High burden of invasive group A streptococcal disease in the Northern Territory of Australia

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SUMMARY
Although the incidence of invasive group A streptococcal disease in northern Australia is very high, little is known of the regional epidemiology and molecular characteristics. We conducted a case series of Northern Territory residents reported between 2011 and 2013 with Streptococcus pyogenes isolates from a normally sterile site. Of the 128 reported episodes, the incidence was disproportionately high in the Indigenous population at 69·7/100 000 compared to 8·8/100 000 in the non-Indigenous population. Novel to the Northern Territory is the extremely high incidence in haemodialysis patients of 2205·9/100 000 population; and for whom targeted infection control measures could prevent transmission. The incidences in the tropical north and semi-arid Central Australian regions were similar. Case fatality was 8% (10/128) and streptococcal toxic shock syndrome occurred in 14 (11%) episodes. Molecular typing of 82 isolates identified 28 emm types, of which 63 (77%) were represented by four emm clusters. Typing confirmed transmission between infant twins. While the diverse range of emm types presents a challenge for effective coverage by vaccine formulations, the limited number of emm clusters raises optimism should cluster-specific cross-protection prove efficacious. Further studies are required to determine effectiveness of chemoprophylaxis for contacts and to inform public health response.

Key words: Infectious disease epidemiology, public health emerging infections, streptococcal infections, Streptococcus pyogenes, vaccines.

INTRODUCTION
Invasive group A streptococcal (iGAS) disease has a high fatality of 7–25% and is associated with three severe clinical outcomes: streptococcal toxic shock syndrome (STSS), necrotizing fasciitis and bacteremia [1–7]. The USA, Australia, Fiji and New Zealand have reported disproportionately higher rates of iGAS disease in their Indigenous populations [2, 6–8]. In Australia, tropical regions of northern Queensland and the Northern Territory (NT) have the highest reported rates, with incidence in Indigenous populations ranging from 23·9 to 82·5/100 000 and non-Indigenous from 4·7 to 10·3/100 000 [8–10]. The state of Victoria in Australia and other
developed countries report much lower incidence, ranging between 1.3 and 3.5/100,000 population [1, 3, 5, 11]. Reasons for this difference are not known but possible factors include climatic variations (tropical vs. temperate climates) and population composition (higher proportion of Indigenous population in northern Australia with high levels of socioeconomic disadvantage and household crowding) [12, 13]. Queensland and the NT have a much higher prevalence of other group A streptococcal (GAS)-associated infections including rheumatic heart disease and acute post-streptococcal glomerulonephritis [14–16]. To inform prevention strategies in the NT further data are needed to identify specific at-risk populations, burden of disease in tropical and semi-arid regions and molecular characterization of GAS strains causing invasive disease. Multivalent GAS vaccines are currently undergoing clinical trials and are expected to reduce the burden of GAS-associated diseases [17, 18]. As over 200 *Streptococcus pyogenes* emm types have been identified, confirmation of strains causing disease in the NT will inform efficacy of various vaccine formulations [17].

**METHODS**

**Study setting**

This study was conducted in the NT of Australia, which encompasses a geographical area of 1 346 200 km² and has a population of about 227 900 people [19]. The tropical ‘Top End’ comprises the northern third of the NT while the southern two-thirds, referred to as ‘Central Australia’ has a semi-arid climate. Indigenous people comprise 27% of the population with many living in remote communities [20]. By contrast, Indigenous people represent 2.5% of the total Australian population. In 2012, about 479 people were receiving haemodialysis in the NT, equating to a rate of 2.0/100,000 population; a rate four times higher than other Australian jurisdictions [21]. In the NT, haemodialysis patients are predominantly Indigenous (91%) and receive services through 10 haemodialysis units or home dialysis.

**Design**

A case series between 11 May 2011 and 11 May 2013 of NT residents reported to the NT Notifiable Diseases System. Notifications were made by laboratories following isolation of *S. pyogenes* from a normally sterile body site. Cases were excluded if *S. pyogenes* had been isolated from a sterile site in the same individual in the preceding 30 days.

