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Epidemiology of invasive *Streptococcus pneumoniae* infections in adults in Finland

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SUMMARY

Laboratory-based surveillance of invasive pneumococcal infections in adults in Finland from 1983 to 1992 identified 862 episodes of pneumococcal bacteraemia and 97 episodes of meningitis. The overall incidence of invasive pneumococcal infections was 9·1 per 100000 for all adults per year, but 27·1, 35·8, and 44·5 per 100000 in those aged 65 years or over, 75 years or over, and 85 years or over, respectively. Most (99·7%) of the pneumococcal strains were sensitive to penicillin. Ninety-five percent of the strains belonged to serogroups/types present in the 23-valent pneumococcal polysaccharide vaccine. Group/type distribution was different in patients aged 16–64 years compared to those 65 years or over ($P < 0{\cdot}001$), in bacteraemia compared to meningitis ($P < 0{\cdot}001$), and in the years 1983–7 compared to 1988–92 ($P < 0{\cdot}05$).

INTRODUCTION

Despite antimicrobial treatment and availability of a safe vaccine, infections caused by *Streptococcus pneumoniae* remain an important cause of morbidity and mortality among adults, and especially the elderly. Pneumococcus is the most common bacterial cause of community-acquired pneumonia in adults, and among the most frequent causes of bacterial meningitis and bacteraemia [1–3]. A substantial proportion of pneumococcal pneumonia and nearly all pneumococcal meningitis are bacteraemic [4, 5]; on the other hand, approximately 75–90% of pneumococcal bacteraemias in adults have been associated with pneumonia [6–9]. The case fatality rate in bacteraemic pneumococcal disease increases with advancing age, from about 20% in young adults to over 50% in the elderly [10]. In the United States about 40000 deaths annually are caused by pneumococcal pneumonia or meningitis [11]. The worldwide emergence of pneumococci resistant to penicillin and other antibiotics complicates treatment strategies for pneumococcal infections and emphasizes the need for and the use of an efficient vaccine [12, 13].

To provide detailed, age- and sex-specific background information for the use of pneumococcal vaccine, we present here epidemiologic data on invasive pneumococcal infections in adults in Finland obtained over a 10-year period.

MATERIALS AND METHODS

Surveillance of invasive pneumococcal infections

A national surveillance of invasive pneumococcal infections was undertaken at the National Public Health Institute (KTL, Kansanterveyslaitos) from January 1983 to December 1992. All clinical microbiology laboratories in Finland were asked to send pneumococcal strains isolated from normally sterile

body sites to KTL for confirmation and further analyses. The present analysis is based on the strains and information provided by three major laboratories in the cities of Helsinki, Tampere, and Oulu, representing different geographical areas (Southern, Central, and Northern Finland), and exclusively investigating samples from one third of the Finnish population. The completeness of the reporting was verified by reviewing the laboratory log books of these three laboratories for possible unsubmitted invasive pneumococcal strains, and if found, their number was included in the incidence calculations.

Only strains isolated from cerebrospinal fluid (CSF) and/or blood of adult patients aged 16 years or over were included in the present analysis; corresponding data for Finnish children 0–15 years old have been published previously [14].

Patient and demographic data and definitions

Pneumococcal strains sent to KTL were accompanied with a case report form containing information on the age and sex of the patient, date and site of the original sample, and the strain's susceptibility to penicillin (MIC).

If the same pneumococcal serotype was isolated from several CSF or blood samples during a single episode of meningitis or bacteraemia, it was registered only once, but if isolated from samples taken more than 30 days apart, the second isolate was considered to represent a new episode ($n = 8$). Isolates from both CSF and blood during the same episode ($n = 52$) were registered as a CSF isolate. If another serotype was isolated from a new sample at any time after the first one, it was considered to represent a new episode ($n = 17$).

Data on the age and sex distribution of the population in 1983–92 were obtained from the Statistics, Finland.

