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REGULAR ARTICLE

Incidence and risk factors of lower respiratory tract illnesses during infancy in a Mediterranean birth cohort

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Abstract

Aim: To investigate the incidence rate, viral respiratory agents and determinants of lower respiratory tract illnesses (LRTIs) in infants younger than 1 year.

Methods: A total of 487 infants were recruited at birth for the Asthma Multicenter Infant Cohort Study in Barcelona (Spain). Cases of LRTIs were ascertained through an active register including a home visit and viral test in nasal lavage specimens during the first year of life. Cotinine in cord blood, household aeroallergens, indoor NO_2 and maternal and neonatal IgE were measured. Other maternal and infants' characteristics were obtained from structured questionnaires.

Results: The incidence rate of at least one LRTI was 38.7 infants per 100 persons-years. The most frequently isolated viral agent was respiratory syncytial virus (44.7%). The risk of LRTIs was higher in infants with a maternal history of asthma and in those with siblings (OR = 2.4; 95% CI: 0.98–6.08 and OR = 1.8; 95% CI: 1.04–3.21, respectively). The risk of LRTIs was lower in infants who were breast fed for more than 12 weeks (OR = 0.26; 95% CI: 0.26–0.86) and in those from a low socioeconomic class (OR = 0.16; 95% CI: 0.06–0.42).

Conclusion: Viral LRTIs are frequent in infants younger than 1 year of age and there is an inter-relationship between maternal asthma, siblings, breast feeding and socioeconomic status.

INTRODUCTION

Acute illnesses of the respiratory tract are the most common diseases during childhood and most of them involve the upper respiratory tract. However, the incidence of lower respiratory tract illnesses (LRTIs) could be considerable, as well. In developed countries, a LRTI occurs in 20–39% of infants and children under 3 years of age (1–3). Moreover, LRTIs not only constitute a burden on health care costs (4), but are also a possible risk factor for developing asthma and allergy during early childhood (5) and may lead to chronic obstructive pulmonary disease in late adulthood (6).

Recent studies reporting incidence and risk factors for LRTIs in early infancy are based on hospitalized infants (7), on infants with a predisposition to allergy (8,9), on a particular type of LRTI (with or without wheezing) (10) or on a causal agent (such as respiratory syncytial virus [RSV]) (11).

The aim of the present study was to determine the incidence rate of LRTIs during infancy, identify viral respiratory agents and ascertain the association of LRTIs with different risk factors in a Mediterranean population.

Abbreviations

AMICS, asthma multicenter infant cohort study; *Der p1*, *Dermatophagoides pteronyssinus 1*; ETS: environmental tobacco smoke; *Fel d1*, *Felus domesticus 1*; LRTI, lower respiratory tract illness; NO_2, nitrogen dioxide; NO-LRTI, no lower respiratory tract illness; NPA, nasopharyngeal aspirate; RSV, respiratory syncytial virus; SES, socioeconomic status.

METHODS

Design and subjects

The Barcelona birth cohort consisted of 487 infants from the Asthma Multicenter Infant Cohort Study (AMICS). The AMICS study was designed to investigate the effects of several pre- and postnatal environmental exposures on the inception of atopy and asthma, and included four cohorts in different European countries. Mothers and their infants were recruited during the prenatal visit to the Hospital del Mar, Barcelona, Spain. Participants were invited to join the study if they anticipated living in the city during the study period and had a telephone. The clinical research ethics committee (CEIC-IMAS) approved the study protocol and mothers signed a written informed consent form. Data collection on LRTI was conducted between January 1996 and October 1999, when infants were recruited prenatally and followed up until they reached 1 year of age. Data on the presence of LRTI were obtained from two sources.

Diagnoses established by study paediatricians

On enrolment, the mother was instructed to contact the local 24-h coordinating centre if her infant developed relevant symptoms lasting at least two consecutive days

(runny nose, fever, dry cough, wet cough and difficulty breathing). Within 24 h, a home visit was arranged and infant visited by a study paediatrician. The event was classified as no LRTI (NO-LRTI) or LRTI. LRTI was further stratified according to the clinical features previously described (1) into laryngotracheobronchitis, bronchitis, bronchiolitis and pneumonia. A fifth diagnosis of non-specific LRTI was made when the infant could not be classified within the other four diagnoses (these infants often only had wheezing). A new LRTI was recorded if the infant was symptom free for at least 14 days between two episodes. A nasopharyngeal aspirate (NPA) sample was obtained only in infants with a LRTI diagnosed by the study paediatrician, instilling 2 mL of normal saline into the nasopharynx and aspirating with a sterile syringe. The NPA sample was preserved at 4°C in a sterile container for transport to the laboratory and was analysed within 4–8 h.

