reporting their infant being sad or in pain (**Supplementary Table 3**). The proportion of parents reporting any impairment of usual activities was similar, while moderate-severe impairment of usual activities was more common in medically attended RSV ARIs (43.1% vs. 25.8%; p=0.01). Parental work absenteeism and any medication use were more frequently reported in medically attended RSV ARIs (28.1% vs. 10.8%, p=0.009, and 81.2% vs. 52.6%; p<0.001, respectively; **Table 3**). The number of infants with at least one or multiple wheezing episodes during the first year of life was similar between those who did and did not seek medical attention for the RSV ARI (**Supplementary Table 5**).

When comparing non-medically to medically attended RSV cases, sensitivity analysis excluding hospitalized infants (n=9) yielded outcomes consistent with the main analysis (**Supplementary Table 5** & **Supplementary Table 6**).

DISCUSSION

We previously showed that non-medically attended RSV infections are very common, affecting nearly 1 in 8 healthy term born infants during the first year of life[1]. This study illustrates that such RSV infections pose a substantial clinical and societal burden. We show that the majority of infants experience at least two weeks of respiratory symptoms. Even when RSV infections are managed without medical consultation, they generate considerable parental worries, impairment of usual activities and absenteeism from work. These findings emphasize that the burden of infant RSV infection extends beyond medically attended disease and hospitalization.

To the best of our knowledge, this is the first study to extensively describe the clinical and societal burden of non-medically attended RSV infections. Three previous studies conducted in Finland included, but were not limited to, non-medically attended RSV cases. The first, a community-based cohort study of children aged 0-24 months, demonstrated that about 1 in 3 symptomatic RSV infections did not require medical attention[2]. However, reported disease characteristics and family life impact were not stratified by presence or absence of medical consultation, limiting the ability to draw conclusions on medically and non-medically attended cases separately. The two other observational cohort studies required parents to visit the medical clinic for RSV testing and physical examination in case of any ARI symptoms of their child, even if symptoms may normally not have led to doctor consultation[4,5]. It is therefore impossible to distinguish between non-medically and medically attended RSV cases, which means that we can only make limited comparisons. Nevertheless, reported durations of 'all-severity' RSV illness in these three studies, with a mean of 12-13 days, were comparable to median illness duration of 15 days in our study.

Interestingly, our study showed that durations of any respiratory symptoms and moderate-severe respiratory symptoms did not significantly differ between infants with a medically and non-medically attended RSV ARI. Yet, parent-reported symptom severity was on average slightly higher in medically attended cases. This implies that more severe illness does not necessarily correspond with longer duration of illness. Furthermore, only shortness of breath and feeding difficulties were more frequently reported during medically attended RSV ARIs, suggesting that these symptoms are important drivers for parents to consult a doctor. In addition, as medically attended infants were more often from families with no other siblings, their parents may have felt less experienced in managing ARI symptoms and may thus have been more inclined to seek medical advice.

Although non-medically attended RSV ARIs do not lead to concurrent healthcare resource expenses, they could incur societal costs through parental work absenteeism. Parental work absenteeism in both non-medically and medically attended RSV ARIs was, however, relatively low (10.8% and 21.7%, respectively), especially compared to two previous Finnish studies (52%-78.6%) mentioned before[2,5]. Yet, these two studies also included children older than one year of age. In our study, a substantial proportion of parents in our study was still on maternity/paternity leave during their infant's RSV ARI. Also, we observed that frequently another family member took care of the infant. Nonetheless, a recently published cost- and HRQoL-analysis, also based on data from the RESCEU birth cohort study, estimated mean societal costs of €44.20 per individual non-medically attended episode, and a mean loss of 1.3 quality-adjusted life-days[11]. Given the high incidence of non-medically attended RSV infections, the costs and HRQoL loss for society at large are substantial.

The association between severe RSV infection and wheezing has been described earlier[16,17], yet our results suggest that wheezing is also associated with milder, non-medically attended, RSV disease. We report wheezing during the first year of life in 38.9% of infants with non-

medically attended RSV ARI, which is substantially higher than previously reported 20.2% of infants with RSV-negative ARIs[1]. However, it remains uncertain whether this association also extends to the development of childhood asthma and whether immunization against RSV would prevent wheezing in later childhood.

