The burden of RSV in healthy term-born infants in Europe: a prospective birth cohort study

Authors:

Joanne G. Wildenbeest, MD[1], Marie-Noëlle Billard, MSc[1#], Roy P. Zuurbier, MD[1,2#], Koos Korsten, MD[1,3], Annefleur C. Langedijk, MSc[1], Peter M. van de Ven, PhD[1,4], Matthew D. Snape, MD[5], Simon B. Drysdale, MD[5,6], Prof Andrew J. Pollard, FMedSci[5], Hannah Robinson, DipHE[5], Prof Terho Heikkinen, MD[7], Prof Steve Cunningham, MBChB[8], Thomas O'Neill, BMBS[9], Bishoy Rizkalla, PhD[10], Ana Dacosta-Urbieta, MD[11,12,13], Federico Martinón-Torres, MD[11,12,13], Marlies A. van Houten, MD[2], Prof Louis J. Bont, MD[1], for the RESCEU Investigators.

Affiliations:

[1] Department of Paediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands

[2] Spaarne Gasthuis Academy, Hoofddorp and Haarlem, the Netherlands

[3] Department of Medical Microbiology and infection prevention. Amsterdam University Medical Centre, Amsterdam University, Amsterdam, the Netherlands

[4] Department of Data Science and Biostatistics, University Medical Center Utrecht, Utrecht, the Netherlands.

[5] Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR Oxford Biomedical Research Centre, Oxford, United Kingdom

[6] Centre for Neonatal and Paediatric Infection, Institute for Infection and Immunity, St George's, University of London, London, United Kingdom

[7] Department of Pediatrics, University of Turku and Turku University Hospital, Turku, Finland

[8] Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom

[9] Children's Clinical Research Facility, Royal Hospital for Children and Young People, NHS Lothian, Edinburgh, United Kingdom

[10] Glaxo Smith Kline, Wavre, Belgium

[11] Translational Pediatrics and Infectious Diseases, Pediatrics Department, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain

[12] Genetics, Vaccines and Infections Research Group (GENVIP), Instituto de Investigación Sanitaria de Santiago, University of Santiago de Compostela, Spain

[13] Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain

[#] Both authors contributed equally

Corresponding author:

Louis J. Bont

Department of Paediatric Immunology and Infectious Diseases

Wilhelmina Children's Hospital/University Medical Center Utrecht,

Lundlaan 6

3584 EA Utrecht

the Netherlands

email: L.Bont@umcutrecht.nl

Phone: 0031 88 7555555

Abstract

Background

Respiratory syncytial virus (RSV) is a major cause of hospitalization in infants. The burden of RSV infection in healthy term infants has not yet been established. Accurate healthcare burden data in healthy infants are necessary to determine RSV immunization policy when RSV immunization becomes available.

Methods

We performed a multicenter prospective, observational birth cohort study in healthy term-born infants (≥37 weeks of gestation) in five sites located in different European countries to determine the healthcare burden of RSV. The incidence of RSV-associated hospitalizations in the first year of life was determined by parental questionnaires and hospital chart reviews. We performed active RSV surveillance in a nested cohort to determine the incidence of medically-attended RSV infection.

Findings

In total, 9154 infants born between July 2017 and April 2020 were followed during the first year of life and 993 participated in the nested active surveillance cohort. The incidence of RSV hospitalization in the total cohort was 1·8% (95% CI 1·6-2·1). There were eight pediatric intensive care unit admissions, corresponding to 5·5% of RSV hospitalizations and 0·09% of the total cohort. Incidences of RSV infection confirmed by any diagnostic assay and medically-attended RSV infection in the active surveillance cohort were 26·2% (95% CI 24·0-28·6) and 14·1% (95% CI 12·3-16·0), respectively.

Interpretation

RSV-associated acute respiratory infection causes substantial morbidity, leading to the hospitalization of one in every 56 healthy term-born infants in high-income settings. Immunization of pregnant women or healthy term-born infants during their first winter season could have a significant impact on the healthcare burden caused by RSV infections.

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Research in Context

Evidence before this study

We searched PubMed, using the terms "RSV" or "respiratory syncytial virus", "hospitalizations", and "infant" or "first year of life", on May 31st 2022, for studies published in the last 30 years, with no language restrictions. The results included mostly retrospective analyses of RSV-coded hospitalizations from health registries or prospective studies conducted in a single country. These studies emphasized the large morbidity and mortality burden in young children associated with RSV. In a recent systematic review and meta-analysis from *The Lancet*, RSV was estimated to be associated with 3.6 million hospitalizations for acute lower respiratory infections and 101,400 in- or out-of-hospital deaths in children younger than 5 years annually worldwide. A gap exists in the knowledge of the RSV burden in healthy term infants, the largest population of RSV infected infants. We identified ten birth cohort studies that reported RSV-associated hospitalization in infants with estimates varying between 0.6% to 5%. These birth cohorts had relatively small sample sizes with 156 to 1,143 participants, and only two included only healthy term-born children. The reliability and the precision of these estimates can be improved by large prospective birth cohorts conducted in multiple countries. Several maternal vaccines and passive immunization against RSV are currently at advanced stage of clinical development or under review for licensure. To decide how these new prevention strategies should be included in national vaccination programs, precise estimates of the healthcare burden of RSV infections in the first months of life are required.

Added value of this study

The RESCEU birth cohort study is the largest multicenter prospective birth cohort that evaluated the incidence of RSV-associated hospitalizations and medically-attended acute

respiratory infections. It was designed to provide a precise and recent estimate of the total RSV incidence and healthcare burden in Europe. Almost 10,000 participants were enrolled in five European countries and 97% were successfully followed during the first year of life. To estimate the incidence of medically-attended RSV infection, we actively followed a nested cohort of ~1,000 participants. The incidence of RSV-confirmed hospitalization in the first year of life was 1·8% (95% CI 1·6-2·1). About half of hospitalizations for respiratory tract infection in the first year of life were associated with RSV. The majority (57·9%) of RSV hospitalizations occurred in children <3 months of age. The incidence of medically-attended RSV infection was 14·1% (95% CI 12·3-16·0).

Implications of all the available evidence

This study provides the precise estimates of the healthcare burden of RSV required to decide on future RSV immunization programs. The healthcare burden of RSV among healthy infants is considerable in Europe, with one in 56 healthy term-born infants hospitalized for RSV infection annually. As the incidence of severe RSV infection is highest in the first months of life, maternal vaccination as well as passive infant immunization could have a major impact on the health of healthy term infants.

Introduction

Respiratory syncytial virus (RSV) causes a substantial burden of disease among infants worldwide with an estimated annual mortality of 101,400 in children under the age of five years.[1] Although >97% of RSV-attributable deaths occur in low-income and middle-income countries, the healthcare burden of RSV infection in high-income countries is considerable with an estimated annual hospitalization rate of 3 per 1000 children under 5 years old in the USA.[2] Passive immunization against RSV with palivizumab is available for high-risk groups including premature infants and children with congenital heart disease or bronchopulmonary dysplasia. Because the majority of children hospitalized with RSV have no pre-existing conditions, a high morbidity is seen in infants <6 months of age despite the availability of palivizumab.[2] Various maternal vaccine and passive immunization trials which aim to protect all infants in the first months of life are currently in phase 3 or submitted for regulatory approval.[3–5] Expectations are that within 1-3 years one or several of these products will be approved by regulatory authorities and governments will have to decide whether these newly available prevention strategies should be implemented into their national immunization schedule.[6] Accurate information about RSV healthcare burden in healthy infants is essential for decision-makers to evaluate the health and economic benefit of these new prevention strategies.

