The epidemiology of invasive group A streptococcal disease in Victoria, 2007–2017: an analysis of linked datasets

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Abstract

Objective: To describe the incidence and severity of invasive group A streptococcal disease (iGAS) in Victoria, Australia.

Methods: Retrospective analysis of iGAS cases identified in linked datasets, 2007–2017: laboratory data from the Victorian Hospital Pathogen Surveillance Scheme; hospitalisation data from the Victorian Admitted Episodes Dataset; and deaths reported by the Australian Coordinating Registry.

Results: There were 1,369 confirmed and 610 probable cases of iGAS identified from 2007 to 2017 in Victoria, Australia. The median annual incidence was 3.1 (range 2.4–5.2) per 100,000 population. The incidence was highest in 2017, with 5.2 (95%CI: 4.6–5.8) cases per 100,000 population. The median length of stay in hospital was 10 days, with 33.1% (578/1,744) of cases admitted to the intensive care unit, of whom 49.5% (286/578) were mechanically ventilated. The case fatality rate was 5.6% (110/1,979), reaching 13.5% (51/378) among those aged 75 years or older.

Conclusions: There was an increased incidence of iGAS in 2017 in Victoria, with substantial healthcare utilisation and a high case fatality rate among older Victorians.

Implications for public health: These data support mandatory notification of iGAS, which will enable better characterisation of the disease, rapid identification of changes in epidemiology and targeted public health responses.

Key words: infectious disease epidemiology, invasive group A streptococcal disease, linked data

Invasive group A streptococcal disease (iGAS), defined as GAS infection of a normally sterile site, is associated with significant morbidity and mortality.[1] Necrotising fasciitis and toxic shock syndrome are particularly severe forms of iGAS, with case fatality rates ranging from approximately 20–50%.[1,2] Complex medical and surgical care is often required.[1] Certain groups have an increased risk of iGAS, particularly the very young and old.[1] Household contacts of iGAS cases are at a higher risk of secondary infection than the general population,[3,4] with a Victorian study reporting an incidence rate ratio of 2,011 (95%CI: 413–5,929) for the 30 days following onset of disease in the index case,[5] and a UK study reporting a similar incidence rate ratio of 1,940 (95%CI:1,240–2,880).[3] Chemoprophylaxis to prevent secondary disease in close contacts is recommended in Canada,[6] but not in the UK[7] or US.[8] Australia has no national guidelines for the prevention of secondary disease with antibiotic prophylaxis, though some Australian sources, including the Royal Children's Hospital in Melbourne, recommend antibiotic prophylaxis for close contacts.[9-11]

Inequitably high rates of iGAS for Aboriginal and Torres Strait Islanders in Australia have been demonstrated, with annual incidence of 69.7 (95%CI: 51.6–92.0), 79.9 (95%CI: 62.6–97.2) and 82.5 per 100,000 population reported in the Northern Territory,[12] Western Australia[13] and North Queensland,[14] respectively. A paediatric cohort study with sites in six states and territories also found that the incidence of iGAS was 2.1-fold higher for Aboriginal and Torres Strait Islander children.[15]

The last statewide characterisation of iGAS in Victoria was published in 2007 and used data from 2002 to 2004, reporting a mean annual incidence of 2.7 (95%CI: 2.3–3.2) per 100,000 population.[16] A more recent study that assessed the trends in iGAS from 2007 to 2017 reported a mean annual incidence of 2.1 (95%CI: 1.8–2.5) per 100,000 population, with a peak incidence of 3.6 (95%CI: 3.2–4.1) cases per 100,000 population in 2017. However, the study did not include all cases in the state and had no clinical or outcome data.[17]

iGAS was added to the National Notifiable Diseases List (NNDL) in Australia in July 2021,[18] paving the way for it to become nationally notifiable. Previously it was

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notifiable in only Queensland and the Northern Territory, but iGAS has since been made notifiable in Victoria, South Australia and Western Australia. In the absence of routinely collected notification data, characterising the incidence and severity (described by indicators such as length of hospitalisation, intensive care requirements and case fatality rate) of iGAS in Victoria has relied on laboratory surveillance that does not cover the entire population, or smaller-scale studies. This limits our understanding of the true burden of disease and our ability to identify and respond to epidemiological trends. Examining linked datasets, this study covers all age groups and geographic locations in Victoria, with maximum case and outcome ascertainment to better describe iGAS incidence and severity than previous studies. We characterise the incidence and severity of iGAS in Victoria from 2007 to 2017.

