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Editorial Manager(tm) for European Journal of Clinical Microbiology & Infectious Diseases  
Manuscript Draft

Manuscript Number: EJCMIID-D-10-00104R1

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

Article Type: Article

Keywords: group A streptococcus; Streptococcus pyogenes; epidemiology; emm typing; outcome; bacteraemia

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**Abstract: Purpose.** In 2006, Finnish nationwide surveillance showed an increase of invasive group A streptococcal (iGAS) disease and clinicians were alarmed by severe disease manifestations, prompting investigation of recent trends and outcome for iGAS.

**Methods.** 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.

**Results.** 1318 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, emm1 replaced emm28 as the most predominant type. The overall case fatality was 8%. Cases with emm1 were associated with high case fatality (14% vs. 8% in other types;  $P<0.02$ ); that of emm28 infections was 2% ( $P<0.01$ ).

**Conclusions.** Changes in emm-type prevalence influenced incidence and case fatality. Differences in age- and sex-specific incidence and seasonal patterns suggest variation in predisposing factors and underlying conditions.

Response to Reviewers: European Journal of Clinical Microbiology & Infectious Diseases

Response to reviewer comments

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Figure A:

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**Cover letter**

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Tuula Siljander

May 20th, 2010

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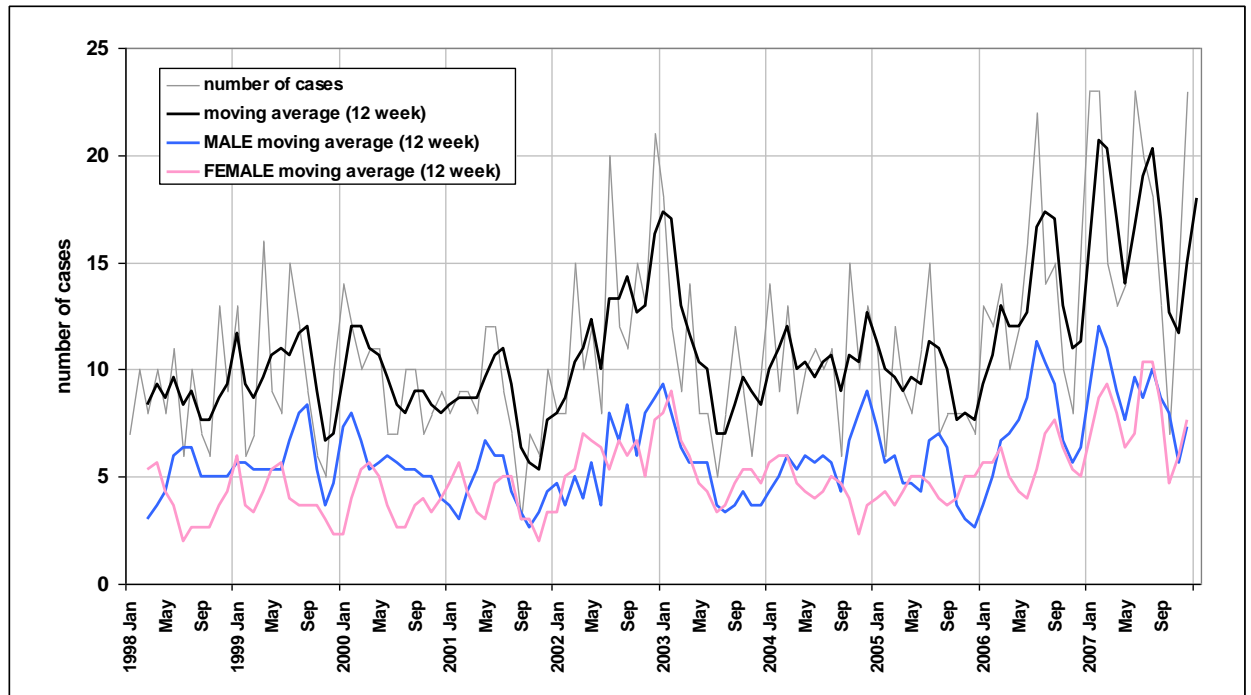




