# The epidemiology of invasive group A streptococcal disease in Victoria, Australia

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## ABSTRACT

**Objective:** To estimate the incidence and severity of invasive group A streptococcal infection in Victoria, Australia.

**Design:** Prospective active surveillance study.

**Setting:** Public and private laboratories, hospitals and general practitioners throughout Victoria.

**Patients:** People in Victoria diagnosed with group A streptococcal disease notified to the surveillance system between 1 March 2002 and 31 August 2004.

**Main outcome measure:** Confirmed invasive group A streptococcal disease.

**Results:** We identified 333 confirmed cases: an average annualised incidence rate of 2.7 (95% CI, 2.3–3.2) per 100 000 population per year. Rates were highest in people aged 65 years and older and those younger than 5 years. The case-fatality rate was 7.8%. Streptococcal toxic shock syndrome occurred in 48 patients (14.4%), with a case-fatality rate of 23%. Thirty cases of necrotising fasciitis were reported; five (17%) of these patients died. Type 1 (23%) was the most frequently identified *emm* sequence type in all age groups. All tested isolates were susceptible to penicillin and clindamycin. Two isolates (4%) were resistant to erythromycin.

**Conclusion:** The incidence of invasive group A streptococcal disease in temperate Australia is greater than previously appreciated and warrants greater public health attention, including its designation as a notifiable disease.

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Over the past two decades, a resurgence of invasive group A streptococcal (GAS) infection has been observed in industrialised countries around the world. This has been attributed to the emergence of highly virulent strains of group A streptococcus.[1,2] With current treatments, mortality still approaches 30% and survivors may be left with chronic sequelae.[3]

Little is known about the epidemiology of invasive GAS infection in Australia. A recent study in northern Queensland reported an annual incidence rate of 10.3 per 100 000 in the non-Indigenous population and 82.5 per 100 000 in the Indigenous population, with an overall mortality rate of 7%.[4] These estimates are substantially higher than those reported from the Top End of the Northern Territory (6.4 per 100 000 in the non-Indigenous population and 32.2 per 100 000 in the Indigenous population).[5] The only data from non-tropical Australia came from a 12-year review of admissions to the Royal Children's Hospital in Melbourne, which identified a clear increase in both disease frequency and severity,[6] consistent with reports from the United States and Europe.

New approaches to the management of invasive infections have emerged, including the use of clindamycin in addition to penicillin and the use of intravenous immune globulin (IVIG) in the treatment of streptococcal toxic shock syndrome (STSS).[7-11] After decades of research, prophylactic candidate GAS vaccines are beginning to show promise and may be available within the next 10 years.[12-17] To evaluate these interventions, comprehensive baseline data on the burden of disease are critical. Therefore, we established intensive, active surveillance of invasive GAS infection in Victoria.

## METHODS

### Setting

The study was conducted in Victoria between 1 March 2002 and 31 August 2004. Victoria has a population of about 4.3 million, a temperate climate, and a demographic profile similar to that of other industrialised countries. About 0.6% of the population identifies as Indigenous, although this is thought to be an underestimate.

### Surveillance system

Active surveillance of invasive GAS infection was performed prospectively via a voluntary, collaborative network of public and private laboratories, hospitals and general practitioners from across Victoria. All laboratories in Victoria that performed bacteriological testing ($n = 65$ in 2001) were approached to participate. In addition to passive reporting, laboratories were contacted twice per month.

To capture cases not reported through established channels, hospital discharge datasets from all Victorian hospitals with an intensive care unit or greater than 200-bed capacity ($n = 45$ in 2001) were reviewed every 3 months for ICD-10 (International classification of diseases, 10th revision) codes indicating GAS disease as a primary or secondary discharge diagnosis.

Confirmed cases were defined as one of the following:

- the isolation of group A streptococcus from a normally sterile site (eg, blood, cerebrospinal fluid, or other sterile fluid or tissue);
- a clinical presentation of necrotising fasciitis with evidence of GAS infection (eg, culture of group A streptococcus or the presence of gram-positive cocci from a tissue specimen or wound swab or positive streptococcal serology);
- a clinical presentation of pharyngeal abscess (quinsy) requiring hospitalisation and parenteral antibiotics with the isolation of group A streptococcus from a throat swab.

STSS was defined according to published criteria (Box 1).[18] Infections were classified as nosocomially acquired if the collection date of the first positive specimen was at least 3 days after the hospital admission date.

Demographic and clinical data were collected from the treating physician and medical record review.