Methods

Data sources and data linkage

All GAS laboratory results reported to the Victorian Hospital Pathogen Surveillance Scheme (VHPSS) with sample collection from 1 January 2007 to 31 December 2017 were included. The VHPSS is coordinated by the Microbiological Diagnostic Unit Public Health Laboratory and collects voluntary notifications of GAS isolated from human blood and cerebrospinal fluid samples from public, private, metropolitan and regional laboratories in Victoria.[17] The scheme was estimated to have approximately 60% coverage of eligible isolates in the state in 2009, increasing to 80% in 2017.[17]

Population-level hospitalisation and death data from 1 January 2007 to 31 December 2017 were obtained from the Victorian Admitted Episodes Dataset (VAED) and the National Cause of Death Unit Record File. The VAED included data on all admitted patient episodes in all Victorian public and private hospitals. This was the only dataset that included Indigenous status. The deaths data were supplied by the Australian Coordinating Registry, on behalf of the Australian state and territory Registrars of Births, Death and Marriages.

Data linkage was performed by the Centre for Victorian Data Linkage. Individuals in the hospitalisation and death datasets were identified using a project-specific linkage ID. Laboratory records were matched to linkage IDs based on a 2x2 first name/last name code, sex and birthdate, along with month of specimen collection and hospitalisation (Supplementary File 2).

Cases were identified using the definitions in Box 1.

Statistical analysis

Annual incidence rates were calculated per 100,00 population using the Australian Bureau of Statistics mid-year population estimates,[19,20] to account for the increasing population. Negative binomial regression models were used to investigate whether iGAS incidence varied significantly according to Indigenous status, year, sex and age, generating incidence rate ratios (IRRs) with 95% confidence intervals.

Length of hospital stay, duration in the ICU and duration on mechanical ventilation were calculated using all hospital admission data for all probable and confirmed iGAS cases. Case fatality rates were calculated using deaths that occurred during the same hospital episode or within one month of hospital separation and/or microbiological diagnosis, and were calculated using both probable and confirmed cases.

Statistical analysis was performed using Stata version 16.1 (StataCorp, College Station, Texas). Ethics approval was obtained from the University of Melbourne Medicine and Dentistry Human Ethics Committee (ID: 1852332.2).

Box 1: iGAS case definitions.

A confirmed case was defined by a Victorian Hospital Pathogen Surveillance Scheme (VHPSS) laboratory record indicating the isolation of GAS from a blood or cerebrospinal fluid specimen.

A probable case was defined as a hospitalisation record with no VHPSS laboratory confirmation and the following combination of ICD-10 codes: (1 OR 2) AND 3

1. A400, sepsis due to Streptococcus, group A

2. B950, Streptococcus, group A, as the cause of diseases classified to other chapters, listed immediately after one of the following codes:
- A483, toxic shock syndrome
- A491, streptococcal and enterococcal infection, unspecified site
- G002, streptococcal meningitis
- J154, pneumonia due to other streptococci
- J390, retropharyngeal and parapharyngeal abscess
- J860, pyothorax with fistula
- J869, pyothorax without fistula
- M002x, other streptococcal arthritis and polyarthritis
- M726x, necrotising fasciitis
- M86xx, osteomyelitis
- O85, puerperal sepsis

(where x further specifies the disease type or site)

3. The absence of diagnostic codes for other pathogens as the cause of disease classified to other chapters (all codes from B951 to B978)

Results

Victoria's population grew from approximately 5.1 million in 2007 to 6.3 million in 2017. In 2016, Aboriginal and Torres Strait Islanders represented 0.9% of the estimated resident population of Victoria.

Characteristics of iGAS cases

Between 1 January 2007 and 31 December 2017, 1,979 cases of iGAS were identified, comprising 1,369 (69.2%) confirmed and 610 (30.8%) probable cases (Table 1). Almost all confirmed cases were identified through isolation of GAS from blood (1,367/1,369, 99.9%); 235 confirmed cases (11.9% of all cases) had no associated hospitalisation data. More cases were identified in males (1,073, 54.2%) compared to females (906, 45.8%). Among the 1,744 cases with hospitalisation data, 23 (1.3%) were in people who identified as Aboriginal and/or Torres Strait Islander. One-quarter of hospitalised cases were located at regional hospitals (439/1,744, 25.2%). Twenty-eight individuals (28/1,949, 1.4%) had two episodes of iGAS over the study period and one individual had three confirmed episodes.

