Epidemic of Group A Streptococcus M/emm59 Causing Invasive Disease in Canada

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Background. The incidence of invasive group A Streptococcus (GAS) disease can vary over time and geographic region, possibly reflecting the population’s susceptibility to particular strains but also variation in the predominant M/emm types. Canadian surveillance documented an epidemic of an uncommon M/emm59 type from 2006 to 2009.

Methods. Invasive GAS isolates are submitted by Public Health Laboratories in Canada to the National Centre for Streptococcus for M/emm typing. Patient age, sex, geographic location, and the anatomical source of isolate are provided with the isolate. When it was recognized that M/emm59 strains were increasing in prevalence, clinical information was collected on M/emm59 cases captured in Alberta and compared with cases of other M/emm types occurring in this province.

Results. From January 2006 through December 2009, 539 (13.0%) of 4150 invasive GAS cases were identified as M/emm59: 164 from British Columbia, 146 from Alberta, 62 from Saskatchewan, 82 from Manitoba, 68 from Ontario, 14 from Quebec, 1 from New Brunswick, 1 from Newfoundland, 1 from Yukon, and 1 from Nunavut. The predominant clinical presentation was bacteremia (45.0%) followed by cellulitis (41.4%). Compared with concurrent cases of invasive GAS disease caused by all other M/emm types, identified risk factors for M/emm59 disease were alcohol abuse (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.4–3.8), homelessness (OR, 2.0; 95% CI, 1.2–3.4), hepatitis C virus infection (OR, 2.0; 95% CI, 1.1–3.5), and illicit drug use (OR, 1.7; 95% CI, 1.0–3.0).

Conclusions. Western Canada has witnessed the rapid emergence of a rare GAS strain causing invasive disease predominately in a select population of disadvantaged persons.

Group A streptococci (GAS; also known as Streptococcus pyogenes) cause a variety of diseases ranging from non-life-threatening pharyngitis to necrotizing fasciitis and streptococcal toxic shock syndrome. The M protein, which is encoded by the emm gene, is an important virulence factor and is also an epidemiological marker that is used worldwide to characterize GAS isolates [1, 2]. A correlation has been found between some specific disease manifestations, age of the patients, and M/emm types. For instance, streptococcal toxic shock syndrome and necrotizing fasciitis are particularly associated with M/emm1 and M/emm3 [3–5].

In Canada, the most prevalent M type identified from clinical specimens since the early 1990s has been M/emm1 [6–8]. M1 has also been the most prevalent in high income countries such as the United States and those in Europe [3, 5, 9, 10]. Before 2006, strains of GAS M/emm59 were only rarely described as a cause of infections in humans. We report here the emergence of invasive GAS M/emm59 in Canada from 2006 to 2009.
METHODS

Isolate and case demographics collection. The National Centre for Streptococcus located in Edmonton, Alberta, has provided Canadian national reference services for GAS M typing/emm typing since 1993. There are 10 provinces and 3 territories in Canada. The population of Canada increased from 32,723,000 in 2006 to 33,894,000 in 2009 [11]. Invasive GAS disease is a nationally notifiable disease in Canada. Clinical microbiology laboratories are requested to submit isolates from
Figure 3. Invasive group A Streptococcus M/emm59 and M/emm1 cases, by age and sex, 2006–2009. For M/emm59 (A), there were 531 cases with the patient’s age identified and 468 with the patient’s sex identified. For M/emm1 (B), there were 716 cases with the patient’s age identified and 499 with the patient’s sex identified.

Invasive GAS infections to the National Centre for Streptococcus for M/emm typing as these isolates are found. Invasive GAS isolates are defined as those isolated from a normally sterile site [12]. Data available to the National Centre for Streptococcus are limited to geographic location descriptors, date of birth, sex, and anatomical source of the isolate.

Laboratory data collection. GAS isolates previously identified by clinical diagnostic microbiology laboratories were confirmed by β hemolysis on sheep blood agar, grouping of carbohydrate antigen, large colony size, and bacitracin susceptibility and stored at −70°C [13]. Serological M and T typing was performed as described elsewhere [14]. In September 2006, the National Centre for Streptococcus replaced serological M typing with emm gene sequencing. The emm typing assay was performed as described by Beall et al [2], and emm sequences were compared with the Centers for Disease Control and Prevention data bank (http://www.cdc.gov/ncidod/biotech/strep/strepblast.htm).

