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# A cluster of acute rheumatic fever cases among Aboriginal Australians in a remote community with high baseline incidence

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**A**cute rheumatic fever (ARF) is a post-infectious immune-mediated complication of pharyngitis, and possibly skin infections, caused by group A *Streptococcus* (GAS).<sup>1,2</sup> Rheumatogenic strains of GAS can lead to ARF in susceptible individuals with untreated infections. ARF most commonly affects children and young people aged 5–15 years.<sup>3,4</sup> Joint, skin and neurological manifestations and fever are all self-limited, but carditis associated with ARF can cause permanent damage to the mitral, aortic and tricuspid valves, leaving the individual with rheumatic heart disease (RHD). The long-term sequelae of RHD in some cases include heart failure, stroke and early death.<sup>5,6</sup>

While the incidence of ARF is declining globally, it remains endemic in low and middle-income countries and in disadvantaged populations in high-income countries where GAS infections and household crowding are common, resulting in high prevalence of RHD in relatively young cohorts in these settings.<sup>7–9</sup> Social determinants of health, including household crowding and socioeconomic disadvantage, are associated with an increase in risk of GAS and subsequent ARF and RHD.<sup>10</sup> Australia's Indigenous population of Aboriginal and Torres Strait Islander people are at significantly increased risk of ARF and RHD compared to non-Indigenous Australians.<sup>6,11</sup>

## Abstract

**Objectives:** We report a cluster of acute rheumatic fever (ARF) cases and the public health response in a high-burden Australian setting.

**Methods:** The public health unit was notified of an increase in ARF cases in a remote Australian Aboriginal community. A multi-disciplinary group coordinated the response. Household contacts were screened for ARF or group A *Streptococcus* (GAS) infection by questionnaire and swab collection, offered an echocardiogram if aged 5–20 years, and intramuscular benzathine benzylpenicillin if aged over one year or if less than one year with impetigo.

**Results:** Fifteen definite and seven probable ARF cases were diagnosed in the community in July–December 2014 (all-age incidence of definite ARF: 1,473/100,000). The public health response identified two additional cases of ARF. A total of 81 contacts were screened; GAS was detected in 3/76 (4%) throat swabs and 11/24 (46%) skin swabs. Molecular typing revealed high GAS strain diversity.

**Conclusions:** The incidence of ARF during this cluster was very high. Carriage and infection with GAS was observed, but no outbreak strain identified.

**Implications for public health:** A national public health guideline has since been developed that includes advice on the investigation of an ARF outbreak/cluster. Sustained efforts with strong community engagement are required to tackle high ARF rates.

**Key words:** acute rheumatic fever, rheumatic heart disease, group A *Streptococcus*, cluster, public health response

ARF is a notifiable condition in the Northern Territory (NT), and an RHD Register is maintained by the NT Centre for Disease Control. The incidence rate of ARF in Aboriginal people aged 5–14 years in the NT is estimated at 194 per 100,000 people per year; one of the highest documented rates internationally. More than 60% of those with ARF go on to develop RHD within 10 years,

representing a large burden of morbidity and mortality in this high-risk population.<sup>11</sup>

GAS types associated with ARF are difficult to define due to the delay between presence of GAS infection and onset of ARF. Studies from the US in past decades indicated that the *emm* gene encoding cluster types A, B and C, considered to be 'throat specialists', were associated with ARF.<sup>12</sup> More recent studies

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from high-burden Southern Hemisphere settings have found that *emm* types D and E, which infect skin and throat, occur in high ARF-burden settings;<sup>13</sup> in previous NT research, high diversity of circulating GAS types has been found, rather than any dominant 'rheumatogenic' strains.<sup>14</sup>