Bacteriological methods

In KTL, the strains were confirmed as *S. pneumoniae* by optochin-sensitivity test, and if necessary, by bile-solubility test. In case the strain was non-viable on receipt in KTL, a new subculture was obtained from the clinical microbiology laboratory. Serotyping was performed by using counterimmunoelectrophoresis, or, for the neutral serogroups/types 7 and 14, latex agglutination [14]. The capsular swelling test was used for confirmation. A strain reacting with the omniserum and/or antiserum pool, but not with a type- or group-specific antiserum, was considered as non-typable. All antisera and antiserum pools were purchased from Statens Seruminstitut, Copenhagen. Factor sera for subtyping the strains included in the serogroups were not available. The sensitivity of the strains to penicillin was screened by the breakpoint method using plates containing 0·06μg/ml of penicillin, and, if the strain was able to grow on the screening plate, MIC was determined by the agar dilution method.

Statistical methods

Statistical analyses were done with SPSS for Windows software (SPSS, Chicago), and CIA program (Gardner SB, Winter PD, Gardner MJ; London, 1992). The Mann–Whitney U test, Pearson's χ^2-test, and confidence interval (CI) analysis were used for comparisons.

RESULTS

Patients

From January 1983 to December 1992, KTL received from the three study laboratories 959 pneumococcal strains responsible for an equal number of bacteraemia or meningitis episodes in 934 adult patients. Eight hundred and sixty-two (89·9%) isolates were from blood only, 45 isolates (4·7%) from CSF, and 52 isolates (5·4%) from both CSF and blood (registered as CSF isolates).

The median age of patients was 59·6 years (mean 57·7 years, range 16–100 years). Six hundred and four (63·0%) of the patients were men, and the male:female ratio among the patients was 1·7:1 (for comparison, the ratio was 0·9:1 in the whole adult population in the same period). The age distribution differed between male and female patients (Mann–Whitney U test; $P < 0·001$) (Fig. 1). The median age of men was 54·4 years (mean 54·1 years, range 16–93 years), and that of women 67·7 years (mean 63·7 years, range 18–100 years); 67·1% of men but only 43·1% of women were younger than 65 years. In patients aged less than 65 years, the male:female ratio was 2·6:1.

Incidence of invasive pneumococcal infections

When the log books of the three major microbiology laboratories from the years 1983–92 were reviewed, 86 additional strains fulfilling the case definition criteria

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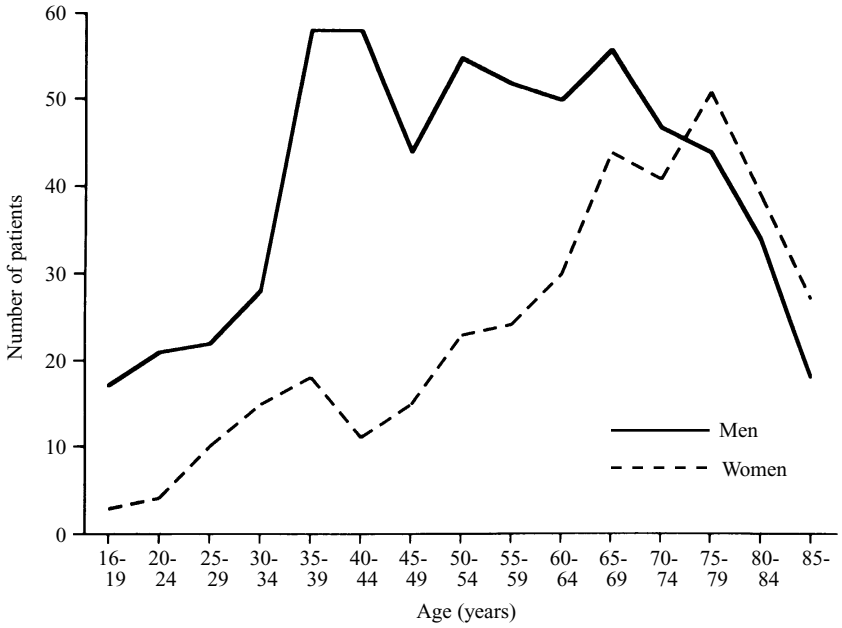

Fig. 1. Age distribution of Finnish men and women with invasive pneumococcal infection, 1983–92.