The main strength of our study is the intensive RSV surveillance during the first year of life in a large birth cohort during three RSV seasons. This enabled us to capture non-medically attended RSV episodes, which are typically overlooked when estimating the burden of RSV. In addition, the prospective nature of symptom and quality of life data collection mitigated the risk of recall bias, and high data completeness reduced the risk of selection bias. As such, we were able to accurately characterize the clinical course and impact of non-medically attended RSV episodes in the community.

Some aspects of our study, however, deserve further consideration. First, our follow-up of 15 days for individual ARI episodes proved to be relatively short, considering that half of infants still reported respiratory symptoms on the last recorded day. Consequently, the reported symptom duration is likely an underestimation of true symptom duration. Second, we may have missed RSV episodes due to unreported ARI episodes or false-negative PCR results. Anyhow, we believe this number to be minimal because the retention rate was high, with 89% of parents completing the questionnaire at age one year. In addition, we obtained most samples (87.7%) within 7 days of symptom onset, ensuring high diagnostic sensitivity[18]. Third, only a subset of European countries was represented in the study and participants may not be fully representative of their country's population, as the educational level of parents was high with 70% reporting university education. Fourth, healthcare seeking behavior may differ between countries, yet we were unable to draw valid comparisons due to the limited number of cases per country. Fifth, the availability of the RSV test result and study visit may have influenced healthcare seeking behavior, yet this could have had an effect in both directions. On one hand, parents may have been more inclined to seek medical care following RSV diagnosis, while, on the other hand, the visit by a member of the study team could have unintentionally reassured parents. Sixth, since we did not test for viral pathogens other than RSV, we were neither able to compare non-medically attended ARI RSV episodes with non-medically attended ARI episodes caused by other viruses in our study, nor were we able to determine the incidence and impact of co-infection. However, a recent systematic review and meta-analysis did not find an association between co-infection and clinical severity in medically attended RSV ARIs[19]. Finally, this study only included infants with RSV infections. Our findings are, therefore, not applicable to older children with RSV, yet there might be a substantial outpatient burden of RSV in older children as well[5,20].

The findings of our study are timely since preventive options against RSV infection in young infants are expected to be available in the near future[12]. A first long-acting monoclonal antibody has recently gained market approval in Europe and Canada[21–23], and a maternal RSV vaccine was shown to be safe and effective in a phase III clinical trial[24]. Health care

policymakers will soon decide whether to implement these immunization interventions in a national immunization program. Interestingly, it is unknown how long-acting monoclonal antibodies and maternal vaccines will affect the incidence and clinical course of non-medically attended RSV infections, since recent clinical trials did not include these infections as an outcome measure. However, non-medically attended cases play a significant role when evaluating cost-effectiveness of RSV interventions, as was demonstrated by a recent modeling study[25]. We, therefore, recommend future studies on the efficacy and cost-effectiveness of RSV vaccines to capture data on non-medically attended RSV episodes to fully quantify the burden of RSV disease.

To conclude, even when medical consultation is not required, RSV infections have a considerable impact on infants and their parents, thus adding to the total burden of RSV disease. These findings are important for policymakers when deciding on the implementation of RSV immunoprophylaxis or maternal vaccination in a national immunization program.

Acknowledgements : We gratefully thank all infants and parents who participated in this study. We thank the local study teams who were responsible for local patient recruitment and follow-up.

FOOTNOTES

PROMISE investigators: The PROMISE investigators are as follows: Sarah Hak; Roderick Venekamp; Joanne Wildenbeest; Marie-Noëlle Billard; Marlies van Houten; Louis Bont (University Medical Center Utrecht); Andrew Pollard, (University of Oxford); Ana Dacosta-Urbieta; Federico Martinón-Torres (Servicio Galego de Saude); Terho Heikkinen (University of Turku and Turku University Hospital); Steve Cunningham; Harish Nair (University of Edinburgh); Margaret Miller (Children's Clinical Research Facility, NHS Lothian, Edinburgh); Peter Openshaw (Imperial College); Philippe Beutels (Antwerp University); Hannah Nohynek (Finnish Institute for Health and Welfare); Anne Teirlinck (National Institute for Public Health and the Environment Netherlands); John Paget (Netherland Institute for Health Services Research); Leyla Kragten (The ReSViNET Foundation); Carlo Giaquinto (Fondazione PENTA – for the treatment and care of Children with HIV-ONLUS); Javier Diez-Domingo (Fundacio per al Foment de la Investigacio Sanitaria i Biomedica); Rafael Mikolajczyk (Martin Luther University Halle-Wittenberg); Gael Dos Santos (GlaxoSmithKline); Tin Tin Htar (Pfizer); Jeroen Aerssens (Janssen); Charlotte Vernhes, Rolf Kramer (Sanofi Pasteur); Veena Kumar (Novavax); Bahar Ahani (AstraZeneca); Eva Molero (Team-It Research).

