Getting to grips with invasive group A streptococcal infection surveillance in Australia: are we experiencing an epidemic?

Well publicised, rapid onset deaths in previously healthy children from invasive group A streptococcal disease (iGAS) in Australia in recent years have highlighted the emerging burden of iGAS.[1-3] Here we explore the evidence and knowledge gaps to inform clinicians, public health units and the Australian public regarding iGAS definition and epidemiological trends in Australia.

iGAS is associated with high morbidity, mortality and substantial health expenditure.[4,5] Clinical forms include sepsis, streptococcal toxic shock syndrome, necrotising fasciitis, pneumonia/empyema, bacteraemia and postpartum endometritis.[6] Group A *Streptococcus* (GAS) infections are not currently vaccine preventable, but through the Australian Strep A Vaccine Initiative, the Australian Government and global philanthropic partners have invested heavily in accelerating the vaccine development.[7,8] Although GAS remains susceptible to penicillin and most β-lactam antibiotics, mortality rates as high as 70–80% have been reported for iGAS necrotising fasciitis, and overall case fatalities remain high (8–16%) for the other phenotypes.[5,9]

Global increase in incidence of iGAS, local epidemiology and possible explanations

In December 2022, the World Health Organization (WHO) released a statement noting increasing iGAS incidence including fatalities in at least five of its European member states during the latter half of 2022.[10] France, Ireland, the Netherlands, Sweden and the United Kingdom reported an increase in cases of iGAS, predominantly affecting children under 10 years of age.[10] The United States also reported an increase in iGAS in 2022, relative to case numbers during the pandemic years.[11] In the UK, where iGAS surveillance has been occurring since 2010,[12] 29 paediatric deaths were recorded from October to December 2022 (an average of 116 annualised), compared with 27 annual deaths during the last comparably high season in 2017–2018.[13] Excess deaths in children were also reported in Ireland,[14] the US[15] and the Netherlands.[16]

iGAS became nationally notifiable in Australia in July 2021, preceded by Queensland since 2005[17] and Northern Territory since 2011.[18] The remaining jurisdictions commenced notification between August 2021 and September 2022. This potentially complicates our assessment of whether the WHO advisory on increased iGAS globally also applies in Australia. In December 2022, Victoria[19] issued an advisory to clinicians in response to an increase in cases of iGAS being notified locally. New South Wales,[20] Western Australia[21] and Australian Capital Territory[22] followed with similar advisories in January 2023. According to the National Communicable Disease Surveillance (NCDS) dashboard, there were 1180 cases of iGAS notified in 2022 with Queensland having the highest number (386 cases, 33%).[23] The Australian total for the first two quarters of 2023 was 1185 cases (updated as of 20 July 2023), including 339 cases from NSW, 253 cases from Queensland (highest year-to-date total of 5-year records available online) and 308 cases in Victoria, indicating that the higher numbers being observed are not yet slowing down (Box).

The incidence of iGAS has been steadily increasing over the past two decades worldwide.[24] The drivers of widespread and sharp increases seen in iGAS incidence across the world in late 2022 are uncertain, although several hypotheses are plausible. First, the emergence of $M1_{UK}$, an *emm1* strain of GAS, in many parts of the world including Australia has been implicated, at least temporally, with an increase in invasive infections.[25] This lineage has acquired several bacteriophage-encoded superantigens, and their relationship with virulence and pathogenicity in iGAS is being further elucidated.[25] Second, some health authorities have suggested that non-pharmaceutical interventions

Invasive group A streptococcal disease cases by jurisdiction, extracted from the National Notifiable Disease Surveillance System (NNDSS) via the National Communicable Disease Surveillance dashboard (20 July 2023)*,[23]

Jurisdiction	Notification counts		Annualised incidence rate†
	2022	2023 Q2	
Australian Capital Territory	2	5	2.2
New South Wales	168‡	339	8.2
Northern Territory	105	66	52.8
Queensland	386	253	9.4
South Australia	83‡	70	7.6
Tasmania	7	18	6.3
Victoria	201‡	308	9.1
Western Australia	228	126	8.9
National total	1180‡	1185	9.0