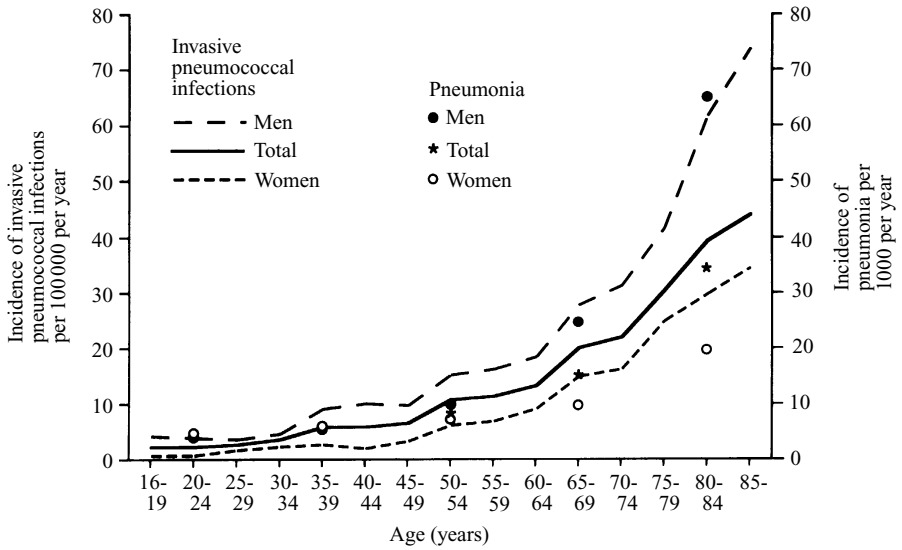

Fig. 2. Age-specific incidences of invasive pneumococcal infections in Finnish men and women, and for comparison, age- and sex-specific incidences of community-acquired pneumonia according to Jokinen and colleagues [15].

of the present study were found; thus these laboratories had sent to KTL strains from 959 (91·8%) of the total of 1045 invasive pneumococcal infections in adults during the 10-year period analysed. The annual incidence rates based on the total of 1045 detected episodes of invasive pneumococcal infections were calculated in the coverage area of these three laboratories, in which the average number of adults aged 16 years or over during 1983–92 was 1146843 (28·7% of the total adult population in Finland). This gave an overall annual incidence of invasive pneumococcal infections of 9·1 per 100000 adults aged 16 years or over: 0·9 per 100000 for meningitis and 8·2 per 100000 for bacteraemia. The incidence of invasive pneumococcal infections was 6·2 per 100000 in those aged 16–64 years, 27·1 per 100000 in those aged 65 years or over, 35·8 per 100000 in those aged 75 years or over, and 44·5 per 100000 in the oldest age group of 85 years or over.

Men had a greater risk for invasive pneumococcal infection than women in all age groups: the relative risk (RR) of men compared to women aged 16–64 years was 2·6 (95% CI 2·2–3·1), and among those aged 65 years or over, 1·8 (95% CI 1·5–2·1) (Fig. 2). In

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Table 1. *Pneumococcal serogroups/types causing invasive infections in adults, 1983–92*

Order of frequency	Serogroup/ type*	No. of isolates	% of total	% accumulated
1	*3*	120	12·5	12·5
2	*9*	108	11·3	23·8
3	*4*	98	10·2	34·0
4	*7*	91	9·5	43·5
5	*14*	82	8·6	52·0
6	*19*	76	7·9	60·0
7	*23*	61	6·4	66·3
8	*6*	59	6·2	72·5
9	*8*	52	5·4	77·9
10	*12*	27	2·8	80·7
11	*15*	23	2·4	83·1
12	*22*	20	2·1	85·2
13	*10*	19	2·0	87·2
14	*11*	19	2·0	89·2
15	*18*	16	1·7	90·8
16	*20*	13	1·4	92·2
17	*17*	10	1·0	93·2
18	35	8	0·8	94·1
19	*1*	7	0·7	94·8
20	31	7	0·7	95·5
21	16	6	0·6	96·1
Others†		37		
Total		959		

* Italicized serogroups/types are present in the 23-valent vaccine.