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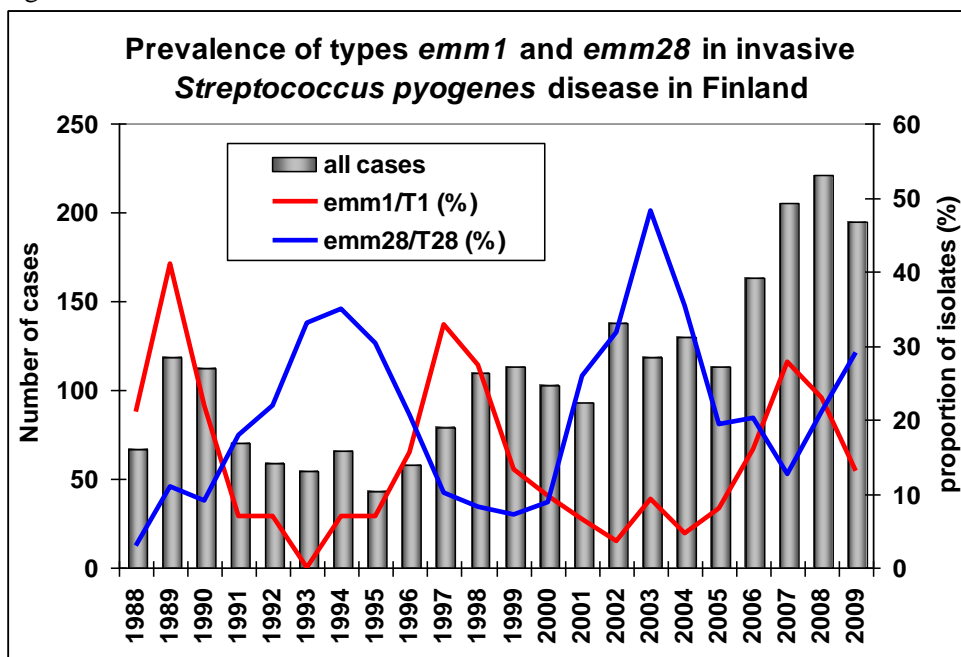
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10 5 <sup>1</sup> Bacteriology Unit, Department of Infectious Disease Surveillance and Control, National Institute for  
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40 19 Category:  
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42 20 Word count for abstract: 200  
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44 21 Word count for text: 2347  
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## 25 ABSTRACT

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6 28 investigation of recent trends and outcome for iGAS.  
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42 43 **Key words:** group A streptococcus; *Streptococcus pyogenes*; epidemiology; *emm* typing; outcome;  
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## 46 INTRODUCTION

1  
2 47 *Streptococcus pyogenes* (group A streptococcus, GAS) causes a wide array of infections ranging in  
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4 48 severity from mild pharyngitis and skin/soft tissue infections to severe invasive infections. In the late  
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6 49 1980s, a change in the epidemiology of severe GAS infections, with an increase in the incidence and  
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8 50 severity of disease was documented [20]. The role and increased pathogenic potential of type M1 in  
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10 51 epidemics were of specific interest [13, 25]. The incidence of severe GAS disease shows variations  
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12 52 over time and geographic region, possibly reflecting the population's susceptibility to particular strains  
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14 53 with diverse virulence properties [9, 17, 26]. Dynamic changes in the type distribution of GAS may  
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16 54 also influence the case fatality of these infections.  
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21 55 In Finland, the incidence rate of invasive group A streptococcal (iGAS) disease has also shown  
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23 56 fluctuations during this and the previous decade, and an increasing trend has been noticed [21]. In  
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25 57 2006, clinicians contacted the National Institute for Health and Welfare and described suddenly  
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27 58 encountering more severe disease manifestations with a poor outcome. These events prompted us to  
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29 59 investigate the recent trend and outcome of iGAS infections and *emm* type distribution in Finland in  
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31 60 more detail.  
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## 33 34 35 61 METHODS