Q2 = first half of the year (January–June). * NNDSS data caveat notes that data in the dashboard "are reliant on the provision of data from states and territories to the Australian Government Department of Health. Backlogs in notifications at the state or territory level may contribute to delays in reporting to the NNDSS".[23] This is likely to explain discrepancies between NNDSS case counts and publicly reported counts by jurisdictions. † Notifications per 100 000 person-years based on Q2 case numbers. As per the caveat detailed in the preceding footnote, changes to the case numbers can occur retroactively due to delays in reporting. This can significantly change the annualised incidence rate, especially in states and territories with relatively low background numbers. ‡ Partial year of data collection as only became notifiable in 2022. ◆

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during the COVID-19 pandemic response — such as hand hygiene practices, face masking, and social distancing — may have contributed to a temporary reduction in the rate of iGAS cases, which has since rebounded to pre-pandemic levels with the easing of those restrictions.[26] However, increases in some parts of the world have been well above a pre-pandemic high season. Third, surges in respiratory viral infections were observed in Australia and internationally following the easing of COVID-19 restrictions.[27-29]

Predisposition to iGAS following viral infections such as influenza and varicella zoster virus are well described.[9] The reduction in all respiratory viruses that followed the pandemic non-pharmaceutical interventions created the environment in which iGAS declined, but with the return of respiratory viruses as well as reduced population immunity during the 3 years when people were not exposed to viral or bacterial infections may have created this niche. Predisposition to iGAS following COVID-19 infection is plausible, although the association is yet to be fully elucidated. A recently published time series analysis found that the increase in iGAS cases in late 2022 also coincided with a major outbreak of respiratory viruses (including SARS-CoV-2) in the paediatric population, suggesting a contributory predisposition towards the observed surge in iGAS cases.[30]

Imperfect surveillance data in its infancy

The Communicable Diseases Network Australia (CDNA) surveillance case definition for notification of iGAS is the detection of GAS from a normally sterile site by culture or nucleic acid detection.[26] While this definition is well placed to capture GAS bacteraemia, empyema, bone and joint infections, or infections involving otherwise sterile sites, it does not currently capture many common forms of iGAS. For example, in necrotising skin and soft tissue infections and invasive peripartum infections, GAS may not be isolated from the bloodstream and may only be isolated from non-sterile sites such as superficial skin tissue or the cervix. Global experts offer a broader iGAS case definition, which recommends capturing confirmed (isolation of GAS from a sterile site) as well as probable cases (clinically congruent with severe GAS illness with GAS isolated from a non-sterile site; for example, maternal sepsis with GAS isolated from the cervix or the placenta). These definitions are intended to provide a comprehensive picture of the burden of iGAS that is consistent with traditional surveillance definitions.[31]

Given that the national CDNA case definition does not capture some forms of iGAS, and the relative infancy and the incompleteness of surveillance across all states and territories, the iGAS numbers reflected currently in the NCDS dashboard are likely to be a significant underestimate of the true burden of disease.

Lack of consensus in public health management of iGAS

iGAS was made nationally notifiable before the development of the CDNA Series of National Guidelines (SoNG; https://www.health.gov.au/resources/collections/cdna-series-of-national-guidelines-songs) or surveillance plan for the disease. This has complicated the response to the current apparent increase in cases, requiring ongoing use of jurisdictional or institutional clinical guidelines, which vary in their case definitions and clinical recommendations. The risk of secondary iGAS cases among household contacts of a confirmed case is up to 2000 times higher in the 30 days following exposure compared with the general population,[32,33] with the highest reported risk in mother–neonate pairs and older people.[33,34] Currently, management of iGAS contacts and outbreaks is left to respective state public health units (PHUs), resulting in a wide variation in advice among PHUs. In guidelines for chemoprophylaxis for close contacts, the definition of iGAS can differ from that of the CDNA and from other PHUs, and variations can also occur in the definition of a close contact and the recommendation for prophylactic regimen (Supporting Information). The CDNA has convened a working group to develop a SoNG for iGAS. This work will be critical to a harmonised national response to iGAS, including addressing the variation in existing guidelines, particularly the definition of close contacts and indications for chemoprophylaxis.