Antibiotic susceptibility was performed and interpreted using reference disk diffusion methods as described by Clinical and Laboratory Standards Institute [15]. The disk diffusion zone sizes were used to interpret susceptibility for GAS on the basis of the guidelines [16]. The following antimicrobial agents were assayed: penicillin, chloramphenicol, erythromycin, clindamycin, and vancomycin. All antimicrobial disks were purchased from BBL, Oxoid, England.

Clinical data collection. In Alberta, invasive GAS disease is a notifiable disease reportable to the Office of the Chief Medical Officer of Health. Cases of invasive GAS disease were identified by the diagnosing laboratory or the patient’s physician and were further investigated by the Medical Officer of Health or designate where the case resided. The clinical information collected by the local communicable disease control staff was reported using the notifiable disease report form which included the patient name, age and place of residence, as well as disease presentation and patient risk factors. Risk factor definitions accompanied the notifiable disease report form. Risk factors captured were alcohol abuse, chronic disease, diabetes mellitus, hepatitis C virus (HCV) infection, human immunodeficiency virus (HIV) infection, homelessness, illicit drug use, immunocompromise, postpartum infection, surgical wound infection, nonsurgical wound infection, none identified, unknown, and other. M/emm1 cases from across Canada were used as a comparator for age and sex distribution and timeline comparison. M/emm1 was selected to compare against M/emm59, because M/emm1 was the most comparable M type to M/emm59 with respect to case numbers during the analysis period and is usually the most common M/emm type reported in Canada.

Statistical analysis. Differences between groups were compared using the χ² test or the Fisher exact test. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute). P values <.05 were considered to indicate statistical significance.

RESULTS

Geography. Figure 1 shows the provincial distribution of M/emm59 cases from 2004 to 2009. There were 7 cases of M/emm59 invasive GAS disease captured from September to November 2004, including 6 from the province of Quebec and 1 from Ontario. From January 2006 to December 2009, 539 (13.0%) of 4143 Canadian cases of invasive GAS disease were attributed to M/emm59, with the majority of M/emm59 occurring in the western half of the country. There were 164 cases of M/emm59 (21.5%) out of 764 cases of invasive GAS disease from British Columbia, 146 (16.3%) of 895 from Alberta, 62 (22.6%) of 274 from Saskatchewan, 82 (24.5%) of 335 from
Manitoba, 68 (4.8%) of 1420 from Ontario, and 14 (4.3%) of 329 from Quebec. Of the 68 isolates from Ontario, 56 were from the Northwestern area of the province. The majority of cases (13 [93%] of 14) from Quebec were identified as occurring in 2009. During the same time period, there were single isolates referred from New Brunswick, Newfoundland, Yukon, and Nunavut.

Analysis of data from 1993 to September 2004 identified only 2 isolates of M/emm59 in Canada of 10,766 isolates submitted. One was collected from Quebec in April 1996, and the other was collected from Ontario in December 1997.

Demographic characteristics. There were 77 different M/emm types identified in Canada from 2004 to 2009. The 20 most frequent M/emm types seen during this time period are shown in Figure 2. From 2004 to 2007, M/emm1 was the most prevalent M type seen in Canada, accounting for 27.2% in 2004 and decreasing to 19% in 2007. In 2008, M/emm59 became the most prevalent type, accounting for 23.4% of isolates and decreasing to 9.2% in 2009.

Of the 539 M/emm59 cases, age was reported for 531 cases (98.5%) and sex was reported for 468 (86.8%) (Figure 3). The ratio of male to female patients was 1.3:1 for M/emm59 and 1.2:1 for M/emm1. There were 26 M/emm59 cases (4.9%) in children aged <1 year; for M/emm1, only 17 cases (2.4%) oc-
2 isolates were collected from cerebrospinal fluid specimens; of 57.1% of isolates were from blood culture, and 39.2% were as a single large cluster during 2006–2009.