An increase in transmission of a rheumatogenic strain of GAS within a community, because of introduction of a new strain, or because of changes to the social or physical environment, creates the potential for an outbreak of ARF. Rapid spread of GAS has been demonstrated in outbreaks of GAS pharyngitis, which have been associated with new cases of ARF, often in low-risk communities.<sup>15-17</sup> In these instances, an increase in GAS pharyngitis preceded an ARF outbreak, and two or three predominant GAS strains were identified. In other instances, an increase in ARF incidence has been observed, and subsequent investigation identified high rates of detection of asymptomatic GAS carriage among cases and their contacts.<sup>18-21</sup> Some outbreaks of ARF have been reported in the absence of clear evidence of epidemic spread of rheumatogenic GAS strains.<sup>22-24</sup> The public health response to clusters or outbreaks of ARF has varied. In some instances, no specific response has been reported.<sup>19,22-24</sup> In other outbreaks, administration of penicillin, usually in the form of long-acting benzathine penicillin G (BPG), has been either targeted at those with positive GAS throat swabs<sup>18</sup> or offered as clearance antibiotics to all members of the affected community.<sup>17,20</sup>

In contrast to these reports of GAS or ARF outbreaks in low-risk populations, there is limited literature regarding outbreak potential in settings where the baseline incidence of ARF is already very high.<sup>17</sup>

We report a cluster of ARF cases that occurred in a remote community with endemic ARF, which prompted a public health response.<sup>25</sup> We describe the public health response and the findings it generated with considerations for future management of detected clusters of ARF.

## Methods

### Setting

The affected community in Northern Australia had a population of 2,292; 2,036 (88%) residents were Aboriginal.<sup>26</sup> Permission to publish these findings was obtained from the local health board of the Aboriginal

community in which the cluster was identified. The mean number of cases of definite ARF over the five years from 2009–2013, based on ARF notifications to the NT RHD Register, was 6.4 cases per year with all cases reported in Aboriginal people, resulting in a baseline all age incidence of ARF in the Aboriginal population of 314 per 100,000 per year (95% confidence interval (CI) 221–445).

### Case definitions

We defined a cluster case as any resident of community X notified with definite ARF between 1 July 2014 and 31 December 2014. A resident was defined as any person living in the community for at least four weeks prior to symptom onset. Cases of ARF were characterised as either definite, probable or possible ARF based on Australian guidelines,<sup>27</sup> which are consistent with internationally recognised and revised Jones criteria.<sup>28</sup>

### Standard treatment

We treated cases as per Australian recommendations for people with a diagnosis of ARF or mild RHD, which includes intramuscular BPG injections every 28 days until the age of 21 years, or until 10 years after the last episode of ARF, whichever is longer. People with moderate or severe RHD should be prescribed intramuscular BPG injections every 28 days at least until the age of 35 years or until 10 years after the last episode of ARF, whichever is longer.<sup>26</sup> 'Days at risk' are defined as the number of days greater than 28 since the most recent BPG injection.<sup>29</sup>

### Public health response

The increased incidence of ARF was recognised by clinicians based in the community following the notification of case seven. An expert consultative group was convened by the NT Centre for Disease Control (NT CDC). This group included specialists in public health, pathology, cardiology, paediatrics and infectious diseases. A public health response was initiated within one week of recognition of the cluster, with the aims of early detection of additional ARF cases, prevention of further transmission of GAS and identification of circulating strains of GAS in cases and contacts if possible. Community and clinical staff education was conducted, focusing on the signs and symptoms of ARF, the role of primordial and primary prevention and the importance of ensuring all people currently prescribed BPG were up to date. An

educational video was produced in English and in the most common local Aboriginal languages to inform the community about signs and symptoms of ARF and the importance of presenting to the clinic with sore throats or impetigo.

### Case finding methods

Household contacts were screened by a standard questionnaire that was developed to record any current symptoms of sore throat, skin sores, arthralgia, fever or chorea. Screening echocardiography (looking at cardiac valves and left ventricular function, to identify RHD) was conducted by a paediatric cardiologist (single reporter) for household contacts aged 5–20 years, as part of the public health response. This age group was targeted for screening as it is the one where ARF is most common, and cases of recent ARF with associated carditis were the main target.

### Laboratory investigations

Throat swabs for GAS were collected from all contacts (where possible) and skin swabs from those with clinical evidence of impetigo. Throat swabs and skin sore swabs from cases were cultured using standard microbiological techniques. If GAS was cultured, deoxyribose nucleic acid (DNA) was extracted from isolates using a QIAmp DNA mini-kit (Qiagen, Australia), and *emm* typing was carried out as described by Boyd et al.<sup>30</sup>

### Contact prophylaxis

A single dose of BPG was offered to all household contacts aged greater than one year, and to infants under one year who had evidence of impetigo.