Inequitable epidemics

The apparent increase in iGAS in southern jurisdictions has attracted media and public health attention. However, the burden of iGAS in Northern Australia is a longstanding epidemic, with a disproportionate incidence in Aboriginal and Torres Strait Islanders, who experience iGAS at 6–10 times the rate of non-Indigenous people.[18,35,36] This inequity is mirrored in the Kimberley region of Western Australia.[37] The devastating impacts have attracted relatively little public attention or action. This slower moving epidemic is almost certainly driven by the high rates of skin infections, potentiated by household crowding and inadequate access to health hygiene infrastructure.[38] It is essential that action to understand and address the iGAS burden focuses on the ongoing and unmet needs of Aboriginal and Torres Strait Islander people in Australia. Consideration should be given to collection of Indigenous status as part of the National Notifiable Disease Surveillance System to assess progress of this inequitable epidemic across Australia.

Urgent need to synthesise clinical, public health and preventive priorities

While evidence-based guidelines are being formulated to inform the public health response, critical research and clinical gaps remain. There is an unmet need for more comprehensive surveillance data that reflect the true incidence of iGAS in Australia with the capacity for clinical data linkage, enabling PHUs to respond to cases and clusters of iGAS in real time. Surveillance at a microbiological level has enabled the global community to track emerging virulent lineages such as the $M1_{UK}$ strain. Such surveillance distinguishes between locally and internationally acquired spread.

The Australian Pathogen Genomics Program (https://www.auspathogen.org.au) is currently building Australia's molecular surveillance for iGAS nationally, to build on jurisdictional reports of local molecular epidemiology.

GAS causes a wide spectrum of disease from superficial infections through to invasive and post-infectious conditions, such as acute rheumatic fever and rheumatic heart disease. Global concerted effort for a GAS vaccine is underway and its success is eagerly awaited; however, a successful candidate will historically take several years to pass late phase clinical trials and regulatory approvals.[8] Detailed epidemiological understanding of iGAS is critical to facilitate planning for more definitive preventions such as a GAS vaccine rollout or chemoprophylaxis measures, while continuing to monitor their impacts on epidemiology and antimicrobial resistance.

To target iGAS when a GAS vaccine becomes available, current epidemiology suggests it should be preferentially provided as an infant series with a booster dose during pregnancy, to reduce the burden of puerperal and neonatal sepsis. This schedule would also be optimal to prevent iGAS in Northern Australia where the early onset and lifelong burden of skin infections drive iGAS incidence.[38] An additional dose before school entry may be considered in this population for prevention of acute rheumatic fever as this post-infectious condition predominantly affects 5–14-year-olds.[39] Lastly, a booster dose for people over 60 years of age should also be considered given the propensity for iGAS in the extremes of age. Ultimately, the development and implementation of a GAS vaccine will require ongoing investment in discovery science, good baseline epidemiological understanding, and a clear economic argument for the investment, all of which rely on a representative disease burden provided by a well functioning iGAS surveillance system. Recent events provide further impetus for these needs to be urgently prioritised by the public health, clinical and research communities in Australia.

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1 Coroner's Court of Western Australia. Inquest into the death of Aishwarya Aswath Chavittupara. 22 Feb 2023. https://www.coronerscourt.wa.gov.au/I/inquest_into_the_death_of_aishwarya_aswath_chavittupara.aspx (viewed Mar 2023).

2 Weber D, O'Flaherty A. Parents of girl who died at Perth Children's Hospital say apology from Health Minister not good enough. ABC News, 13 May 2021. https://www.abc.net.au/news/2021-05-13/call-for-roger-cook-resign-over-aishwarya-death-at-pch/100136904 (viewed Mar 2023).

3 Formica S. The warning to Qld parents after girl dies after missed diagnosis. 4BC Brisbane, News, 6 Mar 2023. https://www.4bc.com.au/two-year-old-child-unexpectedly-dies-after-a-diagnosis-was-missed (viewed Mar 2023).

4 Cannon JW, Jack S, Wu Y, et al. An economic case for a vaccine to prevent group A streptococcus skin infections. *Vaccine* 2018; 36: 6968-6978.

5 Wong CJ, Stevens DL. Serious group a streptococcal infections. *Med Clin North Am* 2013; 97: 721-36, xi-xii.

6 Stevens DL, Bryant AE. Severe *Streptococcus pyogenes* infections. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. *Streptococcus pyogenes*: basic biology to clinical manifestations [internet]. 2nd ed. Oklahoma City: University of Oklahoma Health Sciences Center, 2022. https://www.ncbi.nlm.nih.gov/books/NBK587112/ (viewed Feb 2023).

