Epidemiology of invasive Streptococcus pyogenes infections in France, 2007

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2 **Key words:** *Streptococcus pyogenes*, Group A streptococcus, invasive infection, epidemiology, *emm* sequence-type
Abstract

Invasive group A streptococcal (GAS) infections causes significant morbidity and mortality. A national survey was initiated to assess the burden of invasive GAS infections in France, describe their clinical characteristics, and assess the molecular characteristics of GAS strains responsible for these infections.

The survey was conducted in 194 hospitals, accounting for 51% of acute care hospital admissions in France. Clinical, predisposing factors and demographic data were obtained and all GAS isolates were emm sequence-typed.

We identified 664 cases of invasive GAS infections with an annual incidence of 3.1 per 100,000 population. The case-fatality ratio was 14%, and rose to 43% in case of streptococcal toxic shock syndrome. Bacteremia without identified focus (22%) and skin/soft tissue infections (30%) were the most frequent clinical presentations.

Necrotizing fasciitis was frequent in adults (18%) and uncommon in children (3%). The 3 predominant emm types were emm1, emm89 and emm28 accounting for 33%, 16%, and 10% of GAS isolates, respectively. emm1 type was associated with fatal outcome and was more frequent in children than in adults. Six clusters of cases were identified, each cluster involving 2 invasive cases due to GAS strains which shared identical GAS emm sequence-types. Four clusters of cases involved 8 postpartum infections, one family cluster involved mother and child, and one cluster involved two patients in a nursing home. Invasive GAS infection is one of the most severe bacterial diseases in France, particularly in persons aged ≥ 50 years or when associated with toxic shock syndrome.
INTRODUCTION

*Streptococcus pyogenes* (group A streptococci [GAS]) causes a wide variety of diseases ranging from mild pharyngitis and impetigo to severe invasive infections including streptococcal toxic shock syndrome (TSS) and necrotizing fasciitis. The lethality of severe GAS infections remains high, ranging from 14% to 19% in high-income countries (8,11,12,16,22,29). In addition, outbreaks of invasive GAS infections have been described in the community, in nursing homes, and in hospitals (7,13,17,24,26). Although rarely reported, secondary transmission occurs among household contacts (9,18,25).

In France, invasive GAS infections surveillance relies on the Epibac national hospital-based laboratory network, and on the characterization of GAS strains sent to the French National Reference Center for Streptococci. Epibac network has been collecting data since 1987 from participating hospital-laboratories on bacteremic infections and meningitis due to 6 bacterial species, including GAS. These infections are defined as the isolation of the bacterium from blood (bacteremia) or cerebrospinal fluid (meningitis). The participating hospitals account for more than 75% of French acute care admissions as described at [http://www.invs.sante.fr/surveillance/epibac/default.htm](http://www.invs.sante.fr/surveillance/epibac/default.htm).

The French National Reference center for Streptococci has been collecting GAS strains isolated from invasive and non-invasive GAS infections since 1995 (28).

According to Epibac data, between 2000 and 2006, the incidence of GAS bacteremia and meningitis increased by 32% in France, from 1.5 to 2.0 cases per 100,000 population (National Institute for Public Surveillance, unpublished data). National guidelines for the prevention of secondary cases of invasive GAS infection in the
community and hospitals were issued in 2005 and 2006, respectively (5,6). Antibiotic prophylaxis is recommended to all household contacts of a patient with invasive GAS infection when one of them presents a predisposing factor to invasive GAS infection.

In order to better characterize the epidemiology of invasive GAS infections, we conducted a national prospective survey of invasive GAS infections in metropolitan France. The main goals were to: 1) estimate the burden of invasive GAS infections with or without positive blood culture; 2) characterize the clinical presentations; 3) assess predisposing factors and outcomes; 4) describe the molecular characteristics and antibiotic susceptibility of GAS strains isolated from invasive infections; and 5) assess the level of implementation of the recommendations on antibiotic prophylaxis among household contacts (6).

**MATERIAL AND METHODS**

**Design**

We conducted a cross sectional survey over a one-year period from November 2006 to November 2007. Among the 332 hospital laboratories eligible for Epibac surveillance, 194 laboratories located throughout the 22 French administrative regions participated on a voluntary basis. Participating hospitals accounted for 51% of French acute care inpatients admissions in 2007.