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38 62 **Surveillance.** The national healthcare system of Finland (population 5.3 million) is organised into 20  
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40 63 healthcare districts (with catchment populations ranging from 58,000 to 1.5 million), forming five  
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42 64 tertiary care districts. Since 1995, all clinical microbiology laboratories have mandatorily notified all  
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44 65 isolations of *S. pyogenes* from blood or cerebrospinal fluid (CSF) to the National Infectious Disease  
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46 66 Register (NIDR). With each notification, the following information is transmitted (generally  
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48 67 electronically) to the NIDR: date and type of specimen, unique national identity code of the patient  
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50 68 (since 2004), date of birth, sex, and place of treatment. Within an interval of three months,  
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52 69 notifications concerning the same patient are merged into a single case. The corresponding *S.*  
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54 70 *pyogenes* isolates are submitted to the national reference laboratory.  
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77 the Lancefield group A antigen was identified using Streptex latex agglutination (Remel Europe Ltd,  
78 U.K.). *emm* typing was performed for all isolates according to guidelines by the Centers of Disease  
79 Control and Prevention ([http://www.cdc.gov/ncidod/biotech/strep/protocol\\_emm-type.htm](http://www.cdc.gov/ncidod/biotech/strep/protocol_emm-type.htm)) as  
80 previously described [22]. Susceptibility to erythromycin, clindamycin, and tetracycline was  
81 determined with agar dilution method for all isolates. Susceptibility was assigned according to  
82 interpretative criteria for MIC as recommended by the Clinical and Laboratory Standards Institute [2].

83 **Data analysis and statistics.** Data on the cases of iGAS, their outcome, and *emm* typing and  
84 antimicrobial susceptibility data (where available) were linked using the national identity code of the  
85 case-patient and the date of specimen. Where the national identity code was unavailable, other  
86 available information was used for linkage. Average annual incidence rates were calculated for 1998-  
87 2007 using the population census at the end of the previous year, as obtained from Statistics Finland.  
88 Age- and sex-specific incidence rates and male-to-female ratios with 95% confidence intervals (CI)  
89 according to Poisson distribution were calculated. 7-day case fatality was calculated for 2004-2007  
90 and for each *emm* type separately.  $\chi^2$  and Kruskal-Wallis tests were applied where appropriate to test  
91 for statistical significance between subgroups and distributions. Differences were considered  
92 significant when  $P < 0.05$ . Data were analyzed with Intercooled Stata™ 9.1 software for Windows  
93 (StataCorp, U.S.) and R statistical software version 2.9.0 (R Development Core Team, Austria).

## 94 **RESULTS**

95 **Incidence rates.** From January 1998 to December 2007, 1318 cases of iGAS (range by year, 100-207)  
96 were identified (Table 1). The median age of case-patients was 52 years (range, 0-95 years); 55% were  
97 males. The average annual incidence rate of iGAS was 2.5 cases per 100,000 population. The rate was



98 higher in males than in females and in males of adult age groups it increased with age (Table 2). The  
99 highest rates were observed among the elderly patients. Males had a significantly higher rate of  
100 infection than females especially among persons aged 45-64 years, whereas females had a higher rate  
101 than males among persons aged 25-34 years.

102 The annual incidence rate fluctuated (range by year, 1.9-3.9 cases per 100,000 population) but showed  
103 an increasing trend during the study period. Peaks occurred in 2002 (2.9 cases per 100,000) and in  
104 2006-2007 (3.1-3.9). The average annual incidence rate in the five tertiary care districts varied  
105 between 1.8-3.1 cases per 100,000. Of all cases, 41% were localized in the tertiary care district around  
106 Helsinki, where the annual incidence rate varied within the range of 2.2-4.4 cases per 100,000.  
107 Variation in the seasonal activity of iGAS disease could be identified, with occasional peaks of cases  
108 occurring during the midwinter (for both sexes) and midsummer (with male cases dominating; Figure  
109 1a and 1b).