**Data collection**

Data were collected from individual medical records and included demographic features, clinical presentation and outcome, chronic medical conditions, malignancy, immunosuppressive illnesses, history of tobacco smoking ≥5 times per week, medications and known contact with a person infectious with iGAS disease in the 30 days preceding symptom onset. Dates of hospitalization, specimen collection and 10-day surgical, dialysis and childbirth history were recorded. Infection was classified as nosocomial if the first positive specimen was collected ≥72 h after admission to hospital, or if the person had undergone surgery, dialysis or given birth in the 10 days preceding symptom onset. Secondary transmission was defined as infection occurring in a person who had contact with an infectious case within the preceding 30 days. If a case was not identified as nosocomial or secondary transmission, it was assumed the *S. pyogenes* had been acquired in the community. STSS was defined according to criteria of the working group on severe streptococcal infections with only definite cases included. Fulfilment of the definite STSS case definition required hypotension and the presence of ≥2 of the following: acute renal impairment, coagulopathy, liver abnormalities, acute respiratory distress syndrome, extensive tissue necrosis and/or rash [22]. Mortality was identified if a person died within 30 days of laboratory isolation of GAS from a sterile site; and GAS infection or sepsis was included as a cause of death on the death certificate.

**Characterization of GAS isolates**

GAS isolates causing invasive disease were provided by the five NT public hospital laboratories. DNA was extracted from 1 ml of overnight broth culture using a QIAamp DNA mini-kit (Qiagen, Australia) with the addition of mutanolysin and hyaluronidase. emm polymerase chain reaction (PCR) was conducted according to the USA Centers for Disease Control and Prevention (CDC) protocol [23]. PCR products were purified using a Qiagen PCR purification kit and DNA sequencing was conducted by Macrogen Inc. (Korea). Sequences were compared with the CDC emm sequence database and new subtypes.
submitted to the moderator for assignment. *emm* types encoding proteins of similar binding and structural properties were grouped by cluster, details of which have been described previously [24].

**Data analysis**

Data were analysed using Stata v. 13.1 (StataCorp, USA). Incidence was calculated using NT population projections based on Australian Bureau of Statistics data [25]. Population estimates for dialysis patients were obtained from the Australian and New Zealand Dialysis and Transplant Registry [21]. The \( \chi^2 \) test was used to compare proportions, while Fisher’s exact test was used if any of the cells had <5 cases. Median age and length of hospital stay were compared using the Mann–Whitney \( U \) test. Annualized incidence was calculated by dividing the average number of cases per year by the study population.

**Ethics**

Ethical approval was gained from the Human Research Ethics Committees of Central Australia, NT Department of Health and Menzies School of Health Research, and the Australian National University.

**RESULTS**

Over the 2-year period, 128 episodes of iGAS disease occurred in 121 people. Indigenous people accounted for 99 (77%) episodes and haemodialysis patients for 21 (16%) episodes.

Site of specimen collection was blood \((n = 118, 92\%)\), joints \((n = 7, 5\%)\), peritoneal fluid \((n = 2, 2\%)\) and pleural fluid \((n = 1, 1\%)\).

**Incidence**

Annualized incidence for the non-Indigenous, Indigenous and haemodialysis populations are shown in Table 1 and were similar for both Top End and Central Australian regions. Incidence in the Indigenous population was significantly higher than the non-Indigenous [risk ratio 7.8, 95% confidence interval (CI) 4.4–13.8].

*Figure 1* shows frequency of cases and incidence by Indigenous status and age group. For Indigenous adults, incidence was higher in those aged >30 years while incidence in non-Indigenous adults was higher only after 65 years. In children, incidence was high in the Indigenous population aged <5 years (68.2/100 000, 95% CI 23.6–153.3), a pattern not observed in non-Indigenous children (4.1/100 000, 95% CI 0–38.6).

**Laboratory typing of GAS isolates and clinical presentation**

Of the 128 isolates, 82 (64%) were available for *emm* typing. *Figure 2* shows the 28 *emm* types and clusters identified by geographical region, and includes two previously unidentified subtypes (114.7 and 197.4). There was no predominant *emm* type and half the *emm* types appeared in both Central Australia and the Top End. No individual *emm* type was associated with greater severity of disease as identified by STSS (12/14 isolates from people with STSS were typed) or death (5/10 isolates from people who died were typed).

Classification of isolates by *emm* cluster shows the majority of isolates 63/82 (77%) were from four *emm* clusters, i.e. A-C2, D4, E3 and E6 [24].

*Table 2* shows the clinical presentation and outcome of cases by prevalence of the five most commonly identified *emm* types. *emm* type was not a predictor of clinical presentation or death.

