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Invasive group A, B, C and G streptococcal infections in Denmark 1999–2002: epidemiological and clinical aspects

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ABSTRACT

Group A streptococci (GAS) have been described frequently as an emerging cause of severe invasive infections in population-based surveillance studies, whereas the descriptions of group B, C and G streptococci (GBS, GCS and GGS) have been less frequent. Enhanced surveillance for invasive GAS, GBS, GCS and GGS was performed in Denmark in 1999–2002. A detailed questionnaire was completed for 1237 (98%) of 1260 invasive infections. GAS infections dominated (40%), followed by GGS (32%), GBS (23%) and GCS (6%). Most (74%) patients had predisposing factors, and there were no significant differences between the four serogroups when comparing the prevalence of cancer, diabetes mellitus, chronic heart or lung diseases, immunodeficiency or alcohol abuse. The overall case fatality rate at day 30 was 21%, increasing significantly to 59% for patients with streptococcal toxic shock syndrome (STSS). STSS was significantly more frequent in GAS patients (10%) than in GCS (4%), GBS (2%) and GGS (2%) patients. Regression analyses showed that, despite a younger median age among GAS patients, the probability of developing septic shock and mortality was significantly higher among GAS patients than among GBS and GGS patients. These analyses showed no significant differences between GAS and GCS infections. Invasive infections caused by GAS, GBS, GCS and GGS are still a major challenge for clinicians. Continued epidemiological and microbiological surveillance is important to assess the development of these infections and to improve preventative strategies.

Keywords Case fatality rates, β-haemolytic streptococci, Denmark, invasive streptococcal infections, surveillance

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INTRODUCTION

β-Haemolytic streptococci (BHS) groups A, B, C and G (GAS, GBS, GCS and GGS) are a transient part of the normal flora of the pharynx, skin, intestinal tract and vagina, and can cause a variety of invasive and non-invasive infections [1–7]. It is not possible to differentiate between invasive infections caused by GAS, GBS, GCS or GGS solely on the clinical presentation [1–7]. However, GBS remain one of the most significant causes of invasive neonatal infections during the period before, during and after delivery [8]. GBS, together with GCS and GGS, have also been described as frequent invasive pathogens in elderly patients, often in association with alcohol abuse, diabetes mellitus, malignant diseases, and cardiac and peripheral vascular diseases [6,7,9]. In comparison, GAS have been described since the mid-1980s as an emerging cause of potentially fatal infections, such as necrotising fasciitis (NF), myositis and streptococcal toxic shock syndrome (STSS), described originally in healthy young individuals [10]. The same severe clinical presentations have been described subsequently for GBS, GCS and GGS in several case series, but more often in elderly patients with predisposing factors.

The emergence of severe GAS infections has resulted in enhanced surveillance of invasive

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GAS infections in Europe, the USA and Canada since 1986 [2,11–15]. In the present study, a nationwide prospective surveillance, designed originally for invasive GAS infections, was used to monitor invasive infections caused by GAS, GBS, GCS and GGS. The aim was to estimate the incidence of these infections and to determine the frequency of symptoms, predisposing factors, clinical presentation, treatment, complications and outcome, in order to delineate any differences between invasive infections caused by GBS, GCS, GGS and GAS in the same area during the same period.

MATERIALS AND METHODS

Surveillance and specimens

The Streptococcus Unit at the Statens Serum Institut (Copenhagen, Denmark) serves as the National Streptococcus Reference Centre. During the study period, invasive BHS (groups A, B, C and G) isolates were submitted from patients admitted to all hospitals in Denmark (population 5.3 million). The isolates were received as pure isolates, on a voluntary basis, from all Danish clinical microbiological departments. All invasive BHS cultures from normally sterile sites (e.g., blood, cerebrospinal fluid, synovial fluid, pleural fluid, ascites and tissue obtained during surgery) between 1 January 1999 and 31 December 2002 were collected.

Based on information concerning the number of BHS-positive blood cultures from ten of the 15 clinical microbiological departments, the Streptococcus Unit received a constant proportion of these blood isolates, which on average was 79% for GAS, 58% for GBS, 56% for GCS and 66% for GGS (overall average 72%).