Diagnoses established by family paediatricians

During the follow-up, the mother was called every month by a nurse, who inquired whether the infant had been diagnosed with a LRTI during the previous month by the family paediatrician without the 24-h coordinating centre being informed. The occurrence of a LRTI was defined as a positive answer to the question, 'Has a doctor told you that your son/daughter has laryngotracheobronchitis, bronchitis, bronchiolitis, pneumonia or wheezing, since we spoke with you last?' A negative answer was registered as NO-LRTI.

Respiratory virus detection in NPA samples

NPA samples were analysed at a local virology research laboratory (Hospital Vall d'Hebron, Barcelona) and were classified as positive when a respiratory virus was identified by at least one of the following procedures:

- Rapid detection for RSV and coronavirus with direct fluorescent monoclonal antibodies (Bartels Immunodiagnostics Supplies, Inc., Bellevue, WA, USA).
- Virus culture in human epidermal carcinoma (HEp-2 line) and Madin–Darby canine kidney (MDCK) cells and indirect fluorescent antibody identification with a pool of monoclonal respiratory viral antibodies for RSV, adenovirus, influenza virus types A and B, and parainfluenza types 1, 2 and 3 (Bartels Immunodiagnostics Supplies, Inc.).
- Conventional tissue culture in HEp-2, MDCK and the LLC-MK2 line of rhesus monkey kidney cells for examination of the characteristic cytophatic effect.

Questionnaire information

At the first prenatal care visit to the hospital, usually during the third trimester of pregnancy, a detailed questionnaire including information on smoking habits, sociodemographic characteristics and parental history of asthma was completed. Social class was defined by paternal occupation using the UK Registrar General's 1990 classification, which groups people with similar levels of occupational skill.

Upon delivery, general information (gestational age, gender, weight, length and head circumference at birth) was recorded from medical files.

One year after birth, a total of 381 (82.5%) mothers were contacted for a structured telephonic interview to record the approximate frequency of respiratory symptoms such as wheezing, cough and noisy breathing in the preceding months caused by airway secretions, as well as information on the duration of breast feeding (regardless of whether other foods were given), number of siblings, day care attendance and parental smoking.

Exposure assessment

Specific IgE to *Dermatophagoides pteronyssinus* (*Der p1*) were determined in maternal blood samples (62.2%) obtained in the third trimester of pregnancy by the Pharmacia CAP System RAST-FEIA (Pharmacia, Freiburg, Germany) and total IgE levels in umbilical cord blood (85.4%) were determined by Pharmacia CAP System low-range FEIA (Pharmacia). Maternal atopy was defined by detectable serum levels (>0.35 UI/mL) of specific IgE to *Der p1* and elevated cord blood total IgE levels were defined at concentrations of >0.35 UI/mL.

Umbilical cord serum (75.1%) was analysed to determine cotinine concentration by radioimmunoassay as a biomarker of exposure to tobacco smoke during pregnancy. A cut-off of 1 ng/mL was used for cord serum cotinine to distinguish exposed from non-exposed mothers (12).

Dust samples and passive NO_2 filter badges (Toyo Roshi NO_2 filter badges, Tokyo, Japan) were collected 6 months after birth (78%). Concentrations of household dust mite (*Der p1*) and cat (*Felus domesticus* [*Fel d1*]) allergens were determined using an enzyme-linked immunoabsorbent assay according to standard procedures described elsewhere (13) and grouped in categories with potential relevance for sensitization to *Der p1* and *Fel d1* (>2 μg/g and >1 μg/g of dust, respectively) as reported in the international literature (14). Indoor NO_2 concentration was measured by colorimetric reaction and spectrophotometric analysis described previously (15).

Statistical analysis

The incidence rate was estimated by incidence density and calculated as I/PT, where I is the number of infants with at least one LRTI during the observation period, and PT is the amount of population time observed in the population during this period.

