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ARTICLE

Epidemiology, outcome and *emm* types of invasive group A streptococcal infections in Finland

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Abstract In 2006, Finnish nationwide surveillance showed an increase of invasive group A streptococcal (iGAS) disease and clinicians were alarmed by severe disease manifestations, prompting the investigation of recent trends and outcome for iGAS. A case of iGAS was defined as *Streptococcus pyogenes* isolated from blood or cerebrospinal fluid. Cases during 1998–2007 and isolates during 2004–2007 were included. Case-patients' 7-day outcome was available for 2004–2007. Isolates were *emm* typed. A total of 1,318 cases of iGAS were identified. The average annual incidence was 2.5/100,000 population. The rate was higher in males than females in persons aged 45–64 years, but lower in persons aged 25–34 years. The annual incidence was highest in 2007 (3.9/100,000). Occasional peaks occurred during midwinter and midsummer. The most common *emm* types were 28 (21%), 1 (16%), 84 (10%), 75 (7%) and 89 (6%). During 2004–2007, *emm*1 replaced *emm*28 as the most predominant type. The overall case fatality was 8%. Cases with *emm*1 were associated with high case fatality (14% vs. 8% in other types; $p<0.02$); that of *emm*28 infections was 2% ($p<0.01$). Changes in *emm* type prevalence influenced incidence and case fatality. Differences in age- and sex-specific incidence and seasonal patterns suggest variations in predisposing factors and underlying conditions.

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Introduction

Streptococcus pyogenes (group A streptococcus, GAS) causes a wide array of infections, ranging in severity from mild pharyngitis and skin/soft tissue infections to severe invasive infections. In the late 1980s, a change in the epidemiology of severe GAS infections, with an increase in the incidence and severity of disease, was documented [1]. The role and increased pathogenic potential of type M1 in epidemics were of specific interest [2, 3]. The incidence of severe GAS disease shows variations over time and geographic region, possibly reflecting the population's susceptibility to particular strains with diverse virulence properties [4–6]. Dynamic changes in the type distribution of GAS may also influence the case fatality of these infections.

In Finland, the incidence rate of invasive group A streptococcal (iGAS) disease has also shown fluctuations during this and the previous decade, and an increasing trend has been noticed [7]. In 2006, clinicians contacted the National Institute for Health and Welfare and described suddenly encountering more severe disease manifestations with a poor outcome. These events prompted us to investigate the recent trend and outcome of iGAS infections and *emm* type distribution in Finland in more detail.

Methods

Surveillance

The national healthcare system of Finland (population 5.3 million) is organised into 20 healthcare districts (with catchment populations ranging from 58,000 to 1.5 million), forming five tertiary care districts. Since 1995, all clinical microbiology laboratories have mandatorily notified all isolations of *S. pyogenes* from blood or cerebrospinal fluid (CSF) to the National Infectious Disease Register (NIDR). With each notification, the following information is transmitted (generally electronically) to the NIDR: date and type of specimen, unique national identity code of the patient (since 2004), date of birth, sex and place of treatment. Within an interval of three months, notifications concerning the same patient are merged into a single case. The corresponding *S. pyogenes* isolates are submitted to the national reference laboratory.

Case definition and outcome

A case of iGAS was defined as *S. pyogenes* isolated from blood or CSF. In this study, iGAS cases from January 1998 to December 2007 and isolates from January 2004 to December 2007 were included. Case-patients' vital status at 7 days of positive blood or CSF culture was obtained for 2004–2007 from the Population Information System through the use of the national identity codes.

Identification and characterisation of isolates

Isolates were tested for sensitivity to bacitracin and the Lancefield group A antigen was identified using Streptex latex agglutination (Remel Europe Ltd., UK). *emm* typing was performed for all isolates according to guidelines by the Centers for Disease Control and Prevention (http://www.cdc.gov/ncidod/biotech/strep/protocol_emm-type.htm) as previously described [8]. Susceptibility to erythromycin, clindamycin and tetracycline was determined with the agar dilution method for all isolates. Susceptibility was assigned according to interpretative criteria for the minimum inhibitory concentration (MIC) as recommended by the Clinical and Laboratory Standards Institute [9].

