

Consumption of asthma medication after RS-virus epidemic – A population based survey

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It has been suggested that a respiratory syncytial virus (RSV) infection in infancy increases the likelihood of development of asthma in childhood. The RSV epidemics have a special 2-yr pattern in Finland and this allows the evaluation of the association of RSV and asthma by epidemiological means. We evaluated whether being 0–6 months of age during an RSV epidemic has an impact on the use of asthma medication later in the childhood. The consumption of asthma medication at the age of 3–16 yr and the number of those entitled to special reimbursement for asthma medication were identified for a total of 637,922 children. These subjects were grouped in cohorts according to whether they had been aged 0–6 months (exposed) or not (unexposed) during an RSV epidemic. The means of the proportions taking asthma medication and of those receiving reimbursement were calculated for each cohort. The means of the proportions in the unexposed vs. exposed cohorts were 20.5% vs. 20.3% for consumption and 4.8% vs. 4.9% for reimbursement. These differences were insignificant. In conclusion exposure to a RSV epidemic in infancy does not increase the consumption of asthma medicines at the population level.

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Respiratory syncytial virus (RSV) is a common cause of respiratory tract infections in infants, and the infection rate is high during epidemics (1). Several follow-up studies have indicated that there is a causal relationship between RSV bronchiolitis in infancy and the subsequent development of asthma (2–7). A possible mechanism for the increased risk of asthma might be a permanent immunomodulatory effect induced by the virus during the first 6 months of life, which is considered a critical period for the development of immune responses (8–10). Another possibility is that the immunomodulatory effects of RSV infection may be transient and the infection picks out those individuals who would anyway develop asthma later in childhood. In one large cohort survey, the risk of recurrent wheezing up to 6 yr of age increased after an

RSV infection but disappeared by the age of 13 (11). We have found recently that those who had RSV bronchiolitis in infancy had less allergic sensitization at 8 yr of age than their controls (12).

There is a special 2-yr epidemiological pattern in RSV epidemics in Finland (13) which offers a special opportunity to compare children who are 0–6 months old in same calendar months with and without RSV exposure. As drug sales and reimbursements for medication are centrally registered, we were able to analyze the impact of RSV exposure at the population level in the whole country from the sales of asthma medicines. We hypothesized that if RSV was able to modulate the development of immune responses permanently in favor of asthma to a significant extent, a high seasonal exposure would be reflected in

increased use of asthma medication and the prevalence of diagnosed asthma later in childhood as measured by the reimbursement rate.

Methods

Each person in Finland is registered at birth with a unique social insurance identification (ID) in a database maintained by the Social Insurance Institution. The same institution also records the total sales of prescription-only and over-the-counter medicines at pharmacies throughout the country. Prescription-only medicines are recorded against the ID of the patient, and data on those receiving a special reimbursement of 75% of the costs of asthma medication are also available. To receive this reimbursement, a patient must apply for it by presenting a physician's certificate confirming the diagnosis and the severity of asthma. Total sales data are available from 1995 onwards, and data of those receiving a special reimbursement for asthma medication costs are available from 1977.

Monthly data on RS-virus epidemics was obtained from the Department of Virology, University of Turku, which supplies laboratory services throughout the country (Fig. 1) (13). These data are available from 1979 onwards.