Most large studies that aimed to determine RSV-associated hospitalization rates in young children included children with comorbidities, were country-specific, and partly based on estimates instead of actual numbers.[2,7,8] Birth cohort studies estimate disease incidence more accurately, but previous prospective birth cohorts in healthy infants were relatively small (158-1143 participants) and done in one center and/or country, limiting generalizability.[9–18] To our knowledge, the largest prospective birth cohort determining RSV burden was a South-African single center study that reported 54 RSV hospitalizations among 1143 children (17% with comorbidity) in the first 2 years of life.[13] To prepare for the introduction of RSV immunization,

the RESCEU (Respiratory Syncytial virus Consortium in Europe, https://resc-eu.org/) international consortium was funded by the European Union Commission to obtain accurate data on the incidence and long-term consequences of RSV infection in healthy term infants.

The primary objective of this study was to determine the incidence of medically-attended and hospitalized RSV-associated respiratory infections in healthy term infants in Europe. Secondary objectives included to estimate the incidence of symptomatic RSV infections, the incidence of all-cause respiratory infections and the proportion of respiratory infections attributable to RSV.

Methods

Study design

The study design and protocol have been described previously (ClinicalTrials.gov, Identifier: NCT03627572).[19] In short, healthy term-born infants were enrolled at birth between July 2017 and July 2020 in in five sites each located in a different European country representing Western, Northern, and Southern Europe (Spain, Finland, England, Scotland, and the Netherlands). Children born at ≥37 weeks of gestation with no evidence of significant cardiovascular, respiratory, renal, gastrointestinal, hematological, neurological, endocrine, immunological, musculoskeletal, oncological, or congenital disorders were considered healthy term-born.[18] All participating children were followed-up for at least one year. Children diagnosed with comorbidities later were not systematically excluded. We used parental questionnaires to screen for hospitalization for acute respiratory infection (ARI) during the first year of life at the age of one year. Hospital records, including RSV testing results, were retrospectively assessed in case of hospitalization for ARI. All participating hospitals tested for RSV during the RSV season as part of standard care and were situated in a distinct geographic area to ensure that children were preferentially referred to that hospital if inpatient care was needed. For infants whose parents

did not complete the 1-year questionnaire, hospital records were screened for ARI hospitalizations within the first year of life in participating hospitals.

At enrollment at all five sites, participants to the birth cohort were also invited to participate in a nested cohort (referred to as active surveillance cohort). Participants to the birth cohort and the active surveillance cohort were recruited on voluntary basis and therefore were a convenience sample of term-born children living in the catchment area of the sites. To obtain a cohort with evenly distributed months and years of birth over the recruitment period, sites were instructed to recruit 15-20 participants per week including 2 participants in the active surveillance cohort. Enrollment in the active surveillance cohort continued until the planned sample size was reached in each site (200 per site). Infants were actively followed until their first birthday during the RSV seasons of 2017-18, 2018-19 and 2019-20. Between 1 October and 1 May (or longer if RSV was still circulating), parents were contacted weekly to report ARI symptoms of their child. In case of an ARI, a study visit was planned within 72 hours of notification to obtain a nasal swab for RSV testing. Parents completed a diary with respiratory symptoms and health care usage for 14 days after onset.[18] Written or electronic informed consent was obtained from the parents of all study participants.

RSV detection in active surveillance cohort

At all sites, a nasal sample was collected during each ARI episode by using microtipped flocked swabs (FLOQSwab™, Copan diagnostics), and directly stored in viral transport medium (MicroTest™ M4RT® (Remel, 3 ml)). All samples were stored at -80 Celsius degrees. After the end of the study all samples were tested with in-house RSV quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR, suppl methods).[20,21] In addition, a point of care test (POCT, Alere™ i RSV assay (Alere Inc., Waltham, MA, USA) was performed at the time of sample collection at the 3 sites in Spain, England and the Netherlands. If the infant had an RSV positive ARI episode, POCT was not performed during further ARI's. An RSV

positive ARI episode was defined as a positive test result from either in-house RT-qPCR or POCT or both.

Outcome definitions

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.[19] Episodes were associated with RSV if a POCT or in-house PCR test was positive for RSV. Samples taken more than 10 days after onset were excluded from analysis. Medically attended (MA)-ARI were defined as ARI episodes with at least one visit to a healthcare provider (outpatient clinics, emergency department visits, general practitioner visits) or hospitalization. RSV-associated hospitalizations, RSV-ARI and RSV-MA-ARI were reported as incidence (i.e. the proportion infants experiencing the event at least once during their first year of life) and as incidence rate per 1000 infant-months (number of events per 1000 infant-months of follow-up). The use of incidence rates in addition to incidence was pre-defined in the statistical analysis plan to account for possible variation in follow-up time due to early drop-outs of participants and for participants experiencing outcomes more than once (Suppl B). 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

Statistical analyses were performed according to the predefined statistical analysis plan (suppl. B). For sample size calculation of the total cohort, a yearly incidence of hospitalizations of 0·7% was assumed based on previous literature.[2,22] A sample size of 8700 would produce a two-sided 95% Clopper-Pearson confidence interval with a half-width of 0·2% for this

incidence. If accounting for 10% loss to follow-up 10,000 infants were to be included.[19] Similarly, a sample size of 1,000 infants was estimated for the active surveillance cohort, which would produce a two-sided 95% Clopper-Pearson confidence interval with a half-width of 2%, for an assumed incidence of MA-ARI of 10%.[2,9,22] Baseline characteristics and clinical parameters were summarized by frequency and percentage for categorical variables and mean (+/-SD) and/or median (interquartile range) for continuous variables. Baseline characteristics were compared between groups using chi-square tests for categorical variables, Student's t-tests for normally distributed continuous variables and Mann-Whitney U tests for not normally distributed continuous variables. RSV status was assumed negative when hospitalization occurred outside of the RSV season. RSV status of hospitalizations during the RSV season and ARI in the active surveillance cohort with invalid or missing RSV test results were imputed using multiple imputation based on site, gender, age and meteorological season at time of hospitalization or ARI. Any missing observations for medical attendance of ARIs was subsequently imputed using the same set of predictors to which RSV status was added. Imputation yielded ten complete datasets for each of the two cohorts. After imputation, pooled 95% Wilson-score confidence intervals were calculated for the proportion of infants with at least one RSV hospitalization or ARI in the first year. Incidence rates were calculated together with 95% confidence intervals based on a Poisson distribution and compared between subgroups of infants using Poisson generalized linear models. Statistical analyses were performed using SPSS version 26 and R statistical software version 3.5.1.

Ethical 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).

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies (Suppl. B).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report or the decision to submit for publication.

Results

Study population

Between July 2017 and July 2020, 9466 healthy term infants were recruited at birth, of whom 9154 (96·7%) were included in the primary analysis (Figure 1). Due to the COVID-19 pandemic, 223 infants born after 1 April 2020 were excluded as RSV was not circulating during their first year of life. Between September 2017 and November 2019, 1041 infants were enrolled in the active surveillance cohort and 993 (95·4%) who participated for at least four weeks were included in the analysis (Figure 1). Five deaths occurred among study participants, none were related to RSV. There was substantial and expected variation in baseline characteristics between countries (Table 1). Non-exhaustively, the most common ethnic origin was according to country geographic location, smokers in the family were more common in Spain and maternal vaccination was almost never reported in the Netherlands where it was not recommended at the time. Compared to the rest of the cohort, participants of the active surveillance cohort more frequently reported maternal vaccination against influenza or pertussis, multiple births, a family history of atopy and parental university level of education,

whereas parental smoking and parental origin from Northwest Europe were reported less frequently. They also had fewer siblings and were born later in the year than other participants.