**Case definition**

GAS invasive infection was defined as the isolation of the bacterium from a usually sterile site (e.g., blood, cerebrospinal fluid, joint, bone or synovial fluid), or from samples obtained from deep body site aspirates, intra-operative specimens, or from a non sterile site in association with one of the followings clinical conditions: necrotizing fasciitis, clinically ascertained pneumonia, endometritis, salpingitis, or...
TSS, not attributable to any other cause and defined according to the US Working Group on Severe Streptococcal Infections definitions (31).

Invasive GAS infections identified during the hospital stay or within the 7 days following the hospital discharge were presumed to be nosocomial if they occurred at least 48 hours after the time of admission, or if the patient underwent a surgical operation during the 7 days preceding the onset of GAS infection. Postpartum infections were presumed to be nosocomial if occurring during the hospital stay or within 7 days after discharge.

A confirmed GAS infection in a case-contact was defined as isolation of GAS from the site of infection or, in case of acute pharyngitis, as a positive rapid antigen detection testing for GAS.

**Data collection**

Cases were identified by the local microbiologist who completed a standardized questionnaire for each case meeting the case definition with the support of the local infectious diseases specialist and of the attending physician. Data collected included age, sex, clinical presentations, predisposing factors and outcomes at the time of discharge from hospital. Information regarding the occurrence of a GAS infection among close contacts 30 days before or after the onset of disease of the identified case was also collected. Close contacts were defined as individuals living in the same household or institution as the case or having close and/or repeated contact, during the 7 days preceding the onset of the index case (5). In hospitals, close contacts were patients hospitalized in the same ward (6). Additional information regarding possible clusters of nosocomial invasive GAS infection was retrieved from mandatory notifications of nosocomial invasive GAS infection and from available
investigation reports. The surveys’ questionnaires were sent to the Public Health Institute staff who reviewed the inclusion criteria and the completeness of the data. The microbiologists were reminded to report cases by regular phone calls and mailings.

**Microbiological methods**

GAS isolates were confirmed to be *S. pyogenes* by β-hemolysis on sheep blood agar, presence of Lancefield group A antigen and production of pyrrolydonyl arylamidase (20). Antibiotic susceptibility to penicillin, amoxicillin, vancomycin, erythromycin, tetracycline and clindamycin was determined according to the French Society for Microbiology guidelines as described at [http://www.sfm.asso.fr](http://www.sfm.asso.fr). All available isolates were also screened for streptococcal pyrogenic exotoxin speA, speB and speC and *ssa* genes by multiplex PCR assay. When identical isolates on these markers were obtained from any given patient, only the first invasive isolate was further characterized by molecular typing. The *emm* gene sequencing was performed as described by Beall *et al.* 1996 (1) with modifications described at [www.cdc.gov/ncidod/biotech/strep.htm](http://www.cdc.gov/ncidod/biotech/strep.htm).

**Data analysis**

The incidence of invasive GAS infections in France was estimated by applying a correcting factor yielded by the survey to the incidence of GAS bacteremic infections and meningitis in 2007 ascertained by Epibac surveillance (IncEPI). IncEPI is calculated by dividing the number of reported cases by the population covered by Epibac surveillance, corrected for the under-reporting rates of cases which is evaluated by 3 sources capture-recapture analysis (2,3,10,14,23). The population
coverage was assessed at 78% in 2007 and a 20% underreporting rates was assumed.

Invasive GAS incidence was therefore computed as IncEPI / (1 – k), where k is the correcting factor corresponding to the proportion of invasive GAS infections in the survey where GAS has not been isolated from blood or cerebrospinal fluid and IncEPI is the incidence estimated through Epibac. Age specific incidence rates for invasive GAS infections were estimated by applying to the specific age groups considered the same methodology as described above for the all-ages invasive GAS infections incidence rate.

A cluster of invasive GAS infections was defined as the occurrence of ≥ 2 invasive GAS infections cases in close contacts within 30 days for community-acquired invasive GAS infections and within 6 months for institutionalized invasive GAS infection cases. Clusters were confirmed if the related invasive GAS infections cases were due to GAS strains of identical emm sequence-types.