Data analysis and statistics

Data on the cases of iGAS, their outcome and *emm* typing and antimicrobial susceptibility data (where available) were linked using the national identity code of the case-patient and the date of the specimen. Where the national identity code was unavailable, other available information was used for linkage. Average annual incidence rates were calculated for 1998–2007 using the population census at the end of the previous year, as obtained from Statistics Finland. Age- and sex-specific incidence rates and male-to-female ratios with 95% confidence intervals (CIs) according to the Poisson distribution were calculated. Seven-day case fatality was calculated for 2004–2007 and for each *emm* type separately. χ^2 and Kruskal–Wallis tests were applied where appropriate to test for statistical significance between subgroups and distributions. Differences were considered to be significant when $p<0.05$. Data were analysed with Intercooled Stata™ 9.1 software for Windows (StataCorp, College Station, TX, USA) and R statistical software version 2.9.0 (R Development Core Team, Vienna, Austria).

Results

Incidence rates

From January 1998 to December 2007, 1,318 cases of iGAS (range by year, 100–207) were identified (Table 1). The median age of case-patients was 52 years (range, 0–95 years); 55% were males. The average annual incidence rate of iGAS was 2.5 cases per 100,000 population. The rate was higher in males than in females and among males of adult age groups, it increased with age (Table 2). The highest rates were observed among the elderly patients. Males had a significantly higher rate of infection than females, especially among persons aged 45–64 years, whereas females had a higher rate than males among persons aged 25–34 years.

The annual incidence rate fluctuated (range by year, 1.9–3.9 cases per 100,000 population) but showed an increasing trend during the study period. Peaks occurred in 2002 (2.9

Table 1 Annual incidence of invasive group A streptococcal (iGAS) disease and the number of cases and isolates studied, Finland, 1998–2007

Year	Rate[a] of invasive disease	Number of cases (isolates)
1998	2.1	105
1999	2.2	116
2000	2.2	116
2001	1.9	100
2002	2.9	153
2003	2.3	119
2004	2.5	130 (128)
2005	2.1	110 (110)
2006	3.1	162 (161)
2007	3.9	207 (203)
All	2.5	1,318 (602)

[a] Average annual incidence (cases per 100,000 population)

Table 2 Age- and sex-specific incidence of iGAS disease, Finland, 1998–2007

Age group (years)	Rate[a] of invasive disease (no. of cases)						Rate ratio (RR)[b]	95% CI[c] of RR
	Male		Female		Total			
<1	2.7	(8)	2.2	(6)	2.5	(14)	1.3	0.4–3.9
1–14	1.2	(51)	0.9	(38)	1.0	(89)	1.3	0.8–2.0
15–24	0.8	(26)	1.2	(39)	1.0	(65)	0.6	0.4–1.0
25–34	1.2	(40)	2.7	(86)	1.9	(126)	0.4	0.3–0.6*
35–44	3.0	(112)	2.7	(97)	2.8	(209)	1.1	0.9–1.5
45–54	4.2	(168)	1.8	(69)	3.0	(237)	2.4	1.8–3.2*
55–64	4.8	(151)	2.4	(79)	3.6	(230)	2.0	1.5–2.6*
≥65	5.1	(163)	3.8	(185)	4.3	(348)	1.4	1.1–1.7*
All	2.8	(719)	2.2	(599)	2.5	(1,318)	1.3	1.1–1.4*

[a] Average incidence (cases per 100,000 population)

[b] Male-to-female incidence rate ratio

[c] CI, confidence interval. Statistical significance ($p<0.05$) is indicated with an asterisk (*)

cases per 100,000) and in 2006–2007 (3.1–3.9 cases per 100,000). The average annual incidence rate in the five tertiary care districts varied between 1.8–3.1 cases per 100,000. Of all cases, 41% were localised in the tertiary care district around Helsinki, where the annual incidence rate varied within the range of 2.2–4.4 cases per 100,000. Variation in the seasonal activity of iGAS disease could be identified, with occasional peaks of cases occurring during the midwinter (for both sexes) and midsummer (with male cases dominating; Fig. 1a, b).

emm sequence types

For 602 out of 609 cases during 2004–2007, a corresponding isolate was received. A total of 46 *emm* types were encountered (range by year, 23–28 types). The annual proportion of non-typable isolates varied within 1–5%. The five most common *emm* types were 28, 1, 84, 75 and 89, together accounting for 60% of isolates (Table 3). Type *emm*28 was the most predominant type in 2004, but its proportion declined each year, while that of *emm*1 increased, and by 2007, *emm*1 became the most common type. Type *emm*1 isolates were mainly of subtypes 1.0 and 1.10, but sporadic cases of other subtypes were also encountered. A new and uncommon type, *emm*84, emerged in 2005 and became the second most common type by 2007.

