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Original article

Recent trends in invasive group A *Streptococcus* disease in Victoria

Jane Oliver, Mathilda Wilmot, Janet Strachan, Siobhan St George, Courtney R Lane, Susan A Ballard, Michelle Sait, Katherine Gibney, Benjamin P Howden and Deborah A Williamson

Abstract

Background

Invasive Group A *Streptococcus* (iGAS) disease can cause permanent disability and death. The incidence of iGAS has increased in many developed countries since the 1980s. iGAS disease is not nationally notifiable in Australia or at the state level in Victoria. The Victorian Hospital Pathogen Surveillance Scheme (VHPSS) is a voluntary laboratory-based surveillance system established in 1988. We assessed the trends and molecular epidemiology of iGAS disease in Victoria from 2007-2017.

Methods

A case of iGAS was defined as an individual for whom Group A *Streptococcus* (GAS) was isolated from a normally sterile body site. Data on all iGAS cases, as reported to the VHPSS, between 1 January 2007 and 31 December 2017 were examined.

Results

A total of 1,311 iGAS cases had associated isolates, and M Protein Gene (*emm)* typing was performed for 91.6%. The mean annual incidence was 2.1 (95% CI: 1.8-2.5) per 100,000 population per year, increasing 2.7-fold over the study period. In total, 140 different iGAS *emm*-types were observed, with the 10 most prevalent types comprising 63.1% of the sample.

Conclusions

Despite limitations in this surveillance data, we observed increasing rates of iGAS disease in Victoria. iGAS incidence exceeded the mean annual incidence for invasive meningococcal disease, calculated using Victorian data from the National Notifiable Diseases Surveillance System (2.1 vs. 0.6 cases per 100,000 population per year, respectively). Mandatory case notification could enhance disease control and prevention. Further, the diversity in *emm*-types emphasises the importance of effective secondary chemoprophylaxis in prevention, alongside GAS vaccine development.

Keywords: Invasive disease, group A *Streptococcus*, invasive group A *Streptococcus* disease, Victoria public health, disease control, surveillance, disease prevention, infectious diseases, epidemiology

Introduction

GAS is a major human pathogen. GAS infections are associated with considerable global morbidity and mortality. In particular, invasive Group A *Streptococcus* (iGAS) disease (when GAS is isolated from a normally sterile body site) has been associated with case fatality rates of around 15% in developed countries and higher still in developing countries.[1] Those at highest risk of iGAS disease include the very young and elderly, Indigenous populations, and patients with medical co-morbidities such as diabetes, immunosuppression, obesity and malignancy.[1,2] Further, the incidence of iGAS disease varies geographically, with reported annual rates of between 2 and 4 cases per 100,000 population per year in developed countries, including Canada, the United Kingdom (UK) and the United States (USA).[3-5] Data from several regions suggest that the incidence of iGAS disease has increased since the 1980s, following a decline over the previous century.[6-13]

A recent study from the UK demonstrated that household contacts of an iGAS case (defined as someone who had direct person-to-person contact with the case in their household during the 7 days before the case's onset of illness) have a considerably increased risk of subsequently developing iGAS themselves (secondary iGAS disease).[14] These authors observed an approximately 2,000-times increased risk of iGAS disease in the close contacts of index cases (RR: 1,940, 95% CI; 1,240-2,880) compared with the background risk. Assuming that index cases were notified quickly and effective chemoprophylaxis could be provided, it was estimated that the number of close contacts needed to treat (NNT) in order to prevent one secondary iGAS case was 407 (95% confidence interval, CI: 273–807). The NNT was much lower for mother-neonate pairs and cohabitating couples aged 75+ years old, however, at 50 (95% CI: 27-393) and 82 (95% CI: 46-417) respectively.[14]

iGAS disease is notifiable to public health authorities in several developed countries, including Canada, Sweden, UK, and the USA.[10,15-17] In Australia, iGAS disease is not nationally notifiable, although it is notifiable in Queensland and the Northern Territory. There are no national Australian guidelines regarding the prevention of secondary iGAS disease, and jurisdictional variation in chemoprophylaxis recommendations exists (Table 1).