Associations between outcomes, clinical presentations, predisposing factors, and strains characteristics were tested using Fisher’s exact test for binominal data. Associations between each specific clinical presentation or predisposing factor with death was tested irrespectively of the presence of other clinical presentations or predisposing factors. Death predictors were evaluated using logistic regression modelling. Statistical analysis was performed using Stata 9.2 (Stata Corporation, College Station, Texas).
RESULTS

Number of cases, demographic characteristics, incidence

We identified 664 invasive GAS infections meeting the case definition. GAS strains were isolated from blood cultures alone (n = 345, 52%), blood cultures and other sterile sites (n = 47, 7%), blood cultures and non-sterile sites (n = 75, 11%), sterile sites other than blood (n = 127, 19%), and non-sterile sites (n = 70, 11%); the latter were included on the basis of the presence of at least one of the following clinical manifestations: toxic shock syndrome (n = 21), necrotizing fasciitis (n = 22), endometritis (n = 23), salpingitis (n = 2) or pneumonia (n = 2).

The median age of patients was 55 years (range, 28 days - 103 years). Male to female ratio was 0.9.

The estimates of invasive GAS infections incidence in 2007 by age-group are presented in Fig. 1. On the basis of Epibac surveillance the incidence of GAS bacteremic infections and meningitis was 2.2 cases per 100,000 population in 2007. Moreover, GAS invasive infections where GAS was not isolated from blood or cerebrospinal fluid accounted for 29% (n = 193) of the total invasive GAS infections reported in the survey. Therefore, the overall incidence of invasive GAS infections in France was estimated to be 3.1 (95% CI, 2.9 to 3.2) cases per 100,000 population in 2007. The highest incidence occurred in children < 5 years (5.7 per 100,000) and in adults ≥70 years (8.4 per 100,000). Incidence rates were similar for men and women except in those aged 50-69 years where incidence was higher in men than in women (3.5 vs. 2.2 per 100,000, P < 0.001).

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Clinical presentations

Among the 664 invasive GAS infections included, various clinical presentations were reported (Table 1). Non-necrotic skin or soft tissue infections were the most frequent, accounting for 30% of the cases; blood cultures were positive in 82% of these cases. Necrotizing fasciitis was reported in 16% of cases, pleuro-pulmonary infection in 11%, septic arthritis in 9%, and postpartum sepsis in 5%. Other clinical presentations such as intra-abdominal infections, osteomyelitis, and gynaecological infections were reported in less than 5% of cases. No identified focus of invasive GAS infection was reported in 22% of cases although a portal of entry was clinically suspected in 71% (n = 105), to be the skin in 60%, the respiratory tract in 30% or other sites in 10%.

Septic arthritis, osteomyelitis and pleural infection were observed more frequently in children (<15 years, n = 109) than in adults (≥ 15 years, n = 554), being reported in 20%, 15% and 12% of children, respectively and in 7%, 1% and 2% of adults, respectively (P < 0.001 each). Necrotizing fasciitis was mostly observed in adults and uncommon in children (18% vs 3%, P < 0.001). Postpartum cases accounted for 32% (32 /100) of cases in women of childbearing age (15-49 years).

A TSS was associated in 20% of cases (Table 2). It was 3- and 1.9-fold more frequent in the presence of necrotizing fasciitis and pulmonary infection, respectively (P < 0.001 and P < 0.01) than in other clinical presentations. TSS was reported in children (15%) and in adults (21%) but it was more frequent in persons aged 50-69 years than in other age-groups (31% vs. 17%, P < 0.001)(Table 2).

Predisposing factors

Predisposing factors were ascertained for 657 (99%) cases; 507 (77%) presented at least one predisposing factor for invasive GAS infection (Table 4).
pathology (e.g., burns, varicella, skin disease and wounds) was reported in 247 (38%) cases and in 114 (52%) of those aged ≥ 70 years. A chronic medical condition such as diabetes, malignancy, liver or cardiac chronic disease was reported in 234 (36%) cases. Among children (<15 years), 55 (51%) presented a predisposing factor; varicella was reported in 20 (19%), primarily in those under 5 years of age (19/20), and other lesion or disease of the skin was reported in 19 (18%). Only 6 (6%) children presented a chronic medical condition. Ninety-six cases (15%) were considered nosocomial, among them 32 (5%) were postpartum infections cases.

**emm sequence typing and antimicrobial susceptibility**

Among the 664 cases, at least one GAS strain for 623 cases (94%) was sent to the National Reference Center for Streptococci which analyzed only one representative strain per case. A total of 48 different *emm* types were identified and 3 types accounted for 59% of isolates: *emm*1 (n = 203, 33%), *emm*89 (n = 100, 16%) and *emm*28 (n = 65, 10%), followed by *emm*4 (n = 34, 5%) and *emm*12 (n = 33, 5%) (Fig. 2). No association was observed between the distribution of *emm* types and geographical location. *emm*1, *emm*3 and *emm*12 types were more frequently identified in children than in adults (44% vs. 30%, *P* < 0.05, 7% vs. 2%, *P* < 0.05 and 12% vs. 4%, *P* < 0.01, respectively), while *emm*89 type was less frequently identified in children than in adults (9% vs. 18%, *P* < 0.05).