Type *emm*28 infections were over-represented in females compared to males (55% vs. 45%; $p<0.01$) and the same was true for *emm*4 infections (73% vs. 27%, respectively; $p<0.05$). Specifically, females of child-bearing age (15–44 years) had a significantly larger proportion of infections by *emm*28 than males of the same age (48% vs. 21% of *emm*28 infections, respectively; $p<0.01$).

Outcome

During 2004–2007, 48/609 case-patients died within 7 days of the positive blood or CSF culture (overall case fatality,

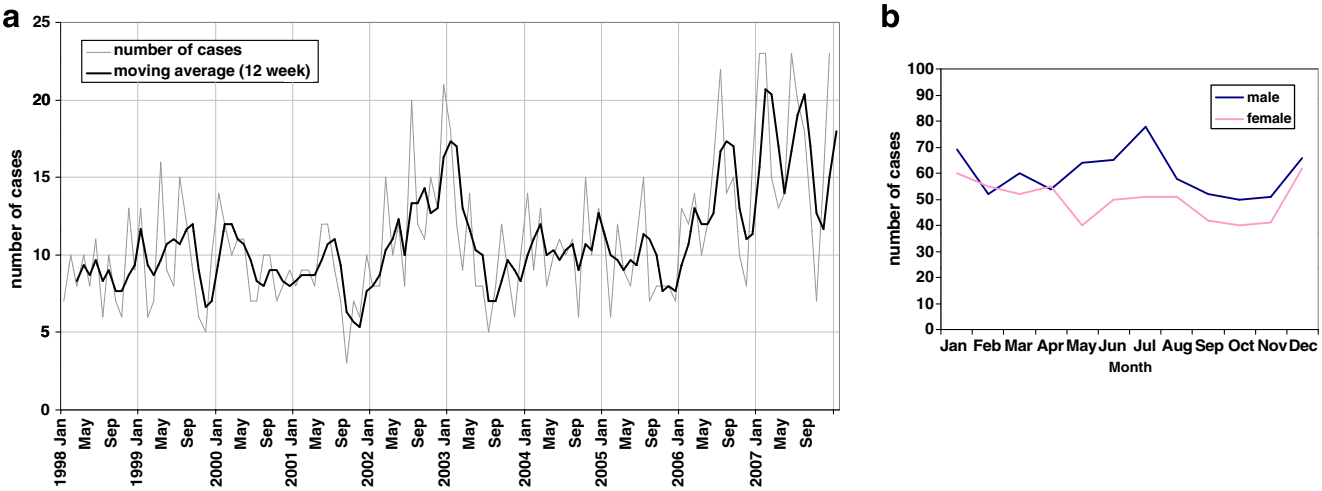

Fig. 1 **a** Cases of invasive group A streptococcal (iGAS) disease during 1998–2007 in Finland. *Thin line*, number of cases; *bold line*, number of cases (12-week moving average). **b** Monthly cases of iGAS during 1998–2007 in Finland (all years combined) in males and females

Table 3 The number and proportion (% of total number) of the most common *emm* types encountered in the order of overall prevalence and case fatality (%) by *emm* type, 2004–2007, Finland

emm type	Number of isolates (%)										Fatal cases (%)	
	2004 (n=128)		2005 (n=110)		2006 (n=161)		2007 (n=203)		2004–2007 (n=602)		2004–2007 (n=48)	
28	46	(35.9)	22	(20.0)	32	(19.9)	25	(12.3)	125	(20.8)	3	(2)
1	6	(4.7)	9	(8.2)	26	(16.1)	57	(28.1)	98	(16.3)	14	(14)
84	0	(0.0)	1	(0.9)	24	(14.9)	32	(15.8)	57	(9.5)	4	(7)
75	10	(7.8)	17	(15.5)	12	(7.5)	4	(2.0)	43	(7.1)	6	(14)
89	10	(7.8)	4	(3.6)	11	(6.8)	12	(5.9)	37	(6.1)	2	(5)
79	10	(7.8)	12	(10.9)	4	(2.5)	2	(1.0)	28	(4.7)	4	(14)
12	2	(1.6)	6	(5.5)	6	(3.7)	12	(5.9)	26	(4.3)	2	(8)
81	7	(5.5)	3	(2.7)	5	(3.1)	8	(3.9)	23	(3.8)	0	(0)
27G	3	(2.3)	1	(0.9)	4	(2.5)	11	(5.4)	19	(3.2)	2	(11)
Other[a]	34	(26.6)	35	(31.8)	37	(23.0)	40	(19.7)	146	(24.2)	11[b]	(7)