† Others include groups/types 13, *33* and 34 (5 isolates each); *5*, 36 and 38 (three isolates each); 25 and 28 (two isolates each); 29, 37, 39, 42 and 48 (one isolate each). Four isolates were untypable.

the men, the incidence of invasive pneumococcal infections started to increase from the age of 35 years, and more rapidly from the age of 65 years. In the women, the incidence started to increase from the age of 50 years with a faster rate after age of 75 years. The highest incidence was observed in men aged 85 years or over: 74·7 per 100000 per year. For comparison, the incidence rates of community-acquired pneumonia in Finland reported by C. Jokinen and colleagues [15] are included in Figure 2.

Susceptibility to penicillin and capsular groups/types

All but 3 out of the 959 strains were sensitive (MIC < 0·06 μg/ml) to penicillin; the 3 strains (0·3%) were intermediately resistant (MIC 0·12–1 μg/ml).

The 959 pneumococcal strains belonged to 36 different serogroups/types. Only one serotype at a time was isolated during each episode. Four strains (0·4%) were untypable. The seven most common groups/types were 3 (12·5%), 9 (11·3%), 4 (10·2%), 7 (9·5%), 14 (8·6%), 19 (7·9%), and 23 (6·4%), and these accounted for 66·3% of the cases (Table 1). Serotype 2, included in the 23-valent pneumococcal vaccine, was not found at all. Serotype 5, also in the vaccine, was rare, found in only three (0·3%) isolates. Type 1 was the 19th in order causing only 0·7% of the invasive infections. The groups/types related to the 23-valent vaccine covered 94·8% of the strains.

The serogroup/type distribution of invasive pneumococci in patients aged 16–64 years was significantly different from that among elderly patients aged 65 years or over (χ^2-test, $P < 0{\cdot}001$). This difference was mainly due to groups/types 3, 6 and 14 which caused more infections in the elderly (Fig. 3). The seven most common groups/types in the age group 16–64 years were 9 (causing 12·0% of all invasive infections), 3 (11·5%), 4 (10·8%), 7 (10·2%), 14 and 19 (both 7·0%), and 8 (6·3%); together accounting for 64·7% of the cases. In the elderly, the most common groups/types were 3 (14·0%), 14 (10·7%), 9 (10·2%), 4 and 6 (both 9·5%), 19 (9·2%), and 7 (8·5%); these seven groups/types caused 71·6% of the invasive infections.

The serogroup/type distribution of the 862 bacteraemia cases differed from that of the 97 meningitis cases (χ^2-test, $P < 0{\cdot}001$). Serogroups/types 10, 11, 15 and 23 caused proportionally more meningitis than bacteraemia. Type 3 was the most common among blood isolates whereas group 23 was most commonly isolated from CSF (Fig. 3).

Temporal and geographical variation

A comparison between the periods 1983–7 and 1988–92 showed a slight change in the serogroup/type distribution (χ^2-test, $P < 0{\cdot}05$). The nine most common groups/types were the same in both periods, but serogroups/types 9 and 14 were more common in the later period and group 19 rarer (Fig. 3). No temporal clustering of a single serogroup/type was observed. There was no difference in the group/type distribution between Southern, Central and Northern Finland.

Every year, there was a marked seasonal variation in the number of invasive isolates with a major peak in December–January (mean 11·3 cases per month) and a trough in July–August (mean 4·4 cases per month). No seasonal trends were found for individual groups/types.