110 ***emm* sequence types.** For 602 out of 609 cases during 2004-2007, a corresponding isolate was  
111 received. A total of 46 *emm* types were encountered (range by year, 23-28 types). The annual  
112 proportion of non-typable isolates varied within 1-5%. The five most common *emm* types were 28, 1,  
113 84, 75 and 89, together accounting for 60% of isolates (Table 3). Type *emm*28 was the most  
114 predominant type in 2004, but its proportion declined each year while that of *emm*1 increased, and by  
115 2007, *emm*1 became the most common type. Type *emm*1 isolates were mainly of subtypes 1.0 and  
116 1.10, but sporadic cases of other subtypes were also encountered. A new and uncommon type, *emm*84,  
117 emerged in 2005 and became the second most common type by 2007.

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

122 **Outcome.** During 2004-2007, 48/609 case-patients died within 7 days of the positive blood or CSF  
123 culture (overall case fatality, 8%). The case fatality did not significantly differ between males and  
124 females (9% vs. 6%,  $P=0.172$ ). The case fatality was the lowest in 2004 (3%), increasing to its highest

125 in 2005 (12%), and then declined by 2006 (10%) and 2007 (7%). The case-patients with fatal outcome  
126 were older than those who survived (median age, 60 vs. 54 years;  $P<0.01$ ). No fatalities occurred in  
127 patients aged  $<1$  and 15-24 years.

128 Overall, infections by *emm1* were significantly associated with higher case fatality (14% vs. 8% with  
129 all other types;  $P<0.02$ , Table 3). Cases by *emm75* and 79 were also associated with higher than  
130 average case fatality (14% for both). In contrast, *emm28* was associated with lower case fatality (2%  
131 vs. all other types,  $P<0.01$ ) along with type 81 (0%, respectively).

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

## 136 **DISCUSSION**

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

144 The observed incidence rate of 3.9 cases per 100,000 population in 2007 is the highest in Finland since  
145 1995. This study together with our earlier research shows that the incidence of iGAS disease has  
146 fluctuated since the 1990s but continued its increasing trend [21, 23]. During 2003-2004, the U.K.,  
147 Sweden, Denmark and Finland had the highest rates of infection (range 2.5-3.3 per 100,000) in a  
148 European study [9]. Since then, indications of an increase in the incidence are seen in Sweden to 4.5  
149 cases per 100,000 by 2007 ([http://www.smittskyddsinstitutet.se/in-english/statistics/beta-hemolytic-](http://www.smittskyddsinstitutet.se/in-english/statistics/beta-hemolytic-group-a-streptococci-gas-invasiv-infection/)  
150 [group-a-streptococci-gas-invasiv-infection/](http://www.smittskyddsinstitutet.se/in-english/statistics/beta-hemolytic-group-a-streptococci-gas-invasiv-infection/)) and very recently in the U.K. [11]. In contrast, the  
151 incidence of iGAS disease in the U.S.A. has remained relatively stable, at an average of 3.5 cases per