### Environmental assessment

An environmental health officer was engaged to conduct assessments of housing conditions, report faults and reinforce the importance of hygiene behaviours to maintain healthy skin.

## Results

### Cluster description

The cluster started in July 2014 (Figure 1) with a 32-year-old male who was diagnosed with a first episode of definite ARF (case one). In September 2014, four children and two adults were diagnosed with ARF over a two-week period (cases 2–7). Case three, the 10-year-old daughter of case one, was diagnosed with

recurrent ARF despite being prescribed BPG prophylaxis with only three days at risk in the preceding two months.<sup>29</sup> Cases four and five lived in houses adjacent to cases one and three, and were biologically related to each other.

Active case finding was instituted in affected households as part of the public health response, resulting in the detection of two additional cases of definite ARF in the month of September, both in 15-year-old girls. The first had mild carditis (case eight), and the second had severe carditis with aortic and mitral valve disease and required urgent interstate referral for cardiac surgery (case nine). Another two cases of ARF were diagnosed in October (cases 10 and 11), two in November (cases 12 and 13), and two in December (cases 14 and 15).

Of the 15 cases (Table 1), eight were female; median age was 14 years (range: 5–44; interquartile range: 10–15). All cases were Australian Aboriginal people. This represented the first ARF diagnosis for 10 of the 15 definite cases; recurrent ARF occurred in two cases who were prescribed BPG prophylaxis to be administered every 28 days, and in three cases where BPG had been ceased according to guideline recommendations.<sup>27</sup> Of the two prescribed BPG prophylaxis, one had 29 days at risk in the eight weeks preceding presentation; the other had only three days at risk. Acute carditis was diagnosed by echocardiography in 9/15 (60%) cases; 3/15 (20%) had acute on chronic RHD; 3/15 (20%) had a normal echocardiogram. Two cases with definite ARF and severe RHD underwent cardiac surgery within 12 months of their ARF diagnosis, another is awaiting cardiac surgery. In addition to the 15 definite cases of ARF diagnosed between July and December 2014, there were seven probable cases of ARF during the same period who were managed with ongoing BPG prophylaxis. One of the probable cases subsequently presented with definite recurrent ARF and severe carditis and required cardiac surgical intervention in 2017.

### Epidemiological results

The all-age incidence rate of definite ARF in the Aboriginal population of the community for the six-month period of July–December 2014 rose to 1,473 cases per 100,000 people per year (95%CI 873–2,438). The age-specific incidence rate for children aged 5–14 years was 3,326 cases per 100,000 people per year (95%CI 2,017–5,376), and for people aged

15–44 years it was 1,122 cases per 100,000 people per year (95%CI 651–1,893).

### Case finding results

Symptom-based screening was undertaken in 81 individuals, which identified two additional definite ARF cases (cases eight and nine). Screening echocardiography was conducted for 49 individuals, with a further case of probable ARF identified as a result.

### Laboratory results

Of 76 throat swabs sent from household contacts, GAS was isolated from 3/76 (4%)

and non-GAS beta-haemolytic *Streptococcus* from 12/76 (16%), see Figure 2A. Skin swabs were collected from 24 household contacts with active or recent impetigo; GAS was isolated from 11/24 (46%). Of ten isolates submitted for typing, seven different *emm* types were identified, all belonging to the classical Groups D and E clusters (Figure 2B).

### Environmental assessment results

Of the 10 households assessed by the environmental health officer, all had running water and the majority had electricity supply, but almost all households lacked consumable hygiene items such as soap and toilet paper.

