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Previous respiratory tract infections and antibiotic consumption in children with long- and short-term carriage of penicillin-resistant *Streptococcus pneumoniae*

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SUMMARY

Previous respiratory tract infections (RTI) and antibiotics consumption as possible risk factors for extended duration of PRP carriage were investigated in 24 children (cases) with previous carriage of penicillin-resistant pneumococci (PRP) for a duration exceeding 120 days (median 168 days) and a control group of 53 children with a duration of PRP carriage less than 90 days (median 21 days). The cases had experienced 0·99 episodes of acute otitis media (AOM) per life-year compared to 0·79 episodes in the controls ($P = 0{\cdot}32$). For antibiotic-treated RTI other than AOM, the corresponding numbers were 0·49 and 0·29 episodes per life-year, respectively ($P = 0{\cdot}01$). No differences in antibiotic consumption in the 3 months preceding the carriage, nor during the carriage period were noted. Other factors than impaired host defence to respiratory tract pathogens or antibiotics consumption seem to be more important in determining the duration of PRP carriage.

INTRODUCTION

During the last 20 years emergence and spread of penicillin-resistant and multiply antibiotic-resistant *Streptococcus pneumoniae* have become an increasing world-wide problem [1]. Young age is a significant risk factor for infection with antibiotic-resistant pneumococci [2, 3], and epidemic spread of these bacteria have been noted in several outbreaks in day-care settings [4, 5]. A significant number of small children are asymptomatic carriers of *S. pneumoniae* [6, 7], and these children may act as a reservoir and source of spread of susceptible as well as antibiotic-resistant pneumococci.

As part of the South Swedish Pneumococcal Intervention Project, we have previously studied the duration of nasopharyngeal carriage of penicillin-resistant pneumococci with MICs to benzyl penicillin $\geqslant 0{\cdot}5$ mg/l (PRP) in 678 individuals (mostly pre-school age children) [8]. In this study the median duration of carriage was 19 (range 3–267) days. Significant risk factors for extended duration of PRP carriage were young age, carriage during the winter months (October–March), a history of acute otitis media (AOM) before the age of 1 year, and a history of more than six episodes of AOM. No differences in duration of carriage were noted between the sexes, between strains with different levels of MICs to penicillin, or serogroups (after adjusting for age). The study data on previous infections in the carriers were collected from questionnaires answered by the patients/parents, and no details from the medical records of each child were available to us. The present study was undertaken in order to further assess the possible importance of increased susceptibility to respiratory tract pathogens and antibiotics consumption as risk factors for extended PRP carriage.

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METHODS

The South Swedish Pneumococcal Intervention Project

This project was initiated by regional health authorities in early 1995 as a set of public health actions in response to an increasing prevalence of PRP in southern Sweden during the early years of the 1990s [9, 10]. Shortly, all patients living in Malmöhus county in the southernmost part of Sweden (817000 inhabitants), with a nasopharyngeal culture yielding PRP (MICs to benzyl penicillin $\geqslant 0{\cdot}5$ mg/l) are directly reported from the three bacteriology laboratories in the county to the regional Centre of Communicable Disease Control in Malmö. According to present guidelines, nasopharyngeal specimen is obtained from patients (mostly children) with recurrent otitis media and failure of initial antibiotic treatment of acute otitis media. The 0·5 mg/l limit was chosen in order to have a margin to the highly resistant strains (MIC $\geqslant$ 2·0 mg/l), and strains with MIC $\geqslant 0{\cdot}5$ mg/l are also notifiable by Swedish law since January 1996. Contact is then established with the local primary health care centres and the patients are followed with weekly nasopharyngeal cultures until they have produced two consecutive cultures, yielding no growth of PRP (PRP-negative).

Nasopharyngeal cultures are obtained from family members and other close contacts of the index patients. All health-care contacts due to the PRPs are free of charge for the patients. If the index case is a child attending any form of group day-care, nasopharyngeal cultures are also obtained from the other children and staff. All pre-school children carrying PRP are denied attendance at regular day-care until they are PRP-negative. If alternative day-care could not be arranged, parents staying home to take care of their PRP-carrying children are reimbursed through the social security system. School children and adults carrying PRP are advised to stay home when having ongoing respiratory tract infection (RTI). The parents of PRP-carrying children are instructed to have them avoid in-door contacts with other small children and elderly people. Antibiotic treatment of a long-term carrier is considered when the duration of carriage has exceeded 2–3 months [11]. The handling of nasopharyngeal samples and bacteriology have been described previously [8, 11].