Chi-square tests were used to assess differences between infants with NO-LRTIs and LRTIs in maternal, neonatal and postnatal characteristics. Statistical significance was set at $p < 0.05$.

Multivariate logistic regression was used to evaluate associations between predictor variables and LRTIs. Variables were chosen for the multivariable model if they entered at a level of $p \leq 0.1$; odds ratios (OR) with 95% confidence intervals (95% CI) were estimated.

All analyses were performed using the Stata 7.0 statistical package (StataCorp, College Station, TX, USA).

RESULTS

Study population characteristics

More than half of the newborns (52.7%) were male. The mean maternal age was 29 years (SE: 5.4). The maternal ethnic distribution (74.9% Spanish vs. 25.1% non-Spanish) reflected the demographics of the population attending the Hospital del Mar. Socioeconomic status (SES) measured by paternal profession was broadly distributed as follows: 18.5% of fathers were in professional, managerial or technical occupations (classes I and II); 21.5% were in skilled non-manual occupations (class III, NM); 41.5% were in skilled manual (class III, M) occupations and 18.5% were in partly skilled or unskilled occupations (classes IV and V).

LRTI distribution and incidence rate

A total of 149 infants had at least one LRTI during the first year of life (Fig. 1). Of these, 106 infants (71.1%) had one LRTI and 43 (28.8%) had two or more other episodes of LRTI. The study paediatrician directly identified at least one LRTI in 99 infants (66.4%), and the monthly calls by the nurse identified retrospectively at least one LRTI in 50 infants (33.6%). The incidence rate of at least one LRTI was of 38.7 infants per 100 persons-years during the follow-up. The most frequent clinical diagnosis was bronchitis (Table 1).

Table 1 Distribution of lower respiratory tract illnesses (LRTIs) in infants based on diagnosing paediatrician

Distribution of LRTIs	LRTIs by study paediatricians (n = 99)* (%)‡	LRTIs by family paediatricians (n = 50)† (%)‡
Non-specific LRTIs	10	6
Pneumonia	6	10
Bronchitis	84	82
Bronchiolitis	17	10
Laringotracheobronchitis	5	4

*A total of 136 LRTI episodes in 99 infants.
†A total of 71 LRTI episodes in 50 infants.
‡Sum of percentages is not 100% because some infants could have had more than one LRTI during this period.

Clinical diagnosis in the infants with an NPA sample

Out of the 99 infants with an NPA sample, one virus was detected in 43 infants (43.4%) and two viruses were detected

