Persistence of upper respiratory tract infections in a cohort followed from childhood to adulthood

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Objective. To assess (1) prevalences of recurrent URTIs (rURTIs) and relapsing/persistent rURTIs and associated medical consumption between 0 and 21 years of age and (2) whether rURTIs experienced in early life predispose to upper airway disease later in life.

Methods. A cohort of all children born in Nijmegen, The Netherlands, between September 1982 and September 1983, was assessed repeatedly from 2 to 21 years of age with questionnaires regarding infections of the upper respiratory tract (URTIs), use of antibiotics, ENT operations and known risk factors for URTIs.

Results. One hundred and sixty-one of the 693 cohort member (23%) suffered from relapsing rURTIs between 0 and 21 years of age, whereas only 7 (1%) suffered from persistent rURTIs throughout this period. Two hundred and six (30%) had used antibiotics more than once; and 220 (32%) had undergone at least one ENT operation. Of the 166 participants with rURTI between 8 and 21 years, 140 (84%) had had rURTI before.

Conclusions. rURTIs are highly prevalent throughout early life and associated medical consumption is substantial. The challenge therefore is to develop therapeutic/preventive strategies that will prevent rURTIs in the first years of life.

Keywords. Upper respiratory tract infections, cohort, antibiotics, ENT operations

Introduction

Infections of the upper respiratory tract (URTIs), presenting as the common cold, rhinosinusitis, tonsillopharyngitis or otitis media are highly prevalent among young children.1–3 These infections not only have an impact on children's health and well-being, but also generate high medical costs and indirect costs for the family and the society.4,5 Children experience, on average, 4–6 URTIs per year.6 When they grow older, the incidence of these infections decreases, probably as a result of a more mature immune defence and improved anatomical conditions, for instance, of the Eustachian tube. A subgroup of children, however, will develop persistent URTIs.

Population studies have provided important information on the epidemiology of URTIs in children. Little is known, however, about its persistence through adolescence since most of these studies have focused on the period between 0 and 6 years of life and follow-up was restricted to a few years.1,2,7 For example, it is unknown whether recurrent URTIs (rURTIs) experienced in early life tend to persist through adolescence and whether rURTIs in adulthood are related to recurrent infections earlier in life.

In a large prospective population-based cohort of Dutch children followed from 2–21 years of age, we assessed (1) prevalences of rURTIs and relapsing/persistent rURTIs and associated medical consumption between 0 and 21 years of age and (2) whether
rURTIs experienced in early life tend to persist through adolescence.

Methods

Participants
The study members were part of a cohort of 1439 children born in Nijmegen, The Netherlands, between September 1982 and September 1983. Of these children, 1328 participated in the first assessment at 2 years of age, including the history of upper respiratory tract infections and medical consumption (i.e. use of antibiotics due to URTIs and ENT operations) in the first 2 years of life.

Between ages 2 and 4 years, children were visited at home every 3 months by a trained study nurse. At each visit upper respiratory tract infections during the previous 3 months were documented and tympanometry was performed. At the age of 8 years children were re-evaluated and a history of upper respiratory disease experienced between 4 and 8 years was taken. At 21 years of age, the home addresses of the cohort members were traced via the City Council of Nijmegen and a standardized respiratory disease questionnaire (covering the period between 8 and 21 years of age) was sent. The study was approved by the medical ethical committee of the University Medical Center, Utrecht.

Outcome measurements
Recurrent infections of the upper respiratory tract before the age of 2 years (rURT1o–2) were defined as the occurrence of four or more ear infections (otalgia with fever and/or otorrhoea) and/or four or more throat infections over that period and/or six or more common colds in the past 12 months.

At ages 2–4 years, the number of 3-monthly episodes in which the child had experienced an upper respiratory tract infection was counted. Recurrent infections of the upper respiratory tract (rURT1–2) were defined as at least four 3-monthly episodes with an ear infection and/or throat infections and/or at least six episodes with a severe common cold. Recurrent infections of the upper respiratory tract between ages 4 and 8 years (rURT4–8) were defined as the occurrence of four or more ear infections and/or four or more throat infections and/or six or more severe common colds.

Recurrent infections of the upper respiratory tract between ages 8 and 21 years (rURT8–21) were defined as the occurrence of four or more ear infections and/or four or more throat infections and/or six or more episodes of common cold or flu like symptoms with fever and/or four or more episodes of sinusitis.

The cut-off points for recurrent infections of the upper respiratory tract were predetermined at the 75th-percentile of the distribution of each infection at each assessment.

Antibiotic treatment for upper respiratory tract infections before the age of 2 years, between ages 2 and 4, 4 and 8, and 8 and 21 years, was defined as at least one course of antibiotics in the corresponding periods. ENT surgery—insertion of tympanostomy tubes, adenoidectomy, tonsillectomy, or any other ENT operation—was documented for the same periods.

Relapsing rURTIs was defined as two or more assessments with rURTIs between 0 and 21 years of age, whereas persistent rURTIs was defined as rURTIs at all four assessments.

Statistical analyses
The characteristics of the study members, prevalences of rURTIs between 0 and 2, 2 and 4, 4 and 8, and 8 and 21 years of life, relapsing/persistent rURTIs, antibiotic use and ENT surgery were described with summary statistics. The data were analysed with SAS version 8.0 (SAS Institute, Cary, NC, USA).

Results

Study sample
At the age of 2 years, 1328 children of the birth cohort participated, at 2–4 years from 1321 (99%), at 8 years 1006 children (76%), and at 21 years 693 (52%) study members completed the questionnaires (Fig. 1).
Representativeness of the sample

There were no significant differences in sex, history of breast feeding, family size, day care attendance, parental smoking habits, maternal educational level and, most important, the number of recurrent upper respiratory tract infections in the first 2 years of life between the 693 study members followed through 21 years of life and the original cohort of 1328 children (Table 1). The most important reason for loss to follow-up was that study members had moved and could not be traced.