Funding: This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) [grant agreement number 101034339]. The JU receives support from the EU's Horizon 2020 research and innovation programme and European Federation of Pharmaceutical Industries and Associations.

Disclaimer: This manuscript reflects only the views of the authors. The European Union and the Innovative Medicines Initiative (IMI) are not responsible for any use that may be made of the information it contains.

Author contributions

JGW, AP, TH, SC, FMT, and LJB designed the study.

JGW, MvH, TH, SC, FMT, MM and ADU collected data.

SH, JGW, MB, RPV and LJB analyzed and interpreted data.

SH wrote the first draft of the manuscript.

JGW, RPV, MB, LJB, AP, TH, SC, FMT, MvH, MM reviewed and commented on the manuscript.

SH, JGW and MB accessed and verified the data.

Potential conflicts of interest

SH, RPV, MM, and MB report no potential conflicts.

MVH has received honoraria for participation in advisory boards from Sanofi and Moderna and acted as PI in randomized clinical trials for Pfizer.

TH has received honoraria for lectures or participation in advisory boards or data monitoring committees from Janssen, Sanofi, and MSD.

AJP is part of the RESCEU consortium and his University received grant funding from the European Commission IMI programme for this work. Oxford University has also received grant funding from Medical Research Council, Wellcome Trust, Bill & Melinda Gates Foundation, Serum Institute of India and AstraZeneca. AJP is a contributor to intellectual property licensed by Oxford University Innovation to AstraZeneca. AJP is chair of the UK Joint Committtee of Vaccination and Immunisation and was a member of WHO SAGE till 2022.

SC had provided clinical study advice or acted as PI for GSK, Pfizer, MedImmune, Ablynx, Gilead, Ark Biosciences, Shionogi, Janssen/Alios with fees paid to the University of Edinburgh.

FMT has received honoraria from GSK group of companies, Biofabri, Pfizer Inc, Sanofi Pasteur, MSD, Seqirus 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. FMT 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.

ADU has been a sub investigator for clinical trials sponsored by Pfizer and GSK, and observational studies sponsored by Sanofi, with all funds paid to her institution. ADU has received funding for attending the AEP meeting in 2022.

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 (>€100000 per industrial partner) for investigator-initiated studies from AbbVie, MedImmune, AstraZeneca, Sanofi, Janssen, Pfizer, MSD, and MeMed Diagnostics. UMCU has received major funding for the RSV GOLD study from the Bill & 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 from Julius Clinical for participating in clinical studies sponsored by MedImmune and Pfizer. UMCU received minor funding (€1000–25000 per industrial partner) for consultation and invited lectures by AbbVie, MedImmune, Ablynx, Bavaria Nordic, MabXience, GSK, Novavax, Pfizer, Moderna, AstraZeneca, MSD, Sanofi, Genzyme, and Janssen. LJB is the founding chairman of the ReSViNET Foundation.

JGW has been an investigator for clinical trials sponsored by pharmaceutical companies including AstraZeneca, Merck, Pfizer, Sanofi, and Janssen. All funds have been paid to UMCU.

JGW participated in the advisory board of Janssen and Sanofi with fees paid to UMCU.

Preliminary data from this study have previously been presented at the 8th ReSViNET conference in Lisbon on February 22th 2023, and at the European Society of Pediatric Infectious Diseases (ESPID) conference in Lisbon on May 11th 2023.