Figures 1 and 2 show the anatomical source of the M/emm1 isolates. Ninety percent of all M/emm59 isolates occurred in individuals aged ≥18 years, compared with M/emm1, for which 80% of cases occurred in individuals aged ≥18 years.

Figure 3 shows the number of cases of M/emm59 and M/emm1 during the 6 years studied. There was a seasonal periodicity associated with M/emm1, with a predictable peak from December to March and a nadir from August to October. In contrast, M/emm59 cases exhibited no periodicity and occurred as a single large cluster during 2006–2009.

Table 1 presents the risk factors and odds ratios (ORs) associated with M/emm59 versus all other M/emm cases in Alberta. The top 4 risk factors for acquiring M/emm59 invasive GAS disease, comparison with all other M/emm invasive GAS disease cases, were alcohol abuse (OR, 2.3; 95% confidence interval [CI], 1.4–3.8; P < .001), homelessness (OR, 2.0; 95% CI, 1.2–3.4; P = .01), HCV infection (OR, 2.0; 95% CI, 1.1–3.5; P = .02), and illicit drug use (OR, 1.7; 95% CI, 1.0–3.0; P = .04).

Table 2. Comparison of the Diagnosis at Presentation of M/emm59 versus All Other M/emm Cases of Group A Streptococcus Infection in Alberta, Canada, for Which Clinical Information Was Available, January 2006–December 2009

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>M/emm59</th>
<th>All other M/emm types</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>50 (45.0)</td>
<td>327 (54.1)</td>
<td>.08</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>46 (41.4)</td>
<td>185 (30.6)</td>
<td>.03</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10 (9.0)</td>
<td>50 (8.3)</td>
<td>.80</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td>15 (13.5)</td>
<td>58 (9.6)</td>
<td>.21</td>
</tr>
<tr>
<td>Toxic shock syndrome</td>
<td>6 (5.4)</td>
<td>40 (6.6)</td>
<td>.63</td>
</tr>
<tr>
<td>Joint infection</td>
<td>6 (5.4)</td>
<td>70 (11.6)</td>
<td>.05</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1 (0.9)</td>
<td>5 (0.8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>2 (1.8)</td>
<td>9 (1.5)</td>
<td>.68</td>
</tr>
<tr>
<td>Epiglottis</td>
<td>1 (0.9)</td>
<td>3 (0.5)</td>
<td>.49</td>
</tr>
<tr>
<td>Pylonephritis</td>
<td>1 (0.9)</td>
<td>1 (0.2)</td>
<td>.29</td>
</tr>
<tr>
<td>Total</td>
<td>111 (100)</td>
<td>604 (100)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Risk Factors for M/emm59 and All Other M/emm Cases of Group A Streptococcus Infection in Alberta, Canada, January 2006–December 2009