Infections of the upper respiratory tract

By the age of 21 years, 67% of the study members had experienced rURTIs during at least one of the study periods; 23% had suffered from relapsing rUTRI and 1% from persistent rURTIs (Table 2).

Figure 2 shows the course of rURTIs between 0 and 21 years of age. One hundred and eighty-five (33%) cohort members reported no rURTIs at all and 26 (5%) had rURTIs between 8 and 21 years without having suffered from such infections at an early age.

Antibiotic prescription

By the age of 21 years, 68% of the study members had been treated with antibiotics for upper respiratory tract infections in at least one age period and 30% had used antibiotics twice or more (Table 2).

ENT surgery

By the age of 21 years, 32% of the study members had undergone at least one ENT operation and 14% had undergone two or more ENT operations. Adenoidectomy and the insertion of tympanostomy tubes were the operations most often performed.

Discussion

We found that in an unselected Dutch birth cohort followed up to 21 years of age, 23% of the participants suffered from relapsing/persistent rURTIs through these ages. About 30% received antibiotics for this indication more than once and the same proportion underwent an ENT operation. Incidence of rURTIs was highest (43%) between ages 2 and 4 years. Of the 166 participants with rURTIs between 8 and 21 years, 140 (84%) had had rURTIs before.

Although high prevalences of URTIs during early childhood have been reported before, no one has followed its natural course into adulthood. Such information is essential to understand the consequences of these infections in early life regarding upper airway disease and associated medical consumption later in life. This information might also give clues for developing more effective therapeutic and preventive strategies. One in three members of the birth cohort had received antibiotics for upper respiratory tract infections repeatedly. This indicates that, even in The Netherlands, where a restrictive use of antibiotics has been practiced for several decades, URTIs account...
for a sizable proportion of total antibiotic prescription. Similarly, one in three study members had undergone ENT surgery, reflecting high expectations of doctors and patients regarding surgical management of URTIs in The Netherlands.\textsuperscript{11,12} Surgical rates may be slightly larger than in the population at large, since all cohort members had undergone regular ENT examinations, specifically for otitis media with effusion, a condition that often remains unnoticed unless actively screened for.

The major strength of our study is the prospective design and the long follow-up period, i.e. from 0 to 21 years of age. Only 693 of the original 1328 study members, however, were evaluated up to 21 years of age and could be included in the final analysis. This could have caused a bias if the study members who were lost to follow-up formed a selective group, e.g. if study members with rURTIs had been most motivated to attend the follow-up visits. This might have resulted in an overestimation of the prevalence of relapsing/persistent rURTIs and associated medical consumption. The most important reason for loss to follow-up, however, was that a study member could not be traced because he or she had moved. Moreover, a comparison of the baseline characteristics of the study members with complete data and those of the original cohort showed no difference between both groups. We therefore believe that selection bias was minimal.

Some further limitations deserve to be mentioned
First, we have not taken into account seasonal factors in our analyses, whereas it is known that the time of year a questionnaire is administered is important with respect to URTIs (http://www.hpa.org.uk/infections/topics_az/primary_care_surveillance/RCGP.htm).\textsuperscript{13,14} However, as our study is a birth cohort study in which the participants were seen at scheduled follow-up visits, all seasons are represented so that information bias due to a seasonal effect will be minimal.

Second, information on infections of the upper respiratory tract and related environmental factors were based on parental and self-report at ages 2, between 2 and 4, and at 8 and 21 years. It is possible that this information was not accurate enough and therefore some misclassification regarding URTIs cannot be excluded. For example, parents of children with frequent infections at an early stage may be more vigilant for these infections later in life.

Third, experimental studies have shown that many upper respiratory tract infections in children go unnoticed. Some authors therefore claim that these kind of epidemiological studies underestimate the true frequency of affected individuals in the population.\textsuperscript{15} However, if parents do not recall certain infections of the upper respiratory tract, they are most likely to be mild and therefore less relevant. More importantly, we have avoided the problem of consultation bias, i.e. some

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{flowchart.png}
\caption{Flow chart of the course of recurrent upper respiratory tract infections between 0 and 21 years of age. N.B.: The numbers do not add to 693 due to missing values with respect to rURTIs at each assessment}
\end{figure}

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Recurrent upper respiratory tract infections} & \textbf{< 2 years of age} & \textbf{2 to 4 years of age} \\
\hline
Yes & 108 (16%) & 20 (4%) \\
No & 44 (7%) & 34 (6%) \\
\hline
Yes & 58 (9%) & 13 (2%) \\
No & 25 (4%) & 35 (6%) \\
\hline
Yes & 215 (35%) & 75 (13%) \\
No & 106 (17%) & 124 (22%) \\
\hline
Yes & 108 (17%) & 59 (11%) \\
No & 36 (6%) & 211 (38%) \\
\hline
\end{tabular}
\end{table}
parents never visit a doctor for an URTI, whereas others bring their child to the GP for minor reasons. We therefore believe that the data of our study do provide the useful clinical information to doctors involved in the care of children with upper respiratory disease.

In summary, rURTIs are highly prevalent, especially between 2 and 4 years and associated medical consumption is substantial. The challenge therefore is to develop therapeutic and preventive strategies that will prevent rURTIs in the first years of life.

Declaration

Competing interest: none declared.

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Ethics approval: The study was approved by the medical ethical committee of the University Medical Center Utrecht.

References