### Laboratory methods

Available isolates underwent *emm* sequence typing and penicillin susceptibility testing. A subset of 50 randomly selected isolates (sample limited because of cost) underwent testing to determine minimal inhibitory concentrations (MIC) to penicillin, clindamycin and erythromycin using the Etest method

**1 Case definition of streptococcal toxic shock syndrome**

A. Isolation of group A streptococcus

1. From a sterile site
2. From a non-sterile body site

B. Clinical signs of severity

1. Hypotension
2. Two or more of the following clinical or laboratory abnormalities:
   - a. Renal impairment
   - b. Coagulopathy
   - c. Liver abnormalities
   - d. Acute respiratory distress syndrome
   - e. Extensive tissue necrosis
   - f. Erythematous rash

A definite case is defined as A1 + B(1 + 2)

A probable case is defined as A2 + B(1 + 2) ◆

(AB Biodisk, Solna, Sweden). Susceptibility was assigned according to the interpretative criteria for MIC recommended by the Clinical and Laboratory Standards Institute.[19]

### Data analysis

Denominators for the calculation of incidence rates were the Victorian estimated resident population (ERP) for 2002 and 2003 obtained from the Australian Bureau of Statistics. Average annualised rates were calculated by multiplying each year's ERP by the number of months of surveillance for each year (eg, 2002 population by 10 months) and adding these totals. The total number of cases over the 29 months was then divided by the total person-months and multiplied by 12. As data on onset of illness were incomplete, onset was calculated as the earliest of hospital admission date, specimen date or date of death. Data were analysed using Stata, version 9 (StataCorp, College Station, Tex, USA).

### Ethics

The study was approved by the Victorian Department of Human Services' Ethics in Human Research Committee and by more than 70 individual health service ethics committees.

## RESULTS

Forty-five eligible hospitals and 63 laboratories agreed to participate. Two laboratories refused, but serviced hospitals for which discharge data were available.