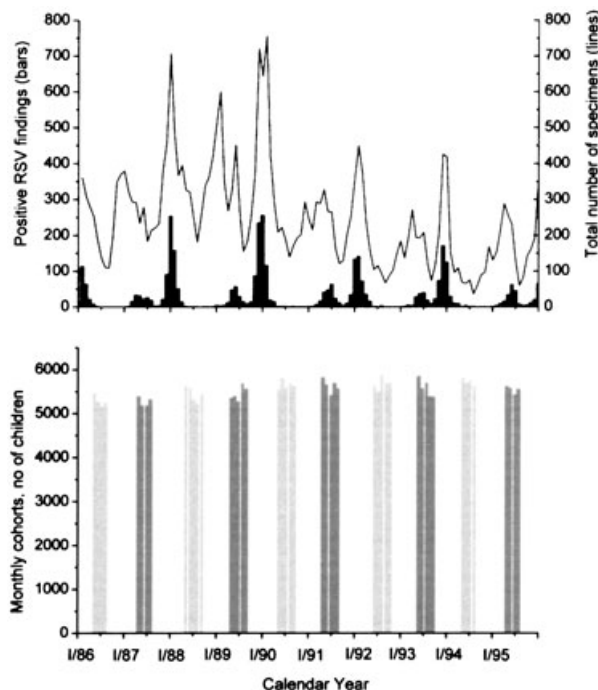


Fig. 1. Respiratory syncytial virus (RSV) epidemics in Finland, total number of specimens during the years 1986–1995 and division of the child cohorts into those exposed or unexposed to RSV at an age younger than 6 months of age. Exposed cases are represented by dark grey bars and unexposed ones by light grey bars.

From January 1986 to December 1995, a total of 29,998 respiratory tract specimens were tested by antigen detection, 3396 specimens from 3249 patients being positive for RSV. The total number of RSV-positive patients during that time was 3351 when diagnoses made by serology and viral culture are included. An indirect enzyme immunoassay was used for antigen detection in 1986 and a direct time-resolved fluoroimmunoassay from January 1987 onwards.

Numbers of children born in Finland in 1986–1995 were obtained from the Population Register Center at Statistics Finland and data of all purchases of asthma medicines and the granting of reimbursements for asthma medication for each individual were obtained from the Social Insurance Institution. Altogether 637,922 children were born in Finland in 1986–1995. The number of patients for whom prescription-only asthma medicines were purchased between 1995 and 2002 at an age older than 3 yr was 133,119. Of these, 12,293 were entitled to a special reimbursement for asthma medication costs.

Study design

The children born in 1986–1995 were arranged in cohorts according to their month and year of birth and the proportions of those who had received asthma medications (Anatomic Therapeutic Chemical code R03 in the register) in 1995–2002 were calculated. The consumption of asthma medication under the age 3 yr was ignored because we wanted to exclude the effect of bronchiolitis or wheezy bronchitis. The child cohorts were grouped according to whether or not they were exposed to an RSV epidemic at the critical age for the development of immune responses (0–6 months of age). The total number of monthly birth cohorts was 120 among which there were more exposed cohorts ($n = 97$) than unexposed ($n = 23$). We chose to make the comparison by calendar months (January vs. January etc.) because of the monthly variation in the purchase of asthma medicines, and to control the birth month of the study population, we included 23 pairs of cohorts in the final analysis (Fig. 2). These 46 child cohorts included 126,303 children who had been exposed to RSV and 127,555 who had not. The numbers receiving reimbursement on account of asthma were 6273 of those exposed and 6020 of the unexposed controls (Fig. 2).

Statistical analysis

We compared the means of the proportions receiving reimbursement or consuming asthma

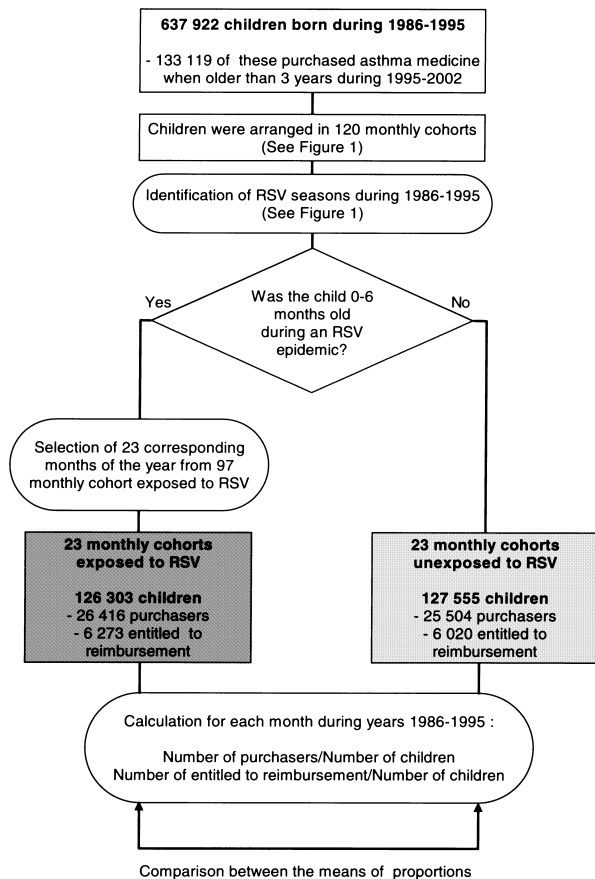


Fig. 2. Study profile.