The most recent epidemiological study of iGAS disease used 2002-2004 data to estimate a mean annual incidence of 2.7 (95% CI: 2.3–3.2) cases per 100,000 population per year in Victoria. This study identified a 2,011-times (95% CI: 413–5,929-times) increased risk of secondary infection for close contacts of cases, very similar to that identified by the UK study.[14,27] An analysis of Victorian Hospital Pathogen Surveillance Scheme (VHPSS) data from 2005-2009 identified a mean annual total of 86 iGAS isolates, and the 5 most common *emm*-types (*emm*-1, -73, -41, -69, -89) comprised 54.7% of the total sample.[28]

Of recent concern is an increase in paediatric iGAS disease in Victoria, with more children hospitalised during the winter of 2017 alone than were reported for either of the preceding 2 years.[29] To date however, there are no contemporary systematic data on temporal trends of iGAS disease in Victoria, and knowledge of the circulating GAS strains associated with iGAS disease is limited. Furthermore, the burden of secondary infection is unknown. Accordingly, using data from a longstanding laboratory-based surveillance system, we sought to assess the trends and molecular epidemiology of iGAS disease in Victoria, over an 11 year period, from 2007 to 2017.

Methods

Minimum risk ethics approval was obtained from the University of Melbourne Biomedical Sciences Human Ethics Advisory Group (ID: 1853000.1).

Setting, data sources and case definition

The VHPSS is a voluntary, laboratory-based surveillance system established at the

Table 1. A summary of clinical guidelines concerning the management of household contacts of severe invasive group A *Streptococcus* disease index cases

Area guidelines are intended for use (Reference)	iGAS disease notifiable to public health authorities (Yes/No)	Guideline recommendations summary
Australian State Guidelines		
Queensland[18]	Yes	All household contacts should receive a fact sheet about iGAS symptoms. Chemoprophylaxis is recommended for mother-neonate pairs in the neonatal period (and for the neonatal twin, if applicable). If there are 2 or more cases of iGAS within a 30 day time period then the entire household (or all residents and staff of the affected institution) should be issued chemoprophylaxis and provided with the iGAS fact sheet.
New South Wales[19]	No (Unless ≥2 related cases occur)	Close contacts should receive information about GAS (e.g. Maternal sepsis fact sheet (http://www.health.nsw.gov.au/Infectious/factsheets/Pages/maternalsepsis.aspx)) and have a heightened awareness of the signs and symptoms of GAS for 30 days after the diagnosis of invasive GAS in the index patient. They should be advised to seek medical advice if they develop symptoms. Chemoprophylaxis of index cases' household contacts may be considered if there is: • A household with 2 or more diagnoses of iGAS linked temporally, • Close contacts with increased susceptibility to severe infection, such as injecting drug users. • Close contacts with symptoms suggestive of localized GAS infection such as sore throat, fever, skin infection.
Victoria[20]	No[20]	At present, the role of antibiotic prophylaxis for close contacts of cases of invasive GAS infection is not established. In certain circumstances, antibiotic therapy may be appropriate for those at higher risk of infection (as left to clinical discretion). Some hospital guidelines recommend antibiotic prophylaxis for close contacts (eg. Royal Children's Hospital Melbourne).
Western Australia	No	No State guidelines identified.
Northern Territory[21]	Yes[21]	All close contacts of patients with iGAS infection should be advised that they are at increased risk of iGAS infection in the next 30 days, and should be aware of the symptoms and of the importance of seeking medical attention promptly should these occur. Chemoprophylaxis is recommended for iGAS cases' household (and homeless) contacts when: • Mother-neonatal pair is affected (or neonatal twins) • iGAS index case has severe disease • Last contact with case was during the period 7 days before onset of symptoms up until 24 hours after the case's commencement of effective antibiotic treatment.

Area guidelines are intended for use (Reference)	iGAS disease notifiable to public health authorities (Yes/No)	Guideline recommendations summary
Tasmania	No	No State guidelines identified.
South Australia	No	No State guidelines identified.
National Guidelines		
USA[22]	Yes[23]	Active surveillance of iGAS needs to continue. No definite recommendations made regarding chemoprophylaxis for household contacts of persons with invasive GAS infection. More data needed to assess risk of subsequent cases and determine optimal chemoprophylaxis regimen. For now, clinicians should base chemoprophylatic decisions on their risk assessment of iGAS disease risk in household contacts for each individual case.
UK[24]	Yes[25]	Provide iGAS fact sheet to household contacts to inform them of iGAS disease symptoms to watch for and seek treatment if signs/symptoms of iGAS disease appear. If household contact has symptoms of GAS infection, or is mother-neonate pair, provide chemoprophylaxis (and hospitalisation, if symptoms of severe disease occur). If there are two or more cases of iGAS within a 30 day time period from index case presentation, then the entire household should be issued chemoprophylaxis and the iGAS fact sheet.
Canada[4]	Yes[26]	Chemoprophylaxis should be offered to household contacts of severe iGAS disease cases if they have been exposed to the case during the period of 7 days before onset of symptoms up until 24 hours after the case's commencement of antimicrobial therapy. Alert household contacts to signs/symptoms of iGAS disease (severe or otherwise), advise them to seek medical attention immediately should they develop clinical manifestations of GAS within 30 days of index case's diagnosis.