Questionnaire

A detailed questionnaire (describing the characteristics of the patient, the infection and the outcome) was completed by the physician responsible for the treatment of each patient. Standard information (age, gender, specimen, serogroup, serotype, date of culture) was included in the statistical analysis even if the questionnaire was not returned. Invasive GBS infections in infants aged <90 days were considered to be a distinct clinical entity and were not included in this study.

Bacteraemia was defined as a clinical entity associated with identification of BHS from blood culture without any specified focus of the infection or complications. NF was defined as necrosis of the fascia and tissue (excluding muscle) and was included as a clinical diagnosis only. A patient with septic shock was defined as a patient with invasive BHS infection and a systolic blood pressure of <90 mm Hg (in adults). The definition of STSS was based on a consensus definition [16], including identification of BHS from a normally sterile site, septic shock and multi-organ failure. An overall case fatality rate (CFR) was assessed at day 1 after the specimen was obtained (1-day CFR; death within day 0 and day 1 after specimen collection), as well as a 30-day CFR.

In order to validate the survey, 41 (3%) of the patients' files were read and the corresponding questionnaires were completed by one of the authors; only insignificant differences between the two questionnaires were found. If a patient had more than one episode of invasive GAS, GBS, GCS or GGS infection during the period 1999–2002, the second episode was only registered in the database if the dates of the cultures were separated by >30 days, or if the second episode was caused by an isolate belonging to a different serogroup. Date of death, or a confirmation that an individual was alive on 1 March 2004, was obtained from the Central Office of Civil Registration for all except nine patients; five patients did not have a personal identification number (i.e., tourists or recent immigrants) and were excluded from the analyses of the CFRs, while four patients were registered as missing or as having left Denmark before 1 March 2004. They were registered as alive, but their details were noted when their registration at the Central Office of Civil Registration ended.

Statistical analysis

Data from the survey were analysed by the SAS System v. 8.2 (SAS Institute, Cary, NC, USA). Spearman rank correlation tests were performed to assess the correlation between the annual incidence rates of GAS, GBS, GCS and GGS, respectively, and the time (in years). For comparisons of proportions between serogroups in relation to outcome of the variables described in the questionnaire, chi-square tests, adjusted for stratification with relation to age (grouped as ≤ 40, 40–65 and >65 years) and gender, were used. However, in situations where outcomes of the response variable were rare, an analogue exact test was conducted. Stratification according to age and gender was used primarily because of a significant difference in the age and gender distribution between the serogroups. Furthermore, only women aged <40 years were included in the statistical analysis regarding fever in relation to delivery, puerperal sepsis and recent delivery.

For the comparison of age distributions between serogroups and other sub-populations of the data, Kruskal–Wallis or Mann–Whitney rank sum tests were used. Two logistic regression analyses were performed to determine factors which were associated significantly with STSS and septic shock without fulfilling the criteria of STSS [16]. Factors included in the analysis were: gender, age (grouped as ≤ 40, 40–65 and >65 years), serogroup, cancer, diabetes, chronic heart or lung diseases, skin lesions, alcohol abuse and immunodeficiency. In order to compare the survival functions between the four serogroups ≤ 30 days after the culture was obtained, a Cox proportional-hazards regression analysis was performed. The following independent variables were included in the model: gender, age (no grouping), serogroups, cancer, diabetes, chronic heart or lung diseases, skin lesions, alcohol abuse and immunodeficiency. The estimated survival function can be considered as a prognosis of mortality when previous knowledge of the patient is available. If a parameter was recorded as 'unknown', or the registration was missing, data were not included in the statistical analyses. A p value of ≤ 0.05 was considered to be significant. Odds ratios and 95% CIs were calculated. Incidence rates were calculated in terms of the incidence/100 000 inhabitants/year.

RESULTS

Study period

Fig. 1 shows the incidence of invasive GAS infections, together with the incidence curves of GBS, GCS and GGS, for 1988–2002. The annual incidence of invasive GAS infections showed considerable variation, but statistical analysis did not reveal a significant trend. The incidence of GBS and GGS showed a constant increase in the study period between 1999 and 2002, but this almost paralleled the increase in the number of blood cultures in the same period (data not shown).