**Table 1: Line list of cases of definite ARF diagnosed in Community X, July–December 2014 (n=15).**

Case	First or recurrent episode	Major criteria	Minor criteria	ASOT <sup>a</sup> /aDNAse-B <sup>b</sup> (KU/L)	Throat swab culture	Echocardiography findings
1; 32y male	First	Carditis; polyarthritides	Fever; elevated CRP	700/3,090	Group G <i>Streptococcus</i>	Moderate mitral regurgitation
2; 10y male	First	Carditis, monoarthritis <sup>c</sup>	Fever; elevated ESR/CRP; prolonged PR interval	843/394		Mild aortic regurgitation
3; 10y female	Recurrent	Carditis, polyarthritides	Fever; elevated ESR/CRP	475/729		Mild mitral regurgitation
4; 5y male	First	Carditis; polyarthritides	Fever; elevated ESR/CRP	842/628		Moderate mitral regurgitation
5; 13y female	First	Carditis; chorea	Elevated ESR	878 / 690		Mild mitral regurgitation
6; 44y female	Recurrent	Carditis; polyarthritides	Fever; elevated ESR/CRP	1,050/852		Moderate mitral regurgitation
7; 44y female	Recurrent	Monoarthritis <sup>c</sup>	Elevated ESR/CRP; prolonged PR interval	1,060/1,680	Group C <i>Streptococcus</i>	Mild mitral regurgitation, mild mitral stenosis, mild aortic regurgitation
8; 15y female	First	Carditis; polyarthralgia <sup>c</sup>	Elevated ESR	697/203	Group A <i>Streptococcus</i>	Severe mitral regurgitation
9; 15y female	First	Carditis	Fever; elevated ESR/CRP	639/538		Severe mitral regurgitation, severe tricuspid regurgitation, moderate aortic regurgitation
10; 14y male	Recurrent	Carditis, polyarthralgia <sup>c</sup>	Elevated ESR/CRP	701/3,190	Group G <i>Streptococcus</i>	Moderate mitral regurgitation
11; 15y male	First	Carditis	Fever; elevated CRP	664/496		Severe aortic regurgitation
12; 10y female	First	Carditis; polyarthralgia <sup>c</sup>	Elevated ESR	609/400		Severe mitral regurgitation, moderate mitral stenosis, mild tricuspid regurgitation, mild aortic regurgitation
13; 24y female	Recurrence	Polyarthralgia <sup>c</sup>	Fever; elevated CRP; prolonged PR interval	725/597		Normal
14; 13y male	First	Polyarthralgia	Elevated ESR/CRP; prolonged PR interval	721/514		Normal
15; 6y male	First	Monoarthritis <sup>c</sup>	Fever; elevated ESR/CRP	456/470		Normal

Notes:

a: reference range <200 KU/L

b: reference range <187 KU/L

c: admissible as a major criterion in high-risk populations (28)

ASOT = anti-streptolysin-O titre; CRP = c-reactive protein; ESR = erythrocyte sedimentation rate

Shaded rows indicate cases diagnosed prior to public health response

## Discussion

This cluster of ARF cases in a setting with endemic GAS transmission and a high baseline incidence of ARF resulted in an incidence of ARF in a single community that rose to more than 1,000 cases per 100,000 per year, before returning to baseline rates (Figure 1). This increased incidence was more than four times the background rate for this community, and more than seven times the mean regional rate for the NT, based on notifications to the NT RHD Register. More than 1.5% of children aged 5–14 years living in this community had definite ARF during a six-month period.

A high proportion of the cases presented with cardiac involvement, with 8/10 first ARF episodes associated with RHD (four severe, two moderate, two mild) in this series. Four patients (three with definite ARF and one who presented initially with probable ARF) required cardiac surgery in the subsequent four years, illustrating the devastating consequences of ARF and RHD in this context, and the importance of adequate treatment, even for cases classified by diagnostic criteria as probable ARF.

This unprecedented situation highlights the ongoing impact of ARF and RHD for

Aboriginal Australians in Northern Australia, despite efforts to implement strategies for primary and secondary prevention.<sup>31,32</sup> The fact that most cases were first episodes of ARF emphasises the need to address primary prevention through provision of prompt antibiotic treatment and infection control strategies for GAS infections. In the NT, skin health is an important focus, as sore throat is infrequently reported, but GAS skin infections (often associated with scabies infestation) are highly prevalent.<sup>33</sup> An association between scabies and ARF has been hypothesised, and demonstrated recently in a cohort of children in New Zealand.<sup>34</sup> Of the three recurrent cases in this series, two occurred in people prescribed secondary prophylaxis with BPG strictly every 28 days, but who had had some recent days at risk. Improving adherence to secondary prophylaxis has been the focus of large programs of work in the NT in recent years.<sup>35</sup>