Incidence

The number of iGAS cases increased from 158 in 2007 to 327 in 2017 (Figure 1a), with an incidence of 3.1 (95%CI: 2.6–3.6) per 100,000 in 2007 compared to 5.2 (95%CI: 4.6–5.8) per 100,000 in 2017. The median annual incidence was 3.1 per 100,000 (range 2.4–5.2). There was weak evidence of a difference in incidence between Aboriginal and Torres Strait Islanders and the non-Indigenous population (IRR 1.41, 95%CI: 0.94–2.13, p=0.100; Supplementary File 3). People aged 75 years and older had the highest incidence of iGAS (9.1 [95%CI: 8.2–10.1] cases per 100,000; Figure 1b). The incidence of iGAS was higher in males than females for all age groups except for those aged 20–39 years (Figure 1b).

Clinical manifestations and risk factors

Among the 1,744 cases with hospitalisation data, the most common diagnosis code was

sepsis due to GAS (1,052, 60.3%), followed by bacteraemia (166, 9.5%) and necrotising fasciitis (155, 8.9%) (Supplementary File 4). The most common risk factor for iGAS was skin infection (692, 39.7%), followed by renal failure (526, 30.2%) and cardiac disease (525, 30.1%) (Supplementary File 5). Very few cases had diagnosis codes indicating co-infection with influenza (20, 1.2%), varicella (5, 0.3%) or HIV (4, 0.2%). Of the 20 iGAS cases with influenza co-infection, 12 (60%) occurred in 2017; influenza was diagnosed in 12/291 (3.7%) iGAS cases with hospitalisation data in 2017 compared to 8/1,453 (0.6%) cases occurring in 2007–2016 ($p<0.001$). Smoking was relatively common (467, 26.8%), however, a diagnosis code indicating drug use was only recorded in 13 cases (0.8%) and alcohol use in four cases (0.2%).

Indicators of severity

The median length of stay in hospital was 10 days (interquartile range (IQR) 5–21, maximum 359 days). One-third of cases were admitted to the ICU (578/1,744, 33.1%). The highest proportions of cases requiring ICU were in 2014 (61 cases in ICU, 38.6% of cases) and 2017 (112 cases in ICU, 38.5%).

Among ICU patients, the median time in the ICU was 95 hours (IQR 46–206, maximum 2,057 hours [86 days]). Admission to the ICU was common for iGAS cases with necrotising fasciitis (112/155, 72.3%) and toxic shock syndrome (52/66, 78.8%). Approximately half of the ICU patients received mechanical ventilation (286/578, 49.5%), accounting for 16.4% of all cases. The median time spent on mechanical ventilation was 108.5 hours (IQR 37–210, maximum 1,147 hours [48 days]).

Deaths

The overall case fatality rate (CFR) was 5.6% (110/1,979), including 75 confirmed and 35 probable cases. The majority of deaths were identified in the hospitalisation dataset [VAED] (105/110, 95.5%); an additional five deaths (4.5%) were identified through data linkage (Supplementary File 2).

The CFR ranged from 3.8% in 2014 to 9.3% in 2008. The greatest number of deaths occurred in 2017 (16/327, CFR 4.9%, Supplementary File 3). The CFR for 2007–2017 reached 13.5% (51/378) for those aged 75 years or older (Supplementary File 3). The relative risk of death was 3.66 (95%CI 2.47–5.42, $p<0.001$) for those aged 75 years or older compared to those aged under 75. No deaths occurred in iGAS cases aged 5–19 years, and three deaths occurred in those aged under 5 years (CFR 1.4%). One death occurred in a case who identified as Aboriginal and/or Torres Strait Islander.

Around one-quarter of deaths had a record identified in the death dataset (32/110, 29.1%). The most common primary cause of death was necrotising fasciitis (13/32, 40.6%) followed by sepsis due to GAS (5/32, 15.6%).