The most common site of initial infection was skin. For haemodialysis patients, 6/21 (29%) had skin lesions specifically on the lower limb. In children aged <16 years, skin sores and infected scabies were predominant (9/15, 60%). All people with infected scabies were Indigenous.

**Risk factors**

In the majority of episodes (66%), the person had a chronic medical condition as shown in Table 3. Comorbidity with diabetes or renal disease was significantly more common in Indigenous people. No cases were reported following varicella infection [26]. Repeat infection was identified in five people, two of whom had three episodes of iGAS disease within 2 years. Average time between episodes ranged from 78 to 532 days (average 273 days). Each episode in the same individual was associated with a different *emm* type except in one person where *emm* type 81.1 was isolated twice. In this individual the interval between infections was 14 months with presentation on both occasions being leg cellulitis.
For haemodialysis patients, presence of a co-morbidity other than renal failure was reported in 18/21 (86%) episodes, most commonly diabetes 16/21 (76%). In 5/21 (24%) episodes the scheduled haemodialysis session prior to onset of illness was missed.

Outcome and severity of disease

The case-fatality ratio (8%) and occurrence of STSS (11% of episodes) was similar for Indigenous and non-Indigenous people (Table 3). All died within 22 days of specimen collection with median time to death 6 days. Age of those who died ranged from 21 to 83 years with half aged ≥60 years. Of the 10 people who died, seven had a history of one or more chronic medical conditions, two had malignancy and one died post-partum. The fatality rate in people with STSS was 29% (4/14). Necrotizing fasciitis was diagnosed in three people of whom two died.

Overall 123 (96%) cases were admitted to hospital with median length of stay 7 days (interquartile range 4–16 days). Surgical intervention was documented in 23/128 (18%) cases, including 16 wound washouts with/without debridement of tissue; drainage of fluid collections for four people and five amputations. Number of surgical procedures per person ranged from 1 to 23.

Nosocomial transmission

In total, six (5%) episodes were acquired in hospital, two of which were acquired after vaginal births. Portals of entry for the remainder were an intravenous catheter site, toe wound and burn sites for two people.

Of 21 episodes in haemodialysis patients, 20 attended a dialysis unit within the 10 days prior to symptom onset. A cluster of three cases was identified in a single dialysis unit, of whom all had onset of

<table>
<thead>
<tr>
<th>Population under study</th>
<th>Entire Northern Territory</th>
<th>Top End</th>
<th>Central Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Incidence (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>Indigenous</td>
<td>99</td>
<td>69.7 (51.6–92.0)</td>
<td>59</td>
</tr>
<tr>
<td>Non-Indigenous</td>
<td>29</td>
<td>8.8 (4.8–14.6)</td>
<td>21</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>21</td>
<td>2205.9 (1080.1–3999.5)</td>
<td>9</td>
</tr>
</tbody>
</table>

iGAS, Invasive group A streptococcal; CI, Confidence interval.
Symptoms within a 2-week period. This cluster, however, was not confirmed through laboratory testing as only one of the three isolates were available for typing.

**Household transmission**

Transmission occurred within a household between twin infants, clinical details of which have been reported previously [27]. Onset of illness was 2 days apart with the common *emm* type 207.1 identified.

A further two separate episodes of iGAS disease occurred in household contacts, with onset of infection between index and secondary cases 4 and 28 days apart. Typing of isolates on both occasions revealed a different *emm* type in index and secondary cases and therefore transmission was not supported.

**DISCUSSION**

Our study provides the first report of the epidemiology of iGAS disease for tropical and semi-arid regions of the NT. Incidence was similar across both regions with over-representation of the Indigenous and haemodialysis populations. Skin infections were the most common sites of initial infection leading to invasive disease. We found evidence supporting transmission in healthcare settings and between infant twins. Typing of isolates showed that a very diverse range of *emm* types contributes to invasive disease in the NT and refuted direct transmission in two household case pairs.