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SpeA, speB, speC and ssa genes were detected in 37%, 100%, 49% and 12% of strains respectively. SpeA gene was carried by 97% of *emm*1 strains (196/203) and
100% of emm3 strains (18/18) whereas it was carried by only 4% (16/399) of other 
emm strains.

emm1 type was associated with a higher frequency of TSS (P < 0.001) and fatal 
outcomes (P < 0.001) than other emm types in univariate analysis. The presence of 
the speA gene was also associated with a higher frequency of TSS (P < 0.001) and 
fatal outcomes (P < 0.001).

All GAS strains were susceptible to penicillin, amoxycillin and vancomycin; 8% were 
resistant to erythromycin, 13% to tetracycline, and 6% to clindamycin. Among GAS 
children isolates (n = 105), 4%, 3% and 1% were resistant to erythromycin, 
tetracycline and clindamycin respectively. A higher prevalence of resistance was 
observed among GAS adults isolates (n = 518), 9%, 15% and 7% being resistant to 
erythromycin, tetracycline and clindamycin, respectively.

Outcomes

Overall, 31% (n = 209) of cases required intensive care admission and 28% (n = 183) 
underwent surgery. The outcome at the time of discharge from hospital was available 
for 646 cases (Table 2). The overall in-hospital lethality was 14% (95% CI, 11% to 
17%) reaching 43% (56/129) in patients who presented with TSS. More than two-
thirds of the deaths (62/91, 68%) occurred within the 4 days following the onset of 
infection.

Among 104 necrotizing fasciitis cases, 64% required intensive care admission and 
69% underwent surgery, 22% (22/102) died and 31% (32/102) had a permanent 
complication at the time of discharge from hospital, such as an amputation (11%) or 
skin soft tissues or muscular defects (14%) due to necrosis. Overall, only 46%
(47/102) of the patients who presented a necrotizing fasciitis recovered without sequelae.

Bacteremia without identified focus, necrotizing fasciitis, pneumonia and TSS were all associated with a higher risk of death in univariate analysis ($P < 0.01$, $P < 0.05$, $P < 0.05$ and $P < 0.001$ respectively).

Death was associated with the presence of a predisposing factor (16% vs. 9%, $P < 0.05$). Among predisposing factors, chemotherapy, diabetes, malignancy or hepatic diseases were all associated with death in univariate analysis ($P < 0.01$, $P < 0.01$, $P < 0.05$ and $P < 0.01$, respectively).

According to the results of multivariate logistic regression analysis, age $\geq 50$ years, pre-existing hepatic disease, TSS, bacteremia without identified focus, and $emm1$ type were all independently associated with an increased risk of fatal outcome (Table 3).

**Antibiotic prophylaxis and cluster of GAS infections in close contacts**

Information on the prescription of an antibiotic prophylaxis to household contacts was available for 451 (68%) cases. Among them, 50 (11%) reported having one or more of their household contacts who presented a predisposing factor for invasive GAS infection; 266 (59%) cases did not report such a factor among their contacts and 135 (30%) lived alone. In following French recommendations, an antibiotic prophylaxis was to be prescribed to each member of these 50 households (i.e: 103 household contacts); it was actually fully respected for all the household contacts in only 7 households (including 11 household contacts), and partially realized in 1 household (1 antibiotic was prescribed to 1 child with varicella while the 5 other household contacts did not receive any). No prophylaxis at all was conducted in 42 households.
(including 86 household contacts). Despite a poor compliance with the recommendations, no subsequent case of invasive GAS infection was reported in the 103 household contacts of these 50 households.

Information concerning the occurrence of a GAS infection in close contacts of the case was available for 518 (78%) cases. A non-invasive GAS infection was confirmed in a close contact of 11 (2%) cases; the contact-case was a member of the household (8 cases), or shared the same hospital-room (1 case) or was a resident of the same nursing home (2 cases).

Subsequent invasive GAS infection cases were identified in the 30 days following the onset of a case among the close contacts of 7 (1%) cases; for 5 of these cases, GAS strains were of identical emm type and for 2 they were of different emm types. In addition to these 5 clusters, a cluster of 3 cases of GAS infection (2 invasive cases and 1 non-invasive case) which shared identical emm89 GAS strains was identified in a delay of 77 days in 3 residents of the same nursing home.