Patients

During the period January 1995–March 1997, data on the duration of PRP carriage was collected for 713 children, 6 years of age or younger. These children had all been subjected to the preventive measures of the intervention project, and followed with weekly nasopharyngeal cultures, until two consecutive nasopharyngeal specimen were negative for PRP. The duration of carriage was defined as the time period from the day of the first PRP-positive culture to the day of the first of the two consecutive PRP-negative cultures.

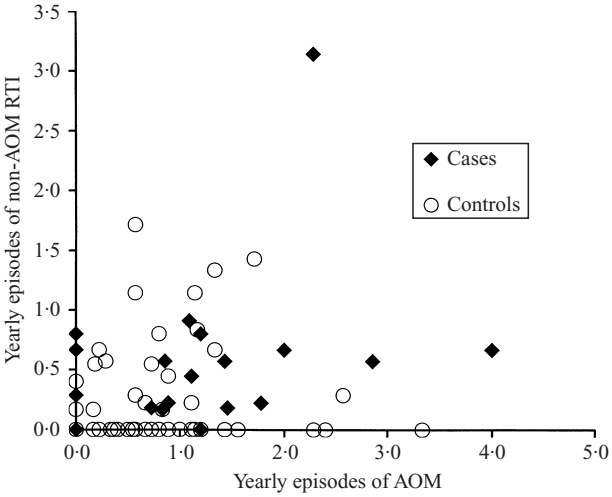

Fig. 1. Average episodes of acute otitis media per year of life in 24 long-term carriers of penicillin-resistant pneumococci (cases) and 53 short-term carriers (controls).

Thirty-eight of the children were 'long-term carriers', with a recorded duration of carriage longer than 120 days, while 647 of the children had carried PRP shorter than 90 days ('short-term carriers'). The parents of all long-term carriers and 80 randomly selected short-term carriers were contacted during the spring of 1997, and asked to have their children included in the study. Twenty-four long-term carriers (cases) and 53 short-term carriers (controls) were included in the study. The cases (8 months–6 years old, mean age 3·2 years at the time of the inclusion in the study) had a median duration of PRP carriage of 168 (range 121–356) days, and the controls (18 months–6 years old, mean age 4·3 years) a median duration of PRP carriage of 21 (range 5–83) days.

Study design

The parents of all study subjects were interviewed, and asked questions about history of AOM and other RTI, before, during and after the PRP carriage. Copies of medical records from consultations due to RTI were obtained and date of infection, diagnosis

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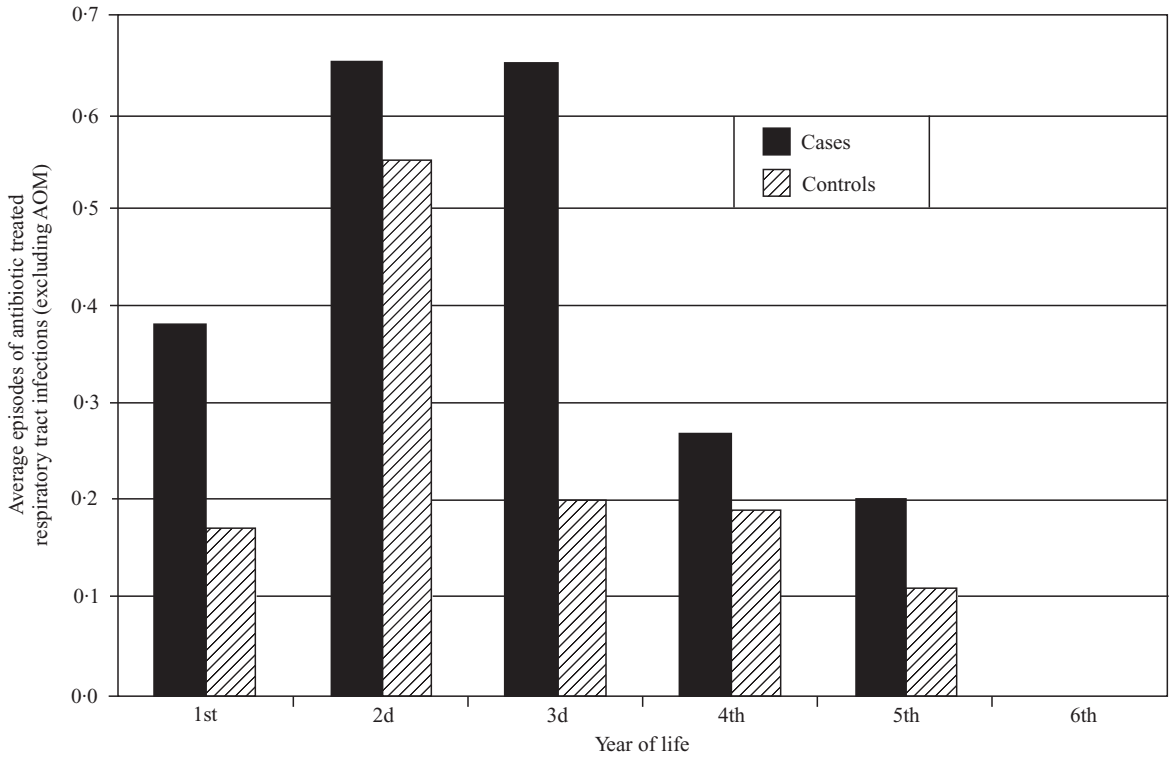