Microbiological Diagnostic Unit Public Health Laboratory (MDU PHL) in 1988 to collect information on invasive cases of bacterial and fungal infections in the Victorian population. The VHPSS includes hospital- and community-acquired invasive infections detected in a range of public, private, metropolitan and regional laboratories using blood or cerebrospinal fluid specimens. At present, the VHPSS is the only public health surveillance system monitoring iGAS in Victoria. Basic data are available for cases reported through VHPSS, including age, sex, date of specimen collection, and name of the reporting laboratory. VHPSS coverage of all eligible blood cultures and cerebrospinal fluid isolates is estimated to have increased from around 60% in 2009 [28] to around 80% in 2017.[30]

A case of iGAS was defined as an individual for whom GAS was isolated from a blood or cerebrospinal fluid specimen. Data on iGAS cases reported to the VHPSS between 1 January 2007 and 31 December 2017 were extracted. All isolates which accompanied VHPSS reports underwent *emm*-typing at MDU PHL. VHPSS also collects data on invasive meningococcal disease (iMD) case isolates, which we obtained for the 11-year period. Data on iMD case notifications for Victoria was also obtained from the Australian National Notifiable Diseases Surveillance System (NNDSS).[31]

Microbiological analysis and molecular typing

Identification of GAS isolates was carried out at individual laboratories prior to specimens being sent to MDU PHL. Polymerase chain reaction (PCR) analysis and DNA sequencing of the *emm* gene was performed using previously described methods.[32] *Emm*-types were assigned using the Blast-*emm* database at https://www2a.cdc.gov/ncidod/biotech/strepblast.asp

Statistical Analysis

Basic descriptive analyses were performed. When investigating whether there was a significant difference in reported proportions, the test of equal or given proportions was used. When calculating population-based iGAS and iMD incidence rates with 95% CI, population estimates based on census data (available from the Australian Bureau of Statistics website)[33] were used as denominator data. The Chi-squared test was used when investigating whether reported rates were significantly different. Differences in proportions and rates were considered statistically significant if $p<0.05$. Poisson regression models were used to investigate whether differences in the iGAS incidence varied according to age group, gender and year. Incidence rate ratios (IRR) were generated from univariate models, including univariate models stratified by age, and adjusted IRRs (aIRR) were generated from a multivariable model that included age group, gender and year (Stata v.14.[34]).

Results

Descriptive epidemiology of cases and trends in iGAS incidence

Between 1 January 2007 and 31 December 2017, a total of 1,311 iGAS cases were identified through the VHPSS. The majority of patients (1,309/1,311; 99.8%) had bloodstream isolates and the remainder were from cerebrospinal fluid. Over one-quarter (27.9%) of cases were aged 70+ years old, with 20.4% of cases aged <20 years; 52.9% of cases were male. A statistically significant variation in the seasonal distribution of cases was not observed ($p=0.0572$, Chi-squared test).

The number of iGAS cases increased from 83 in 2007, to 220 in 2017 (Figure 1), an increase of 165%.

The peak annual incidence rate was 3.63 cases (95% CI: 3.17-4.13) per 100,000 population per year in 2017, a 67% increase from the previous year ($p<0.05$). The mean annual incidence was 2.11 cases (95% CI: 1.78-2.50) per 100,000 population per year. The incidence was 48% higher in the latter part of the study period (2013–2017) than earlier in the study period (2007–2012, IRR: 1.48, 95% CI: 1.33–1.66). People aged 60+ years

had the highest iGAS incidence (4.7 per 100,000 population per year) followed by those aged <5 years (3.9 per 100,000 population per year). Overall, males had higher iGAS incidence than females (IRR: 1.14, 95% CI: 1.03-1.28), however this association was not consistent across age-groups. When stratified by age, among those aged 20–49 years, males had lower incidence than females (IRR: 0.57, 95% CI: 0.43-0.74). Conversely, among those aged 60+ years, males had higher incidence than females (IRR 1.54, 95% CI: 1.31-1.82; Figure 2, Table 2).