7 Telethon Kids Institute. Australian Strep A Vaccine Initiative (ASAVI). https://www.telethonkids.org.au/projects/australian-strep-a-vaccine-initiative-asavi (viewed Feb 2023).

8 Shaw E. $8 million in funding for Strep A collaboration with Moderna. Forbes Australia, 14 Feb 2023. https://www.forbes.com.au/news/innovation/8-million-in-funding-for-strep-a-collaboration-with-moderna/ (viewed Mar 2023).

9 Steer AC, Lamagni T, Curtis N, Carapetis JR. Invasive group a streptococcal disease: epidemiology, pathogenesis and management. *Drugs* 2012; 72: 1213-1227.

10 World Health Organization. Increased incidence of scarlet fever and invasive Group A Streptococcus infection - multi-country. Disease Outbreak News, 15 Dec 2022. https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON429 (viewed Feb 2023).

11 Centers for Disease Control and Prevention. Increase in invasive group A Strep infections, 2022–2023. https://www.cdc.gov/groupastrep/igas-infections-investigation.html (viewed May 2023).

12 UK Health Security Agency. UK guidelines for the management of contacts of invasive group A streptococcus (iGAS) infection in community settings. Version 2.0, March 2023. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1140766/Management-of-contacts-of-invasive-group-a-streptococcus.pdf (viewed Mar 2023).

13 UK Health Security Agency. UKHSA update on scarlet fever and invasive group A strep. 5 Jan 2022. https://www.gov.uk/government/news/ukhsa-update-on-scarlet-fever-and-invasive-group-a-strep-1#full-publication-update-history (viewed Feb 2023).

14 Health Protection Surveillance Centre. Update on Group A streptococcus (12/01/2023). https://www.hpsc.ie/news/newsarchive/2023newsarchive/title-22663-en.html (viewed Feb 2023).

15 Colorado Department of Public Health and Environment. CDPHE monitoring increase in invasive group A strep cases, other bacterial infections, in Colorado [press release]. 15 Dec 2022. https://cdphe.colorado.gov/press-release/monitoring-increase-in-invasive-group-a-strep-cases-other-bacterial-infections (viewed Mar 2023).

16 Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment). Reports of invasive GAS infections in the Netherlands. https://www.rivm.nl/groep-a-streptokokkeninfecties-gas/meldingen-van-invasieve-gas-infecties-in-nederland (viewed Feb 2023).

17 Thangarajah D. Applied epidemiology of infectious diseases in Queensland [thesis]. Chapter 3: Invasive group a streptococcal disease surveillance in Queensland. Australian National University, 2019. https://openresearch-repository.anu.edu.au/handle/1885/216785 (viewed Mar 2023).

18 Centre for Disease Control, Department of Health, Northern Territory. Public health management of invasive group A streptococcal disease in the Northern Territory guideline. https://health.nt.gov.au/__data/assets/pdf_file/0009/1111122/invasive-group-A-streptococcal-disease-northern-territory-guidelines.pdf (viewed Mar 2023).

19 Department of Health (Victoria). Health warning on invasive group A streptococcal disease. 23 Dec 2022. https://www.health.vic.gov.au/health-advisories/health-warning-on-invasive-group-a-streptococcal-disease (viewed Feb 2023).

20 NSW Health. Safety Alert 001/23. Clinician Alert - Invasive group A streptococcal disease. Issue date: 5 Jan 2023. https://www.health.nsw.gov.au/sabs/Documents/2023-sa-001.pdf (viewed Mar 2023).

21 Communicable Disease Control Directorate (WA). Alert for Clinicians: Increase in invasive group A streptococcus (iGAS) infection notifications. 17 Jan 2023. https://www.health.wa.gov.au/~/media/Corp/Documents/Health-for/Infectious-disease-alerts/2023/Increase-in-invasive-Group-A-Streptococcus-17-January-2023.PDF (viewed Feb 2023).

22 Office of the Chief Health Officer (ACT). Invasive group A streptococcal disease. Information for ACT clinicians – 12 January 2023. https://health.act.gov.au/sites/default/files/2023-01/CHO%20alert%20-%20iGAS%20-%20Jan%202023.pdf (viewed Feb 2023).