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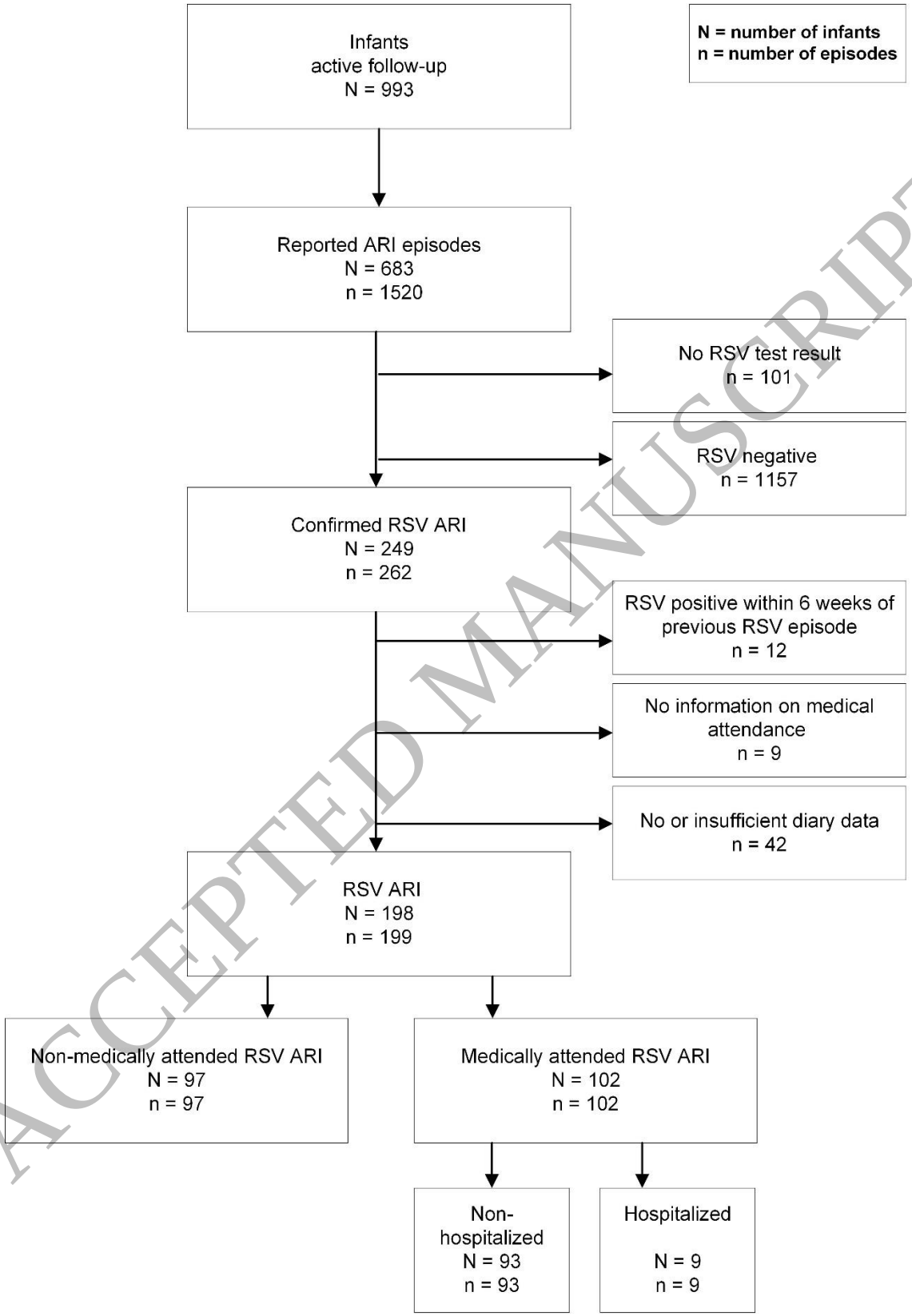