Overall, 6 clusters involving 12 invasive GAS infections cases were confirmed on the basis of epidemiological links and isolation of GAS strains of identical emm types (Table 5). One family cluster due to an emm1 strain (cluster 1) occurred in a 34-years-old mother and her three-year old daughter, both previously healthy; the mother died and the young girl recovered. One cluster of two invasive and one non-invasive infection due to an emm89 strain (cluster 2) occurred in three chronically disabled residents of a nursing-home. Four post-partum clusters involved two women each, who shared the same emm4, emm11, emm28, or emm89 strain. Investigation reports were available for 3 clusters; the suspected route of contamination was direct transmission in the members of the family in cluster 1, indirect transmission from one
resident to another during skin wound care in cluster 2 and intra-hospital patient to
patient contamination during the post delivery period in cluster 5 (Table 5).

**DISCUSSION**

This nationwide prospective survey enables the determination of the incidence of
invasive GAS infections in France. It indicates that cases not captured by routine
surveillance of bacteremia and meningitis account for a substantial part (29%) of
invasive GAS infections. Given this result, the estimated rate was in 2007, 3.1 cases
per 100,000 population, a rate comparable to the 2.2 to 3.8 recently reported from
surveys in Europe, the USA and Canada (11,22,27).

The highest risks of invasive GAS infections were identified in young children and
elderly patients as previously reported (11,27). This study also highlights the high
severity of invasive GAS infections, with a case fatality ratio of 14%, which is also in
agreement with those reported in the USA: 14% (22), Sweden: 14,5% (8), and
Denmark: 16% (16).

This survey allowed a comprehensive assessment of the epidemiology of invasive
GAS infections in France since predisposing factors, outcomes and GAS isolates
were obtained from more than 90% of the cases.

Regarding the representativeness of the survey, although the survey was conducted
on a voluntary basis, the participating hospitals, accounted for 51% of French acute
care admissions in 2007, and were distributed in all French regions. Regarding cases
characteristics, the age and sex distribution of bacteremic invasive GAS cases
included did not differ from those of bacteremic cases identified in Epibac
surveillance in 2007, suggesting no significant bias in the recruitment of cases.

Regarding the estimation of invasive GAS infection incidence, as Epibac results are
regularly validated through 3 sources capture-recapture analysis, we consider that our estimation of global invasive GAS infection incidence based on the Epibac rates for bacteremia or meningitis, corrected by the proportion of invasive GAS infections in our survey where the GAS has not been isolated from blood or CSF fluid, provides the best incidence estimate.

Inclusion of cases with GAS isolates obtained from a non sterile site (i.e. 23 cases of endometritis, 2 cases of salpingitis and 2 cases of pneumonia), accounting for 4% of the total of cases, may hamper comparison of the results with those of surveys which include only cases with GAS isolates from normally sterile sites (8,16,22). However, the design of our survey led to a more comprehensive ascertainment of the burden of invasive GAS infections in our country.

The results emphasize the severity of invasive GAS infections in adults over 50 years of age who accounted for the majority (82%) of fatal invasive GAS infections. This may in part be explained by the high frequency of TSS and pre-existing chronic medical conditions in this age group. On the contrary children and women with postpartum endometritis were less likely to present severe clinical manifestations such as necrotizing fasciitis, TSS, or a fatal outcome. The highest risk of fatal outcome was associated with pneumonia, necrotizing fasciitis and bacteremia without identified focus.

emm1 was the main emm type associated with a higher risk of fatal outcome after adjusting on other predisposive factors, as previously reported in Europe and the USA (15,22). Most of emm1 strains carried the speA gene which was also associated with severe infections and outcomes. However as the presence of speA gene was highly correlated with emm1 type, the role of speA gene in the occurrence of TSS or a fatal outcome could not be distinguished from that of emm1 type. Moreover emm1
strains were more frequent in patients without chronic medical condition (36% vs. 27%, P < 0.02) and in children. These results confirm the high virulence potential of emm1 strains circulating in France and other countries. Second most frequent emm types included emm89 and emm28 which were also frequent in the USA, Denmark, and Sweden (8,16,22). On the contrary, emm3 type which was identified as preponderant and highly virulent in the USA, and other European countries (15,21,22) accounted for only 3% of the strains isolated from invasive infections in our survey.