RSV-associated hospitalization

We observed 388 ARI hospitalizations (Figure 1 and 2, Table S1). Of these, 145 (37·4%) were positive for RSV, 193 (49·7%) were negative or occurred outside the RSV season and 50 (12·9%) occurred during the RSV season but were not tested for RSV (and status was imputed). Among the RSV-associated hospitalizations, RSV was detected during admission by hospital laboratory PCR tests in 71/145 (49·0%) and by POCT in 67/145 (46·2%). The test used was not documented for seven RSV-associated hospitalizations. Overall, 143 (1·6%) children were hospitalized with confirmed RSV, including two who were admitted twice with RSV. After imputing missing RSV test results, the incidence of RSV-associated hospitalization was 1·8% (95% CI 1·6-2·1), corresponding to an RSV hospitalization incidence rate (IR) of 1·6 /1000 infant-months (95% CI 1·3-1·8, Table 2). RSV hospitalization incidence in countries varied between 1·1% (95% CI 0·7-1·5) in Finland and 2·5% (95% CI 1·8-3·4) in Spain (Table 3). RSV hospitalization IR was higher in children born in autumn (2·6/1000 infant-months, 95% CI 2·0-3·3)) than in children born in winter (1·1/1000 infant-months, 95% CI 0·8-1·6, Bonferroni adjusted p=0·002) and spring (0·8/1000 infant-months, 95% CI 0·5-1·3, Bonferroni adjusted p=0·001, Table 3, Figure S1). RSV hospitalization IR was highest in 2017-2018 (2·7/1000 infant-months, 95% CI 1·9-4·0) when the proportion of participating children <6 months of age was high, and lowest in 2019-2020 (1·5/1000 infant-months, 95% CI 1·1-1·8, Table 3).

Out of 145 RSV hospitalizations, 84 (57·9%) were in children <3 months of age (Table S2, Figure S1). In that age group, incidence of RSV hospitalization peaked at 1-<2 month of age (Figure S1). Median duration of hospitalization was 3 days (range 1-19 days). Hospitalizations lasted longer in Spain (median 6 days) than in the Netherlands (median 3 days, p<0·003),

296 Finland, England, and Scotland (median 2 days, p<0·001). Duration of hospitalization and other
297 measures of severity were not found to be associated with the incidence rate of RSV
298 hospitalization. Length of hospitalization was longer in infants <3 months when compared to
299 infants aged 6-<12 months (p=0.004) but not when compared to infants aged 3-<6 months
300 (p=0.27). Eight RSV hospitalizations (5·5%) were admitted to the pediatric intensive care unit
301 (PICU) (0·09% of total cohort, and three (2%) required mechanical ventilation (0·03% of total
302 cohort). Six out of eight infants admitted to ICU were aged <3 months (median age 1 month).
303 Any respiratory support was more frequently used in RSV-positive than RSV-negative
304 hospitalizations (53·1%, 77/145 *versus* 23·3%, 45/193, p<0·001). Coinfections with other
305 respiratory viruses were tested as part of routine care in 85 (58·6%) and found in 34 (23·4%)
306 of RSV hospitalizations. Rhinovirus was most frequently co-detected. In RSV-negative
307 hospitalizations, rhinovirus, influenza and parainfluenza were the 3 most prevalent viruses
308 (Table S2).

309 ***Outpatients***

310 We registered 1520 ARI episodes in 993 infants in the active surveillance cohort (Figure 1 and
311 2). A nasal swab was collected during 1442 episodes (95%). Missed episodes was the main
312 reason for not collecting a swab. Twenty-three samples collected >10 days after start of
313 symptoms were excluded. Most samples (88%) were collected within 7 days after the start of
314 symptoms. In total, 262/1419 episodes (18·5%) were positive for RSV in 249 infants (Figure
315 1). Among the 840 episodes tested by PCR and POCT, RSV was detected only by POCT in
316 five (0.6%).

317 RSV-A was detected in 142 (54·2%) of RSV-ARI and RSV-B in 111 (42·4%). One sample was
318 positive for both RSV-A and RSV-B. RSV subtype was unknown for 10 ARI episodes: five
319 were only tested by POCT, four were only tested in hospital as part of routine care and for one
320 RSV subtype could not be determined. Information about medical attendance was available for

1432 episodes (94·2%). For 1353 ARI episodes (89·0%) both RSV and medical attendance status were available. Medical attendance was reported in 131/251 (52·2%) RSV-positive ARI, which was more frequent than in RSV-negative ARI (298/1102, 27·0%, p<0·001).

After imputing missing RSV test results, the incidence of RSV-MA-ARI was 14·1% (95% CI 12·3-16·0) with an IR of 12·1/1000 infant-months (95% CI 10·2-14·3, Table 2). The incidence of RSV-ARI overall was 26·2% (95% CI 24·0-28·6) with an IR of 23·7/1000 infant-months (95% CI 21·0-26·7). IR of RSV-ARI and RSV-MA-ARI were similar for infants <6 and ≥6 months of age (Table 3). The IRs for RSV-ARI and RSV-MA-ARI episodes were highest in the Netherlands (38·9/1000 infant-months (95% CI 31·5-48·0) and 19·2/1000 infant-months (95% CI 14·2-25·9), respectively) and lowest in Finland (8·8/1000 infant-months, 95% CI 5·7-13·5 and 5·8/1000 infant-months, 95% CI 3·4-9·9 respectively, Bonferroni adjusted p<0·05, Table 3).

Wheezing in first year of life

Information on wheezing in the first year of life was available for 7838 children (85·6% of participants) whose parents completed the 1-year questionnaire (Figure 1). Wheezing was reported in 87/123 (70·7%) infants admitted with RSV. Wheezing was less frequent in infants hospitalized for RSV-negative ARI only (73/134 (54·5%), p=0·008) and in infants never admitted for an ARI (1272/7550 (16·8%), p<0·001, Figure 1). In the active surveillance cohort, wheezing was reported for 56/118 (47·5%) infants with RSV-MA-ARI and 37/102 (36·3%) infants with non-MA RSV-ARI (p=0·09). This was more frequent than in children who had no ARI (8·1%, 20/246, p<0·001 and p<0·001), had MA RSV-negative ARI (23·5%, 38/162, p<0·001 and p=0·03) or had non-MA RSV-negative ARI (20·2%, 43/213, p<0·001 and p=0·002). When adjusted for family history of atopy and smoking household members at birth the difference in wheezing between RSV-positive and RSV-negative or no ARI remained

significant (p=0.003 and p<0.001 for hospitalizations, p<0.001 and p<0.001 for MA-ARI, and p=0.002 p<0.001 for non-MA-ARI¬).

Discussion

This is the first international birth cohort study powered to accurately estimate the healthcare burden of RSV in healthy term-born infants. Our results showed an incidence of RSV-associated hospitalization of 1·8% in the first year of life. Almost half of all ARI hospitalizations in the first year of life were RSV-associated. The burden of RSV-associated hospitalization was highest in infants <3 months of age with an incidence rate of 3·3/1000 infant-months. Children born in autumn had a significantly higher risk of hospitalization than children born in other seasons. One quarter of infants experienced an RSV-ARI, of which half were medically-attended. Wheezing during the first year of life was associated with RSV hospitalization, MA-RSV-ARI, and overall RSV-ARI.