Comparison with invasive meningococcal disease cases

In comparison to iGAS cases, the number of iMD cases reported to VHPSS (with blood and cerebrospinal fluid isolates only) increased from 38 cases in 2007 to 67 in 2017, a 76% increase, with the annual incidence rate peaking at 1.10 (95% CI: 0.86-1.39) per 100,000 population per year (Figure 1). The mean annual incidence rate for the whole study period was 0.60 cases (95% CI: 0.45-0.82) per 100,000 population per year. The annual number of iMD cases notified to the NNDSS for Victoria was also considerably lower than the number of iGAS cases reported to VHPSS throughout the study period, peaking at 89 cases in 2017 (p<0.05).

Emm-type distribution by year

The majority of iGAS cases had *emm*-typing information available (N=1,202, 91.7%). A diverse array of 140 different *emm*-types was identified. The most common was *emm*-1 (n=274 isolates, 22.8%), followed by *emm*-89 (N=115, 9.6%, Figure 3).

Emm-1 comprised the highest proportion of isolates each year. At most, 36.0% of all isolates were *emm-1* in 2009. The lowest *emm-1* prevalence was reached the following year (2010), at 16.9% (Supplementary Table 1).

The 10 most common *emm*-types (*emm*-1, -2, -3.1, -4, -12, -22, -28, -75, -87, -89) comprised 63.1% of the total sample (N=759). Despite the annual number of cases peaking in 2017 (Figure 1), this increase did not appear to be driven by any particular *emm*-type (Figure 4, Supplementary Table 1).

DISCUSSION

Based on data from the VHPSS, the iGAS incidence in Victoria increased over the period 2010-2017, peaking at 3.6 (95% CI: 3.2-4.2) per 100,000 population per year in 2017. This observation is consistent with increases in iGAS incidence across a range of countries with similar Human Development Indices to Australia, such as New Zealand, the US, UK, and Canada.[4,9,11-13,35] The recent increase in iGAS disease is concerning, especially as our estimates likely undercount the true burden of disease by 20-40%, given the voluntary, passively collected surveillance data available from the VHPSS.[28] Why older males had the highest IRR of iGAS is unclear, but similar case distributions have been noted in a number of other studies.[27,36,37]

Despite limitations in the surveillance data, in particular undercounting of iGAS cases, the annual incidence of iGAS exceeded the incidence of notified iMD over the entire study period. While case numbers for both conditions peaked in 2017, the number of iGAS cases was 2.5-times higher than iMD cases that year. This finding is consistent with Steer *et al.'s* 2012 observation that the rate of iGAS disease in industrialised countries is 2-4 times higher than the rate of meningococcal disease.[38] While both conditions share high case fatality rates and potential to cause lifelong disability[39,40], only iMD is presently notifiable in Victoria.[41]

Although efforts to develop a multivalent GAS vaccine targeting the M-protein (encoded by the *emm* gene) are in progress.[42,43], this study observed a diverse range of iGAS *emm*-types, with none in particular appearing to have driven the recent upsurge in cases. To illustrate, the 10 most prevalence *emm*-types comprised <60% of the total sample and 68% in 2017. These findings indicate the emergence of greater diversity in *emm*-types compared to the previous iGAS

Figure 1. Annual numbers and incidence rates of invasive group A *Streptococcus* cases and invasive meningococcal disease cases, Victorian Hospital Pathogen Surveillance Scheme, 2007-2017