During the study period, the Streptococcus Unit received 1263 BHS isolates. In total, 1260 episodes of invasive BHS infections from 1231 different patients were included in the study. Twenty-seven patients had more than one BHS isolate registered at the Streptococcus Unit (n = 59 isolates), with the second isolate from eight patients belonging to a different serogroup than the first isolate. The same serogroup was isolated twice from 15 patients, on three occasions from three patients, and on four occasions from one patient. Three isolates (one GBS, one GCS and one GGS) were discarded because there were <30 days between the dates of the successive cultures. Questionnaires were received in respect of 1237 (98.2%) of the 1260 episodes.

The distribution of invasive episodes among the four serogroups is shown in Table 1. The median age of the patients with invasive GAS infections was 59.8 (range 0.4–97.4) years, compared to 64.7 (range 0.4–95.8) years, 72.8 (range 1.4–94.6) years and 71.7 (range 0.3–99.6) years among patients with GBS, GCS and GGS infections, respectively. The age distribution differed between the four serogroups, as invasive episodes involving GCS and GGS were significantly more prevalent in the older age groups compared to episodes involving both GAS and GBS (p 0.001). Females constituted 268 (54.0%) of 491 patients with GAS infections, compared to 141 (49.6%) of 274, 33 (44.0%) of 73 and 176 (43.5%) of 393 patients with GBS, GCS and GGS infections, respectively. In the group of invasive GBS infections, there were significantly more female than male patients in the younger age groups ($p \leq 0.001$), a tendency that was not found with the other serogroups. The overall gender distribution did not differ significantly between the four serogroups.

Table 1. Invasive group A, B, C and G streptococcal infections in Denmark (1999–2002)

	No (% of isolates)			
Isolates from	**GAS**	**GBS**	**GCS**	**GGS**
Blood	454 (91.5)	273 (95.8)	70 (92.1)	382 (94.1)
CSF	10 (2.0)	3 (1.1)	1 (1.3)	4 (1.0)
Other specimens	32 (6.5)	9 (3.2)	5 (6.6)	20 (4.9)
Total	496 (100)	285 (100)	76 (100)	406 (100)

GAS, group A streptococci; GBS, group B streptococci; GCS, group C streptococci; GGS, group G streptococci; CSF, cerebrospinal fluid.

Fig. 2 shows that the incidence of streptococcal infections increased with increasing age, particularly after the age of 55 years for GAS, after 65 years for GBS and GGS infections, and a decade later for GCS infections.

Predisposing factors

The questionnaire revealed that most patients with invasive BHS infection had underlying predisposing factors, and that the frequencies differed significantly between the serogroups

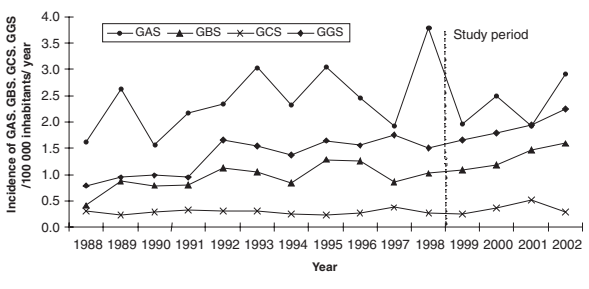

Fig. 1. Incidence/100 000 inhabitants/year of invasive infections caused by group A, B, C and G streptococci in Denmark 1988–2002.

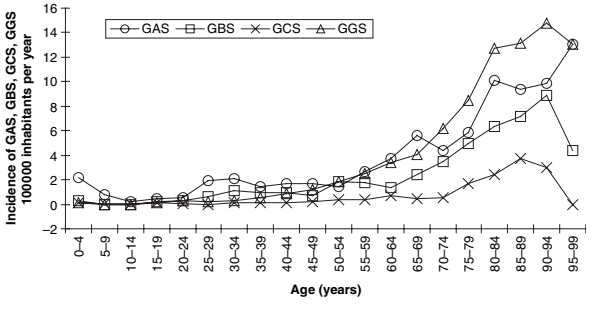

Fig. 2. Incidence/100 000 inhabitants/year by age of invasive infections caused by group A, B, C and G streptococci in Denmark 1999–2002.