Our findings are consistent with previous literature. Although not a birth cohort study, a study conducted in the United States reported an incidence of RSV hospitalizations of 1·7% in infants <6 months (1·5% in our study), and 0·5% in infants 6-<12 months of age (0·4% in our study).[2] The higher admission rate in infants <6 months reported by Hall et al. might be related to the 35% of higher-risk infants included. In our study, incidence of RSV hospitalization per country varied between 1·1 and 2·5%, which was in line with previous findings from these countries.[9,11,18,22] In other birth cohort studies, RSV hospitalization incidence in the first year of life varied between 0·6% and 5%. Some studies also included high-risks infants (Table S3).[10,12–17] The two largest birth cohort studies in healthy term-born infants showed an incidence of RSV hospitalization of 1·9% in an Indian birth cohort of 310 infants and 1% in 298 infants of a Dutch birth cohort.[9,14] Wheezing in the first year of life was associated with RSV infection irrespective of severity. The association between severe RSV infections and wheezing has been described earlier.[23] Whether this is also associated with development of childhood asthma remains

unclear, as well as whether RSV immunization will prevent wheezing during later childhood.[24] Intervention studies are required to define the causal relationship between RSV infection during infancy and wheezing in healthy term-born infants.

The major strength of our study is the prospective design with the power to accurately estimate RSV incidence in European countries over several seasons. We used active surveillance to capture mild RSV disease to provide a precise estimate of total RSV incidence and disease burden. Follow-up rates were high with collection of swabs in 95% of reported ARI episodes and >85% completion of the 1-year questionnaire in the total cohort. In addition to parental report, we screened the study participants' hospital charts to ensure no ARI hospitalization was missed. This study also has limitations. First, in 50/388 ARI hospitalizations during the RSV season no RSV test was performed. When using a cohort study design with RSV testing results as primary outcome, missing test results will systematically lead to an underestimation of true incidence if assumed negative. To avoid this systematic bias, primary outcomes were reported after using multiple imputation for missing RSV test results and medical attendance status. As the proportion of missing information was small, using multiple imputation resulted in a small increase in incidence compared to estimating incidence assuming all cases with missing RSV status were RSV-negative. Two of the five sites did not use POCT which could have led to underestimating incidence in those countries, however that impact was probably small. Among the 840 episodes tested by PCR and POCT, five (0.6%) were detected by POCT only. Assuming a similar rate, two additional RSV cases would have been detected by POCT among the 415 episodes tested by PCR only at the sites not using POCT. Second, data on co-infection with other respiratory viruses were limited. Third, the participants in the study may not be representative of the country population and not all countries in Europe were represented. The education level of participants, especially in the active surveillance cohort, was high with 70% of mothers reporting university education and is therefore not necessarily representative of the

whole population. Lower socio-economic status and younger age of the mother have been reported as risk factors for RSV associated hospitalization in infancy.[25] Other risk factors like parental smoking were less frequently reported by active surveillance cohort participants than the rest of the study population. This could have resulted in an underestimation of RSV incidence in the study population compared to the country population and in the active cohort compared to the entire cohort. Although children with evidence of significant comorbidities at birth were excluded, we cannot rule out that a minority of participants had comorbidities diagnosed later in life. Fourth, it is possible that we missed ARI episodes despite weekly contacts with parents during the period of active surveillance (October to May, or longer if RSV was still circulating). We cannot rule out that some participants may have stopped reporting ARI of their children, which could result in underestimating incidence rate and would be more pronounced in the older infants. However, participation to the first year questionnaire was 89% in the active surveillance cohort, suggesting a high retention rate. ARI episodes occurring outside of the active surveillance period would not have been captured, which likely contributed to the 31% of active cohort participants with no ARI in the first year of life. However, it is unlikely that those uncaptured ARI episodes were associated with RSV infection. Fifth, the COVID-19 pandemic impacted RSV incidence in 2020. The 2019-2020 RSV season was virtually finished in the participating countries when the COVID-19 pandemic started, except for Finland, where the usual continuation of the RSV outbreak into late spring was abruptly terminated due to COVID-19 pandemic.[26,27] The COVID-19 pandemic may have contributed to the lower incidence of RSV-associated hospitalization, MA-ARI and ARI in the study in Finland. Participants born after April 1 2020 were excluded as RSV did not circulate during their first year of life. Follow-up time after November 1 2020 represented less than 3% of total the follow-up time of the cohort and concerned only participants ≥6 months of age. Sixth, healthcare burden does not reflect the total burden of RSV. Healthcare burden is key

information to estimate economic and societal burden, and the incidence of medically-attended and hospitalized RSV infections is expected to be a major part of the healthcare burden in Europe where RSV-related deaths are rare. Overall, study limitations have possibly resulted in a modest underestimation of actual RSV burden.

Conclusions

The healthcare burden of RSV in healthy term-born infants in Europe is considerable with an incidence of RSV-associated hospitalization of 1·8% in the first year of life, which means that one in 56 healthy term-born infants is hospitalized with RSV annually. Because the highest burden is seen in infants in their first months of life, maternal vaccination and passive immunization could have a profound impact on the RSV burden.

Study group members

The RESCEU investigators are as follows: Joanne Wildenbeest; Marie-Noëlle Billard; Roy Zuurbier; Koos Korsten; Marlies van Houten; Annefleur Langedijk; Peter ; Louis Bont (University Medical Center Utrecht); Simon Drysdale; Joseph McGinley; Gu-Lung Lin; Matthew Snape; Andrew Pollard, Andrew Ives, Helen Wolfenden, Sanjay Salgia, Rohoth Shetty (University of Oxford); Ana Dacosta-Urbieta; Irene Rivero-Calle; Alberto Gómez-Carballa; Sara Pischedda; Carmen Rodriguez-Tenreiro; Federico Martinón-Torres (Servicio Galego de Saude); Terho Heikkinen (University of Turku and Turku University Hospital); Steve Cunningham; Harish Nair; Harry Campbell (University of Edinburgh); Thomas O'Neill; Margaret Miller; Julie Baggott; Catherine Beveridge; Rachael McKernan (Children's Clinical Research Facility, NHS Lothian, Edinburgh); Bishoy Rizkalla (GlaxoSmithKline) Philippe Beutels (University of Antwerp); Peter Openshaw (Imperial College London); Adam Meijer (National Institute for Public Health and the Environment); Thea Kølsen Fischer (Statens Serum Institut); Maarten van den Berge (Academisch Ziekenhuis Groningen); Carlo Giaquinto (Fondazione PENTA for the Treatment and Care of Children with HIV-ONLUS); Michael Abram (AstraZeneca); Kena Swanson (Pfizer); Jeroen Aerssens (Janssen); Charlotte Vernhes, Scott Gallichan (Sanofi Pasteur); Veena Kumar (Novavax); Eva Molero (Team-It Research).

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Conflict of interests

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 has provided consultancy and/or investigator roles in relation to product development for Ablynx, Janssen, MedImmune, AstraZeneca, Pfizer, GSK, Vertex, AbbVie, Valneva, Fibrogen, Boehringer Ingelheim, 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.

MDS acts as an investigator on behalf of the University of Oxford on research studies funded by vaccine manufacturers including GlaxoSmithKline, Janssen, MCM vaccines, Novavax, AtraZeneca and Pfizer. He receives no direct personal payment for this work. MDS was an NIHR senior Investigator and received salary support from the NIHR Oxford Biomedical Research Centre during the course of this project. MDS is currently an employee of Moderna.

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. BR is a full time employee of the GSK group of companies and holds shares and restricted shares in the GSK group of companies as part of their employee remuneration. AJP is currently Chair of DHSC's JCVI and was previously a member of WHO's SAGE and chair of the European Medicine's Agency Scientific Advisory Group on Vaccines. Oxford University has partnered with AstraZeneca on development of COVID19 vaccines. Other authors declare no conflict of interests.