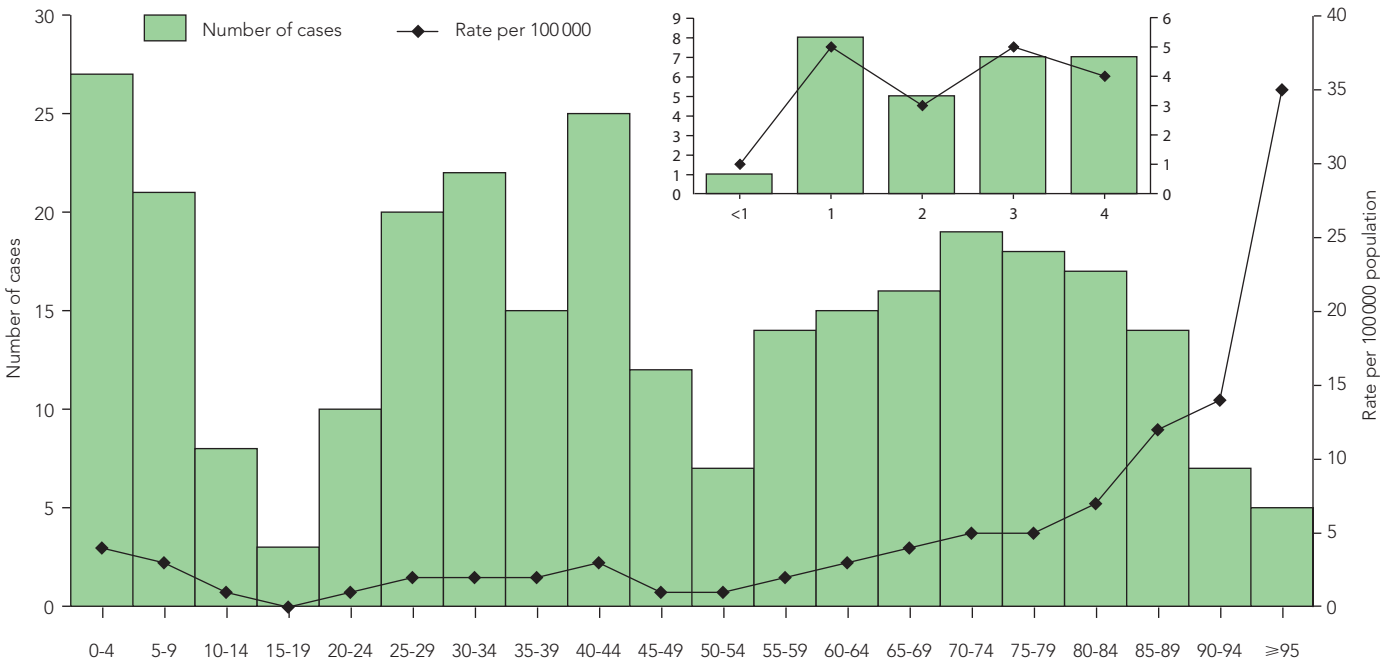
### Epidemiological data

In the 30-month study period, 333 confirmed cases were identified. Three hundred and fifteen (94.6%) were classified by the isolation of group A streptococcus from a sterile site, one was laboratory-confirmed necrotising fasciitis with positive streptococcal serology and group A streptococcus isolated from a deep wound swab, and 17 were pharyngeal abscesses. The average annualised incidence rate was 2.7 (95% CI, 2.3–3.2) per 100 000 population per year. Blood cultures were positive in 240 patients (72.1%) (annualised incidence of GAS bacteraemia, 2.0 [95% CI, 1.6–2.4] per 100 000 population per year).

For the 302 patients whose age was known, the mean age was 45.8 years (95% CI, 42.6–49.0 years); 58 cases (19.2%) occurred in children aged 0–15 years and 134 (44.4%) occurred in people aged 50 years and older. Incidence rates were highest in people younger than 5 years and in those 65 years and older (Box 2). Fifty-three per cent of cases occurred in males. Only two cases were identified in Indigenous individuals (average annual incidence rate, 2.9 per 100 000 population per year).

Among those for whom the information was available, 97.8% (307/314) were hospitalised, the length of stay was ⩾ 10 days for 48.7% (135/277), and 23.3% (67/288) required admission to an intensive care unit. Twenty-one (6.8%) of 307 hospitalised

**2 Confirmed invasive group A streptococcal infection and average annualised incidence rate per 100 000 by age group (years), Victoria, 1 March 2002 to 31 August 2004**




The inset shows data for the 0–4-years age group. ◆

**3 Specified diagnosis* by age group in people with confirmed invasive group A streptococcal infection, Victoria, 1 March 2002 to 31 August 2004**

| Diagnosis | Age group (years) 0–14 (*N* = 58) | 15–49 (*N* = 110) | ⩾ 50 (*N* = 134) | Unknown (*N* = 31) | Total† (%) |
|---|---|---|---|---|---|
| Soft tissue infection | 20 | 56 | 86 | 14 | 176/266 (66.2%) |
| Cellulitis | 11 | 47 | 74 | 14 | 146/182 (80.2%) |
| Necrotising fasciitis | 0 | 14 | 14 | 2 | 30/276 (10.9%) |
| Septic arthritis | 13 | 11 | 19 | 1 | 44/280 (15.7%) |
| Bacteraemia only | 8 | 8 | 15 | 10 | 41/333 (12.3%) |
| Lower respiratory tract | 13 | 16 | 12 | 2 | 43/279 (15.4%) |
| Pneumonia | 8 | 14 | 12 | 2 | 36 |
| Empyema | 5 | 2 | 0 | 0 | 7 |
| Upper respiratory tract | 9 | 20 | 5 | 2 | 36/333 (10.8%) |
| Quinsy | 3 | 12 | 0 | 2 | 17 |
| Pharyngitis | 2 | 2 | 0 | 0 | 4 |
| Sinusitis | 1 | 2 | 1 | 0 | 4 |
| Other | 3 | 4 | 4 | 0 | 11 |
| Surgical site infection | 2 | 9 | 12 | 2 | 25/277 (9.0%) |
| Osteomyelitis | 5 | 3 | 2 | 0 | 10/270 (3.7%) |
| Other site | 1 | 8 | 1 | 0 | 10/134 (7.5%) |
| Peritonitis | 2 | 2 | 1 | 2 | 7/280 (2.5%) |
| Peripartum | 0 | 6 | 0 | 0 | 6/286 (2.1%) |

* More than one diagnosis may be specified per patient. † Denominator denotes number of patients for whom the information was available. ◆