(p 0.014; Table 2). Skin lesions were the most frequent predisposing factor and were found most often among patients with GAS infections ($p \leq 0.001$). Even excluding Caesarian sections, GBS dominated BHS infections because of peri- or post-operative procedures (p 0.010). Cancer was the second most frequent predisposing factor, but there was no significant difference between the serogroups (p 0.129). Likewise, the data showed no significant differences between the serogroups in the prevalence of diabetes mellitus, chronic heart or lung diseases, human immunodeficiency virus or alcohol abuse.

Clinical aspects

The variety of infections associated with the four serogroups is summarised in Table 3.

In total, 208 (17.8%) of 1167 episodes were registered as septic shock; these occurred in 124 (26.9%) patients with GAS, 32 (12.1%) patients with GBS, 12 (17.8%) patients with GCS and 40 (10.7%) patients with GGS ($p \leq 0.001$). All four serogroups caused STSS, which was identified in 68 (5.5%) of 1237 patients. Most (73.5%) of the STSS patients were infected with GAS. Furthermore, GAS was identified in 34 (75.6%) of the 45 patients with NF. Nineteen (1.5%) patients had myositis, again with a significant difference between the serogroups (p 0.036), since 16 (84.2%) patients were infected with GAS. For 381 (30.8%) patients, clinicians recorded bacteraemia as the only diagnosis, and this occurred more frequently with GBS infections ($p \leq 0.001$).

Table 2. Predisposing factors[a] for invasive infection with group A, B, C and G streptococci in Denmark (1999–2002)

	GAS *n* = 472 %	GBS *n* = 271 %	GCS *n* = 72 %	GGS *n* = 386 %	Overall p value
Predisposing factor (≥ 1)	73.7	79.0	75.0	83.9[b]	0.014
Skin lesions	31.6	17.7[b]	33.3	36.5	≤ 0.001
Peri-/post-operative	3.4	9.2[b]	2.8	5.7	0.010
IDU	4.9	1.1[c]	1.4	3.6	0.007
Cancer	13.1	18.5	15.3	19.7	0.129
Diabetes mellitus	11.0	14.0	13.9	15.8	0.904
Chronic heart or lung disease	5.5	6.3	8.3	7.5	0.925
Alcohol abuse	9.3	12.2	6.9	11.4	0.573
Immune deficiency[d]	8.3	12.6	13.9	10.1	0.168
NSAID	6.1	6.3	0.0	6.7	0.146

GAS, group A streptococci; GBS, group B streptococci, GCS, group C streptococci; GGS, group G streptococci; IDU, intravenous drug use; NSAID, non-steroid anti-inflammatory drugs.
[a]A patient can have more than one predisposing factor, and a patient can have more than one episode of invasive streptococcal infection.
[b]$p \leq 0.01$ relative to serogroup A.
[c]$p \leq 0.05$ relative to serogroup A.
[d]Includes patients positive for human immunodeficiency virus and those receiving immunosuppressive treatment.

Table 3. Clinical manifestations and complications of invasive infection with group A, B, C and G streptococci in Denmark (1999–2002)

	GAS *n* = 487 %	GBS *n* = 278 %	GCS *n* = 75 %	GGS *n* = 397 %	Overall p value
Septic shock	26.9	12.1[a]	17.8[b]	10.7[a]	≤ 0.001
STSS	10.3	2.2	4.0	2.3[a]	≤ 0.001
NF	7.0	1.8[a]	2.7	1.0[a]	≤ 0.001
Myositis	3.3	0.4[a]	0	0.5[a]	0.036
Pneumonia	10.3	7.6	4.0	4.8[a]	0.002
Meningitis	4.5	2.9	1.3	3.3	0.542
Arthritis	4.1	6.1	5.3	10.3[a]	0.002
Erysipelas	20.1	8.3[a]	34.7[b]	33.8[a]	≤ 0.001
Bacteraemia only	27.1	41.7[a]	32.0	27.5	≤ 0.001
Puerperal fever[c]	35.9	33.3	0	16.7	0.352
ICU	24.7	14.6[a]	15.1[b]	10.0[a]	≤ 0.001
Mechanical ventilation	14.2	6.3[a]	6.9	4.6[a]	≤ 0.001
Surgery	28.9	19.6[a]	13.7[b]	17.2[a]	≤ 0.001
Renal impairment	30.7	25.2[b]	27.0	22.6[a]	≤ 0.001
Hepatic impairment	30.2	21.6[a]	25.0	21.2[a]	0.006
Coagulator dysfunction	20.7	13.2[a]	18.5	10.2[a]	≤ 0.001