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.

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Author contributions

JGW, AP, TH, SC, FMT, MS and LJB designed the study. JGW, RZ, MvH, TH, SC, MS, SC, FMT, KK, SD, HR, ADU and TON collected data. JGW, MB, PvdV, and LJB analysed and interpreted data. JGW wrote the first draft. AP, TH, SC, FMT, MS, RZ, MvH, KK, SD, HR, ADU, BR and TON reviewed and commented on the manuscript. JGW and MB accessed and verified the data. JGW and LJB were responsible for the decision to submit the manuscript.

Data sharing statement

The anonymized data of the RESCEU birth cohort study will be made available for research purposes after the end of the long-term follow-up. The data will be store on the Elixir data platform. Requests to access the data should be sent via Elixir to the RESCEU consortium.

References

1 Li Y, Wang X, Blau DM, *et al.* Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *The Lancet* 2022; **399**: 2047–64.

2 Hall CB, Weinberg GA, Iwane MK, *et al.* The burden of respiratory syncytial virus infection in young children. *N Engl J Med* 2009; **360**: 588–98.

3 Madhi SA, Polack FP, Piedra PA, *et al.* Respiratory Syncytial Virus Vaccination during Pregnancy and Effects in Infants. *New England Journal of Medicine* 2020; **383**: 426–39.

4 Hammitt LL, Dagan R, Yuan Y, *et al.* Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. *N Engl J Med* 2022; **386**: 837–46.

5 RSV Vaccine and mAb Snapshot. https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/ (accessed March 22, 2022).

6 EMA. New medicine to protect babies and infants from respiratory syncytial virus (RSV) infection. European Medicines Agency. 2022; published online Sept 16. https://www.ema.europa.eu/en/news/new-medicine-protect-babies-infants-respiratory-syncytial-virus-rsv-infection (accessed Sept 26, 2022).

7 Haerskjold A, Kristensen K, Kamper-Jørgensen M, Nybo Andersen A-M, Ravn H, Graff Stensballe L. Risk Factors for Hospitalization for Respiratory Syncytial Virus Infection: A Population-based Cohort Study of Danish Children. *Pediatr Infect Dis J* 2016; **35**: 61–5.

8 Hardelid P, Verfuerden M, McMenamin J, Smyth RL, Gilbert R. The contribution of child, family and health service factors to respiratory syncytial virus (RSV) hospital admissions in the first 3 years of life: birth cohort study in Scotland, 2009 to 2015. *Euro Surveill* 2019; **24**. DOI:10.2807/1560-7917.ES.2019.24.1.1800046.

9 Houben ML, Bont L, Wilbrink B, *et al.* Clinical prediction rule for RSV bronchiolitis in healthy newborns: prognostic birth cohort study. *Pediatrics* 2011; **127**: 35–41.

10 Nokes DJ, Okiro EA, Ngama M, *et al.* Respiratory syncytial virus infection and disease in infants and young children observed from birth in Kilifi District, Kenya. *Clin Infect Dis* 2008; **46**: 50–7.

11 Toivonen L, Karppinen S, Schuez-Havupalo L, *et al.* Respiratory syncytial virus infections in children 0-24 months of age in the community. *J Infect* 2020; **80**: 69–75.

12 Kubale J, Kuan G, Gresh L, *et al.* Assessing the Incidence of Symptomatic Respiratory Syncytial Virus Illness Within a Prospective Birth Cohort in Managua, Nicaragua. *Clin Infect Dis* 2020; **70**: 2029–35.

13 Zar HJ, Nduru P, Stadler JAM, *et al.* Early-life respiratory syncytial virus lower respiratory tract infection in a South African birth cohort: epidemiology and effect on lung health. *The Lancet Global Health* 2020; **8**: e1316–25.

14 Kumar P, Medigeshi GR, Mishra VS, *et al.* Etiology of Acute Respiratory Infections in Infants: A Prospective Birth Cohort Study. *Pediatr Infect Dis J* 2017; **36**: 25–30.

15 Regamey N, Kaiser L, Roiha HL, *et al.* Viral etiology of acute respiratory infections with cough in infancy: a community-based birth cohort study. *Pediatr Infect Dis J* 2008; **27**: 100–5.

16 Kusel MMH, de Klerk NH, Holt PG, Kebadze T, Johnston SL, Sly PD. Role of respiratory viruses in acute upper and lower respiratory tract illness in the first year of life: a birth cohort study. *Pediatr Infect Dis J* 2006; **25**: 680–6.

17 Takashima MD, Grimwood K, Sly PD, *et al.* Epidemiology of respiratory syncytial virus in a community birth cohort of infants in the first 2 years of life. *Eur J Pediatr* 2021; **180**: 2125–35.

18 Thomas E, Mattila J-M, Lehtinen P, Vuorinen T, Waris M, Heikkinen T. Burden of Respiratory Syncytial Virus Infection During the First Year of Life. *J Infect Dis* 2021; **223**: 811–7.

19 Wildenbeest JG, Zuurbier RP, Korsten K, *et al.* Respiratory Syncytial Virus Consortium in Europe (RESCEU) Birth Cohort Study: Defining the Burden of Infant Respiratory Syncytial Virus Disease in Europe. *The Journal of Infectious Diseases* 2020; **222**: S606–12.

20 Korsten K, Adriaenssens N, Coenen S, *et al.* Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study. *Eur Respir J* 2021; **57**: 2002688.

21 Zuurbier RP, Korsten K, Verheij TJM, *et al.* Performance Assessment of a Rapid Molecular Respiratory Syncytial Virus Point-of-Care Test: A Prospective Community Study in Older Adults. *J Infect Dis* 2022; **226**: S63–70.

22 Zomer-Kooijker K, Uiterwaal CSPM, van der Gugten AC, Wilbrink B, Bont LJ, van der Ent CK. Decreased lung function precedes severe respiratory syncytial virus infection and post-respiratory syncytial virus wheeze in term infants. *Eur Respir J* 2014; **44**: 666–74.

23 Blanken MO, Rovers MM, Molenaar JM, *et al.* Respiratory Syncytial Virus and Recurrent Wheeze in Healthy Preterm Infants. *N Engl J Med* 2013; **368**: 1791–9.

24 Brunwasser SM, Snyder BM, Driscoll AJ, *et al.* Assessing the strength of evidence for a causal effect of respiratory syncytial virus lower respiratory tract infections on subsequent wheezing illness: a systematic review and meta-analysis. *The Lancet Respiratory Medicine* 2020; **8**: 795–806.

25 Fitzpatrick T, McNally JD, Stukel TA, *et al.* Family and Child Risk Factors for Early-Life RSV Illness. *Pediatrics* 2021; **147**: e2020029090.

26 Haapanen M, Renko M, Artama M, Kuitunen I. The impact of the lockdown and the re-opening of schools and day cares on the epidemiology of SARS-CoV-2 and other respiratory infections in children - A nationwide register study in Finland. *EClinicalMedicine* 2021; **34**: 100807.

27 van Summeren J, Meijer A, Aspelund G, *et al.* Low levels of respiratory syncytial virus activity in Europe during the 2020/21 season: what can we expect in the summer and autumn/winter? *Eurosurveillance* 2021; **26**: 2100639.

Table 1. Baseline characteristics of participants by recruitment sites based on participants with available information.