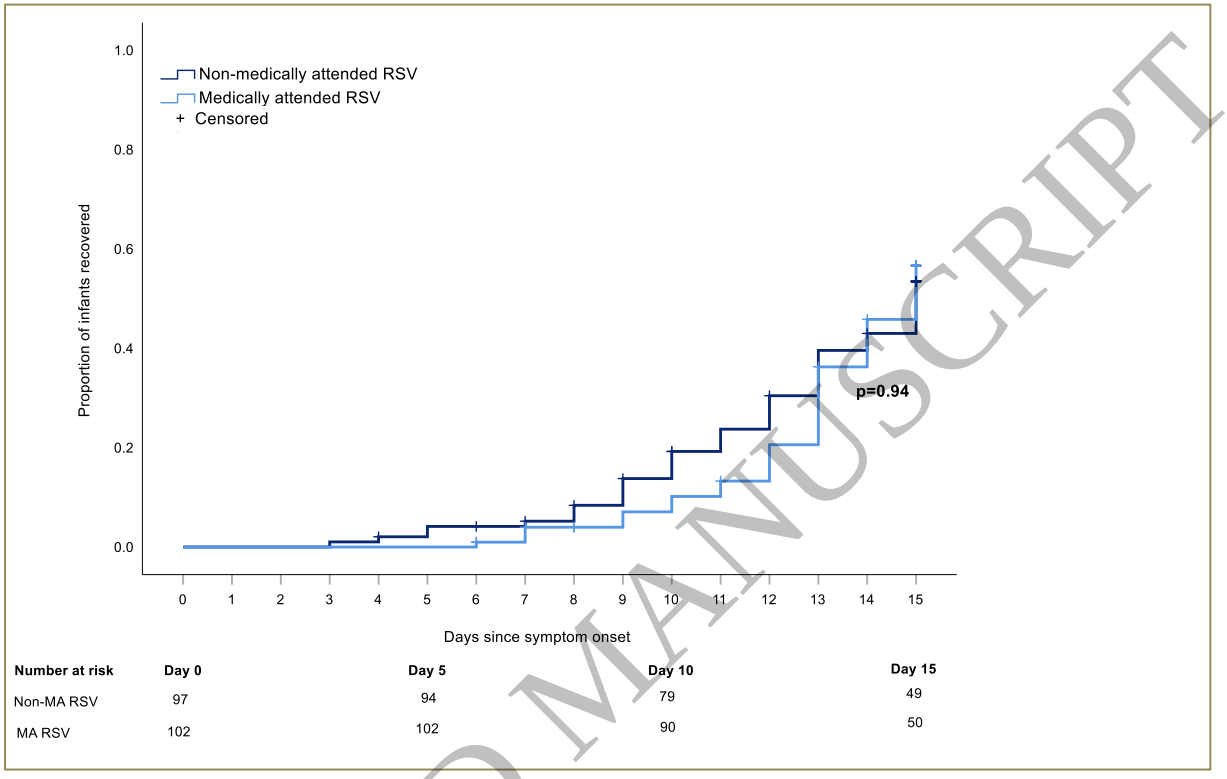
Figure 1. Flowchart (online only).