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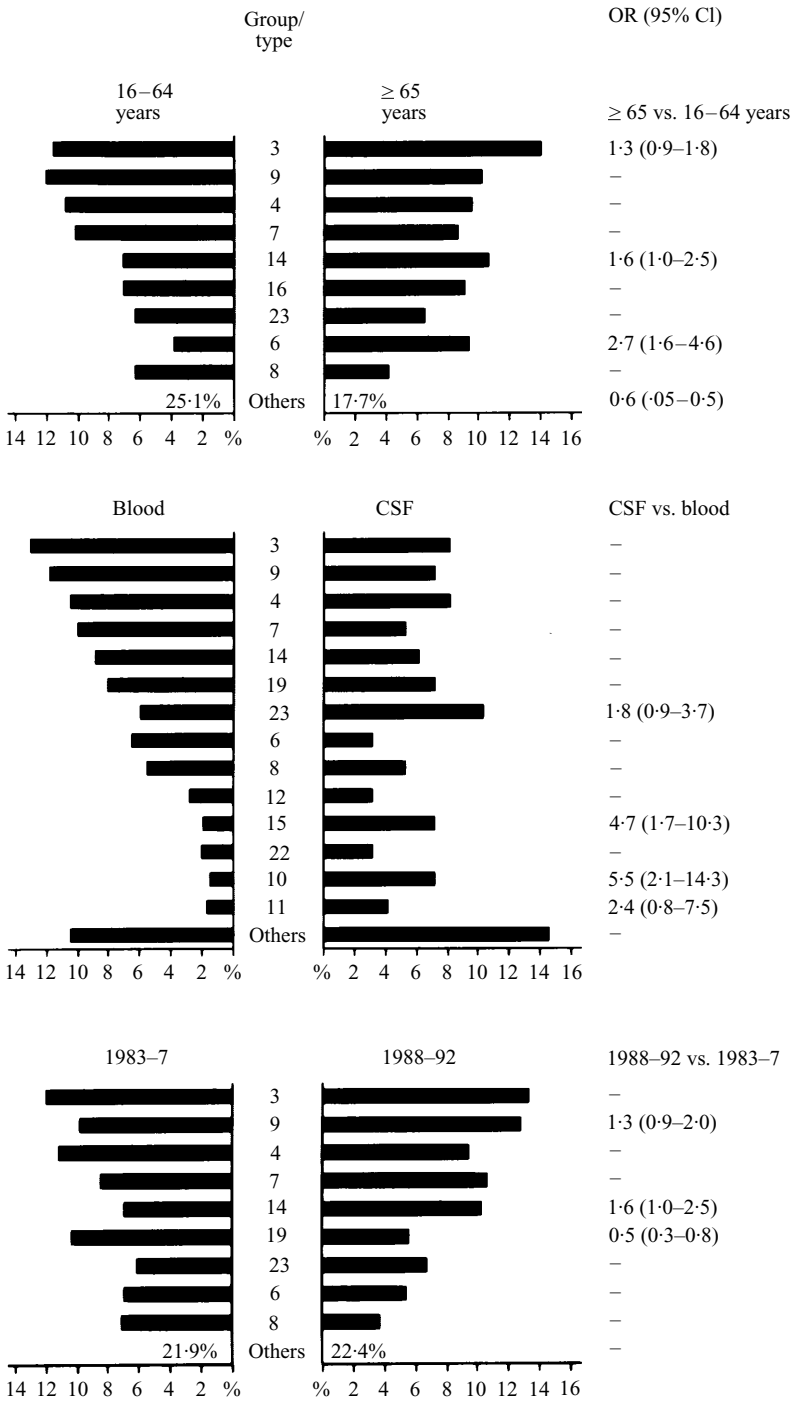

Fig. 3. Comparison of the percentages of pneumococcal serogroups/types causing invasive infections in patients aged 16–64 years or 65 years or over; causing bacteraemia or meningitis; and causing invasive infections among adults in 1983–7 and 1988–92.