[a] Including isolates from a total of 37 other *emm* types and non-typable isolates

[b] Other types causing poor outcome: *emm*4 and *emm*110 (two cases each); *emm*22, *emm*59, *emm*60, *emm*77,*emm*85, *emm*87 and *emm*112 (one case each)

8%). The case fatality did not significantly differ between males and females (9% vs. 6%; p=0.172). The case fatality was the lowest in 2004 (3%), increasing to its highest in 2005 (12%), and then declined by 2006 (10%) and 2007 (7%). The case-patients with fatal outcome were older than those who survived (median age, 60 vs. 54 years; p<0.01). No fatalities occurred in patients aged <1 and 15–24 years.

Overall, infections by *emm*1 were significantly associated with higher case fatality (14% vs. 8% with all other types; p<0.02, Table 3). Cases by *emm*75 and 79 were also associated with higher than average case fatality (14% for both). In contrast, *emm*28 was associated with lower case fatality (2% vs. all other types; p<0.01) along with type 81 (0%, respectively).

Antimicrobial susceptibility

Of the iGAS isolates tested, 1.5% (9/602) were resistant to erythromycin, 0.5% (3/602) to clindamycin and 16% (97/602) to tetracycline. The tetracycline-resistant strains were mainly of *emm* types 81 (20 resistant isolates in total; 87% of this type resistant to tetracycline), 27G (19; 100%), 77 (12; 100%) and 85 (9; 100%).

Discussion

This study presents a comprehensive description of the recent epidemiology and outcome of invasive group A streptococcal (*S. pyogenes*) disease with information on *emm* type prevalence in a well-defined population. The main strength of the study is the nationwide population-based surveillance and the good coverage of isolate collection. We describe how the incidence and case fatality of iGAS infections were influenced by changes in the *emm* type prevalence. Age- and sex-specific differences in the incidence, uncharacteristic seasonal patterns of infections and aspects of vaccine coverage are also discussed.

The observed incidence rate of 3.9 cases per 100,000 population in 2007 is the highest in Finland since 1995. This study together with our earlier research shows that the incidence of iGAS disease has fluctuated since the 1990s but continued its increasing trend [7, 10]. During 2003–2004, the UK, Sweden, Denmark and Finland had the highest rates of infection (range 2.5–3.3 per 100,000) in a European study [4]. Since then, indications of an increase in the incidence are seen in Sweden to 4.5 cases per 100,000 by 2007 (http://www.smittskyddsinstitutet.se/in-english/statistics/beta-hemolytic-group-a-streptococci-gas-invasiv-infection/) and very recently in the UK [11]. In contrast, the incidence of iGAS disease in the USA has remained relatively stable, at an average of 3.5 cases per 100,000 during 1995–2004, with a moderate increase to 3.8 in 2007 (http://www.cdc.gov/abcs/survreports.htm) [5].

The incidence of iGAS disease in Finland generally increased with age as expected, but the rate in the elderly (≥65 years of age) still remained at a lower level than has been reported in Sweden, Denmark, the UK or the USA [5, 12–14]. Males had a higher incidence of iGAS disease compared to females, which has also been noted by some other studies [4, 5]. Differences could also be identified in the age- and sex-specific rates, with males having significantly more infections than females in the age range 45–64 years. In contrast, females had more infections in the age range 25–34 years than males. A similar clear peak in the

incidence of females around the same age has been noticed in earlier studies from Denmark and the UK [13, 14].

The characteristic fluctuation in the incidence of iGAS disease is presumably a reflection of changes in the *emm* type distribution and the population's susceptibility towards particular strains, especially of emerging types [5, 12, 15]. The *emm* type distribution in Finland underwent major changes during 2004–2007 when *emm*1 replaced *emm*28 as the most predominant type. The incidence of iGAS disease increased simultaneously with the increasing prevalence of type *emm*1, as has also been observed by others [3]. However, changes in the prevalence of other types, such as the sudden emergence of *emm*84, also contributed to the increase [10].