GAS, group A streptococci; GBS, group B streptococci; GCS, group C streptococci; GGS, group G streptococci; STSS, streptococcal toxic shock syndrome; NF, necrotising fasciitis; ICU, intensive care unit.
[a]$p \leq 0.01$ relative to serogroup A.
[b]$p \leq 0.05$ relative to serogroup A.
[c]Comparison performed among females aged < 40 years (GAS, *n* = 78; GBS, *n* = 42; GCS, *n* = 3; GGS, *n* = 12).

Case fatality rates

During the first 30 days following collection of the specimen, 21% of patients with invasive BHS infections died (23% of patients infected with GAS, 21% with GCS, 19% with GBS, and 18% with GGS). Patients infected with GAS had a significantly higher 1-day CFR (11%) compared to patients infected with GBS or GGS (both 5%; $p \leq 0.001$); 9% of the GCS patients died within 1 day, with no significant difference between GCS and GAS patients (p 0.296).

The hazard functions for 30-day case fatality (or, equivalently, the 30-day survival functions), as estimated by a Cox proportional-hazards regression, were significantly lower for GBS (p 0.007) and GGS ($p \leq 0.001$) than for GAS (Table 4). No significant difference was observed between the 30-day hazard functions for GAS and GCS. Table 4 also presents the significant 30-day hazard functions for chronic heart or lung disease, alcohol abuse, immunodeficiency and skin lesions.

Septic shock and STSS

Overall, 59% of patients with STSS died within the 30-day period following the collection of cultures, compared to 57% of patients with septic shock without STSS, and 13% of the non-septic

Table 4. Cox proportional-hazards regression analysis of factors associated with fatal outcome within 30 days after invasive infection caused by group A, B, C and G streptococci in Denmark (1999–2002)

	Cox proportional-hazards regression	
	p value	Hazard ratio (95% CI)
Age	≤ 0.001	–
GBS vs. GAS	0.007	0.63 (0.45–0.88)
GCS vs. GAS	0.247	0.73 (0.43–1.24)
GGS vs. GAS	≤ 0.001	0.52 (0.38–0.70)
CHLD	≤ 0.001	2.54 (1.53–3.32)
Alcohol abuse	≤ 0.001	2.38 (1.64–3.45)
Immune incompetence[a]	0.003	1.58 (1.17–2.14)
Skin lesions	0.019	0.70 (0.52–0.94)

GAS, group A streptococci; GBS, group B streptococci; GCS, group C streptococci; GGS, group G streptococci; CHLD, chronic heart or lung diseases.
[a]Includes patients positive for human immunodeficiency virus and those receiving immunosuppressive treatment.

Table 5. Results of logistic regression analyses of predisposing factors associated with septic shock, with or without streptococcal toxic shock syndrome, after invasive infection caused by group A, B, C and G streptococci in Denmark (1999–2002)

	Septic shock including STSS		Septic shock excluding STSS	
	p value	OR (95% CI)	p value	OR (95% CI)
GBS vs. GAS	≤ 0.001	0.19 (0.08–0.45)	0.005	0.50 (0.31–0.81)
GCS vs. GAS	0.101	0.37 (0.11–1.22)	0.530	0.80 (0.39–1.62)
GGS vs. GAS	≤ 0.001	0.20 (0.09–0.42)	≤ 0.001	0.35 (0.22–0.55)
Age	–	–	≤ 0.001	–
CHLD	–	–	0.005	2.42 (1.30–4.48)
Alcohol abuse	–	–	≤ 0.001	2.29 (1.35–3.90)

GAS, group A streptococci; GBS, group B streptococci; GCS, group C streptococci; GGS, group G streptococci; CHLD, chronic heart or lung disease; STSS, streptococcal toxic shock syndrome.

shock patients. Table 5 presents the results of a logistic regression analysis of factors associated significantly with STSS, and a similar analysis of factors associated significantly with septic shock without fulfilling the STSS definition.