Abbreviations: ARI, acute respiratory infection; N, number of infants; n, number of ARI episodes.

Figure 2. Time to recovery of respiratory symptoms in non-medically attended (dark blue) and medically attended (light blue) RSV acute respiratory infections. Time to recovery was compared between groups using a log-rank test. (online only)



Abbreviations: MA, medically attended.

Figure 3. Mean daily symptom severity score in non-medically attended RSV episodes, presented with 95% confidence interval (CI). Cough, wheezing, shortness of breath, rhinitis, vomiting, feeding difficulties (scale 0-3 points), and apnea (3 points if present), and fever (1 point: feeling feverish or temperature 38-38.5°C; 2 points ≥38.5°C) were summed, with a maximum of 23 points (**Supplementary Table 1**).

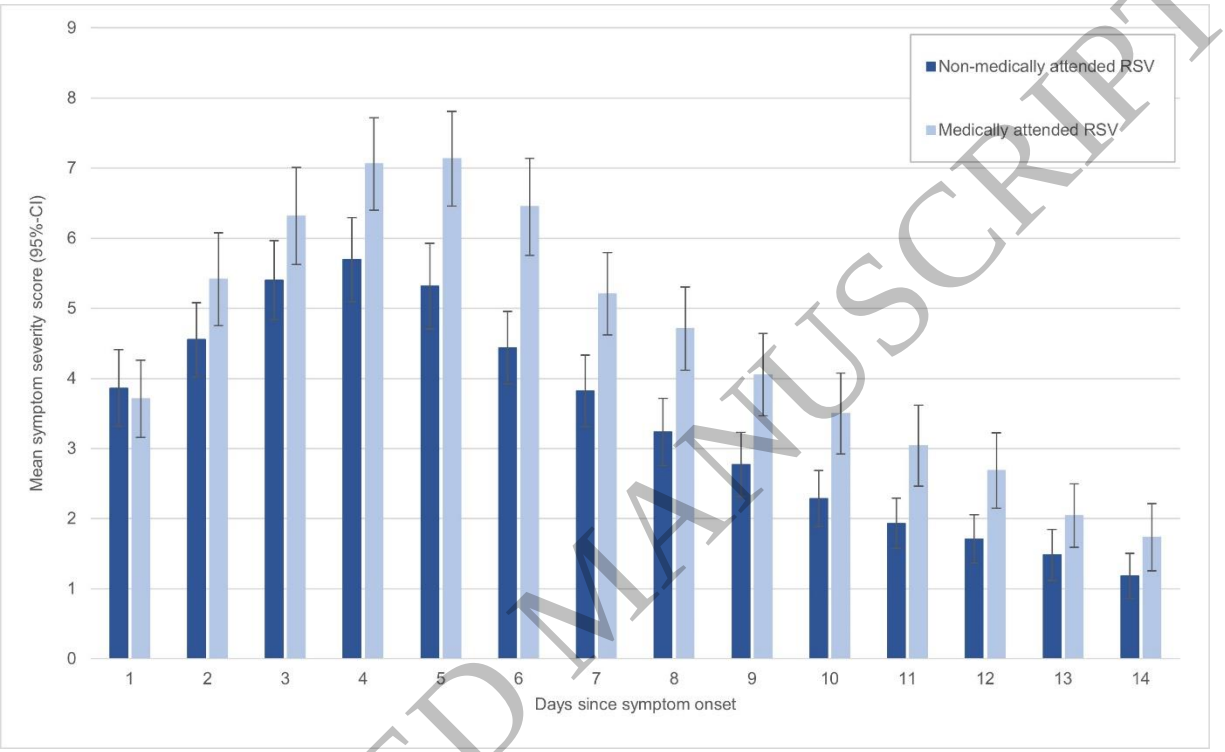
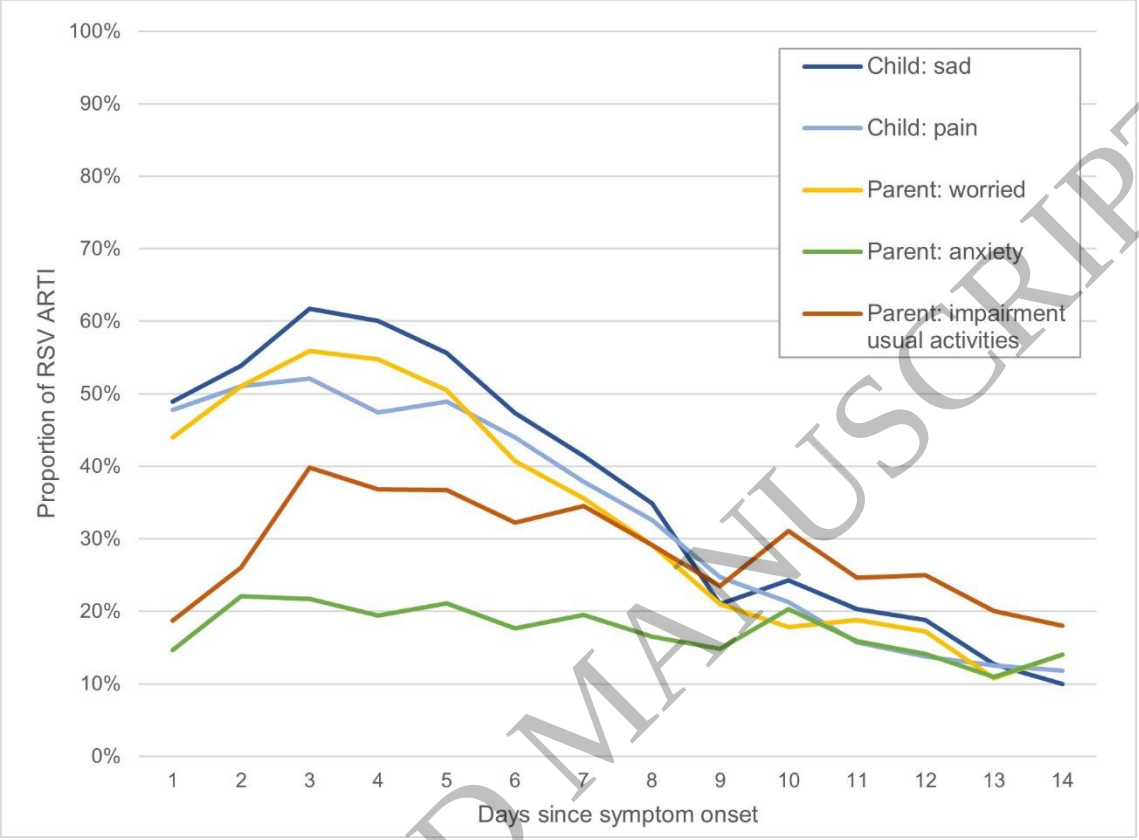