Discussion

This study is the first statewide analysis to characterise the incidence and severity of iGAS in Victoria, Australia using linked administrative datasets. Our analysis demonstrated a significantly higher incidence and substantial critical care requirements in 2017 compared to previous years. We documented an increased iGAS incidence in 2017, rather than a gradual increase over the period. Similar upsurges in iGAS incidence have been reported over comparable time periods in Europe[21-23] and some states in the US,[24] compared to the steady increases in Western Australia[13] and New Zealand.[25]

Temporal variation in iGAS incidence may be caused by changes in population susceptibility or transmission among specific groups such as injecting drug users or homeless populations,[26,27] whereas the introduction of different strains has been shown to drive more sudden increases in disease incidence.[28,29] However, analysis of *emm*-typing of iGAS cases reported to the VHPSS demonstrated that the increase in incidence in 2017 was not driven by one particular *emm*-type.[17] The higher proportion of cases with influenza in 2017 warrants further investigation of the potential for an influenza epidemic to drive a surge in iGAS cases, particularly as the increase in paediatric iGAS cases in Australia in 2017 has been correlated with influenza notifications.[15] Studies have noted ecological associations between influenza and iGAS incidence,[30,31] and identified co-infections during periods with increased iGAS and influenza incidence,[22] with influenza infection increasing susceptibility to secondary bacterial infections.[32,33] The upsurge in iGAS cases in 2017 may have been driven by other factors including random fluctuation, changes in testing or increased adherence to voluntary notification, although we are not aware of any initiative that would have prompted a sudden surge such as this.

These results emphasise the regional variability of iGAS in Australia, with the incidence in Victoria much lower than in Queensland and the Northern Territory.[34] While Aboriginal and Torres Strait Islanders are overrepresented in iGAS cases in Queensland[14,35] and the Northern Territory[12] compared to non-Indigenous people, the overall incidence of iGAS is also higher in non-Indigenous populations in North

Table 1: Characteristics of invasive group A streptococcal disease cases, Victoria, 2007–2017.

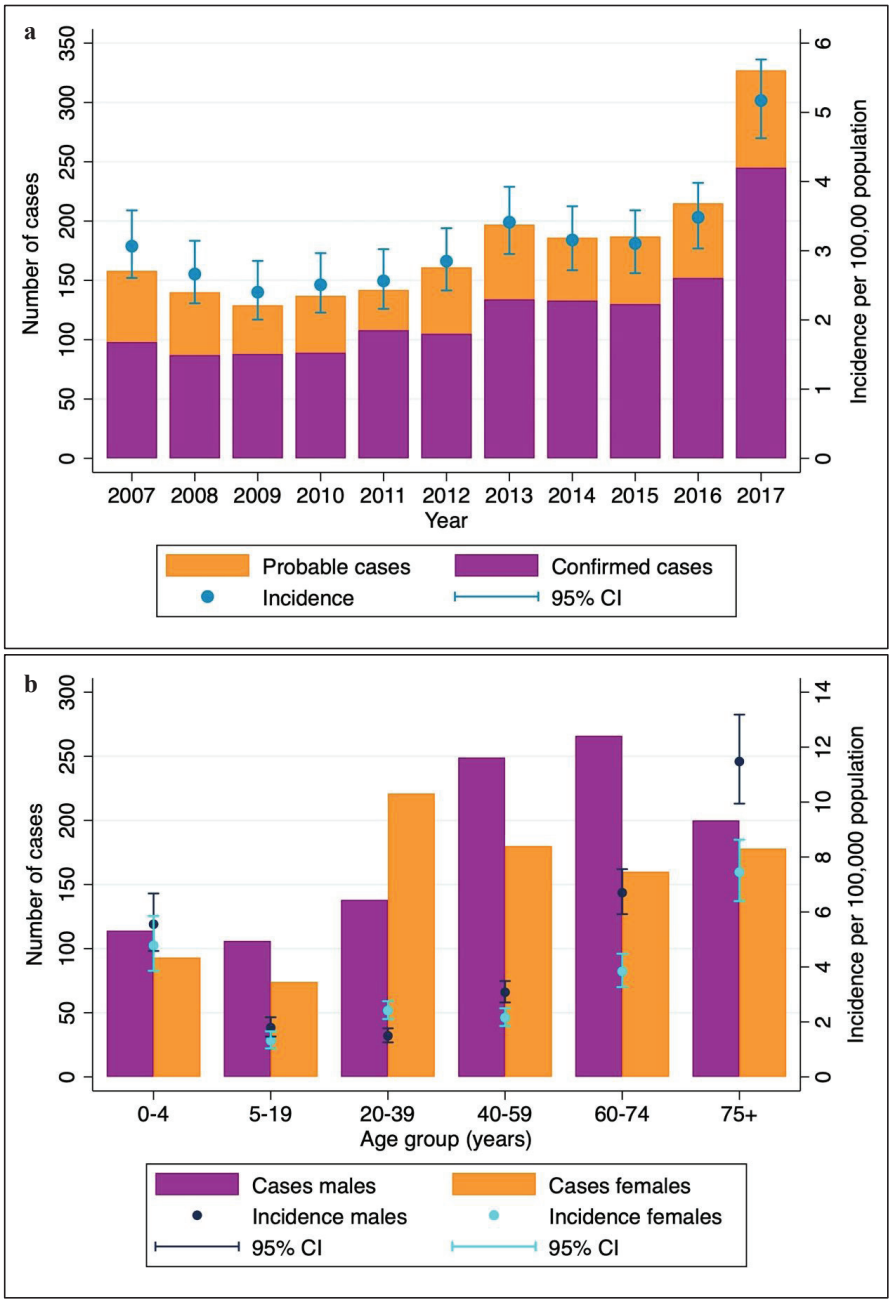
Classification	Confirmed, n (%)	Probable, n (%)	Total, n (%)
Case number	1,369 (69.2)	610 (30.8)	1,979
Sample type	**[N=1,369[a]]**		
Blood	1,367 (99.9)	-	1,367 (99.9)
Cerebrospinal fluid	2 (0.01)	-	2 (0.01)
Hospital record identified	1,134 (82.8)	610 (100.0)	1,744 (88.1)
Sex			
Male	717 (52.4)	356 (58.4)	1,073 (54.2)
Female	652 (47.6)	254 (41.6)	906 (45.8)
Age group, years			
0–4	152 (11.1)	55 (9.0)	207 (10.5)
5–19	121 (8.8)	59 (9.7)	180 (9.1)
20–39	232 (17.0)	127 (20.8)	359 (18.1)
40–59	278 (20.3)	151 (24.8)	429 (21.7)
60–74	303 (22.1)	123 (20.2)	426 (21.5)
75+	283 (20.7)	95 (15.6)	378 (19.1)
Indigenous status	**[N=1,134[b]]**		**[N=1,744[b]]**
Not Aboriginal and/or Torres Strait Islander	1,105 (97.4)	596 (97.7)	1,701 (97.5)
Aboriginal and/or Torres Strait Islander	17 (1.5)	6 (0.1)	23 (1.3)
Unknown	12 (1.1)	8 (1.3)	20 (1.1)