Skin diseases or cutaneous lesions were the most common predisposing factor, especially in elder and younger patients. Skin conditions were reported in more than half of the elderly (52%) and varicella was reported in one fifth of children under the age of 15. This observation highlights the importance of skin breaches as portals of entry for GAS infection, as also noticed in previous reports (12,29,30).

Six clusters of 12 GAS invasive infections with identical emm types were identified; 4 of them involved 8 postpartum cases accounting for 25% (8/32) of postpartum cases. This suggests that a substantial proportion of postpartum GAS infections are preventable. In addition, 10% (64/632) of non postpartum invasive GAS infections were suspected to have been acquired in hospital. The significant number of postpartum cases reported in the survey could partially be related to the mandatory report of nosocomial infections since 2001 and the incentive to investigate postpartum and post surgery GAS infections as recommended in guidelines issued in 2006 (5). Sequencing of emm gene was very important in the investigation of clusters of cases to confirm the links between epidemiologically related cases.

The prescription of antibiotic prophylaxis in household members of GAS infected patients when one of them presents a predisposing factor has been recommended
since 2005 (5,6). This survey suggests that these recommendations were inconstantly applied and strengthens the need to reinforce their implementation in community settings.

In France as in other developed countries invasive GAS infections range among the most severe bacterial infections. Overall we estimated that 1,900 cases of these infections occurred in France in 2007. Assuming that the cases included in the survey were representative of invasive GAS infections in France, we estimated that 270 patients died from it in 2007.

Current strategies to prevent GAS invasive diseases still relies on early detection of GAS infections, rapid and effective medical care and reinforcement of outbreaks investigation and control, particularly in healthcare settings. However, identification of factors associated with mortality can guide disease-prevention efforts. It was estimated that a 26-valent vaccine candidate, which has reached phase II trial in adults could potentially prevent 40-50% of cases and 50%-60% of deaths due to invasive GAS infections among children and the elderly (4,19). In this context, the follow up of GAS strains involved in severe GAS infection is important to adapt current vaccine development strategies.
Acknowledgments

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References


### TABLE 1. Clinical presentations, positive blood cultures and outcomes among 664 invasive group A streptococcal infection cases

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>No. (%) of cases</th>
<th>No. (%)&lt;sup&gt;b&lt;/sup&gt; with positive blood culture</th>
<th>No. (%)&lt;sup&gt;b&lt;/sup&gt; presenting with a TSS</th>
<th>No. with fatal outcome / total no. of cases (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia without identified focus</td>
<td>147(22)</td>
<td>147(100)</td>
<td>24(16)</td>
<td>32/144(22)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Skin or soft tissue infection</td>
<td>196(30)</td>
<td>160 (82)</td>
<td>29(15)</td>
<td>17/193(9)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td>104(16)</td>
<td>49 (47)</td>
<td>45(43)</td>
<td>22/102(22)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pleuro-pulmonary infection&lt;sup&gt;d&lt;/sup&gt;</td>
<td>71(11)</td>
<td>44 (62)</td>
<td>24(34)</td>
<td>15/68(22)</td>
</tr>
<tr>
<td>Postpartum infection</td>
<td>32(5)</td>
<td>12 (38)</td>
<td>0(0)</td>
<td>0/32(0)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intra-abdominal infection</td>
<td>24(4)</td>
<td>11 (46)</td>
<td>5(21)</td>
<td>3/23(13)</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>59(9)</td>
<td>22 (37)</td>
<td>7(12)</td>
<td>2/54(4)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>22(3)</td>
<td>13 (59)</td>
<td>0(0)</td>
<td>0/22(0)</td>
</tr>
<tr>
<td>Other clinical presentation&lt;sup&gt;e&lt;/sup&gt;</td>
<td>48(7)</td>
<td>30 (63)</td>
<td>10(21)</td>
<td>5/45(11)</td>
</tr>
</tbody>
</table>

<sup>a</sup>The total number does not add up to 664 as certain patients presented more than one clinical presentation, percentages are given with respect to the 664 cases.

<sup>b</sup>% of cases presenting the clinical presentation.

<sup>c</sup>Outcome was available for a total of 646 cases. The total number of cases does not add up to 646 as certain patients presented more than one clinical presentation.

<sup>d</sup>Cases presenting a pleuro-pulmonary infection (n = 71) included 48 cases presenting with pneumonia, 12 cases presenting a primary pleural infection and 11 cases presenting with pneumonia and pleural infection.