Figure 4. Proportion of non-medically attended RSV episodes in which parents reported any problem in five health-related quality of life dimensions. (online only)



Abbreviations: ARI, acute respiratory infections.

Table 1. Demographic and clinical characteristics [online only]

Characteristic	Non-medically attended (N=97)	Medically attended (N= 102)	*P*-value
Age at symptom onset, months, mean (SD)	6.3 (2.9)	5.8 (3.1)	0.30
Hospitalized	-	9/102 (8.8)	-
RSV			0.22
A	58/94 (59.8)	53/100 (52.5)	-
B	36/94 (37.1)	47/100 (46.5)	-
Country			0.79
Spain	18/97 (18.6)	18/102 (17.6)	-
Scotland	26/97 (26.8)	23/102 (22.5)	-
England	13/97 (13.4)	16/102 (15.7)	-
Finland	7/97 (7.2)	12/102 (11.8)	-
The Netherlands	33/97 (34.0)	33/102 (32.4)	-
Female sex	48/96 (50.0)	45/102 (44.1)	0.48
Birthweight ≥2500 grams	93/95 (97.9)	100/102 (98.0)	0.94
Pregnancy			
Maternal smoking	2/97 (2.1)	4/102 (3.9)	0.44
Maternal vaccination[a]	69/97 (71.1)	72/101 (71.3)	0.98
Caesarean section	26/96 (27.1)	37/102 (36.3)	0.17
Planned breastfeeding	81/87 (83.5)	93/102 (91.2)	0.10
Daycare attendance	32/89 (36.0)	23/91 (25.3)	0.15
Any siblings in household	61/97 (62.9)	50/102 (49.0)	0.05
Daycare attendance sibling	51/97 (52.6)	46/102 (45.1)	0.29
Smoking in household	9/97 (9.3)	9/102 (8.8)	1.00
Atopy family member	77/97 (79.4)	84/102 (82.4)	0.59
Highest completed education mother			0.19

Primary school	2/97 (2.1)	1/102 (1.0)	-
Secondary school	7/97 (7.2)	2/102 (2.0)	-
Vocational school	14/97 (14.4)	25/102 (24.5)	-
University of applied science	33/97 (34.0)	34/102 (33.3)	-
University	41/97 (42.3)	40/102 (39.2)	-
Highest completed education father			0.11
Primary school	3/95 (3.2)	2/102 (2.0)	-
Secondary school	13/95 (13.7)	9/102 (8.8)	-
Vocational school	17/95 (17.9)	35/102 (34.3)	-
University of applied science	26/95 (27.4)	26/102 (25.5)	-
University	36/95 (37.9)	30/102 (29.4)	-
Parental employment[b]			0.54
One parent employed	33/88 (37.5)	31/93 (33.3)	-
Both parents employed	55/88 (62.5)	61/93 (65.6)	-
Work status during RSV ARI mother			0.103
Unemployed	29/88 (33.0)	32/92 (34.8)	-
Still on maternity leave	22/88 (25.0)	24/92 (37.0)	-
Working	37/88 (42.0)	26 (28.3)	-
Work status during ARI father			0.09
Unemployed	3/87 (3.4)	1/91 (1.1)	-
Still on paternity leave	9/87 (10.3)	3/91 (3.3)	-
Working	75/87 (86.2))	87/91 (95.6)	-
Parental leave, duration, months, mean (SD)[c]			
Maternity leave	5.7 (3.1)	6.3 (3.9)	0.36
Paternity leave	1.8 (3.4)	1.0 (1.9)	0.07

Values are numbers and percentage of cases, unless indicated otherwise. Abbreviations: ARI, acute respiratory infection; SD, standard deviation.

Frequencies were compared between groups using χ^2 tests, or, if the cell count was below ten, Fisher's exact tests were used. Means were compared using Student's t-test.