Notes:
a: Data available only for confirmed cases (from Victorian Hospital Pathogen Surveillance Scheme);
b: Data available only for hospitalised cases (from Victorian Admitted Episodes Dataset)

Queensland (10.3 per 100,000 population)[14] and the Northern Territory (8.8 per 100,000 population)[12] compared to Victoria (3.1 per 100,000 population). The incidence of iGAS among Aboriginal and Torres Strait Islanders in Victoria was not significantly higher than among the non-Indigenous population and was considerably lower than the incidence in Aboriginal and Torres Strait Islanders in northern Australia.[12,14] These regional differences may relate to differences in climate or factors such as socioeconomic disadvantage and housing between Aboriginal and Torres Strait Islander populations in these states,[12] as well as more complete data in Queensland and the Northern Territory due to mandatory notification of iGAS.[34] However, a data linkage study in Western Australia also reported a consistently higher incidence in Aboriginal and Torres Strait Islander populations (IRR 13.1), with incidence also higher in tropical compared to non-tropical areas.[13]

The prevalence of recorded drug and alcohol use was relatively low in this study compared to the 2007 study of iGAS in Victoria, which reported that 11.7% of cases had current or past alcohol misuse and 9.4% had a history of injecting drug use.[16] It is likely that these risk factors are not well captured by ICD-10-AM codes (Supplementary File 1.2), which are loosely defined and do not specifically identify injecting drug use. The potential inadequacy of ICD-10 codes is highlighted by a single-centre study of GAS bacteraemia in Melbourne, Victoria from 2014 to 2017 where 18/43 patients (42%) had a history of injecting drug use,[36] whereas our study, which should include all of these cases and covers additional years, only identified 13 cases with drug use coded. A more detailed analysis of prospectively collected data could examine temporal and geographical variation in the prevalence of comorbidities, rates of co-infection such as influenza, and risk factors such as injecting drug use. Such data could be available through enhanced surveillance now that iGAS has been made notifiable in Victoria and could be used to determine trends or outbreaks among particular groups and to target interventions such as prophylactic antibiotics or future vaccines to the highest-risk groups.[27,37]

Figure 1 (a): Confirmed and probable invasive group A streptococcal disease cases and incidence rate by year, Victoria, 2007–2017 (b): Confirmed and probable invasive group A streptococcal disease cases and incidence rate in Victoria, 2007–2017, by age group and sex.