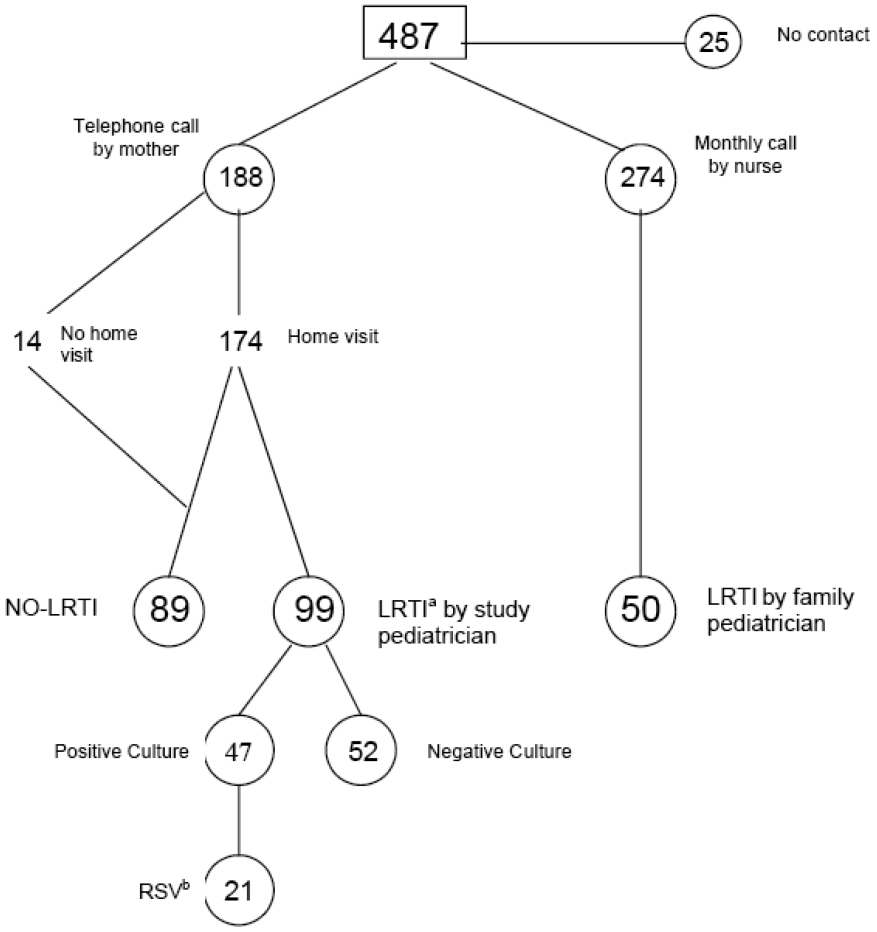

Figure 1 Recruitment and follow-up of infants in the birth cohort. [a]LRTI: lower respiratory tract illnesses; [b]RSV: respiratory syncytial virus.

in the same NPA sample in 4 infants (4.0%). The most commonly detected virus was RSV in 21 infants (44.7%). Adenovirus was detected in seven (14.9%), enterovirus in six (12.8%), influenza A in six (12.8%) and cytomegalovirus in five (10.6%). Other viruses identified in these infants were coronavirus in three (6.4%), parainfluenza in three (6.4%) and influenza B in two (4.3%).

The viral isolation rate in the 136 NPA samples was 50%. The viruses recovered from different respiratory syndromes are shown in Table S1 (in Supplementary material online). Pneumonia and bronchiolitis had a viral isolation rate of approximately 60%, RSV being the most commonly isolated virus. Laryngotracheobronchitis was caused mainly by the parainfluenza virus. Non-specific LRTIs were mainly caused by other viruses.

Respiratory symptoms during the first year of life

When examining the results of the structured telephonic interviews, no significant differences were found in the prevalence of respiratory symptoms reported by the mothers among infants with LRTIs and without LRTIs irrespective of the health professional making the diagnosis.

Determinants of LRTIs

There were no differences between the two groups (LRTI and NO-LRTI) with respect to the maternal age or maternal birth country (see Table S2 in Supplementary material online). LRTIs were less frequent in social classes IV and V, comprising skilled and unskilled occupations. A maternal history of asthma was more frequent in infants with LRTI.

The prevalence of mothers who smoked during pregnancy was very high not only in the NO-LRTI group (50%) but also in the LRTI group (44.2%). Indeed, more than 87% of the total number of infants had cotinine levels in cord blood above 1 ng/mL, suggesting exposure to tobacco smoke during fetal life.

Der p1 and *Fel d1* levels higher than the threshold for sensitization to allergens ($>2\,\mu$g/g and $>1\,\mu$g/g of dust, respectively) were less frequent among the LRTI group. No differences between groups were detected in indoor NO_2 levels.

Infants who were breast fed for more than 12 weeks showed a lower frequency of LRTI. The presence of one or more siblings was more frequent in the LRTI group; also, more children in this group attended day care centres compared to the NO-LRTI group; however, in this cohort, the difference did not reach statistical significance.

Multivariate analysis

In the multivariate model (see Table S3 in Supplementary material online), the risk of LRTIs was 2.4 times higher in infants with a maternal history of asthma (OR = 2.44; 95% CI: 0.98–6.08) and was 1.8 times higher (95% CI 1.04–3.21) in infants with siblings. The risk of LRTIs was lower among infants who were breast fed for more than 12 weeks (OR = 0.26; 95% CI: 0.26–0.86) and among those in social classes IV–V (OR = 0.16; 95% CI 0.06–0.42).

DISCUSSION

We present the first study in a Mediterranean area of infant outpatients with a prospective record of LRTIs, which includes an *ad hoc* register and laboratory diagnosis, and a wide record of possible risk factors. Maternal asthma as a risk factor for the development of LRTI in infants was found to be significant, as was the number of siblings. Breast-fed infants and those from a low social class had a lower risk of LRTIs.