<sup>e</sup>Other clinical presentations included 48 patients presenting 51 clinical presentations:

- meningitis (n = 7), salpingitis/endometritis (n = 14), endocarditis (n = 7), other upper
respiratory tract infection (n = 10), brain abscess (n = 3), renal abscess/pyelonephritis (n = 4), vascular catheter infection (n = 2), urinary catheter infection (n = 2), hip prosthesis infection (n = 1), bacteremia from digestive tract infection (n = 1)

\[^{f}\] P value <0.05 for a positive association between the presence of the specific clinical presentation and death (Fisher exact test for binary data)

\[^{g}\] P value <0.05 for a negative association between the presence of the specific clinical presentation and death (Fisher exact test for binary data).
TABLE 2. Age and outcomes among 664 invasive group A streptococcal infection cases

<table>
<thead>
<tr>
<th>Age-group in years</th>
<th>No. (%) of cases</th>
<th>No. (%) presenting with a TSS</th>
<th>No. with fatal outcome /total no. of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>109 (17)</td>
<td>16 (15)</td>
<td>4/105 (4)</td>
</tr>
<tr>
<td>15-49</td>
<td>188 (28)</td>
<td>27 (14)</td>
<td>12/184(7)</td>
</tr>
<tr>
<td>50-69</td>
<td>142 (21)</td>
<td>44 (31)</td>
<td>35/138(25)</td>
</tr>
<tr>
<td>≥ 70</td>
<td>224 (34)</td>
<td>44 (20)</td>
<td>40/218(18)</td>
</tr>
<tr>
<td>All ages</td>
<td>664 (100)</td>
<td>131 (20)</td>
<td>91/646(14)</td>
</tr>
</tbody>
</table>

a Outcome was available for 646 cases

b P value <0.05 for the test of a difference in the frequency of death compared with the 0-14 years age-group used as reference-group (Fisher exact test for binary data)

c Include one patient without age information
TABLE 3. Predisposing factors, and outcomes among invasive GAS infection cases

<table>
<thead>
<tr>
<th>Predisposing factors</th>
<th>No. (%) of cases</th>
<th>No. (%) presenting with a TSS</th>
<th>No. with fatal outcome / total no. of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppression</td>
<td>49 (7)</td>
<td>9 (18)</td>
<td>9/47(19)</td>
</tr>
<tr>
<td>Steroid use</td>
<td>30 (5)</td>
<td>8 (27)</td>
<td>6/28(21)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>18 (3)</td>
<td>6 (33)</td>
<td>7/16(44)</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>9 (1)</td>
<td>1 (11)</td>
<td>1/9(11)</td>
</tr>
<tr>
<td>Skin disease or wound</td>
<td>247 (38)</td>
<td>48 (19)</td>
<td>33/242(14)</td>
</tr>
<tr>
<td>Varicella</td>
<td>20 (3)</td>
<td>3 (15)</td>
<td>1/20(5)</td>
</tr>
<tr>
<td>Skin wound</td>
<td>193 (29)</td>
<td>41 (21)</td>
<td>27/188(14)</td>
</tr>
<tr>
<td>Skin disease</td>
<td>46 (7)</td>
<td>8 (17)</td>
<td>6/46(13)</td>
</tr>
<tr>
<td>Burn</td>
<td>3 (0)</td>
<td>0 (0)</td>
<td>0/3(0)</td>
</tr>
<tr>
<td>Chronic medical condition</td>
<td>234 (36)</td>
<td>56 (24)</td>
<td>56/226(25)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>88 (13)</td>
<td>22 (25)</td>
<td>21/86(24)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>42 (6)</td>
<td>12 (29)</td>
<td>11/39(28)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>28 (4)</td>
<td>6 (21)</td>
<td>10/28(36)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>25 (4)</td>
<td>6 (24)</td>
<td>7/25(28)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>44 (7)</td>
<td>10 (23)</td>
<td>10/43(23)</td>
</tr>
<tr>
<td>Other chronic medical condition</td>
<td>31 (5)</td>
<td>8 (26)</td>
<td>6/29(21)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>34 (5)</td>
<td>14 (41)</td>
<td>7/33(21)</td>
</tr>
<tr>
<td>Surgery &lt; 8 days</td>
<td>18 (3)</td>
<td>4 (22)</td>
<td>2/16(13)</td>
</tr>
<tr>
<td>Childbirth &lt; 4 weeks</td>
<td>32 (5)</td>
<td>0 (0)</td>
<td>0/32(0)</td>
</tr>
<tr>
<td>No predisposing factor reported</td>
<td>150 (23)</td>
<td>28 (19)</td>
<td>13/149(9)</td>
</tr>
</tbody>
</table>

a Information on the presence of predisposing factor was available for 657 patients

b Patients may have more than one predisposing factor, percentages are calculated using the 657 cases as denominator

c Percentages are calculated using the number of cases presenting the specific predisposing factor as denominator

d Outcome was available for 646 cases The total number of cases does not add up to 646 as certain patients presented more than one predisposing factor.