The type distribution of iGAS isolates in Finland has common features with that of other countries but also some unique characteristics. *emm* types 1, 28 and 89 are common globally, but 75 and 84 are rarer and have not featured among the five most common *emm* types elsewhere [5, 6, 12, 14, 16, 17]. The low prevalence of cases by *emm*3 is of interest, as it is a common type in many countries, and is often associated with high case fatality [5, 6, 14, 17]. The *emm* types included in the putative 26-valent recombinant vaccine would have covered approximately half of the Finnish isolates in 2004–2007, a notably smaller proportion than has been estimated for the USA (79%) and Japan (82%) [5, 17, 18].

Within the last 20 years, a periodic fluctuation of peaks and troughs of the two most common genotypes, *emm*1 and *emm*28, has occurred in Finland. Peaks in numbers of M/*emm*1 have been observed earlier in 1988–1990 and 1997–1998, and in this study in 2006–2007 [7, 19, 20]. Similarly, the prevalence of type *emm*28 has peaked in 1993–1995 and 2002–2004 [7, 20]. Such a pattern of alternating type prevalence may be a reflection of changes in the general immunity of the population.

Types *emm*28 and, more rarely, also *emm*4 have been known to associate with postpartum infections and puerperal sepsis [6, 21, 22]. Also in this study, *emm*28 infections were found to be specifically concentrated in females of child-bearing age. However, estimations of how many of these cases were pregnancy-related infections are beyond the scope of this study.

The overall erythromycin resistance during 2004–2007 was expectedly low, as the rate has declined during this decade in Finland (http://www.ktl.fi/portal/english/projects/fire/finres/finres__antimicrobial_resistance_statistics_/streptococcus_pyogenes/). The Finnish iGAS strains remain susceptible to clindamycin. Similar low resistance rates have been reported, for example, in Denmark and the USA [14, 23]. Tetracycline resistance was associated with certain clones, as has also been found previously, and the resistant strains were mainly of uncommon *emm* types [24].

The overall case fatality of iGAS disease in Finland was relatively low at 8%, compared to those reported by some other European countries and the USA [5, 12, 13, 16]. A sudden four-fold increase in the case fatality occurred from 3% in 2004 to 12% in 2005. During the study, the proportion of infections by types *emm*1 and *emm*75 increased, these types being associated with a high case fatality. In parallel, the proportion of *emm*28, associated with a low case fatality, decreased. Having an infection by *emm* types 1 or 3 has been identified as an independent factor associated with death due to iGAS disease [5]. Also in our study, the case fatality by *emm*1 was higher than average; however, we did not adjust it for age.

Seasonal variation in iGAS disease was observed; in addition to a midwinter peak season, there were also occasional peaks during the midsummer. In the northern hemisphere, peaks of cases are generally observed during the winter and spring [4–6, 12]. There were also sex-specific differences in the peak seasons, with male cases dominating during the summer. These two peak seasons might be associated with different predisposing factors and underlying conditions. However, the unusual pattern and irregularity of the seasonality observed in this study may partly arise from natural variation due to a reasonably small study size.

There are some limitations to this study. Firstly, part of the increase in the incidence may be due to more frequent blood culturing activity [25]. It is also possible but less likely that the incidence would have been influenced by changes in the reporting system, which was established in 1995. Secondly, case definitions of iGAS disease differ between countries and complicate comparisons of incidence rates. Exclusion of non-bacteraemic cases with other sterile site isolations and/or toxic shock by the Finnish case definition may partly explain the observed lower incidence rate. Thirdly, differences in blood culture sampling practices between countries may have an effect on the observed incidence [25]. In addition, the observed differences in fatality may arise from the case definition used, the timing of death considered (7/30-day/in-hospital mortality) and the source of information (e.g. population registry vs. hospital records). In this study, the 7-day mortality information obtained from the Population Information System was used. Finally, the surveillance does not include the collection of clinical data of disease manifestations, possible risk factors and underlying conditions of patients. These data would be needed in order to address reasons behind the observed differences in the age-and sex-specific incidence, and such a study has been undertaken within one healthcare district in Finland [26].

In conclusion, dynamic changes in the *emm* type prevalence influenced the incidence and case fatality of iGAS disease in Finland. An unusual seasonal pattern with

peaks in the midwinter and midsummer was observed. Differences in age- and sex-specific incidence rates and seasonality suggest variations in predisposing factors and underlying conditions.

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Conflict of interest The authors declare that they have no conflict of interest.

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