**4 Frequency of known risk factors for confirmed invasive group A streptococcal infection, Victoria, 1 March 2002 to 31 August 2004**

| Risk factor | *n*/*N** | % |
|---|---|---|
| Chronic medical condition | 182/275 | 66.1% |
| Heart disease | 66/283 | 23.3% |
| Lung disease | 43/280 | 15.4% |
| Diabetes | 31/281 | 11.0% |
| Liver disease (other than cirrhosis) | 21/282 | 7.4% |
| Renal disease | 15/279 | 5.4% |
| Haematological disorder | 6/279 | 2.2% |
| Other† | 137/283 | 48.4% |
| Cigarette smoking | | |
| Current | 52/268 | 19.4% |
| Past | 96/257 | 37.4% |
| Prior use of non-steroidal anti-inflammatory agents | 62/261 | 23.4% |
| Immunosuppression‡ | 52/278 | 18.7% |
| Includes 3 patients with HIV | 3/280 | 1.1% |
| Any history of alcohol misuse | 30/257 | 11.7% |
| Current | 23/269 | 8.6% |
| Past | 29/264 | 11.0% |
| Any history of IV drug use | 26/270 | 9.4% |
| Current | 23/278 | 8.3% |
| Past | 23/277 | 8.3% |
| Recent history of chickenpox (all cases) | 4/275 | 1.8% |
| Age < 15 years | 3/58 | 5.0% |

* Denominator represents patients for whom the information was available. Patients may have had more than one condition. † Includes endocrine disorders, autoimmune disorders, cerebrovascular disorders, mental illnesses, gastrointestinal disorders, glaucoma, metabolic disorders. ‡ Includes systemic lupus erythematosus, HIV, hepatic cirrhosis, splenectomy, transplant, malignancy, sickle cell anaemia. ◆

patients were identified as having potentially nosocomially acquired infections.

Soft tissue was the most common site of infection (*n* = 176) across all age groups (Box 3). Among the patients for whom the information was available, a pre-existing chronic medical condition was reported in 66.2% (182/275); heart and lung diseases predominated. Immunosuppression was reported in 18.7% of patients (52/278), and 23.8% (62/261) reported use of non-steroidal anti-inflammatory drugs within 14 days of symptom onset. Preceding chickenpox was reported in 5% (3/58) of paediatric patients. Other risk factors are listed in Box 4.

### Severity and outcome

STSS was identified in 48 (14.4%) of the 333 patients, and necrotising fasciitis in 30 (10.9%) of 276 patients for whom the information was available (Box 5). Twenty-five deaths were known to have been due to GAS disease (case-fatality rate, 7.8%). Six deaths (24%) occurred in people younger than 65 years, including a 2-year-old child with a history of sore throat who died of streptococcal bacteraemia. All but three died within 10 days of admission to hospital. Of those who died, only one person had received IVIG and only eight had received clindamycin in hospital. Four people who died were immunocompromised; none was HIV positive. The focus of infection in 19 fatal cases (76%) was soft tissue, of which five involved necrotising fasciitis.

Where the information was available (*n* = 285), 138 people (48.4%) required surgery as a result of their GAS disease (including debridement, washout, skin graft, incision and drainage of abscesses, and exploratory surgery) and of these, 13 (9.4%) required amputation of a limb.

### Laboratory data

Among the 255 available isolates on which *emm* sequence typing was performed, 56 different types were identified; the top five are presented in Box 6. Type 1 was the most common in all age groups, and accounted for 42% of isolates from those who died, and 47% of STSS and 70% of necrotising fasciitis cases. Sixty-two per cent of the isolates came from *emm* types included in a 26-valent serotype-specific GAS vaccine currently in clinical trials.[17] *Emm* types were available on 15 of the 21 nosocomial infections: three were type 1, two were type 12, two were type 28, and eight were individual types. No epidemiological links were apparent.

All of the 50 isolates tested were susceptible to penicillin (all MICs < 0.024 μg/mL) and clindamycin (all MICs < 0.20 μg/mL). Two isolates (4%) were resistant to erythromycin (MICs, 16 and 24 μg/mL; all other MICs < 0.20 μg/mL).

## DISCUSSION

Our study provides the first population-based data on the epidemiology of invasive GAS infection in non-tropical Australia. We

**5 Demographic features of patients with necrotising fasciitis or STSS**

| | Necrotising fasciitis | STSS |
|---|---|---|
| Number (%) | 30/276 (10.9%) | 48/333 (14.4%) |
| Age (years) | Mean: 52<br>95% CI: 43–61 | Median: 60<br>Range: 6–88 |
| Sex | | |
| Male | 19 (63%) | 19 (30%) |
| Female | 11 (37%) | 29 (60%) |
| Cases in children < 15 years | 0 | 4 (8%) |
| Case fatalities (%) | 5 (17%) | 11 (23%) |

STSS = streptococcal toxic shock syndrome. ◆

identified an incidence rate of 2.7 per 100 000 population per year and a case-fatality rate ranging from 7.8% for any disease to 23% for STSS. This disease predominantly affected the elderly and young children. The most common focus of infection across all age groups was soft tissue, which also accounted for an increasing proportion of cases as age increased.