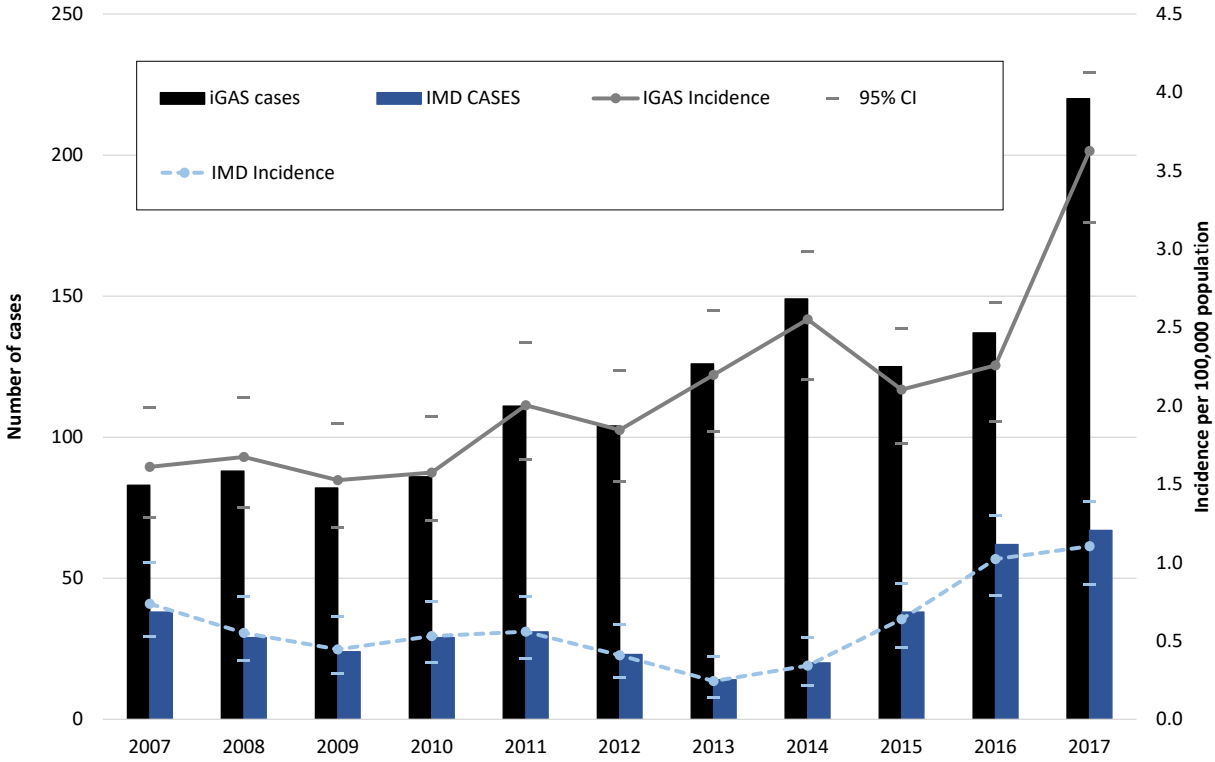


Figure 2. Age range and sex distribution of invasive group A *Streptococcus* cases as reported to the Victorian Hospital Pathogen Surveillance Scheme, 2007-2017