152 100,000 during 1995-2004, with a moderate increase to 3.8 in 2007

1 153 (<http://www.cdc.gov/abcs/survreports.htm>) [17].  
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4 154 The incidence of iGAS disease in Finland generally increased with age as expected, but the rate in the  
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6 155 elderly ( $\geq 65$  years) still remained at a lower level than has been reported in Sweden, Denmark, the  
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8 156 U.K. or the U.S.A. [4, 10, 12, 17]. Males had a higher incidence of iGAS disease compared to females,  
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10 157 which has also been noted by some other studies [9, 17]. Differences could also be identified in the  
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12 158 age- and sex-specific rates, with males having significantly more infections than females in the age of  
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14 159 45-64 years. In contrast, females had more infections in the age of 25-34 years than males. A similar  
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16 160 clear peak in the incidence of females around the same age has been noticed in earlier studies from  
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18 161 Denmark and the U.K. [10, 12].  
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23 162 The characteristic fluctuation in the incidence of iGAS disease is presumably a reflection of changes  
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25 163 in the *emm* type distribution and the population's susceptibility towards particular strains, especially of  
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27 164 emerging types [4, 16, 17]. The *emm* type distribution in Finland underwent major changes during  
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29 165 2004-2007 when *emm1* replaced *emm28* as the most predominant type. The incidence of iGAS disease  
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31 166 increased simultaneously with the increasing prevalence of type *emm1*, as has also been observed by  
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33 167 others [25]. However, changes in the prevalence of other types, such as the sudden emergence of  
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35 168 *emm84*, also contributed to the increase [23].  
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39 169 The type distribution of iGAS isolates in Finland has common features with that of other countries but  
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41 170 also some unique characteristics. *emm* types 1, 28 and 89 are common globally but 75 and 84 are rarer  
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43 171 and have not featured among the five most common *emm* types elsewhere [4, 5, 7, 12, 17, 26]. The  
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45 172 low prevalence of cases by *emm3* is of interest, as it is a common type in many countries, and often  
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47 173 associated with high case fatality [7, 12, 17, 26]. The *emm* types included in the putative 26-valent  
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49 174 recombinant vaccine would have covered approximately half of the Finnish isolates in 2004-2007, a  
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51 175 notably smaller proportion than has been estimated for the U.S.A. (79%) and Japan (82%) [7, 14, 17].  
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56 176 Within the last 20 years, a periodic fluctuation of peaks and troughs of the two most common  
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58 177 genotypes *emm1* and *emm28* has occurred in Finland. Peaks in numbers of M/*emm1* have been  
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60 178 observed earlier in 1988-1990 and 1997-1998, and in this study in 2006-2007 [6, 15, 21]. Similarly,  
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179 the prevalence of type *emm28* has peaked in 1993-1995 and 2002-2004 [15, 21]. Such a pattern of  
1 180 alternating type prevalence may be a reflection of changes in the general immunity of the population.

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4 181 Types *emm28* and more rarely also *emm4* have been known to associate with postpartum infections  
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6 182 and puerperal sepsis [1, 3, 26]. Also in this study, *emm28* infections were found to be specifically  
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8 183 concentrated in females of child-bearing age. However, estimations of how many of these cases were  
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10 184 pregnancy-related infections are beyond the scope of this study.

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14 185 The overall erythromycin resistance during 2004-2007 was expectedly low, as the rate has declined  
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16 186 during this decade in Finland

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18 187 ([http://www.ktl.fi/portal/english/projects/fire/finres/finres\\_\\_antimicrobial\\_resistance\\_statistics\\_/strept](http://www.ktl.fi/portal/english/projects/fire/finres/finres__antimicrobial_resistance_statistics_/streptococcus_pyogenes/)  
19  
20 188 [ococcus\\_pyogenes/](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  
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22 189 resistance rates have been reported for example in Denmark and the U.S.A. [12, 19]. Tetracycline  
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24 190 resistance was associated with certain clones, as has also been found previously, and the resistant  
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26 191 strains were mainly of uncommon *emm* types [8].

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30 192 The overall case fatality of iGAS disease in Finland was relatively low at 8%, compared to those  
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32 193 reported by some other European countries and the U.S.A. [4, 5, 10, 17]. A sudden four-fold increase  
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34 194 in the case fatality occurred from 3% in 2004 to 12% in 2005. During the study, the proportion of  
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36 195 infections by types *emm1* and *emm75* increased, these types being associated with a high case fatality.  
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38 196 In parallel, the proportion of *emm28*, associated with a low case fatality, decreased. Having an  
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40 197 infection by *emm* type 1 or 3 has been identified as an independent factor associated with death due to  
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42 198 iGAS disease [17]. Also in our study, the case fatality by *emm1* was higher than average, however we  
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44 199 did not adjust it for age.