23 Department of Health and Aged Care. National Communicable Disease Surveillance dashboard. https://nindss.health.gov.au/pbi-dashboard/ (viewed July 2023).

24 Craik N, Hla T, Cannon J, et al. Global disease burden of *Streptococcus pyogenes*. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. *Streptococcus pyogenes*: basic biology to clinical manifestations [internet]. 2nd ed. Oklahoma City: University of Oklahoma Health Sciences Center, 2022. https://www.ncbi.nlm.nih.gov/books/NBK587112/ (viewed Mar 2023).

25 Davies MR, Keller N, Brouwer S, et al. Detection of Streptococcus pyogenes M1(UK) in Australia and characterization of the mutation driving enhanced expression of superantigen SpeA. *Nat Commun* 2023; 14: 1051.

26 Communicable Diseases Network Australia. Invasive group A streptococcal (iGAS) disease: Australian national notifiable diseases case definition. https://www.health.gov.au/sites/default/files/documents/2022/06/invasive-group-a-streptococcal-disease-igas-surveillance-case-definition.pdf (viewed Feb 2023).

27 Amar S, Avni YS, O'Rourke N, Michael T. Prevalence of common infectious diseases after COVID-19 vaccination and easing of pandemic restrictions in Israel. *JAMA Netw Open* 2022; 5: e2146175.

28 Eden JS, Sikazwe C, Xie R, et al. Off-season RSV epidemics in Australia after easing of COVID-19 restrictions. *Nat Commun* 2022; 13: 2884.

29 Wan WY, Thoon KC, Loo LH, et al. Trends in respiratory virus infections during the COVID-19 pandemic in Singapore, 2020. *JAMA Netw Open* 2021; 4: e2115973.

30 Lassoued Y, Assad Z, Ouldali N, et al. Unexpected increase in invasive group a streptococcal infections in children after respiratory viruses outbreak in France: a 15-year time-series analysis. *Open Forum Infect Dis* 2023; 10: ofad188.

31 Miller KM, Lamagni T, Cherian T, et al. Standardization of epidemiological surveillance of invasive group a streptococcal infections. *Open Forum Infect Dis* 2022; 9 (Suppl 1): S31-S40.

32 Carapetis JR, Jacoby P, Carville K, et al. Effectiveness of clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive group a streptococcal infections. *Clin Infect Dis* 2014; 59: 358-365.

33 Mearkle R, Saavedra-Campos M, Lamagni T, et al. Household transmission of invasive group A *Streptococcus* infections in England: a population-based study, 2009, 2011 to 2013. *Euro Surveill* 2017; 22: 30532.

34 Adebanjo T, Apostol M, Alden N, Petit S, Tunali A, Torres S, et al. Evaluating household transmission of invasive group A *Streptococcus* disease in the United States using population-based surveillance data, 2013-2016. *Clin Infect Dis* 2020; 70: 1478-1481.

35 Carapetis JR, Currie BJ, Mathews JD. Cumulative incidence of rheumatic fever in an endemic region: a guide to the susceptibility of the population? *Epidemiol Infect* 2000; 124: 239-244.

36 Queensland Health Guidelines for Public Health Units. Invasive group A streptococcal disease. Version 3.0, Oct 2018. https://www.health.qld.gov.au/cdcg/index/igas (viewed Mar 2023).

37 Wright CM, Moorin R, Pearson G, et al. Increasing incidence of invasive group A streptococcal disease in Western Australia, particularly among Indigenous people. *Med J Aust* 2021; 215: 36-41. https://www.mja.com.au/journal/2021/215/1/increasing-incidence-invasive-group-streptococcal-disease-western-australia

38 Davidson L, Knight J, Bowen AC. Skin infections in Australian Aboriginal children: a narrative review. *Med J Aust* 2020; 212: 231-237. https://www.mja.com.au/journal/2020/212/5/skin-infections-australian-aboriginal-children-narrative-review

39 RHDAustralia (ARF/RHD writing group). The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (3.2 edition, March 2022). https://www.rhdaustralia.org.au/system/files/fileuploads/arf_rhd_guidelines_3.2_edition_march_2022.pdf (viewed May 2023). ■

Supporting Information

Additional Supporting Information is included with the online version of this article.