LRTIs and viral agents

In our study, 38.7% infants had at least one LRTI during the first year of life while the incidence of LRTIs reported in other community-based longitudinal studies ranges from 20 to 32.9% (1–3). The higher percentage observed in this study may be the result of using both active follow-up of direct diagnosis and self-reporting.

The viral isolation rate in the NPA specimens (50%) was higher than those reported in other community-based studies (26–42.4%) (1,3,16), probably due to immediate specimen collection. However, the rate was lower than those in hospital-based studies (50–66.2%.) (17), probably because we had antigen tests only for RSV and coronaviruses and no PCR was available. When both antigen tests and PCR are used, the proportion of virus-positive cases is almost 100%.

Viral agents in the present cohort were identified in almost 60% of bronchiolitis and pneumonia episodes while only 47.1% of bronchitis episodes were positive. Virus-negative illnesses could be caused by other viruses not isolated in this study (i.e. the recently discovered metapneumovirus (18) or rhinoviruses (19) detected by the newer PCR techniques). Since both antigen tests for all respiratory viruses and PCR have been introduced, the proportion of virus identified has notably increased. At the follow-up of our cohort, new data about wheezing illnesses and its risk factors, as RSV, or other virus infections or environmental tobacco smoke exposure will be included.

The association between viral isolates and clinical diagnosis in this study was not statistically significant but the distribution was similar to that in other publications (1,2,20–23).

Determinants of LRTIs

Our finding that a maternal history of asthma was associated with LRTIs in infants is in agreement with data from other birth cohort (24). Over-reporting of asthmatic mothers is not a likely explanation, because the association in the current study was evaluated with medical diagnosis and not symptoms.

Similar to other studies (21) we found that the presence of siblings was a significant risk factor for LRTIs due to increased exposure to viral agents. However, unlike other authors (25), we found no significant differences between infants with LRTIs and NO-LRTIs with respect to the frequency of day care attendance. This may be due to the low attendance at day care before the first year of age in our

population (nearly 20% vs. more than 50% in the above-mentioned study).

Of note, nor household dust mite (*Der p1*) or cat (*Fel d1*) allergens higher than the threshold for sensitization were found to be associated with LRTIs. In contrast, it can be hypothesized that high *Der p1* and *Fel d1* levels were less frequent among the LRTI group due to more frequent cleaning in the houses of these infants, whose families were those with higher SES.

Breast feeding for more than 12 weeks was significantly associated with protection against LRTIs in our study, which is in agreement with other birth cohort studies (26) suggesting that specific nutritional, immunoregulatory and immunomodulatory factors in maternal milk may promote maturation of infant immune competence (27).

Our finding that the prevalence of LRTI was lower in infants with low SES than in those with high SES was unexpected. These results could be explained if families with low SES were less likely to call us and therefore would have diminished the frequency due to misclassification. However, the surveillance project designed a monthly call to reduce this effect. Studies describing the inverse relationship between SES and LRTIs provide limited information because only differences in mortality or hospitalization rates were examined (28). Recently, it has been suggested that the relationship between SES and physical health may not be constant across ages. In a cross-sectional interview about acute respiratory conditions in infants and children aged 0–18, a reverse SES gradient was found in early years (low SES – low frequency of respiratory illnesses), whereas an expected SES gradient appeared during adolescence (low SES – high frequency of respiratory illnesses) (29).

Interestingly, in our study cohort, no association between exposure to tobacco smoke and LRTIs was demonstrated, just the fact that nearly all infants were prenatally and postnatally exposed. Indeed, cord serum cotinine concentrations were higher than those in other European birth cohorts (12,30) and the percentage of self-reported postnatal parental smoke was extremely high.

In conclusion, our study highlights important risk factors such as maternal asthma, the number of siblings and SES for the development of LRTIs in infants from a Mediterranean area.

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Supplementary material

The following supplementary material is available for this article:

Table S1 Viruses detected in 136 nasopharyngeal aspirate samples from 99 infants, according to clinical diagnosis.
Table S2 Distribution (%) of study variables according to the presence or absence of lower respiratory tract illness (LRTI).
Table S3 Multivariate association (odds ratio and 95% CI) of study variables with lower respiratory tract illnesses (LRTI) in comparison with NO-LRTI.

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