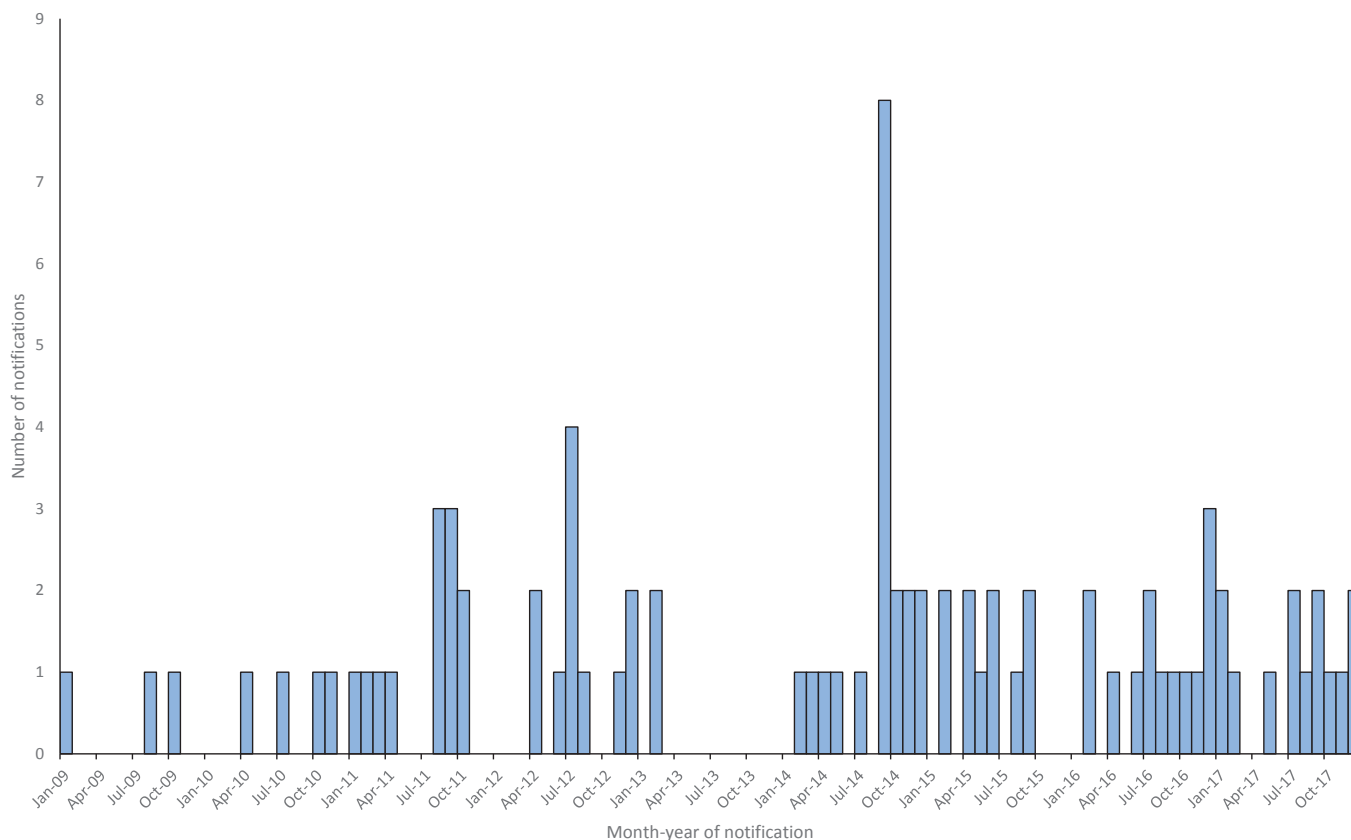
Ultimately, sustained reduction in rates of ARF and RHD require attention to the underlying social determinants, which predispose Aboriginal and Torres Strait Islander people in Australia to diseases of poverty.<sup>10</sup> Addressing socioeconomic disadvantage is the key priority for addressing the primordial prevention of RHD. In the context of ongoing

high rates of ARF and RHD in Northern Australia, renewed efforts to relieve poverty and its flow-on effects are needed. Access to untied funding, employment opportunities and improved housing availability should be prioritised. Reduction in household crowding could be expected to have a significant impact, with additional societal benefits. Ensuring access to functioning health hardware in existing houses, and community initiatives targeting hand hygiene, are also important.<sup>36</sup>