The annual incidence rate varied from 7·9 per 100000 in 1984 and 1991 to 10·5 per 100000 in 1986 (95% confidence interval (CI) analysis, $P < 0{\cdot}05$) (Fig. 4). When the annual incidence rates in the coverage areas of the three major laboratories (in Southern, Central and Northern Finland) were compared, a year-to-year variation was observed in the area of Oulu laboratory in Northern Finland, but not at the two other sites. In Northern Finland, the incidence of invasive pneumococcal infections varied from 4·5 to 14·9 per 100000 per year ($P < 0{\cdot}01$); an average of 13·4 per 100000 in 1986–7 and 7·2 per

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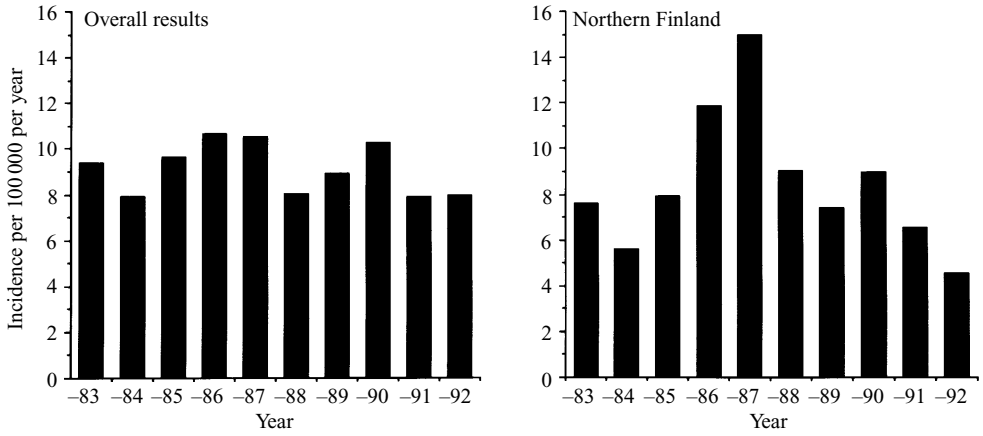

Fig. 4. Incidence rates of invasive pneumococcal infections among adults in the whole of Finland ('Overall results', left column), and in Northern Finland (right column) in 1983–92.

100000 in the surrounding years ($P < 0{\cdot}05$) (Fig. 4). The peak in 1986–7 was not caused by any single serogroup/type.

Recurrent pneumococcal infections

Seventeen patients had 2 and 4 patients had 3 separate episodes of invasive pneumococcal disease within the study period 1983–92 (altogether resulting in 46 episodes in 21 patients). Three of these 21 patients (16 men, 5 women) had recurrent pneumococcal meningitis, and the others recurrent bacteraemia. The median age of patients with recurrent pneumococcal infection at the time of first episode was 52·4 years (mean 52·0 years, range 18–81 years) compared to 59·9 years (mean 57·9 years, range 16–100 years) of those with only one invasive pneumococcal infection. The most frequent serogroups/types in the 21 patients with 46 episodes of invasive pneumococcal infections were 23, 6, 7 and 15 (causing 8, 5, 4 and 4 episodes, respectively). Seven patients had a recurrent infection caused twice or three times by the same serogroup/type (group 23 in two patients, groups 6, 7, 10 and 15 each in one patient).

DISCUSSION

Epidemiological data are essential for defining immunization requirements. In most European countries, pneumococcal vaccine is not included in any vaccination programme. Even in the United States, despite recommendations to vaccinate all the elderly and those adults in certain risk groups, many opportunities for pneumococcal vaccination are missed leading to vaccination coverage of less than 30% among the elderly [11, 16, 17]. We are aware of only a few studies on age- and sex-specific epidemiological characteristics of invasive pneumococcal infections in adults, including those aged 85 years or over. The incidence figures and serogroup/type data in the present study are based on the prospective 10-year collection of all invasive pneumococcal strains isolated in the microbiology laboratories of three geographical areas covering 29% of the total adult population in Finland.

We found an annual incidence of invasive pneumococcal infections to be 9·1 per 100000 in adults aged 16 years or over in Finland in 1983–92. In a contemporary study on Finnish children aged under 16 years, Eskola and colleagues [14] have reported an overall incidence rate of 8·9 per 100000; a figure closely similar to that of adults. By combining these two figures, the estimated incidence in the whole Finnish population would be about 9 per 100000 persons annually. Closely similar figures, 7–7·5 per 100000, have been reported from Sweden [18, 19]. In studies from the United States, incidence rates have ranged from 9 to 19 per 100000 persons [20, 21]. Considerably higher figures have been reported from the native populations in Alaska [22]. An extremely high incidence, 297 per 100000 persons, has been observed among the Australian Aborigines, whereas the incidence among the non-Aborigines was 9·4 per 100000 per year [23], similar to that in Finland. Both in Alaska and Australia, the high incidence has been associated with socio-economic problems, such as malnutrition or alcoholism.