Fig. 2. Average episodes of antibiotic treated respiratory tract infections (other than acute otitis media) per year of life in 24 long-term carriers of penicillin-resistant pneumococci (cases) and 53 short-term carriers (controls).

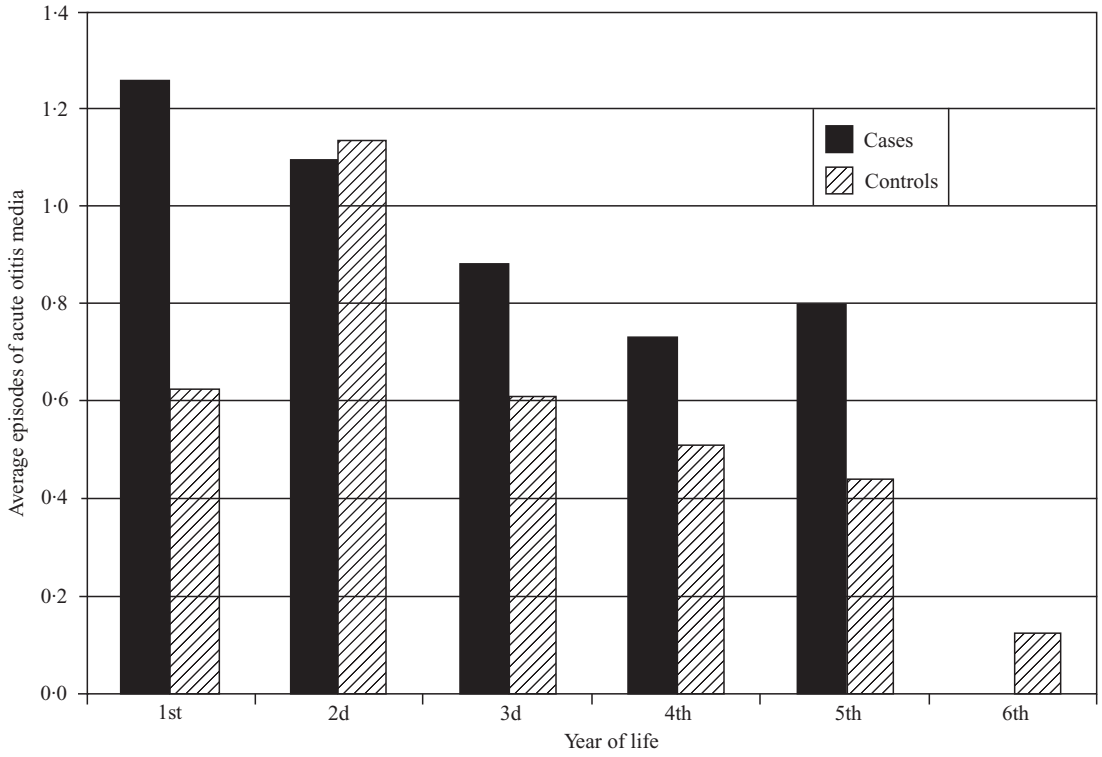

Fig. 3. Average yearly episodes of acute otitis media (AOM) in relation to average yearly episodes of antibiotic treated non-AOM respiratory tract infections (non-AOM RTI) in 24 long-term carriers of penicillin-resistant pneumococci (cases) and 53 short-term carriers (controls).