	Total Cohort						Active surveillance cohort					
Site[#]	**SCO**	**ENG**	**ESP**	**FIN**	**NLD**	**All**	**SCO**	**ENG**	**ESP**	**FIN**	**NLD**	**All**
Total number of participants	n=2130	n=1979	n=1080	n=2093	n=1879	n=9154	n=203	n=198	n=205	n=200	n=187	n=993
Follow-up time (infant-months)	25,498	23,458	12,949	25,119	22,484	109,507	2,408	2,288	2,404	2,384	2,245	11,728
Pregnancy												
Vaccination (n (%))*	85%	91%	61%	45%	34%	64%	93%	93%	59%	65%	31%	69%
Influenza	68%	73%	28%	45%	1%	46%	76%	72%	19%	65%	3%	47%
Pertussis	82%	86%	58%	0%	34%	51%	89%	91%	57%	1%	30%	54%
Smoking during pregnancy (n (%))	7%	5%	10%	5%	4%	6%	4%	5%	9%	7%	2%	5%
Birth												
Month of birth (n (%))*												
Oct - Dec	24%	22%	26%	21%	28%	24%	15%	13%	34%	19%	33%	23%
Jan - Mar	31%	29%	24%	15%	33%	26%	16%	14%	16%	29%	34%	22%
Apr - Jun	22%	28%	15%	29%	16%	23%	34%	30%	14%	34%	16%	26%
Jul - Sept	23%	22%	36%	34%	23%	27%	35%	42%	36%	18%	18%	30%
Male sex (n (%))	52%	53%	51%	52%	50%	52%	52%	55%	52%	53%	45%	52%
Multiple birth (n (%))*	2%	3%	3%	1%	1%	2%	9%	3%	3%	1%	3%	4%
Cesarean delivery (n (%))*	44%	38%	22%	14%	22%	29%	41%	38%	32%	14%	24%	30%
Birth weight <2500g (n (%))	2%	3%	3%	1%	1%	2%	2%	3%	4%	2%	2%	3%
Antibiotics <72h post-partum	0%	7%	1%	5%	2%	3%	0%	7%	0%	4%	1%	2%
Intention to breastfeed (n (%))*	79%	84%	68%	97%	73%	83%	90%	92%	71%	98%	82%	97%
Family												
Any siblings (n (%))	43%	50%	52%	53%	48%	49%	51%	45%	48%	48%	63%	51%
Number of siblings (Median (IQR))*	1 (1-2)	1 (1-2)	1 (1-1)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-2)	1 (1-1)
Sibling(s) in daycare or primary school	38%	42%	45%	41%	45%	41%	45%	35%	42%	35%	57%	43%
Smokers in the family*	15%	14%	28%	13%	16%	16%	7%	10%	28%	12%	11%	14%
Mother	4%	2%	6%	2%	3%	3%	2%	1%	4%	2%	1%	2%
Father	12%	11%	24%	11%	14%	14%	6%	8%	25%	11%	10%	12%

Other family member	1%	2%	3%	0%	1%	1%	0%	2%	3%	0%	1%	1%
Smoking in the house	1%	1%	4%	0%	0%	1%	0%	2%	3%	0%	1%	1%
Family history of atopy*	74%	72%	56%	63%	71%	68%	80%	76%	60%	67%	76%	72%
Sibling(s) uses or used respiratory	8%	11%	11%	8%	11%	9%	5%	8%	8%	5%	15%	8%
Ethnic origin of the mother*												
Northwest Europe	77%	75%	3%	97%	78%	73%	72%	72%	4%	98%	88%	66%
Southern Europe	4%	2%	90%	0%	2%	12%	5%	3%	87%	0%	2%	20%
Other	19%	23%	10%	3%	24%	16%	23%	25%	8%	3%	11%	14%
Ethnic origin of the father*												
Northwest Europe	78%	76%	3%	95%	77%	73%	76%	79%	4%	97%	89%	68%
Southern Europe	4%	3%	90%	1%	1%	12%	3%	2%	88%	0%	1%	29%
Other	18%	23%	9%	5%	24%	16%	20%	20%	7%	4%	11%	12%
Highest level of education of the mother*												
Secondary / vocational school	37%	38%	51%	35%	32%	37%	18%	20%	50%	31%	25%	29%
University of (applied) sciences	63%	62%	45%	63%	67%	61%	82%	80%	46%	67%	75%	70%
Highest level of education of the father*												
Secondary / vocational school	48%	48%	66%	48%	40%	48%	29%	34%	68%	46%	37%	43%
University of (applied) sciences	52%	52%	24%	48%	58%	49%	71%	65%	27%	51%	63%	55%
Employment of the mother before birth												
Full-time	65%	64%	59%	69%	42%	60%	69%	72%	53%	69%	45%	62%
Part-time	24%	26%	16%	13%	49%	26%	25%	24%	19%	15%	50%	26%
Employment of the father before birth												
Full-time	91%	94%	91%	88%	83%	89%	95%	94%	91%	83%	81%	89%
Part-time	4%	2%	4%	4%	13%	5%	1%	4%	3%	4%	17%	6%

* P<0·05 total active surveillance versus total passive (without active) cohort

sites abbreviations correspond to abbreviations of country names: SCO for Scotland, ENG for England, ESP for Spain, FIN for Finland and NLD for the Netherlands.

Table 2: Incidence and incidence rates of RSV-associated ARI, MA-ARI and hospitalized ARI in the first year of life

	RSV incidence after imputation[$]	RSV incidence before imputation[$$]	Cohort size / person-time	Number of hospitalizations/ ARI episodes	Number of RSV-positive (observed)	Number of missings[#] (required imputation)
RSV-associated hospitalization in total cohort						
Incidence*	1·8% (1·6-2·1)	1·6% (1·3-1·8)	9,154 infants	341 infants hospitalized	143 infants with RSV-associated hospitalization	50/388 hospitalizations (12.9%)
Incidence rate per 1,000 infant-months**	1·6 (1·3-1·8)	1·3 (1·1-1·6)	109,507 infants-months	388 hospitalizations	145 RSV-associated hospitalizations	
MA RSV-positive ARI in active surveillance cohort						
Incidence*	14·1% (12·3-16·0)	13·0% (11·0-15·2)	993 infants	683 infants with ARI	129 infants with RSV-associated MA-ARI	166/1520 ARI (10.9%)
Incidence rate per 1,000 infant-months**	12·1 (10·2-14·3)	11·2 (9·3- 13·3)	11,728 infant-months	1520 ARI	131 RSV associated MA-ARI	
RSV-positive ARI in active surveillance cohort						
Incidence*	26·2% (24·0-28·6)	25·1% (22·4-27·9)	993 infants	683 infants with ARI	249 infants with RSV-associated ARI	101/1520 ARI (6.7%)
Incidence rate per 1,000 infant-months**	23·7 (21·0-26·7)	22·3 (19·7-25·2)	11,728 infant-months	1520 ARI	262 RSV-associated ARI	

* Incidence as proportion infants experiencing the event at least once during their first year of life. ** Incidence rate as number of events per 1000 infant-months of follow-up.
$ Missing RSV status imputed using multiple imputation based on site, gender, age and meteorological season at time of hospitalization or ARI and missing medical attendance imputed using site, gender, age, meteorological season at time of hospitalization or ARI and RSV status (observed or imputed) $$ assuming all missing outcomes were negative.
# Outcomes that required imputations included: 50 hospitalizations with missing RSV status, 166 ARI episodes with missing RSV status and/or missing MA status, 101 ARI episodes with missing RSV status.

Table 3. Incidence and incidence rates after imputation for missing RSV test results and missing medical attendance status of RSV-associated hospitalized ARI, MA-ARI and ARI by age group, according to season, recruitment site, cohort, and season of birth.