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49 200 Seasonal variation in iGAS disease was observed; in addition to a midwinter peak season, there were  
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51 201 also occasional peaks during the midsummer. In the northern hemisphere, peaks of cases are generally  
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53 202 observed during the winter and spring [4, 9, 17, 26]. There were also sex-specific differences in the  
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55 203 peak seasons, with male cases dominating during the summer. These two peak seasons might be  
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57 204 associated with different predisposing factors and underlying conditions. However, the unusual pattern

205 and irregularity of the seasonality observed in this study may partly arise from natural variation due to  
206 a reasonably small study size.

207 There are some limitations to this study. Firstly, some of the increase in the incidence may be due to  
208 more frequent blood culturing activity [24]. It is also possible but less likely that the incidence would  
209 have been influenced by changes in the reporting system, which was established in 1995. Secondly,  
210 case definitions of iGAS disease differ between countries and complicate comparisons of incidence  
211 rates. Exclusion of non-bacteraemic cases with other sterile site isolations and/or toxic shock by the  
212 Finnish case definition may partly explain the observed lower incidence rate. Thirdly, differences in  
213 blood culture sampling practices between countries may have an effect on the observed incidence [24].  
214 In addition, the observed differences in fatality may arise from the case definition used, the timing of  
215 death considered (7/30-day/in-hospital mortality), and the source of information (e.g. population  
216 registry vs. hospital records). In this study, the 7-day mortality information obtained from the  
217 Population Information System was used. Finally, the surveillance does not include collection of  
218 clinical data of disease manifestations, possible risk factors and underlying conditions of patients.  
219 These data would be needed to address reasons behind the observed differences in the age- and sex-  
220 specific incidence, and such a study has been undertaken within one healthcare district in Finland [18].  
221 In conclusion, dynamic changes in the *emm* type prevalence influenced the incidence and case fatality  
222 of iGAS disease in Finland. An unusual seasonal pattern with peaks in the midwinter and midsummer  
223 was observed. Differences in age- and sex-specific incidence rates and seasonality suggest variation in  
224 predisposing factors and underlying conditions.

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7  
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16 232 Conference on Applied Infectious Disease Epidemiology (ESCAIDE), October 2007, Stockholm,  
17  
18 233 Sweden (poster number B.A.1.28), at the XVII Lancefield International Symposium on Streptococci  
19  
20 234 and Streptococcal Diseases (LISSSD), June 2008, Porto Heli, Greece (abstract number O 4.4), and at  
21  
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24  
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323 **FIGURE LEGENDS**

1  
2 324 **Fig. 1a** Cases of invasive group A streptococcal disease during 1998-2007 in Finland. Thin line,  
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4 325 number of cases; bold line, number of cases (12-week moving average)  
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7 326 **Fig. 1b** Monthly cases of iGAS during 1998-2007 in Finland (all years combined) in males and  
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329 **TABLES**

1  
2 **Table 1** Annual incidence of invasive group A streptococcal disease and the number of cases and  
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4 isolates studied, Finland, 1998-2007  
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Year	Rate <sup>a</sup> 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	1318 (602)

32 <sup>a</sup> Average annual incidence (cases per 100,000 population)  
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334 **Table 2** Age- and sex-specific incidence of invasive group A streptococcal disease, Finland, 1998-

1 335 2007

Age group (years)	Rate <sup>a</sup> of invasive disease (no. of cases)						Rate ratio (RR) <sup>b</sup>	95% CI <sup>c</sup> 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	(1318)	1.3	1.1-1.4*

28 336 <sup>a</sup> Average incidence (cases per 100,000 population)

29 337 <sup>b</sup> male-to-female incidence rate ratio

30 338 <sup>c</sup> CI, confidence interval. Statistical significance (P<0.05) is indicated with an asterisk (\*).