**Incidence**

Similar to previous reports, we found a significantly higher rate of disease in the Indigenous population (69.7/100 000) compared to non-Indigenous (8.8/100 000) [2, 6–8, 10]. This finding is similar to rates reported in tropical northern Queensland (Indigenous: 82.5, 95% CI 27.4–190.0/100 000 population; non-Indigenous: 10.3, 95% CI 5.5–17.6/100 000 population) [10]. It was speculated that the tropical conditions in northern Australia contribute to the higher rates of iGAS disease seen in these regions [4, 9]. Our findings, however, did not support this hypothesis with incidence in the tropical regions of the NT similar to the semi-arid regions of Central Australia. However, the high rate of iGAS disease in the Indigenous population across the NT is consistent with high rates of other GAS-associated diseases including acute post-streptococcal glomerulonephritis, acute rheumatic fever and rheumatic heart disease [14–16]. Causes are likely multifaceted and include socioeconomic and environmental factors (e.g. house
overcrowding) and greater host susceptibility (e.g. higher prevalence of predisposing chronic diseases) [12, 13, 28–30]. Moreover, onset of chronic diseases occurs at a younger age in Indigenous people. In particular, rates of chronic kidney disease and diabetes begin rising from age 25 years in the Indigenous population compared to 55 years in non-Indigenous people [12]. This is reflected in our cases where the incidence of iGAS disease was higher in those aged >30 and >65 years for the respective populations. A further age group contributing to the higher incidence in the Indigenous population were children aged <5 years. Scabies, which frequently underlies streptococcal pyoderma was described exclusively in Indigenous children and is endemic in many NT Indigenous communities [29–31]. Improving the social determinants of health for Indigenous people, along with greater adherence to treatment, prevention of scabies, skin infections and chronic diseases are of vital importance for decreasing the burden of GAS-associated diseases.

Incidence of iGAS disease in haemodialysis patients is exceedingly high. While chronic kidney disease is a known risk factor for iGAS disease, the high rate (2205.9/100,000) in haemodialysis patients has not been reported outside the NT. A study between 2005 and 2009 reported that 17% of people with GAS bacteraemia in the Top End were on haemodialysis; a result consistent with our finding of 16% of people with iGAS disease [9]. Further, our study found a similar incidence in Top End and Central Australia; suggesting a more widespread phenomenon than a breach in infection control practices isolated to one or two dialysis units. Apart from one cluster of three cases within a single dialysis unit, we were unable to establish nosocomial or community-acquired disease in the

Table 2. Clinical presentation and outcome of Northern Territory residents with iGAS disease by the five most commonly identified emm types

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Total (n = 128) (%)</th>
<th>113·0 (n = 10)</th>
<th>197·0 (n = 10)</th>
<th>81·0 (n = 9)</th>
<th>81·0 (n = 5)</th>
<th>101·0 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue infection</td>
<td>40 (31)</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Skin lesion(s)</td>
<td>18 (14)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Scabies</td>
<td>11 (9)</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Burns</td>
<td>7 (5)</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Vascular access site</td>
<td>4 (3)</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>31 (24)</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Bacteraemia with no focus</td>
<td>16 (13)</td>
<td>–</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12 (9)</td>
<td>–</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Abscess</td>
<td>6 (5)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Septic joint secondary to blunt trauma</td>
<td>5 (4)</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>5 (4)</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>4 (3)</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td>3 (2)</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>2 (2)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Post-partum endometritis</td>
<td>2 (2)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Empyema</td>
<td>1 (1)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Bursitis</td>
<td>1 (1)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Outcome

| Severe disease*                                     | 37 (29)             | 2              | 4              | 2            | 2            | 1            |
| STSS†                                               | 14 (11)             | 1              | 3              | –            | 1            | –            |
| Died‡                                               | 10 (8)              | –              | –              | 1            | –            | –            |

iGAS, Invasive group A streptococcal; STSS, streptococcal toxic shock syndrome.
* Severe disease is defined as iGAS disease presenting as pneumonia, meningitis, necrotizing fasciitis, STSS or any other manifestation requiring intensive care admission or causing death; † Other emm types identified where clinical illness was complicated by STSS included 4·0 (1), 39·4 (1), 73·0 (1), 92·0 (1), 104·0 (1), 207·1 (2). ‡ Other emm types identified where outcome was death included 197·0 (1), 39·4 (1), 4·0 (1) and 87·0 (1).
The high incidence in this population probably reflects both the high rates of GAS infections in the region and susceptibility of the haemodialysis population. Patients on haemodialysis generally had at least two risk factors for iGAS disease, i.e. chronic kidney disease and Indigenous background. Additionally, three-quarters had a third risk factor of diabetes for whom the most common site of initial infection was a skin lesion of the lower limb. Hence regular examination of the skin integrity of the lower limbs of these patients could limit disease progression through early detection and treatment. The susceptibility of this population also highlights the need for stringent implementation of infection control practices including regular auditing to prevent transmission.