	RSV-associated hospitalized ARI				**RSV-associated MA-ARI**				**RSV-associated ARI**			
	< 3 months	**3-<6 months**	**6-<12 months**	**<12 months**	**< 3 months**	**3-<6 months**	**6-<12 months**	**<12 months**	**< 3 months**	**3-<6 months**	**6-<12 months**	**<12 months**
RSV incidence proportion (% (95%CI))												
Overall	0·97 (0·82-1·16)	0·49 (0·38-0·63)	0·39 (0·29-0·52)	1·80 (1·58-2·05)	3·39 (2·56-4·49)	4·55 (3·55-5·80)	6·32 (5·13-7·77)	14·07 (12·31-16·03)	5·05 (4·01-6·33)	9·29 (7·84-10·97)	12·61 (10·93-14·51)	26·22 (23·95-28·63)
Site												
Scotland	1·15 (0·83-1·6)	0·47 (0·28-0·79)	0·73 (0·48-1·1)	2·31 (1·83-2·92)	1·48 (0·59-3·64)	5·72 (3·55-9·11)	6·75 (4·30-10·45)	13·74 (10·17-18·31)	3·5 (1·91-6·33)	12·69 (9·17-17·3)	13·6 (9·88-18·43)	29·21 (24·05-34·97)
England[#]	1·03 (0·71-1·51)	0·71 (0·44-1·14)	0·43 (0·23-0·81)	1·97 (1·50-2·57)	2·58 (1·26-5·20)	5·05 (2·97-8·46)	3·03 (1·48-6·09)	10·4 (7·18-14·84)	3·99 (2·21-7·11)	9·95 (6·89-14·15)	7·61 (4·93-11·55)	20·51 (15·96-25·94)
Spain	1·2 (0·77-1·88)	1·00 (0·6-1·65)	0·28 (0·11-0·69)	2·48 (1·81-3·4)	6·00 (3·77-9·43)	6·65 (4·27-10·21)	5·35 (3·22-8·76)	17·71 (13·65-22·65)	7·71 (5·10-11·49)	11·15 (7·98-15·37)	11·8 (8·50-16·16)	29·56 (24·49-35·19)
Finland	0·62 (0·4-0·97)	0·24 (0·12-0·49)	0·19 (0·08-0·44)	1·05 (0·74-1·49)	1·00 (0·33-2·98)	1·01 (0·33-2·99)	4·95 (2·95-8·19)	6·9 (4·48-10·49)	1·00 (0·33-2·98)	2·51 (1·23-5·07)	7·07 (4·62-10·68)	10·50 (7·45-14·61)
Netherlands	0·97 (0·65-1·43)	0·26 (0·12-0·57)	0·25 (0·11-0·56)	1·47 (1·07-2·03)	6·04 (3·73-9·63)	4·28 (2·43-7·43)	11·66 (8·32-16·10)	21·98 (17·38-27·39)	9·25 (6·30-13·38)	10·16 (7·08-14·38)	23·32 (18·6-28·81)	42·19 (36·35-48·26)
RSV incidence rate (/1000 months (95%CI))												

Overall	3·26 (2·63-4·04)	1·67 (1·23-2·27)	0·65 (0·45-0·92)	1·56 (1·33-1·82)	11·69 (8·34-16·38)	15·21 (11·28-20·52)	10·77 (8·36-13·88)	12·11 (10·24-14·34)	17·55 (13·34-23·1)	31·69 (25·76-38·98)	22·81 (19·16-27·17)	23·7 (21·02-26·73)
Site												
Scotland	3·88 (2·60-5·8)	1·55 (0·82-2·92)	1·21 (0·73-2·00)	1·96 (1·48-2·61)	4·95 (1·6-15·35)	19·1 (10·63-34·32)	11·47 (6·62-19·87)	11·75 (8·06-17·12)	11·70 (5·58-24·56)	44·82 (30·18-66·56)	24·77 (16·78-36·56)	26·52 (20·54-34·25)
England	3·46 (2·20-5·45)	2·56 (1·47-4·47)	0·72 (0·34-1·51)	1·87 (1·38-2·55)	8·61 (3·58-20·71)	17·00 (8·89-32·54)	5·04 (2·09-12·1)	8·98 (5·69-14·18)	13·31 (6·44-27·51)	34·07 (21·68-53·55)	12·99 (7·63-22·1)	18·39 (13·4-25·23)
Spain	4·01 (2·33-6·9)	3·34 (1·81-6·14)	0·46 (0·15-1·44)	2·07 (1·41-3·03)	20·11 (11·37-35·55)	22·22 (12·92-38·24)	8·93 (4·8-16·61)	15·09 (10·82-21·06)	27·46 (16·81-44·88)	37·28 (24·56-56·59)	20·58 (13·77-30·75)	26·49 (20·63-34·03)
Finland	2·07 (1·20-3·56)	0·80 (0·33-1·92)	0·31 (0·1-0·9)	0·87 (0·57-1·33)	3·34 (0·84-13·35)	3·35 (0·84-13·41)	8·24 (4·37-15·52)	5·79 (3·4-9·85)	3·34 (0·84-13·35)	8·38 (3·49-20·14)	11·78 (6·98-19·89)	8·81 (5·74-13·51)
Netherlands	3·23 (2·02-5·18)	0·86 (0·33-2·27)	0·40 (0·14-1·15)	1·23 (0·83-1·81)	21·93 (12·46-38·57)	14·27 (7·14-28·54)	20·28 (13·43-30·64)	19·2 (14·21-25·93)	32·63 (20·57-51·77)	33·9 (21·62-53·15)	44·48 (33·62-58·85)	38·89 (31·49-48·02)
Season												
2017-2018	3·9 (2·51-6·08)	2·49 (1·21-5·09)	0***	2·71 (1·85-3·98)	15·01 (7·81-28·86)	11·98 (4·49-31·94)	0***	12·05 (7·00-20·75)	20·75 (11·75-36·67)	18·08 (8·03-40·72)	0***	17·15 (10·79-27·26)
2018-2019	3·17 (2·30-4·38)	1·41 (0·83-2·41)	0·90 (0·50-1·62)	1·76 (1·38-2·25)	8·36 (4·75-14·71)	9·79 (5·50-17·46)	10·37 (6·64-16·19)	9·60 (7·12-12·95)	12·10 (7·56-19·38)	20·32 (13·60-30·37)	21·3 (15·62-29·05)	18·19 (14·67-22·55)
2019-2020	3·03 (2·1-4·36)	1·79 (1·17-2·76)	0·74 (0·47-1·15)	1·45 (1·14-1·83)	14·90 (8·66-25·64)	21·24 (14·44-31·24)	12·65 (9·26-17·29)	15·06 (12·04-18·83)	24·32 (15·89-37·22)	46·16 (35·79-59·54)	27·2 (21·99-33·66)	31·25 (26·81-36·42)
Cohort												
Cohort A	2·92 (1·48-5·77)	2·45 (1·13-5·29)	0·72 (0·27-1·91)	1·71 (1·08-2·69)								
Cohort P without cohort A	3·30 (2·63-4·14)	1·57 (1·13-2·19)	0·64 (0·44-0·93)	1·54 (1·30-1·82)								