medications in the child cohorts by analysis of covariance adjusted for time, because of the trend for an annual increase in the use of asthma medication. Likewise, the adjusted mean number of purchased packages of inhaled corticosteroids and β_2 -agonists per child was compared between the exposed and unexposed cohorts. The results are presented as differences in the adjusted means of proportions and in the adjusted mean number of packages and 95% confidence intervals (CI) for the differences. The data were analyzed using SPSS (Chicago, IL, USA) for Windows, version 12.0.1.

Results

We found no difference in the adjusted means of the proportions of children consuming asthma medication between the unexposed and exposed cohorts [20.5% vs. 20.3%; difference 0.2% (95% CI for difference: -1.2, 1.5); $p = 0.8$] (Fig. 3a). The adjusted mean number of packages of inhaled corticosteroids purchased per child was 12.7 vs. 12.4 packages in the unexposed and exposed groups, respectively [difference 0.2 (95% CI: -0.4, 0.9); $p = 0.5$] and the corresponding figures

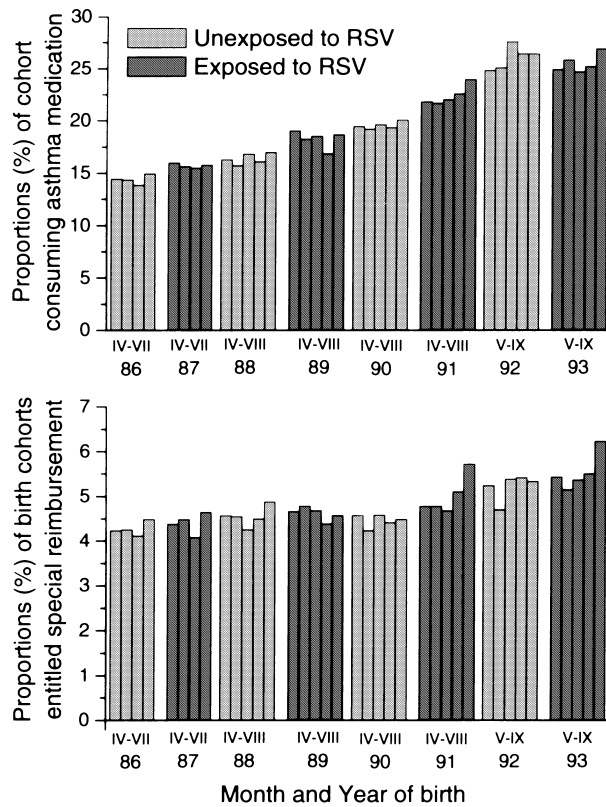


Fig. 3. (a) Proportions of the paired child cohorts consuming asthma medication, and (b) proportions of the child cohorts entitled to special reimbursement for asthma medication costs, grouped as exposed or unexposed to respiratory syncytial virus epidemics in the years in question. Roman numerals on the bars refer to months of the year (i.e., I = January etc.).

for inhaled β_2 -agonists were 4.6 vs. 4.5 [difference 0.1 (95% CI for difference: -0.1, 0.4); $p = 0.4$].

The adjusted means of the proportions of the unexposed and exposed children who received special reimbursement for asthma medications were 4.8% and 4.9% [difference -0.1% (95% CI for difference: -0.3, 0.1); $p = 0.2$] (Fig. 3b). As an overall change in the use of asthma medicines, we found an approximately 1.5-fold increase in purchases from 1995 to 2002.