Age has a strong influence on susceptibility to pneumococcal infections. The highest incidences in the Finnish studies conducted by ourselves and by

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Eskola and colleagues [14] were seen at the extremes of age: 45·3 per 100000 per year in children less than 2 years old, and 44·5 per 100000 in the elderly aged 85 years or over. The rate in those aged 65 years or over was 27·1 per 100000 persons. Similar results for adults aged 65 years or over have been recorded from the United States, where annual rates have ranged from 22–56 per 100000 [20, 21], and from Israel, where a rate of 39 per 100000 persons has been recorded [7].

Invasive pneumococcal infections were more common among men than women in all age groups, the male predominance being particularly strong among the elderly. The higher incidence of invasive pneumococcal infections in men has been noted by others [6–9, 18]. A similar male predominance has been observed in a study of community-acquired pneumonia carried out in Finland at about the same time [15]. The factors contributing to the greater susceptibility of men to invasive pneumococcal infections or to pneumonia are not fully understood. In several studies, alcoholism has been an underlying condition in 3–59% of the adults with invasive pneumococcal infections, and it also increases the risk for pneumonia or pneumococcal infections in general [8, 18, 22–25]. Alcoholism was noted to be significantly more common among men than women with invasive pneumococcal infections in previous studies in Finland and in Sweden [8, 18, 26]. It is possible that this may be contributing to the increase of the number of invasive pneumococcal infections in the men aged 35–49 years reported here. A history of smoking and smoking-related lung diseases, e.g. chronic obstructive pulmonary disease (COPD), is also more common among elderly men than women [27]. These factors also increase the risk for pneumonia or pneumococcal infections [24, 25], and could further contribute to the male predominance in invasive pneumococcal infections. The increased incidence of pneumococcal infections in males observed in childhood [14] suggests that a true sex difference might also pertain.

The majority of pneumococcal bacteraemias in adults are associated with pneumonia [6–9]. It was therefore of interest to compare age- and sex-specific incidence data of invasive pneumococcal infections to corresponding data on community-acquired pneumonia in Finland in 1981–2. The age- and sex-specific incidence rates of community-acquired pneumonia and invasive pneumococcal disease had evident similarities, i.e. the increase by advancing age and the male predominance. In the present study, 90% of the pneumococci were isolated from blood only (thus mostly from patients with pneumonia), corresponding to an overall incidence of pneumococcal bacteremia of 8·2 per 100000 adults. The incidence of community-acquired pneumonia irrespective of aetiology was 9·0 cases per 1000 adults per year, i.e. a hundred times higher, and about 40% of these pneumonias were shown to be caused by pneumococcus (C. Jokinen, unpublished data) by a wide pattern of serological and antigen detection tests [28]. This also corresponds to the present view of the aetiological role of pneumococcus in 30–50% of pneumonias. Comparison of this figure with the incidence rate of invasive pneumococcal infections suggests that not more than 3% of pneumococcal pneumonias would be bacteraemic. This is probably a gross underestimate: blood cultures are not always undertaken on patients with pneumonia especially when treated at home, and preceding oral antibiotics may prevent the isolation of pneumococci from blood.