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

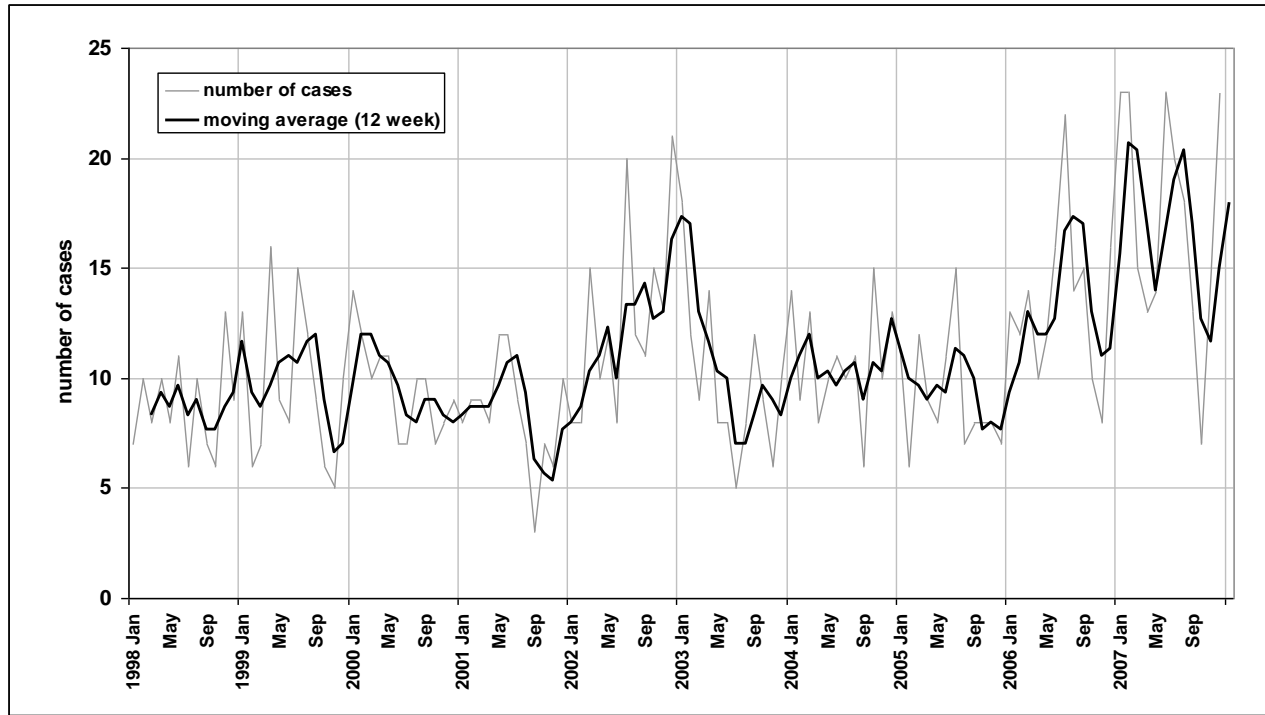
<i>emm</i> type	Number of isolates (%)					Fatal cases (%)	
	2004 (N=128)	2005 (N=110)	2006 (N=161)	2007 (N=203)	2004-2007 (N=602)	2004-2007 (N=48)	
28	46 (35.9)	22 (20.0)	32 (19.9)	25 (12.3)	125 (20.8)	3	(2)
1	6 (4.7)	9 (8.2)	26 (16.1)	57 (28.1)	98 (16.3)	14	(14)
84	0 (0.0)	1 (0.9)	24 (14.9)	32 (15.8)	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 <sup>a</sup>	34 (26.6)	35 (31.8)	37 (23.0)	40 (19.7)	146 (24.2)	11 <sup>b</sup>	(7)

<sup>a</sup> Including isolates from a total of 37 other *emm* types and nontypable isolates.

<sup>b</sup> Other types causing poor outcome: *emm4* and *emm110* (2 cases each); *emm22*, *emm59*, *emm60*, *emm77*, *emm85*, *emm87* and *emm112* (1 case each).

Figure

a



b