The CFR of 5.6% is lower than has been reported in many high-income countries such as the UK and US (around 10–20%[38,39]) and lower than the 2007 Victorian study (7.8%[16]). This relatively low CFR may reflect the relatively low proportion of iGAS cases with manifestations typically associated with a high risk of death such as toxic shock syndrome, or the high standard of care available in Victoria,[12] but could also indicate under-ascertainment of deaths in our study that would result in an underestimation of the true CFR.

In the absence of routinely collected notification data, data linkage has enabled increased case and outcome ascertainment. This is particularly important, as the only available laboratory data in Victoria do not include all isolates in the state, and hospital data may not completely capture outcomes such as iGAS-related deaths after discharge from hospital.[40] Data linkage also enabled analysis of additional demographic and clinical factors, and more accurate estimation of Indigenous status, which is often missing or incompletely reported in laboratory notifications in Victoria.[41]

This study had several limitations. It is unclear whether confirmed cases with no hospitalisation data were not linked due to issues with the data linkage process,

or whether these cases occurred in the community and were not admitted to hospital. While diagnostic coding in Victoria is reported to be of high quality,[42] the reliability of using diagnostic codes to identify iGAS cases and clinical manifestations is uncertain. Our probable case definition, similar to a recent Western Australian data linkage study,[13] favours specificity because the hospitalisation data do not indicate whether GAS has been isolated. While the B950 code (specifying GAS as the cause of disease) suggests laboratory evidence, true iGAS cases may have been missed due to this lack of sensitivity, or if they were not included in the VHPSS laboratory dataset, which has incomplete coverage of isolates in the state. Our study did not include cases with GAS isolated from normally sterile tissues and fluids, apart from CSF, which could explain the lower incidence compared to studies from other states in Australia. However, many of these cases will have been captured by the probable case definition. As the deaths data were selected for relevant diagnostic codes before data linkage, not all mortality within a month of separation from hospital or sample collection was identified, resulting in possible underestimation of the CFR.

The findings of this study highlight the importance of iGAS being notifiable in Victoria and nationally. While the addition of iGAS to the NNDL in July 2021[18] paves the way for iGAS to be nationally notifiable, some jurisdictions are yet to make iGAS notifiable and may choose not to do so. Mandatory notification of iGAS will alleviate the need for conducting discrete studies to understand the disease epidemiology and facilitate more rapid identification of changes in disease incidence or severity. It will also enable the identification of key populations and targeted responses to outbreaks, timely provision of prophylaxis to contacts to prevent secondary infections, analysis of secondary transmission events, and assessment of the impact of interventions. Mandatory reporting at a national level will further enhance identification and response to changes in disease patterns and allow for better comparisons across regions and demographic groups in Australia and internationally.[34]

This analysis is the most comprehensive recent assessment of iGAS in Victoria. The substantial severity and recent increase in incidence provide strong support for the decision to add iGAS to the NNDL and for jurisdictions to make iGAS notifiable. This will enable ongoing characterisation of the disease burden, key populations and identification of changes in incidence, as well as targeted and timely responses.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary File 1: Relevant ICD-10-AM codes.

Supplementary File 2: Merging of datasets, and reasons for excluding records. Before data linkage, hospital admissions and death records were selected based on diagnostic codes relevant to the Straddle-Vic project.

Supplementary File 3: Number of cases of invasive group A streptococcal disease, incidence rates, incidence rate ratios, number of deaths and case fatality rates, Victoria, 2007–2017.

Supplementary File 4: Diagnosis codes of invasive group A streptococcal disease among cases with hospitalisation data (N=1,744), Victoria, 2007–2017.

Supplementary File 5: Potential risk factors for iGAS disease among cases with hospitalisation data (N=1,744), Victoria, 2007–2017.