DISCUSSION

This study provides an overview of invasive GAS, GBS, GCS and GGS infections in Denmark during 1999–2002, based on nationwide enhanced prospective surveillance. The incidence rates obtained reflect the minimum estimates of invasive BHS disease, since national streptococcal surveillance in Denmark is based on voluntary submission of invasive isolates from the local clinical microbiology departments. However, *c.* 72% of invasive BHS isolates were received and 98% of questionnaires were submitted, and incidence rates from the county of Northern Jutland in Denmark [17] were similar to those in the present study.

No increase in invasive GAS infections was identified during the study period (1999–2002). The average annual incidence and fluctuating pattern of invasive GAS infections were both similar to those in previous reports [11,12]. There was a three-fold increase in invasive GBS and GGS infections in Denmark during 1988–2002, and the incidence curves showed similarities with the incidence curve of GAS until 1996. These similarities may reflect improvements in methodology or an overall increase in the number of blood cultures analysed. The incidence curves for invasive GBS and GGS were almost parallel in 1988–2002. The reason for the continuous increases since 1998 remains unclear, although increased awareness or prolonged survival of adults with underlying chronic diseases (diabetes mellitus, cancer and heart disease) may be a contributing factor [4–9,18–20]. The incidence of GGS and the emerging trend of invasive GGS infections, approaching and potentially surpassing the incidence of invasive GAS infections, were similar to those described elsewhere [20–22]. The incidence of invasive GBS infections was lower than that described in Europe and North America [4,5,23], but was similar to the average annual incidence in a recent surveillance study from Finland [8]. This may be a consequence of the moderate submission rate or may be caused by variations in bacterial virulence, host susceptibility, socio-economic factors or demographic variations. Comparisons of the incidence of GCS infection are almost impossible, since only two studies have presented epidemiological data [24,25].

The present study confirmed that GAS patients are generally younger and associated less frequently with predisposing factors when compared to GBS, GCS and GGS patients [4–7,17–20,25–27]. However, no significant differences in the frequencies of cancer, diabetes mellitus, chronic heart or lung diseases or alcohol abuse were identified in the comparisons between the four serogroups in the present study. As described previously [2,4–7,9,17–20,22,25], skin was the most common portal of entry, while skin and soft tissue infections, together with bacteraemia without focal symptoms, were the most prevalent clinical presentations of invasive BHS infections. Patients with invasive GBS infections were infected more often in association with surgical procedures, and were less likely than GAS patients to

have an impaired skin barrier (i.e., skin lesions or intravenous drug users). In the present study, most GBS infections were diagnosed as bacteraemia with an unknown focus of infection, and more frequently than in previous reports [4,19]. In contrast to GBS, GGS were associated particularly with skin infections. Erysipelas was recorded more frequently for patients with GCS and GGS than for patients with GAS and GBS. Similarly, cellulitis occurred in 60% of patients with invasive GGS infections in a study from Israel [21]. This may reflect a new aspect of this clinical entity, since erysipelas has been regarded traditionally as a specific kind of superficial cellulitis caused predominantly by GAS [28,29].

Puerperal sepsis is regarded currently as a minor problem, but the present results indicate that clinicians should still suspect streptococcal infections in relation to delivery, occurring either sporadically or in clusters [30]. Endocarditis and osteomyelitis have also been described among the clinical manifestations of invasive streptococcal infections [3,6,7,12,18,19,31], but these entities were not included in the present prospective survey. Neither was pneumonia, although it was recorded by clinicians in 7% of cases, which resulted in a frequency slightly lower than that reported previously [5,6,20,25,26,32,33]. Pneumonia is not a diagnosis associated normally with BHS, as it was in the pre-antibiotic era, but there may be re-emergence of this entity [33]. However, there are obvious limitations in the diagnosis, since no radiological confirmation was obtained, and objective distinctions between BHS pneumonia and invasive BHS disease complicated by adult respiratory distress syndrome are lacking.