[a] Pertussis or influenza vaccination during pregnancy.

[b] Employment during first year of life, as reported in 1-year questionnaire.
[c] Calculated amongst parents that resumed working during first year of life.

Table 2. Disease characteristics

Characteristic	Non-medically attended (N=97)	Medically attended (N=102)	*P*-value
Presence of symptoms ≥1 day, n (%)			
Any moderate-severe respiratory symptoms[a]	90 (92.9)	98 (96.1)	0.31
Cough	94 (96.9)	101 (99.0)	0.29
Shortness of breath	50 (51.5)	78 (76.5)	<0.001
Wheeze	64 (66.0)	79 (77.5)	0.07
Runny/blocked nose	96 (99.0)	101 (99.0)	0.97
Apnea	11 (11.3)	7 (6.7)	0.46
Feels feverish	32 (33.0)	35 (34.2)	0.84
Measured fever (≥38° Celsius)	29 (29.9)	40 (39.2)	0.17
Feeding difficulties	69 (71.1)	102 (89.2)	0.001
Vomiting	54 (55.7)	61 (59.8)	0.56
Duration of symptoms, days, median (IQR)[b]			
Any moderate-severe respiratory symptoms[a]	6 (5.0-9.0)	7 (4.0-9.0)	0.52
Cough	11 (8.0-13.0)	12 (10.0-14.0)	0.02
Shortness of breath	4 (2.25-7.0)	5 (3.0-10.0)	0.02
Wheeze	5 (3.0-5.0)	6.0 (3.25-10.0)	0.12
Runny/blocked nose	12 (9.0-14.0)	12 (9.0-14.0)	1.00
Apnea	1 (1.0-1.0))	1 (1.0-1.0)	1.00
Feels feverish	2 (1.0-3.0)	2 (1.0-4.0)	0.92
Measured fever (≥38° Celsius)	1.5 (1.0-2.75)	2 (1.0-4.0)	0.12
Feeding difficulties	5 (2.0-7.0)	6 (4.0-8.0)	0.03
Vomiting	2 (1.0-4.75)	3 (1.0-6.25)	0.28

Symptom severity, mean (SD)			
ReSViNET score by study team	3.5 (2.3)	4.6 (2.4)	0.001
Maximum symptom score by parent	7.4 (2.7)	9.7 (3.2)	<0.001

Abbreviations: IQR, interquartile range; SD, standard deviation.

Frequencies were compared between groups using χ^2 tests, or, if the cell count was below ten, Fisher's exact tests were used. Means were compared using Student's t-test. Medians were compared using Mann-Whitney U tests.

[a] Any moderate-severe symptoms indicate presence of at least one of the following: moderate-severe cough, dyspnea, rhinitis or wheezing (score ≥2 out of 4), or presence of apnea.

[b] Duration of individual symptoms calculated only if symptom was reported at least once during ARI, and diary data was complete.

Table 3. Parental work absenteeism and medication use (online only)

Characteristic	Non-medically attended RSV	Medically attended RSV	*P*-value
Parental work absenteeism[a]			
Any caretaker staying at home	24 (25.8)	36 (37.5)	0.08
Father	4 (4.3)	17 (17.7)	0.003
Mother	7 (7.5)	17 (17.7)	0.04
Other family member / caretaker	14 (14.7)	9 (9.4)	0.32
Parental work absenteeism	10 (10.8)	27 (28.1)	0.003
Duration per household, median (IQR)	1 (1.0-4.25)	4 (1.0-4.0)	0.23
Use of medication[b]			
Any	50 (52.6)	82 (81.2)	<0.001
Painkillers	36 (37.9)	47 (46.5)	0.22
Nasal spray	19 (20.0)	47 (46.5)	<0.001
Antibiotics	1 (1.1)	9 (8.9)	0.02
Bronchodilator	0 (0.0)	18 (17.8)	<0.001
Other	4 (4.2)	12 (11.9)	0.07

Values are numbers and percentage of cases unless otherwise indicated.

Abbreviations: IQR, interquartile range.

Frequencies were compared between groups using χ^2 tests, or, if the cell count was below ten, Fisher's exact tests were used. Medians were compared using Mann-Whitney U tests.

[a] Missing: non-medically attended (n=4/97); medically attended (n=6/102)

[b] Missing: non-medically attended (n=2/97); medically attended (n=1/102)