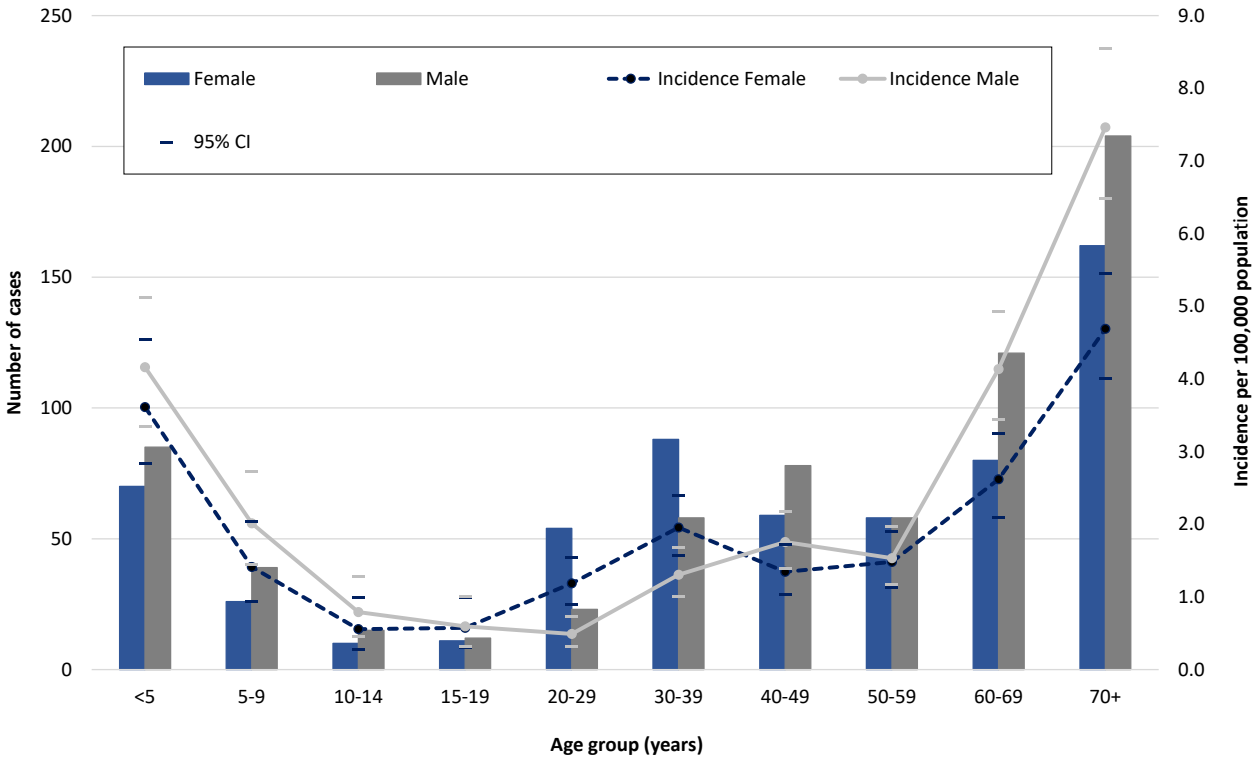


Table 2. Incidence rate ratio and 95% confidence interval of invasive group A *Streptococcus* disease isolates received at Victorian Hospital Pathogen Surveillance Scheme by year, age group and gender

Factor[1]	Comparator	IRR (95% CI)
Univariate analysis		
Year of isolate collection	2007	
2008		0.97 (0.72-1.31)
2009		0.91 (0.68-1.24)
2010		1.01 (0.75-1.35)
2011		1.14 (0.85-1.51)
2012		1.13 (0.85-1.50)
2013		**1.34 (1.02-1.76)**
2014		**1.51 (1.16-1.97)**
2015		1.25 (0.95-1.65)
2016		**1.39 (1.06-1.82)**
2017		**2.12 (1.65- 2.73)**
Mean annual IRR change over study period		**1.07 (1.05-1.09)**
Sex		
Males (all ages)	Female (all ages)	1.14 (1.03-1.28)
Stratified by age-group		
Males <5 years	Females <5 years	1.15 (0.84-1.58)
Males 5-19 years	Females 5-19 years	1.33 (0.92-1.94)
Males 20-39 years	**Females 20-39 years**	**0.57 (0.43-0.74)**
Males 40-59 years	Females 40-59 years	1.20 (0.94-1.54)
Males 60+ years	**Females 60+ years**	**1.54 (1.31-1.82)**
Agegroup	<5 years	
5-19 years		**0.25 (0.20-0.32)**
20-39 years		**0.31 (0.26-0.39)**
40-59 years		**0.40 (0.33-0.49)**
60+ years		**1.20 (1.00-1.43)**
Multivariable analysis		**aIRR (95% CI)**
Year (average annual change)		**1.07 (1.05-1.09)**
Male	Female	**1.18 (1.06-1.32)**
Age-group	<5 years	
5-19 years		**0.26 (0.20-0.33)**
20-39 years		**0.32 (0.26-0.39)**
40-59 years		**0.41 (0.33-0.49)**
60+ years		**1.20 (1.01-1.43)**

Abbreviations: IRR – incidence rate ratio, aIRR – adjusted incidence rate ratio, CI – confidence interval.

[1]Bold lettering indicates p<0.05.

Figure 3. Invasive group A *Streptococcus emm* types reported to the Victorian Hospital Pathogen Surveillance Scheme, 2007-2017