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and antibiotic treatment were recorded. Only antibiotic-treated RTI were considered. Group-wise differences were analysed using the Mann–Whitney *U*-test and the χ^2 test. The numbers of infections per life-year were calculated, and sub-analyses were performed for each year of life. Informed consent was obtained from the parents or guardians of the children, and the study was approved by the Ethics Committee, Faculty of Medicine, Lund University.

RESULTS

The average numbers of episodes of AOM and antibiotic-treated respiratory tract infections other than AOM (non-AOM RTI) in the cases and the controls are shown in Figures 1 and 2. These figures include all infectious episodes, before, during, and after the PRP-carriage. The cases had experienced 0·99 episodes of AOM per life-year, compared to 0·79 episodes per life-year in the controls ($P = 0{\cdot}32$). For non-AOM RTI, the corresponding figures were 0·49 and 0·29 episodes per life-year, respectively ($P = 0{\cdot}01$). For each life-year (except for AOM during the second year of life) the cases had experienced more AOM as well as non-AOM RTI than the controls, although none of these differences per life-year was statistically significant. Of 10 children with more than one episode of AOM per year, but no history at all of non-AOM RTI, nine were control subjects (Fig. 3).

No differences in the antibiotics consumption (number of children that had consumed antibiotics or number of courses consumed by these children) nor in the types of antibiotics consumed during the 3 months period preceding the PRP carriage and during the carriage period were noted between the cases and the controls.

DISCUSSION

Even though asymptomatic carriers are likely to be important transmitters of PRP, little attention has been brought to factors influencing the duration of carriage. We have previously shown that age is the most important factor determining the duration of PRP carriage, with the longest duration of carriage in the youngest individuals [8]. However, within each age group we found very large differences in carriage, age thus not being the only factor influencing the duration of carriage. The reason for the association of age and duration of PRP carriage is probably to be found in the relative immune incompetence seen in young children. The major immunogenic determinant of the pneumococcus is the polysaccharide capsule, and children are unable to mount a specific IgG antibody response to the capsule of many common serotypes before the age of 5 years [12, 13].

Gwaltney and colleagues have shown that the duration of pneumococcal carriage was associated with both pre-colonization antibody titres, and the rise in titre of antibody due to the colonization [14].

In our previous study, PRP carriage longer than 2 months in adults was rare (two of 70 individuals). One of these individuals, with PRP carriage during more than 9 months, was a woman with common variable immunodeficiency, treated with subcutaneous gammaglobulin once very 3 weeks. Patients with immunoglobulin deficiencies have also been found to be carriers of non-encapsulated *Haemophilus influenzae* during extended periods of time [15]. This led us to hypothesize that immature immune defence or immunodeficiencies could be important factors explaining also differences in carriage between individuals of the same age. If this hypothesis was true children with long-duration carriage would likely have experienced more respiratory tract infections than children with short-duration PRP carriage.

We found a tendency to more infections in the cases than in the controls. These differences were small, and for AOM not significant. The incidences of RTI were highest, and the differences between the groups the least, during the second year of life (the age when most Swedish children start attending day-care). This could possibly be explained by small immunological differences during this second year of life being 'drowned' by the massive exposition to respiratory tract pathogens and high incidences of RTI.

Different immunodeficiencies such as immunoglobulin deficiencies [16], complement aberrations [17], deficient immune responses to pneumococcal polysaccharide antigens [16, 18, 19], as well as depressed polymorphonuclear leucocyte function [20] are more common in children with recurrent AOM, than in non-otitis prone children. A number of children in our study, mainly belonging to the control group, had a history of several episodes of AOM, but had never been treated with antibiotics for other RTI. In this group of children non-immunological reasons for the AOM (i.e. local anatomic factors) may instead have been of importance.

In several studies previous antibiotics consumption has been identified as a risk factor for carriage as well

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as infection with antibiotic-resistant pneumococci [2, 21, 22]. To our knowledge the present study is the first attempt to establish if antibiotics consumption also is a risk factor for extended duration of carriage. Theoretically, the altered nasopharyngeal microbial flora after antibiotic treatment might favour the continued presence of antibiotic-resistant pneumococci before other susceptible bacteria. However, the results of this study do not favour such a hypothesis.

There are probably multiple factors determining the duration of PRP carriage, age being the most important and impaired immune competence, as indicated by susceptibility to RTI, being of less importance. Several studies have highlighted the importance of adherence to mucosal surfaces for the colonization of *S. pneumoniae* [23–25]. A main clue to the different durations of carriage in children of the same age may be found here.

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