The incidence of disease, case-fatality rate, predominance of cases in the elderly and people with underlying medical conditions, foci of infection and frequency of *emm* type 1 among invasive isolates are consistent with epidemiological data from other industrialised countries.[20-23] The incidence of invasive GAS infection in non-Indigenous people in tropical northern Australia is two to four times greater than in Victoria.[4,5] It is not clear if these differences are attributable to factors related to host susceptibility (eg, increased prevalence of chronic conditions and alcohol use), differences in environmental exposures, or differences in the virulence of prevalent GAS strains. The differences in *emm* type distribution between northern Australia and Victoria reflect their divergent epidemiologies. Cases in the north are largely due to underlying skin infections,[5] and the extreme diversity in *emm* types in invasive GAS disease reflects the same diversity in skin strains.[5,24] The limited *emm* type distribution in Victoria parallels that seen in other industrialised countries.

The proportion of infections that were nosocomially acquired is of concern. Invasive GAS infection in health care settings can be highly transmissible[25] and is associated with an increased risk of a fatal outcome;[26,27] institutional outbreaks are not uncommon.[28] In the US, it is recommended that one nosocomial postpartum or postsurgical invasive GAS infection should initiate enhanced surveillance and two or more should prompt an epidemiological investigation that includes carriage studies of health care workers.[29] Our data suggest these recommendations are prudent and should be considered in Australia.

We found a low proportion of varicella-associated childhood cases compared with between 15% and 27% of paediatric cases reported elsewhere.[30-32] The reasons for this are unclear. Hospitalisation for childhood varicella in Victoria occurs relatively late in the illness,[33] suggesting that the low rate of varicella-associated invasive GAS infections is not due to different behaviour in seeking health care. However, at the time of this study there was considerable public concern surrounding invasive meningococcal disease in Australia; it is possible that this may have led parents of children with fever and rash to present early to primary care practitioners.

Under-reporting is usually the most common problem with the use of surveillance systems for providing burden of disease data. Our system of reviewing hospital data and regular contact with diagnostic laboratories suggests we are not likely to have missed many confirmed cases. We included in our case definition 18 cases that were not confirmed by the isolation of group A streptococcus from a sterile site. One of these was a patient with necrotising fasciitis who had both positive streptococcal serology and group A streptococcus isolated from a deep wound swab, and developed STSS. The other 17 had pharyngeal abscesses (quinsy), which are accepted invasive infections for which the most common single pathogenic species is group A streptococcus;[34] all these patients had positive throat swabs. Both conditions require management as intensive as for group A streptococcus confirmed by sterile site isolates, and their exclusion would underestimate disease burden.

The incidence of invasive GAS disease in Victoria is similar to that of invasive meningococcal disease before the introduction of meningococcal C vaccine.[35] Invasive meningococcal disease has been legally notifiable in all parts of Australia since 1991, with comprehensive treatment and management guidelines developed at a national level.[35] Given the similarities, there is a case for making invasive GAS infection notifiable in Australia. This would be strengthened if an increased risk of disease could be demonstrated in close contacts of cases; we are analysing our data to determine if this is the case in Victoria. The frequency of nosocomial infections provides impetus for the development of guidelines to manage GAS disease in institutions. The lack of use of IVIG or clindamycin in fatal cases, despite recommendations that they be used in patients with severe invasive GAS infections,[36-38] suggests a need for standard treatment guidelines and education of health professionals. A review of the approved indications for IVIG in Victoria is required, as these do not currently include severe GAS disease, potentially delaying the release of the product for immediate use. The ongoing development of vaccines, concerns about antibiotic resistance and a growing body of evidence that suggests disease is becoming more severe in recent decades necessitate ongoing population-based surveillance systems to monitor these trends and to inform both clinical management and public health policy.

**6 The five most frequent *emm* types by age group in patients with confirmed invasive group A streptococcal infection, Victoria, 1 March 2002 to 31 August 2004**

| | *emm* type (%) | | |
|---|---|---|---|
| Rank | 0–14 years | 15–49 years | ⩾ 50 years |
| 1 | 1 (32.6%) | 1 (21.3%) | 1 (26.1%) |
| 2 | 3.1 (11.6%) | 12 (8.8%) | 28 (15.7%) |
| 3 | 28 (7.0%) | 22 (8.8%) | 12 (7.0%) |
| 4 | 4 (4.7%) | 28 (5.0%) | 75 (6.1%) |
| 5 | 75 (4.7%) | 3.1 (5.0%) | 4 (4.4%) |

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## COMPETING INTERESTS

None identified.

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