e The total of subcategories does not add up to 247 as certain patients presented more than one type of skin disease or wound

f The total of subcategories does not add up to 234 as certain patients presented more than one chronic medical condition
P value $<0.05$ for a positive association between the presence of the specific predisposing factor and death (Fisher exact test for binary data).

P value $<0.05$ for a negative association between the presence of the specific predisposing factor and death (Fisher exact test for binary data).
TABLE 4. Results of multivariate logistic regression analysis of factors associated with death in invasive GAS infection (n = 600)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 years</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>2.9 [1.5-5.6]</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Toxic shock syndrome</td>
<td>9.9 [5.6-17.5]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bacteremia without identified focus</td>
<td>2.5 [1.4-4.7]</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>3.9 [0.9-16.2]</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.8 [0.9-3.6]</td>
<td>0.10</td>
</tr>
<tr>
<td>Liver disease</td>
<td>3.7 [1.3-10.5]</td>
<td>0.02</td>
</tr>
<tr>
<td>emm 1 type</td>
<td>2.2 [1.2-3.8]</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Note: Clinical presentations, predisposing factors, emm types and patients characteristics were entered in the model if associated with an increased or a decreased frequency of death on univariate analysis (p < 0.20) and retained in the model if associated with death (p < 0.10). Finally factors were considered to be independently associated with death if associated with a p value of 0.05 or less (Wald test). Patients with missing data (n = 64) were excluded from the analysis. Two-way interactions were evaluated.
<table>
<thead>
<tr>
<th>Cluster No.</th>
<th>Setting</th>
<th>No. invasive case (clinical presentation)</th>
<th>No. non-invasive cases (clinical presentation)</th>
<th>Duration (days)</th>
<th>emm types (No. of strains /total no. of strains)</th>
<th>Suspected mode of transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Household</td>
<td>2 (1 pneumonia with empyema, 1 pneumonia and TSS)</td>
<td>1 (pharyngitis)</td>
<td>7</td>
<td>emm1 (3/3)</td>
<td>Intra-familial</td>
</tr>
<tr>
<td>2</td>
<td>Nursing home</td>
<td>2 (2 bacteremic skin infections)</td>
<td>1 (lower genital tract infection)</td>
<td>77</td>
<td>emm89 (3/3)</td>
<td>Indirect transmission from patient to patient during the care of skin wounds of the 3 patients by hand borne transmission or by transmission from a carrier among healthcare staff (not screened)</td>
</tr>
<tr>
<td>3</td>
<td>Postnatal ward A</td>
<td>3 (1 cesarean wound infection and endometritis, 2 endometritis)</td>
<td></td>
<td>20</td>
<td>emm11 (2/3), emm1 (1/3)</td>
<td>Unknown</td>
</tr>
<tr>
<td>4</td>
<td>Postnatal ward B</td>
<td>2 (1 bacteremic endometritis, 1 endometritis)</td>
<td></td>
<td>3</td>
<td>emm89 (2/2)</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>Postnatal ward C</td>
<td>2 (1 bacteremic endometritis, 1 endometritis)</td>
<td></td>
<td>2</td>
<td>emm4 (2/2)</td>
<td>Patient-to-patient in the post-delivery period where the 2nd case shared the same room as the index case</td>
</tr>
<tr>
<td>6</td>
<td>Postnatal ward D</td>
<td>2 (1 bacteremic endometritis, 1 endometritis)</td>
<td></td>
<td>3</td>
<td>emm28 (2/2)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

2 A confirmed cluster was defined as the occurrence in 30 days (in the community) or 6 months (in institutional settings) of ≥ 2 invasive GAS cases due to GAS strains sharing identical emm sequence types.

3 The mode of transmission was suspected on the basis of the results of investigations of the infection control staffs.
Legends of the figures

1. Figure 1. Age-specific rates and case-fatality ratio of invasive group A streptococcal infections in France in 2007.

2. Figure 2. Distribution of emm types among 623 GAS strains responsible for invasive infections in children and adults.