Only a minor variation in the annual incidence of invasive pneumococcal infections was observed in adults in Finland during 1983–92. This is at discordance with a recent report from Sweden, which showed a successive increase in the incidence of invasive pneumococcal infections from 3·2 to 10·2 cases per 100000 persons of all ages during 1988–92 [29]. We are confident that our finding of a stable incidence among adults in Finland over this time is reliable for several reasons. Firstly, there were no changes in the policy of obtaining blood or CSF cultures during the 10-year period analysed. Secondly, we made a considerable effort to find all positive blood or CSF cultures for our calculations by reviewing the laboratory log books thoroughly. Thirdly, the incidence figures are based on three geographical districts from different parts of the country which included one third of the whole adult population, thus giving a reliable picture of the whole country. Incidence figures in the Swedish study were based on a requirement from 1988 for microbiology laboratories to report pneumococcal bacteraemia cases. No verification on the completeness of reporting was done [29] and it is possible that considerable underreporting occurred in the early stages of this new initiative.

Contrary to our observations elsewhere, a significant transient increase in the incidence of pneumococcal bacteraemias among adults was noticed in Northern Finland in 1986–7. There were no changes in the practice of obtaining blood cultures during these years in the area, and the number of

bacteraemias caused by other bacteria in 1986–7 did not show a similar change (our unpublished observations). The observed increase in the incidence may have been due to an intensive *Chlamydia pneumoniae* epidemic, which occurred in Northern Finland in 1986–7 [30]. In those years, a mixed infection caused by *C. pneumoniae* and *S. pneumoniae* together was a common finding among the pneumonia patients [31], showing that infections caused by *C. pneumoniae*, like many viral infections, may predispose to pneumococcal infections. This interpretation is also consistent with the fact that no epidemic spread of a single serotype was observed during those 2 years.

The composition of the 23-valent pneumococcal polysaccharide vaccine has been kept constant since its introduction in 1983. Of the 959 pneumococcal isolates from invasive infections of Finnish adults, 94·8% belonged to 21 serogroups/types included in the vaccine. Reports from studies from the United States [32, 33], Denmark [34], Sweden [29, 35], and Belgium [36] have shown that 86–98% of invasive pneumococcal infections have been caused by vaccine-related or vaccine-type pneumococci. Vaccine serotypes 2 and 5 were extremely rare among the Finnish adults, with zero and three isolates, respectively. The seven most common serogroups/types were 3, 9, 4, 7, 14, 19 and 23. Groups/types 3, 9, 4 and 7, in descending order, were the most common ones in blood isolates of Swedish adults, too [26]. Except for the rare occurrence of serotype 1 among adults in Finland (19th in the rank order), the group/type distribution was quite similar to previous reports from industrialized countries. In an extensive study on more than 10000 invasive pneumococcal strains from several European countries in 1982–7, the most common serotypes in adults were 3, 1, 14, 7F, 4 and 8 [37]. Minor temporal changes in the serotype distribution were also observed during the 10-year period in this study, emphasizing the need for continuous surveillance of the serotype distribution.

The present study showed differences in the serogroup/type distribution between bacteraemia and meningitis. Groups 23, 10, 11 and 15 were more frequently isolated from CSF whereas type 3 was more common in blood. Similar to the results of the current study, group 23 was the most frequent isolate from the CSF from 31 patients with pneumococcal meningitis in Sweden [4]. Less invasive serogroups may cause meningitis rather than bacteraemia, as predisposing factors like skull fractures, sinusitis or chronic mastoiditis may facilitate the spread of these strains to the meninges [4, 5]. In the present study, group 23 pneumococci were also the most common isolates in the patients with recurrent invasive infections, who probably have serious predisposing conditions as well.

The first moderately penicillin-resistant pneumococcal strain was identified in Finland in 1979 [38], and in the present study only 0·3% of the invasive pneumococcal strains of adults had a decreased susceptibility to penicillin during 1983–92. In Finnish children, 1·7% of otitis-related strains during 1987–90 were moderately resistant to penicillin (MIC 0·12–1 μg/ml) [12], but in the beginning of the year 1995, 6% of otitis-related pneumococci were noted to have decreased sensitivity to penicillin, and 2% of the strains were highly resistant (MIC $> 1\mu$g/ml) (A. Nissinen, unpublished observation). Thus the warning signs of emergence of resistant pneumococci in Finland are evident, and the importance of strict policies for antibiotic use as well as continuous surveillance of antibiotic resistance cannot be overstressed.

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