This cluster investigation shows that there is a potential for spikes in case numbers of ARF, even in the context of ongoing high baseline rates. While it is not clear exactly what factors contributed to this increase in incidence, a number of possible explanations can be hypothesised. Increased clinical recognition of ARF may have occurred due to higher than usual healthcare provider awareness. This appears less likely since the cases were not subtle in presentation and there were no changes to staff preceding the increase in incidence.

The detection of two additional definite cases and one additional probable case through active case finding highlights the fact that under-detection is an issue. Introduction of

Figure 1: Notifications of definite ARF cases by month, 2009–2017 (data provided by NT RHD Register).



a new rheumatogenic strain of GAS into the community could have occurred, although we did not identify one predominant strain of GAS. However, the rate of culture positivity from skin and throat samples was unexpectedly low; loss of bacterial viability might have occurred due to prolonged storage time of swabs prior to transfer to the laboratory, diminishing our ability to identify any true outbreak strain. This highlights the challenges of providing microbiology results in the remote setting. Point-of-care GAS testing was unavailable and would not have provided isolates for typing. It is possible that, given the delay between GAS infection and ARF onset, the opportunity to detect an outbreak strain of GAS was missed by the subsequent public health response, which commenced after the cluster was identified and seven cases were diagnosed.

Other environmental factors may also contribute to increased GAS transmission pressure, even in the absence of a specific, circulating, rheumatogenic GAS strain. It is possible that this cluster of cases was influenced by community movements and household crowding, which provided the conditions for multiple different circulating strains of GAS to infect closely located individuals who shared environmental and genetic<sup>37</sup> risk factors, with a large proportion going on to develop ARF as a result. However, no specific antecedents or changes to community movements and exacerbations of household crowding, such as funerals or festivals, were identified. Fulfilment of Jones criteria requires exclusion of alternative diagnoses such as autoimmune conditions or arboviral infections before confirmation of a diagnosis of ARF. Given the high streptococcal titre results, and the high proportion of cases with documented carditis or first-degree heart block, other aetiologies are unlikely to explain any of the cases in this cluster.

The GAS types identified from contacts were all cluster D or E. These were classically considered to be predominant skin types, but with the ability to also infect throats.<sup>12</sup> While it was not possible to determine whether any of these identified types may have been triggers for ARF cases, our findings are consistent with the large body of evidence implicating GAS skin infection as a precursor of high community ARF rates in Southern Hemisphere high-burden settings.<sup>1,2,34,38,39</sup>

Regardless of the contributing factors to this cluster of cases, it is clear that a robust public health response is needed in such instances.

Although ARF is a notifiable condition in the NT, monitoring systems lacked the sensitivity to detect this increase in notifications prior to it being apparent clinically. In addition, there were no published guidelines available to inform investigation and management of a possible outbreak of ARF in a community setting.

The Communicable Diseases Network of Australia (CDNA) maintains a Series of National Guidelines (SoNG) that inform the response to notifiable communicable diseases that is expected from public health units throughout Australia. A guideline for ARF and RHD has since been developed and endorsed.<sup>40</sup> The guideline recognises that the high burden of ARF and RHD in remote communities in Australia points to the urgent need to address social determinants of health and recommends that the public health response to even individual cases of ARF or RHD should include an environmental health evaluation, coupled with education and advocacy to improve household living conditions for patients, families and communities.