It is possible we under-ascertained the total number of people with iGAS disease as people with milder symptoms receiving antibiotic treatment in primary care without collection of a specimen may not have been identified.

**Typing**

Similar to other GAS-associated diseases in the NT, molecular typing showed a very diverse range of *emm* types causing invasive disease [32–34]. These data are consistent with developing regions of the Pacific and Africa which also report high diversity of *emm* types causing GAS-associated diseases [35].

**Table 3. Characteristics of Northern Territory patients diagnosed with iGAS disease by Indigenous status**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 128)</th>
<th>Indigenous (n = 99)</th>
<th>Non Indigenous (n = 29)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>71 (55)</td>
<td>66 (67)</td>
<td>5 (17)</td>
<td>9·6 (3·4–27·4)</td>
<td>&lt;0·01</td>
</tr>
<tr>
<td>Age, median</td>
<td>47 years</td>
<td>46 years</td>
<td>51 years</td>
<td>–</td>
<td>0·07</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic medical condition*</td>
<td>84 (66)</td>
<td>67 (68)</td>
<td>17 (59)</td>
<td>1·5 (0·6–3·5)</td>
<td>0·37</td>
</tr>
<tr>
<td>Type II diabetes mellitus</td>
<td>46 (36)</td>
<td>42 (42)</td>
<td>4 (14)</td>
<td>4·6 (1·5–14·2)</td>
<td>&lt;0·01</td>
</tr>
<tr>
<td>Renal disease†</td>
<td>36 (28)</td>
<td>34 (34)</td>
<td>2 (7)</td>
<td>7·1 (1·6–31·5)</td>
<td>&lt;0·01</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>21 (16)</td>
<td>21 (21)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Heart disease</td>
<td>33 (26)</td>
<td>25 (25)</td>
<td>8 (28)</td>
<td>0·9 (0·3–2·3)</td>
<td>0·80</td>
</tr>
<tr>
<td>Liver disease</td>
<td>29 (23)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lung disease</td>
<td>24 (19)</td>
<td>19 (19)</td>
<td>5 (17)</td>
<td>1·1 (0·4–3·4)</td>
<td>0·81</td>
</tr>
<tr>
<td>Human T-lymphotropic virus 1</td>
<td>4 (3)</td>
<td>4 (4)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Other medical/behavioural</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>8 (6)</td>
<td>7 (7)</td>
<td>1 (3)</td>
<td>2·1 (0·3–18·1)</td>
<td>0·68</td>
</tr>
<tr>
<td>Immunosuppressive agents‡</td>
<td>4 (3)</td>
<td>4 (4)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cigarette smoking§</td>
<td>7/121 (6)</td>
<td>4/92 (4)</td>
<td>3/29 (10)</td>
<td>0·4 (0·1–1·9)</td>
<td>0·30</td>
</tr>
<tr>
<td>Current</td>
<td>25/121 (21)</td>
<td>20/92 (22)</td>
<td>5/29 (17)</td>
<td>1·3 (0·5–3·9)</td>
<td>0·79</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>123 (96)</td>
<td>94 (95)</td>
<td>29 (100)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Days hospitalized, median</td>
<td>7 days</td>
<td>7 days</td>
<td>9 days</td>
<td>–</td>
<td>0·28</td>
</tr>
<tr>
<td>ICU admission</td>
<td>26 (20)</td>
<td>17 (17)</td>
<td>9 (31)</td>
<td>0·2 (0·2–1·2)</td>
<td>0·11</td>
</tr>
<tr>
<td>STSS</td>
<td>14 (11)</td>
<td>9 (9)</td>
<td>5 (17)</td>
<td>0·5 (0·1–1·6)</td>
<td>0·22</td>
</tr>
<tr>
<td>Died</td>
<td>10 (8)</td>
<td>6 (6)</td>
<td>4 (14)</td>
<td>0·4 (0·1–1·5)</td>
<td>0·23</td>
</tr>
</tbody>
</table>

iGAS, Invasive group A streptococcal; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; STSS, streptococcal toxic shock syndrome.