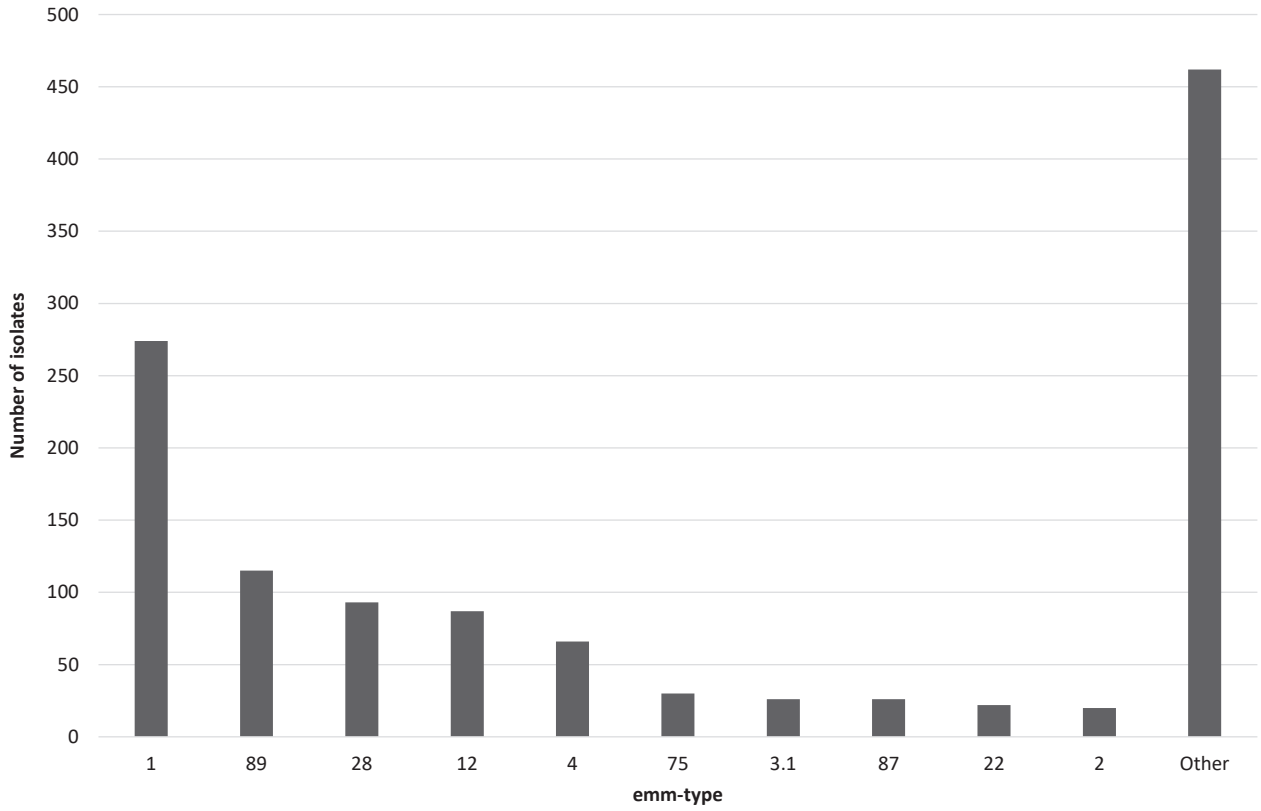
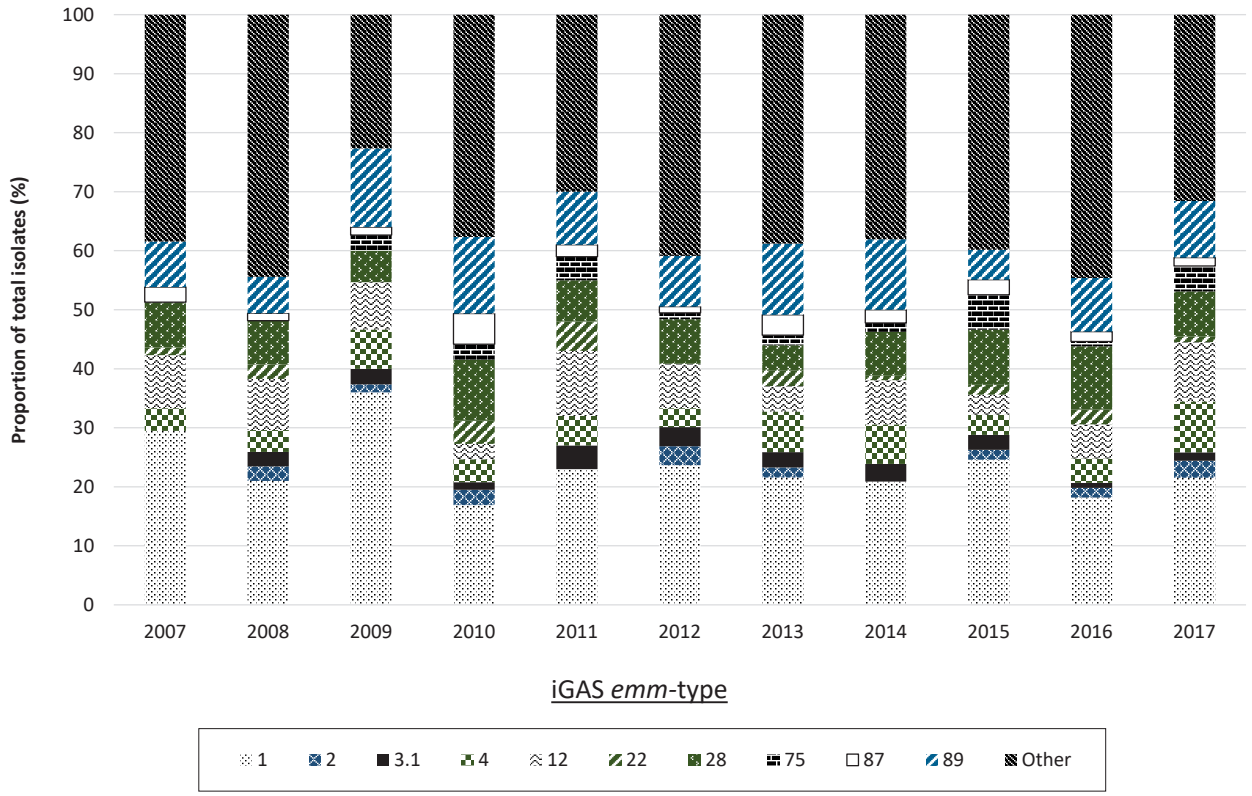


