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# Nationwide study of recurrent invasive pneumococcal infections in a population with a low prevalence of human immunodeficiency virus infection

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## ABSTRACT

Recurrent invasive infections caused by *Streptococcus pneumoniae* are rare, and often considered to be indicative of serious underlying illness. However, the prevalence of this problem, and the relevance of specific predisposing conditions, can be hard to assess, since many of the studies are based on specific risk groups. A population-based study of recurrent invasive pneumococcal disease in Iceland during the 30-year period 1975–2004 was performed. Clinical information, including mortality and vaccine use, was analysed retrospectively. Invasive pneumococcal isolates were serotyped and susceptibility testing was performed. During this period, 36 (4.4%) of 819 patients who survived an initial infection experienced recurrence, with a median time between episodes of 9.7 months. Pneumonia with bacteraemia was the most common clinical diagnosis (48% of cases), followed by bacteraemia without a clear focus (21%) and meningitis (13%). Most (94%) of the patients had identifiable predisposing conditions, most commonly, multiple myeloma in adults, and antibody deficiencies in children. Compared with children, adults were more likely to present with pneumonia (65% vs. 18%; p 0.0001). No significant change in the 30-day mortality rate was observed during the three decades of the study. Only 26% of eligible patients received pneumococcal vaccination. Patients with recurrent invasive pneumococcal disease should be investigated thoroughly for underlying diseases. Greater use of pneumococcal vaccines should be encouraged among high-risk patients. More effective preventive and therapeutic measures are needed to improve outcomes.

**Keywords** Bacteraemia, invasive infections, meningitis, pneumococci, recurrent infections, *Streptococcus pneumoniae*

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## INTRODUCTION

Infections caused by *Streptococcus pneumoniae* are common, and invasive infections, such as bacteraemia and meningitis, caused by this organism are associated with high rates of morbidity and mortality [1,2]. Although the incidence of pneumococcal disease is increasing in some countries [3,4], the use of a seven-valent pneumococcal conjugate vaccine in a childhood vaccination programme in the USA has reduced the rate of invasive pneumococcal disease in both children and adults [5]. Many risk-factors for pneumococcal infection have been well-established, such as antibody deficiencies [6,7], defective antibody formation [8], complement deficiencies [9], asplenia [10], age (higher likelihood with extremes of age) [3], malnutrition [11], alcoholism [12,13], tobacco use [14], infection with human immunodeficiency virus (HIV) [15–18], renal insufficiency [19] and chronic disease [20].

Recurrent invasive pneumococcal disease has been described in numerous case reports and case series [21–31]. It has been stated that recurrence is a rare event [20,26–28], with a documented risk of 2.3–5.3% [17,26–28]. Recurrence is often considered to be a strong indicator of serious underlying illness [26,28], with a mortality rate as high as 47% during the recurrent episode [26], although

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the significance of these recurrences may depend, in part, on the age of the patient. One study found that recurrent invasive pneumococcal infections in young children did not indicate the presence of an unsuspected immunodeficiency [29]. Similarly, one case series described five children with recurrent invasive pneumococcal disease, two of whom had no detectable underlying disease [30]. Thus, the prevalence of various conditions that predispose to recurrent pneumococcal infections may be highly age-dependent. However, studies of this clinical entity have been limited by small patient numbers, short follow-up periods, and a primary focus on selected patient populations such as children and individuals with HIV infection [26,28,31].

The aim of the present study was to investigate the epidemiological trends, clinical characteristics and microbiological findings among children and adults with recurrent invasive pneumococcal infections in Iceland during a 30-year period. Because the annual incidence of HIV infection in Iceland is low, it was possible to assess the contributions of other risk-factors to recurrent disease.

## PATIENTS AND METHODS

### Setting and patient selection

Iceland is an island in the mid-Atlantic ocean, with a population that increased from 219 033 at the end of 1975 to 293 291 by the end of 2004. The socio-economic status is high and the inhabitants have universal access to a government-based healthcare system. The country has two university or university-affiliated hospitals and 14 county hospitals, as well as numerous smaller health clinics. All hospitals and clinics were included in this study. Blood cultures were processed at two or three sites in the country, and a single reference laboratory performed serotyping on all invasive *S. pneumoniae* isolates. All patients, adults and children (aged ≤16 years), with pneumococci cultured from blood, cerebrospinal fluid, joint fluid or peritoneal fluid, or patients with a positive Gram-stain cerebrospinal fluid smear and a positive latex agglutination test for pneumococci, were recorded in an electronic database that was used to identify recurrences.

### Definitions

Individuals at risk of recurrent invasive pneumococcal disease were those who survived for 30 days after the initial episode of infection [17]. Recurrent pneumococcal disease was defined as two or more episodes of invasive pneumococcal infection separated by >4 weeks, or episodes separated by <4 weeks but caused by different pneumococcal serotypes, during a 30-year period (1 January 1975 to 20 September 2004).

### Data registration

The following clinical data were collected by chart review: age, gender, socio-economic status, tobacco use, alcohol consumption and vaccination status. Each episode of infection was reviewed to determine the type of infection, presenting signs, previous medication, physical examination, complete blood count and biochemical profile, treatment and diagnosis at discharge. Results of radiological, immunological and histopathological investigations, including autopsies, were documented. The numbers and types of bacterial cultures were documented. Outcome (mortality at 30 days) was calculated from hospital charts and the national population register.

### Microbiology

Serotyping of available invasive isolates was performed by coagglutination with antisera from the Statens Serum Institute (Copenhagen, Denmark). The invasive isolates were screened for penicillin resistance by the oxacillin disk-diffusion test [32]. Penicillin MICs were determined for all oxacillin-resistant isolates by Etest (AB Biodisk, Solna, Sweden). Isolates with a penicillin MIC ≥0.1 mg/L were defined as penicillin non-susceptible. Four patients had two separate infections with the same pneumococcal serotype; six of these eight isolates were available for DNA fingerprinting by pulsed-field gel electrophoresis following DNA restriction with *Sma*I [33].

### Statistical analysis

The chi-square test was used for statistical comparison of the incidence of recurrence during the two halves of the study period. Fisher's exact test was used for comparison of types of infection among adults and children. Statistical significance was set at $p < 0.05$. All tests were two-tailed.

### Ethical approval

The study was approved by the National Bioethics Committee of Iceland and the Data Protection Authority of Iceland.

## RESULTS

### Epidemiology

Invasive pneumococcal infections were diagnosed in 933 patients during the study period. Of these 933 patients, 819 survived for >30 days after the initial episode, and 36 (4.4%) of the survivors had one or more invasive pneumococcal infections subsequently (total of 77 episodes). These 36 patients included 12 children with 28 infections (primary and recurrent), and 24 adults with 49 infections. The median ages of children and adults were 2.5 years and 65.3 years, respectively. The mean time between episodes was 15.4 months, with a median of 9.7 months (range, 15 days to 7.7 years). Two patients had infections separated by <1 month, but with different pneumococcal