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>M/emm59 No. (%)</th>
<th>All other M/emm types No. (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol abuse</td>
<td>28 (25.2)</td>
<td>77 (12.7)</td>
<td>2.3 (1.4–3.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Homelessness</td>
<td>22 (19.8)</td>
<td>67 (11.1)</td>
<td>2.0 (1.2–3.4)</td>
<td>.01</td>
</tr>
<tr>
<td>HCV infection</td>
<td>18 (16.2)</td>
<td>54 (8.9)</td>
<td>2.0 (1.1–3.5)</td>
<td>.02</td>
</tr>
<tr>
<td>Illicit drug use</td>
<td>22 (19.8)</td>
<td>75 (12.4)</td>
<td>1.7 (1.0–3.0)</td>
<td>.04</td>
</tr>
<tr>
<td>Nonsurgical wound</td>
<td>37 (33.3)</td>
<td>143 (23.7)</td>
<td>1.6 (1.0–2.5)</td>
<td>.03</td>
</tr>
<tr>
<td>Surgical wound</td>
<td>9 (8.1)</td>
<td>33 (5.5)</td>
<td>1.5 (0.7–3.3)</td>
<td>.28</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (11.7)</td>
<td>66 (10.9)</td>
<td>1.1 (0.6–2.0)</td>
<td>.81</td>
</tr>
<tr>
<td>Chronic disease</td>
<td>23 (20.7)</td>
<td>117 (19.4)</td>
<td>1.1 (0.7–1.8)</td>
<td>.74</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>13 (11.7)</td>
<td>57 (9.4)</td>
<td>1.3 (0.7–2.4)</td>
<td>.46</td>
</tr>
<tr>
<td>HIV infection</td>
<td>3 (2.7)</td>
<td>15 (2.5)</td>
<td>1.1 (0.3–3.8)</td>
<td>.75</td>
</tr>
<tr>
<td>Postpartum infection</td>
<td>0 (0)</td>
<td>25 (4.1)</td>
<td>5.5 (0.3–88.3)</td>
<td>.29</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>0 (0)</td>
<td>2 (0.3)</td>
<td>5.5 (0.3–88.3)</td>
<td>.29</td>
</tr>
<tr>
<td>Eczema</td>
<td>1 (0.9)</td>
<td>1 (0.2)</td>
<td>5.5 (0.3–88.3)</td>
<td>.29</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (5.4)</td>
<td>32 (5.3)</td>
<td>1.0 (0.4–2.5)</td>
<td>.96</td>
</tr>
<tr>
<td>None identified</td>
<td>17 (15.3)</td>
<td>145 (24.0)</td>
<td>0.6 (0.3–1.0)</td>
<td>.04</td>
</tr>
</tbody>
</table>

NOTE. Cases may have presented with >1 risk factor. CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; OR, odds ratio.

DISCUSSION

Prior to 2004, M/emm59 had been rarely recognized in Canada, and it currently remains uncommon in other parts of the world, with 1–8 isolates reported in a very small number of countries (United States, Mexico, Brazil, England, and Belgium) [3, 5, 9, 17–20]. Additional evidence of the rarity of M/emm59 was demonstrated by figures posted by the Streptococcus Laboratory in the Center for Disease Control and Prevention [21]. These figures showed that M/emm59 was among the top 25 M/emm types only in Latin America; it was absent from this ranking in Africa, Asia, the Middle East, and the Pacific Island Countries/Indigenous Australian region. In Latin America, emm59 ranked 21 of 25 types, accounting for ∼2% of the emm types listed—far less than the 23.4% seen in Canada in 2008.

The diversity of M/emm types present in different geographic regions suggests an M/emm-based component vaccine against GAS infection would need to be modifiable, allowing M/emm substitutions in such a vaccine to be implemented as required. However, the rapid increase and decrease in the prevalence of M/emm59 suggests that vaccine substitutions may not be achievable in relevant time frames in all cases.

The M/emm59 strain in this epidemic was recovered in higher percentages from persons with abscess and soft-tissue infections than all other M/emm types suggesting this M/emm59 strain may have a preference for abscess formation and soft-tissue infection. A similar observation was made in the only other documented M/emm59 outbreak which occurred in Dun dee, Scotland [22]. In this outbreak of M/emm59 GAS disease, 8 slaughterhouse workers contracted M/emm59 GAS infections presenting as skin lesions/wound infections on fingers, hands and arms, with infection associated with inadequate hygiene practices in the facility [22]. This predominance of skin infections was observed in the Alberta cohort; M/emm59 was diagnosed more frequently in cases of cellulitis infection than all other M/emm types (Table 2). In the initial descriptions of M/emm59 by Dillon and Dillon [23], M/emm59 was found to be associated with pyoderma and acute glomerulonephritis. The association of M59 with pyoderma is mirrored in our epidemic and the one from Dundee, Scotland [22]. However, unlike Dillon and Dillon, we failed to find any descriptions of acute glomerulonephritis in the cases for which we had clinical information [23].

The increased frequency of M/emm59 isolates recovered from abscess or soft-tissue sites, as opposed to all other M/emm types, may relate to one of the major risk factors: illicit drug use, which was identified in this epidemic. The documentation of illicit drug use as a risk factor for invasive GAS disease is similar to previous reports that have described increased cases of invasive GAS disease in association with injection drug users [24, 25].