From the clinicians' point of view, it may be difficult to distinguish between STSS and a straightforward case of septic shock, as similar CFRs were found, and these were comparable to CFRs for septic shock caused by other pathogens [34]. The case definition of STSS may identify individuals with toxic septic shock, as well as those who develop multi-organ failure when subjected to the stress of sepsis without toxicity, although this was not the intention of the consensus definition [16]. Severe infections such as septic shock (with or without STSS) and NF were more likely to be caused by GAS than by GBS, GCS and GGS. GAS was the only independent predictor for the development of STSS, whereas septic shock without STSS was associated with increased age and predisposing factors such as chronic heart or lung diseases and alcohol abuse, as well as GAS. Moreover, GAS STSS patients were younger than GAS patients with septic shock without STSS, perhaps because a certain level of immune response is required for progression of multi-organ failure involved in STSS. This may be seen as analogous to the association between the HLA class II allotype of infected patients and disease progression; that is, the allotype influences the in-vitro immune response induced by streptococcal superantigens, and thereby identifies high and low responders to superantigens [35]. The elderly, with potential immune senescence, or patients with immune deficiency, are associated with poor prognosis for other more obvious reasons [7]. Both the frequency of GAS STSS and the 30-day CFR were comparable with those in other studies [11,12]. The occurrence of STSS caused by GBS, GCS or GGS has been reported primarily in case series studies [36–42], but data from population-based studies has not been presented previously in comparison with GAS STSS.

NF was predominantly a disease caused by GAS, and occurred at a frequency similar to that in previous reports [12,31]. Since the present surveillance study included primarily blood isolates, with only a few isolates from surgical tissue, the real prevalence will probably be higher [11,43]. A large surveillance study of invasive GBS infections [9] reported a GBS NF prevalence of 0.3%, compared with 2% of patients with GBS in the present study and elsewhere [19]. In the present study, NF occurred in 3% and 1% of the patients with GCS and GGS infections, respectively. NF caused by GBS, GCS and GGS has been described previously in several case series [36,41,44–47]. As the clinical presentations of NF and STSS caused by GBS, GCS and GGS are indistinguishable from those caused by GAS, the underlying mechanisms are likely to be related. Some researchers consider that the possible acquisition of GAS-related virulence genes, especially by GGS, is consistent with the hypothesis that GGS may be an emerging pathogen with increased virulence potential [48,49].

The overall 21% CFR for invasive BHS infections was similar to that found previously in population-based studies [2,7,9,17,18,20,26], although other studies have reported lower fig-

ures [4,19]. Because information regarding patient mortality was obtained from the Central Office of Civil Registration, the cause of fatalities, and the link with BHS infection, was not investigated. However, it has been estimated that *c.* 90% of deaths which occur within 30 days are related directly to the infection [22]. In addition to the serotype involved, the prognosis of invasive BHS infection was associated independently with increased age and the precise predisposing factor (i.e., chronic heart or lung diseases, alcohol abuse or immunodeficiency). However, patients with skin lesions were associated negatively with death compared to patients without skin lesions. This was interpreted as a difference between patients with primary bacteraemia (no skin lesions and without any obvious focus of the initial infection) and secondary bacteraemia (with skin lesions and therefore an obvious site of initial infection).

In conclusion, invasive infections caused by BHS remain a major challenge for clinicians. The clinical manifestations vary, and the CFR of 21% increases to *c.* 60% in patients with septic shock. An ageing population, and progress in the treatment of chronic medical conditions, provides an expanding number of patients at risk of invasive BHS. In order to improve preventive strategies and therapeutic procedures, further investigation of the interactions between host and pathogen is needed. Continued epidemiological and microbiological surveillance is important to assess the future development of invasive BHS infections.

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