The guideline also addresses response to possible outbreaks, but retains a strong focus on addressing primordial, primary and secondary prevention for families and communities affected by ARF and RHD even in the setting of a possible outbreak. Community education is crucial to the success of the public health response to an outbreak, both to enable effective contact identification, management and active case finding, and to promote a community-driven response to addressing the underlying causes of high rates of ARF and RHD. As recommended in the guideline, the response to possible outbreaks should, where possible, include research to improve understanding of ARF clustering and distribution of GAS types.<sup>40</sup> Our experience serves to highlight some of the challenges associated with implementing public health responses, and incorporating investigation into possible causes of clustering in remote settings.

The NT RHD Control Program has established an electronic surveillance system to detect two or more cases of definite ARF occurring in a single community with onset within

Figure 2a: Beta-haemolytic streptococcal isolates from throat and skin swabs from household contacts.

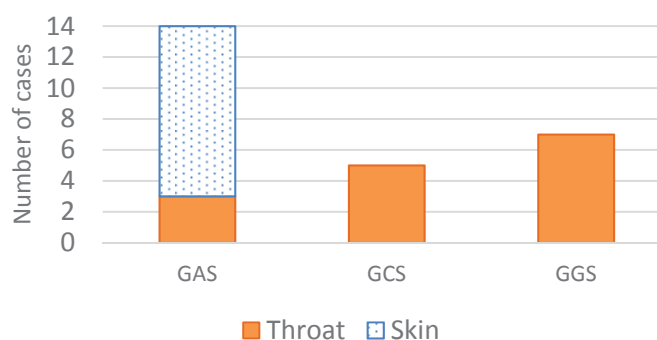
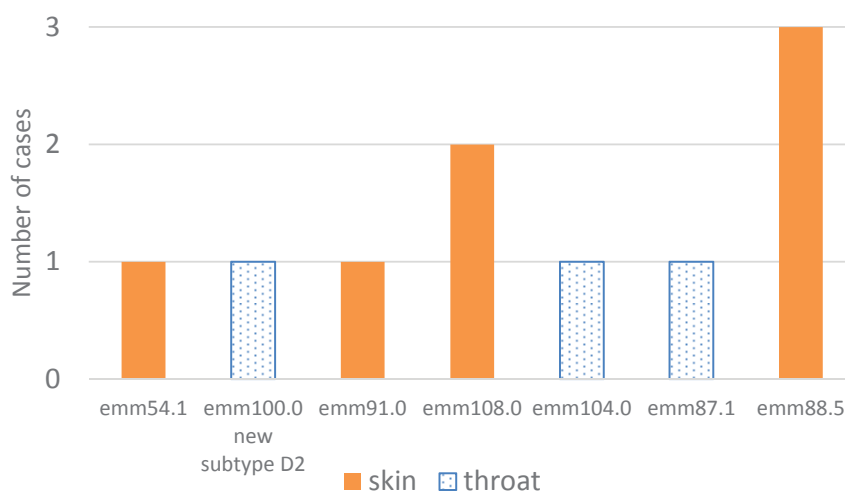


Figure 2b: Types of Group A Streptococcus isolates obtained from household contacts showing emm type and cluster type (D or E).



60 days of each other. This has triggered an alert several times and investigations have occurred. If a higher than usual level of ARF activity seems to be occurring, verbal contact is made with the primary health clinic, supported by a letter, which makes several recommendations. The recommendations are aimed at ensuring local health staff are aware of a rise in case numbers, the symptoms of ARF, the importance of early treatment for sore throats and skin sores for all members of the community, and the importance of ensuring people already prescribed antibiotic prophylaxis are up to date. Additional resources are required to effectively deliver on these measures. There have been no further significant clusters of ARF in the NT since 2014, up to the end of 2018. The direct impact of the public health response (including BPG administration to household contacts of cases) is uncertain.

## Conclusion

The high burden of ARF and RHD among the Aboriginal and Torres Strait Islander population of Australia was further compounded by this unprecedented cluster of ARF cases in a small community. Further research is needed to define the epidemiological factors that contribute to the endemicity and outbreak potential of this life-limiting disease. In the meantime, public health efforts should include advocacy for improved living conditions for those at high risk, specifically to reduce household crowding and improve access to functioning health hardware in homes, as well as ensuring access to early, effective antibiotic treatment of GAS infections, and effective delivery of antibiotic prophylaxis to those with ARF or established RHD.

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