A report from the United Kingdom describes increased rates of invasive GAS disease in the injection drug user population,
with a high proportion being reported in 2003–2004 [24]. Interestingly, unlike our epidemic, the cases from the United Kingdom were not attributed to any single M/emm type but, rather, to multiple M types, with M83 causing a higher proportion of disease (22%) in the injection drug user population than in the non–injection drug user population [24]. The information gleaned from the United Kingdom study suggested that the increase in invasive GAS infections among intravenous drug users was a mixture of sporadic and clustered infections. The investigators were unable to provide a clear explanation for the increase [24].

Another survey of invasive GAS disease amongst injection drug users was performed in Barcelona, Spain, in the fall seasons of 2000, 2002, and 2003 [25]. Similar to the UK findings, no single M type was attributed to the outbreaks; however, 22 (50%) of the 44 cases from these clusters were attributed to a single clone, emm25.2. Not unexpectedly, the patients from Spain had an HCV infection rate of 88.2% and an HIV infection rate of 58.5%—conditions that are often associated with the use of injection drugs. This is in sharp contrast to our Alberta cohort M/emm59 clinical study group, which had an HIV infection rate of 2.7% and an HCV infection rate of 16.2%, indicating that although illicit drug use maybe an important risk factor in the M/emm59 epidemic in Canada, it is most likely only one of many factors involved.

The risk factor analysis from Alberta showed that alcohol abuse, homelessness, HCV infection, and illicit drug use to be major risk factors, suggesting that the M/emm59 epidemic was focused on a very specific disadvantaged population. Again, this is in contrast to M/emm1, which generally targets a much wider general population as a whole rather than any one specific group. A select population focus may also be supported by the ages affected. The M/emm1 age distribution is broader across the age spectrum, whereas the M/emm59 age distribution is more focused on middle-aged individuals—a population more likely to be associated with illicit drug use, homelessness, and alcohol abuse.

A recent description of an erythema outbreak involving an extremely infective M81 GAS strain in Israel found a major risk factor to be crowding with poor hygienic conditions. Similar observations are reflected in the outbreak involving M/emm59 described here, with a large number of cellulitis infections in a disadvantaged population with presumably poorer hygiene [26].

It is interesting that the sudden increase in cases involving M/emm59 did not lead to replacement of other M/emm types but, rather, appeared to occur in addition to the M/emm types already circulating. When comparing M/emm59 to M/emm1, usually the most prevalent M/emm type in North America, M/emm1 was fairly constant in number of isolates recovered in Canada from 2004 to 2009, with no major decrease or increases other than the expected seasonal cycling in number of cases. This is in contrast to M/emm59, which exhibited a clear epidemic curve from 2006 to 2009.

A strength of the study is the ability of a centralized GAS typing laboratory to document major epidemiological changes in invasive GAS disease in Canada. If M/emm typing was regionalized, the capture of M/emm59 cases may have been difficult, and the magnitude of the epidemic may have gone unrecognized. This is not the same for the capture of clinical data for invasive GAS disease, because these data are not centralized. Nonetheless, to provide important clinical data for the epidemic, we gathered data from Alberta, which accounted for 21% of the cases in Canada. Although not providing a national picture, it does provide a clear description for cases in Alberta, a province with significant number of cases.

We have not determined why the number of M/emm59 cases increased, why the number has decreased, or why the epidemic was focused in western Canada. Although the waxing and waning of clones of GAS causing disease have been well-recognized events in the past, the reasons for these have never been well defined [27, 28]. It has been suggested that the emergence of a new clone may evolve slowly through the accumulation of point mutations or by acquisition of new genetic material through horizontal gene-transfer events [29]. A decrease in the prevalence of a particular clone may be the result of decrease in virulence, an increase in host defence (herd immunity), and/or serotype replacement by a more “fit” clone [27, 28, 30].

In conclusion, we documented a single, large epidemic of invasive GAS disease in Canada caused by a single unique strain of invasive GAS, M/emm59. The epidemic in Alberta targeted primarily a disadvantaged group comprised of the homeless, illicit drug user, alcohol abuse population.

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