* One or more chronic medical conditions.
† Includes people receiving haemodialysis.
‡ Includes chemotherapy (3) and radiotherapy (1).
§ Smoking status only known for 121 episodes.
predominant *emm* types causing invasive disease [3–5, 35]. The reason for this differing molecular epidemiology is unclear. Potentially the diversity of *emm* types reflects the NT’s demographic and geographical setting that supports a high proportion of Indigenous people, many of whom are of lower socioeconomic status and live in remote communities associated with household overcrowding [12, 20]. Overcrowding provides opportunity for circulation of GAS strains. We did not find tropical climate to be a contributing factor as a diverse range of *emm* types were found in both the tropical and semi-tropical regions of the NT. As our study was limited to a 2-year period and small sample size, further study is required to rule out tropical setting as a contributing factor. The diversity of *emm* types has implications for potential effectiveness of GAS vaccine formulations [18]. In rat trials, a 30-valent GAS vaccine has shown cross-protection against molecularly related non-vaccine *emm* types which has led to interest in the concept and use of *emm* clustering to further inform vaccine coverage [24, 36]. As most isolates (77%) in our study fell within four *emm* clusters, introduction of a GAS vaccine formulation covering these clusters may potentially reduce the incidence of iGAS disease in the NT significantly. Nevertheless the theoretical cross-protection across *emm* clusters remains speculative and requires robust studies in diverse locations to justify support for a GAS vaccine that directly covers only a minority of *emm* types in regions with high rates of GAS-related disease [35]. Our study is the first to describe the difference between *emm* ST and *emm* cluster coverage in a whole population analysis, but our data were limited to a 2-year period and ongoing typing of isolates is required to inform the evolution of circulating *emm* types causing disease.

**Risk factors predisposing to disease**

Consistent with previous reports, the majority of people had a risk factor predisposing them to iGAS disease [1, 4, 5, 8]. Risk factors included Indigenous ethnicity, age >65 years, presence of an underlying chronic or immunosuppressive medical condition, history of smoking and previous episode of iGAS disease. A limitation of this study was the inability to quantify alcohol consumption due to variable recording of alcohol intake in medical records. Excessive alcohol consumption, however, has been identified as a risk factor for iGAS disease [1, 3–5], and is likely also to be a risk factor in the NT which reports a higher alcohol consumption *per capita* than other Australian jurisdictions [37]. Identification of risk factors alerts clinicians for early detection and treatment and identifies populations who should be considered for vaccination and education.

**Public health response**

We identified only one episode of secondary transmission to a household contact. Due to lack of evidence of the efficacy of chemoprophylaxis and uncertainty regarding the number of people needed to treat to prevent one case, recommendations for managing contacts vary from no follow-up of cases to chemoprophylaxis of household members with a predisposing risk factor [3, 38, 39]. In 2014, the NT adopted similar guidelines to Canada, restricting chemoprophylaxis to close contacts of people with severe iGAS disease [39, 40]. Accordingly, contacts of 37 cases in our study would have received chemoprophylaxis, including the secondary case identified in the same household. However, due to the short timeframe of 2 days between infection in the index and secondary cases it is doubtful that diagnosis and public health response would have occurred prior to the secondary infection. To rationalize deployment of scarce public health resources, further studies on the potential effectiveness of chemoprophylaxis are needed. Studies should encompass timeliness of response, potential virulence of the organism, carriage status and extent of likely transmission.

**Outcomes**

Invasive GAS disease continues to cause severe illness in the Indigenous population of the NT. Outcomes and clinical course were similar regardless of Indigenous status. The case-fatality ratio of 8% was comparable to other Australian reports of 7–8% and lower than the rates reported from the United States, Europe and Fiji which were between 13% and 32% [3–5, 7, 11]. This potentially reflects universal access to advanced healthcare including intensive care facilities in Australia increasing the chance of survival. Severe complication of STSS in 11% of cases is similar to previous Australian findings, as were the large number of cases requiring hospital admission and surgical interventions [4, 8, 10]. People who died were more often older and had a pre-existing chronic medical condition. Similar to previous reports, development of STSS or necrotizing fasciitis was associated with
high mortality [3–5]. Invasive GAS disease continues to place significant burden on the individual, community and healthcare system.

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DECLARATION OF INTEREST

None.

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