Discussion

In this ecological survey the purchase of asthma medicines among children who were exposed to an RS-virus epidemic early in their life was of the same magnitude as among those not exposed. There were no differences between the exposed and unexposed cohorts in the amounts of inhaled corticosteroids or β_2 -agonists purchased, these being the most frequently prescribed asthma medicines in Finland. If exposure to RSV in infancy were an important risk factor for the

development of asthma or asthma-like symptoms, it should have been reflected in an increase in the consumption of asthma medication at the population level. All the asthmatics who required continuous medication would have been included in the special reimbursement data, because the costs of regular asthma medication are high and special reimbursement allows a 75% discount. Special reimbursement for asthma medication costs did not differ between the exposed and unexposed children, however. These results may indicate that the exposure to RSV in infancy most probably does not affect the clinical severity of asthma in the childhood.

Asthma is an immune-mediated disease, and the development towards an allergic phenotype takes place mainly during the first year of life, the first 6 months being considered the most important period (14, 15). We thus wanted to evaluate the effect of the exposure to an RSV epidemic in particular on infants under 6 months of age. The link between RSV and asthma is thought to imply damage to local immunity caused by the virus and the subsequent imbalance between Th1/Th2 lymphocyte subpopulations (16, 17). It has been shown in clinical studies that RSV bronchiolitis often precedes recurrent wheezing during childhood (2, 3, 5, 18–20). In a case-control study with 47 subjects who were hospitalized for RSV bronchiolitis under the age of 6 months the frequency of asthma and allergy was still higher in the subjects at the age 13 yr (21). Yet recent data suggests that an RSV infection merely increases the risk of asthma-like symptoms up to the age of 6 yr but not that of atopic asthma lasting into adolescence (11). This is supported by our present results, which show that RSV epidemics had no impact on the purchase of asthma medicines at the population level in the age group of 3–16 yr. Similarly we have found earlier that children who had been hospitalized because of RSV bronchiolitis in infancy had more asthma under the age of 3 yr. But at the age of 8 yr the rates of asthma did not differ and they had less atopic sensitization than their age- and sex-matched controls (12).

During an RSV-epidemic more than two-thirds of infants under 12 months of age will catch the infection and virtually all children will be infected at least once by 24 months of age (1). Thus, if an RSV infection in infancy were to lead to asthma, this should be seen in the use of asthma medication at the population level, because the infection is so common. The epidemiology of RSV in Finland, with its 2-yr pattern, is well established as we have already

had a systematic monthly follow-up of viral infections since 1979 (22, 23). The specimens are collected mainly from hospitalized children in pediatric and infectious disease clinics, mostly (61%) in the south western part of the country, the region served by Turku University Hospital, with a population of about 1 million. The rest were from other regions of Finland up to the northernmost central hospital in Rovaniemi on the Arctic Circle. From these data we were able to identify the times when exposure to RSV was most probable. The results of this ecological survey do not support the hypothesis that RSV is capable of permanently modulating the immune system towards asthma if exposure has taken place before 6 months of age.

Inhaled asthma medication is the recommended form in Finland even for young children. Systemic steroids are being rarely prescribed for children, so that our data on the consumption of inhaled anti-inflammatory treatment covers most of the children for whom anti-inflammatory asthma medication was prescribed. Annual sales of asthma medicines to children born between 1986 and 1995 increased by approximately 1.5-fold overall from 1995 to 2002, mostly reflecting changes in the policies of treating asthma and asthma-like symptoms, and also the availability of better asthma medicines and devices for children. Asthma-like symptoms, especially together with acute respiratory viral infections, are common in infancy, but a remission in these recurrent obstructive symptoms is seen in most of the children after 3 yr of age (24, 25). According to the current guidelines for well-controlled asthma, the use of β_2 -agonists should not exceed two packages per year (26). In our survey, the number of packages of inhaled corticosteroids was higher than that of β_2 -agonists which indicates that the treatment of asthma in children is in accordance with current guidelines (27).

We conclude that the exposure to an RSV epidemic in early infancy does not increase the proportion of those who consume asthma medication later in childhood. As the proportions of those receiving special reimbursement for asthma medication costs were the same in the exposed and unexposed children, such an epidemic seems not to have any clinically significant impact on the severity of asthma.

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