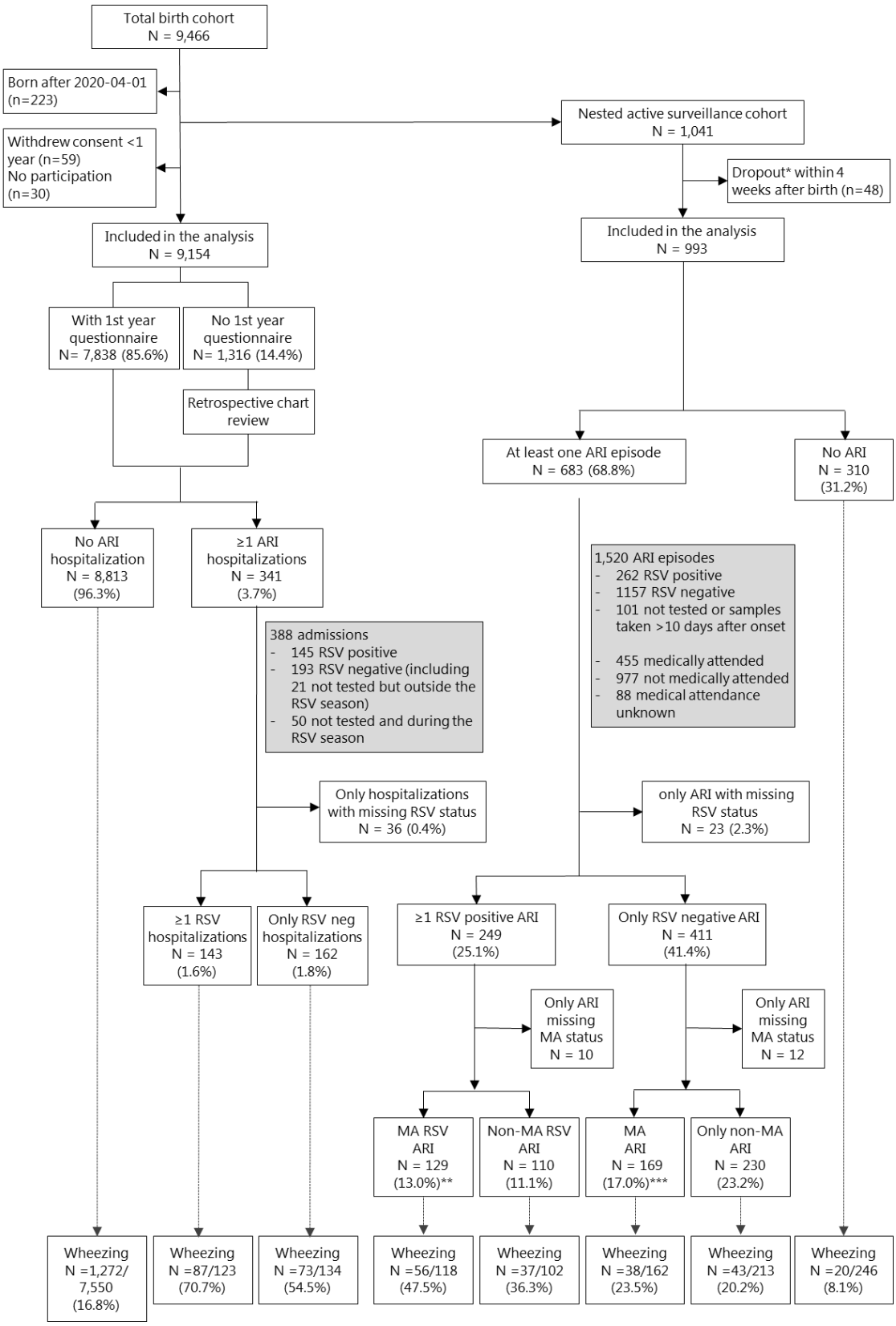
Sex												
Female	3·16 (2·31-4·32)	1·44 (0·9-2·3)	0·55 (0·32-0·93)	1·42 (1·13-1·8)	10·68 (6·45-17·71)	11·37 (6·94-18·63)	11·49 (8·07-16·37)	11·26 (8·77-14·46)	17·39 (11·66-25·92)	28·39 (20·73-38·89)	23·99 (18·8-30·61)	23·43 (19·71-27·84)
Male	3·38 (2·53-4·51)	1·89 (1·24-2·88)	0·74 (0·47-1·17)	1·69 (1·37-2·08)	12·65 (8·05-19·86)	18·82 (12·87-27·52)	10·09 (7·04-14·48)	12·92 (10·31-16·19)	17·73 (12·08-26·03)	34·16 (25·81-45·21)	21·72 (16·98-27·78)	23·82 (20·16-28·14)
Season of birth**												
Spring	0·47 (0·15-1·45)	0·77 (0·31-1·95)	1·02 (0·56-1·83)	0·82 (0·51-1·31)	0***	6·15 (2·45-15·4)	18·52 (12·77-26·86)	10·72 (7·60-15·12)	0***	16·71 (9·70-28·77)	42·87 (33·49-54·87)	25·43 (20·31-31·83)
Summer	1·55 (0·86-2·8)	4·24 (2·92-6·15)	0·29 (0·10-0·82)	1·6 (1·18-2·16)	8·17 (3·90-17·14)	36·82 (25·64-52·88)	2·03 (0·65-6·3)	12·32 (9·01-16·83)	14·99 (8·66-25·95)	78·13 (61·17-99·79)	4·92 (2·39-10·15)	25·81 (20·85-31·95)
Fall	8·53 (6·60-11·04)	1·35 (0·7-2·61)	0·17 (0·04-0·65)	2·57 (2·03-3·25)	31·56 (20·95-47·55)	11·37 (5·69-22·73)	1·48 (0·37-5·91)	11·55 (8·19-16·27)	46·95 (33·56-65·67)	17·83 (9·98-31·88)	4·22 (1·90-9·4)	18·41 (13·99-24·23)
Winter	2·03 (1·18-3·48)	0·15 (0·02-1·05)	1·17 (0·7-1·95)	1·13 (0·78-1·62)	7·23 (2·71-19·29)	0***	25·22 (17·4-36·55)	14·41 (10·17-20·41)	7·23 (2·71-19·29)	0***	46·33 (35·24-60·9)	24·97 (19·17-32·51)
Birthweight												
<2500 g	5·78 (1·86-17·91)	0***	0***	1·49 (0·48-4·63)	0***	38·45 (11·15-132·56)	6·94 (0·98-49·29)	13·42 (4·87-36·98)	0***	72·07 (30·01-173·09)	7·44 (1·05-52·97)	22·04 (9·96-48·75)
≥2500 g	3·18 (2·55-3·96)	1·69 (1·25-2·3)	0·66 (0·47-0·95)	1·55 (1·32-1·82)	12·04 (8·59-16·88)	14·72 (10·77-20·12)	10·94 (8·47-14·13)	12·16 (10·25-14·43)	18·1 (13·75-23·82)	30·54 (24·63-37·87)	23·17 (19·43-27·62)	23·73 (21·01-26·81)

* p<0·05 between groups, cohort P = passive surveillance cohort, cohort A = active surveillance cohort;

** season of birth was defined as follows: spring from March 21st to June 20th, summer from June 21st to September 20th, autumn from September 21st to December 20th, winter from December 21st to March 20th;

*** IR estimated as 0, 95% CI not determined because of 0 cases

Figure 1. Flow chart of participants in RESCEU birth cohort study for total cohort and active surveillance cohort.



Notes

Abbreviations; N= Number of infants

Wheezing: number of children with wheezing of total number of children with known wheezing status

* Dropout: did not continue with active surveillance

** Including 16 RSV admissions (also counted in RSV admissions)

*** Including 7 ARI admissions (also counted in RSV neg admission)

Figure 2. Number of all-cause and RSV-associated ARI by months for ARI (A), MA-ARI (B) and hospitalized ARI (C). Figure (A) and (B) are derived from the active surveillance cohort, figure (C) from the passive surveillance cohort.