Figure 4. Invasive group A *Streptococcus emm* types as a proportion of the total annual *emm* types reported to the Victorian Hospital Pathogen Surveillance Scheme, 2007-2017



study that used VHPSS data from 2005-2009.[28] The *emm*-1 strain remained the most commonly identified in both studies.[28] Considerable diversity in GAS *emm*-types has also been reported for Africa and the Pacific region as a whole.[44] An iGAS study in Sydney in 2008 and 2010 identified somewhat greater diversity than our study, but was limited to 2 years of data collection. The authors identified 72 cases with 27 different *emm*-types[11], while we identified 174 cases and 46 strains for the same years (Figure 4). Our results highlight the role of chemoprophylaxis in disease control, as an iGAS vaccine would need to have extremely broad coverage in order to effectively prevent all cases. The J8-DT vaccine may provide a promising means of generating broad protection against a diverse range of GAS strains.[45] This vaccine is still in development, but streptococcal infection following its administration in mice has been demonstrated to boost vaccine-induced immunity.[46] The recent data from the UK highlighted the potential benefits and challenges of chemoprophylaxis in preventing secondary iGAS cases.[14] The evidence of increased risk of secondary disease among close contacts, in conjunction with rising incidence rates of iGAS, demonstrate the urgent public health need to make iGAS notifiable, both in Victoria and nationally. Potential benefits of making iGAS notifiable would include improved epidemiological surveillance; enhanced follow-up of cases - including contact tracing and chemoprophylaxis provision; and a requirement for laboratories to send isolates for additional characterisation. Ideally, this would encompass whole genome sequencing of isolates, which, in addition to *in silico emm* typing, would enable assessment of relatedness between isolates. This would provide a deeper understanding of possible outbreaks and/or transmission networks, as has been previously described overseas.[14]

In summary, high-quality surveillance information is needed to better inform effective control and prevention measures for this condition. Introducing a mandatory requirement for case notification, in conjunction with enhanced laboratory characterisation of isolates could facilitate such improvements.

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Supplementary Table

Supplementary Table 1. Number of iGAS *emm*-types received at the Victorian Hospital Pathogen Surveillance Scheme, 2007-2017

Year	Invasive GAS emm-type cases (N)										
	Emm-1	Emm-2	Emm-3.1	Emm-4	Emm-12	Emm-22	Emm-28	Emm-75	Emm-87	Emm-89	Other[1]
2017	45	6	3	18	21	2	16	9	3	20	66
2016	22	2	1	5	7	3	13	1	2	11	54
2015	29	2	3	4	4	2	11	7	3	6	47
2014	28	0	4	9	10	1	10	2	3	16	51
2013	25	2	3	8	5	3	5	2	4	14	45
2012	22	3	3	3	7	0	7	1	1	8	38
2011	23	0	4	5	11	5	7	4	2	9	30
2010	13	2	1	3	2	3	8	2	4	10	29
2009	27	1	2	5	6	0	4	2	1	10	17
2008	17	2	2	3	7	2	6	0	1	5	36
2007	23	0	0	3	7	1	6	0	2	6	30
Total	274	20	26	66	87	22	93	30	26	115	443

1 'Other' includes 130 different emm-types, none of which were identified in >19 cases at most.