

## The dynamic nature of group A streptococcal epidemiology in tropical communities with high rates of rheumatic heart disease

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### SUMMARY

Prospective surveillance was conducted in three remote Aboriginal communities with high rates of rheumatic heart disease in order to investigate the epidemiology of group A  $\beta$ -haemolytic streptococci (GAS). At each household visit, participants were asked about sore throat. Swabs were taken from all throats and any skin sores. GAS isolates were *emm* sequence and pattern-typed using standard laboratory methods. There were 531 household visits; 43 different *emm* types and subtypes (*emmST*) were recovered. Four epidemiological patterns were observed. Multiple *emmST* were present in the population at any one time and household acquisition rates were high. Household acquisition was most commonly via 5- to 9-year-olds. Following acquisition, there was a 1 in 5 chance of secondary detection in the household. Throat detection of *emmST* was brief, usually <2 months. The epidemiology of GAS in these remote Aboriginal communities is a highly dynamic process characterized by *emmST* diversity and turnover.

### INTRODUCTION

Remote tropical Aboriginal communities of northern Australia have among the highest reported rates of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) in the world; yet, the epidemiology of streptococcal infection in these settings appears to differ from that seen in temperate climates [1]. Specifically, symptomatic group A streptococcal (GAS) pharyngitis is rare whereas GAS pyoderma is common.

Much of what we know about the epidemiology of GAS comes from studies conducted in temperate climates [2–4], although there are data from tropical

and subtropical settings [5, 6]. One of the most comprehensive studies, with relevance to remote Aboriginal populations, was that done in the 1960s and 1970s at the Red Lake Reservation [7]. Using M protein serotyping, investigators demonstrated the introduction, dissemination and waning of successive serotypes in schoolchildren of an indigenous US community. The mean number of new strain acquisitions per child was 4.7 (range 1–9) per 24 months. Some serotypes lingered in the community for extended periods whilst others moved rapidly through the population. The phenomenon of rapid strain replacement has also been described in a US farming community [8].

One of the limitations of M serotyping is the proportion of strains that are non-typable, particularly in Australian Aboriginal communities [9]. In the 1990s, Beall and others developed *emm* sequence

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typing based on the nucleotide sequence of the variable 5'-end of the *emm* gene encoding for M protein. M serotypes and *emm* types appeared to be concordant [10] and a comprehensive online *emm* database is now available [11]. Bessen and others have also used a polymerase chain reaction (PCR)-based mapping technique to identify different arrangements of *emm* and related genes within the *mga* regulon, or *emm* pattern typing. Patterns A–C are associated with GAS strains recovered from the throat, pattern D from the skin and pattern E from both throat and skin [12]. With few exceptions, GAS with a given *emm* sequence type have a predictable *emm* pattern [13].

A previous longitudinal study of GAS epidemiology in a remote Aboriginal island community also used a typing method based on the *mga* regulon (*vir* typing) [14]. This showed high strain diversity and turnover. It also demonstrated simultaneous colonization with multiple *vir* types and used a model to estimate that each child carried a specific *vir* type for an average of 4 months. We now report a longitudinal study, using *emm* sequence typing, of three mainland Aboriginal communities with exceptionally high rates of ARF and RHD. One of the aims of the study was to collect throat swabs and pyoderma swabs from children in households at high risk for ARF. If anyone subsequently developed ARF, it could be determined whether GAS pyoderma or GAS pharyngitis was the antecedent infection. We also aimed to examine the household and community epidemiology of pharyngitis and pyoderma and determine whether there were features unique to the study population, including household and personal acquisition, length of carriage, secondary transmission and the effect of age.

## METHODS

### Study sites and consultation

The study was conducted in three communities, separated by at least 400 km, located in the Top End of the Northern Territory (NT), Australia. At the request of community elders, the community names have not been disclosed. Each has an all-age prevalence of RHD >25/1000 population compared to 0.26/1000 in the non-Aboriginal population. A prolonged period of community consultation preceded approval of the study protocol by the regional ethics committee. Household and individual consent

was obtained and surveillance was commenced in communities 1 and 2 in August 2003. Researchers encountered logistic problems in community 2 and the study was transferred to community 3 in June 2004. Surveillance was completed in July 2005.

### Surveillance

Researchers endeavoured to visit each study household on a monthly basis. Each person present was asked about sore throat and skin sores in the local language. All throats were examined and swabbed for culture. Limbs and exposed areas were also examined and any pyoderma lesions swabbed according to a standard protocol. Each individual episode was defined as a 'consultation'. People with pyoderma, symptomatic pharyngitis or other medical conditions of concern were transported to the Community Health Centre and provided with treatment. Specimens were transported by air in a cold container to a central laboratory.

### Household units and definitions

It was not feasible to follow individuals over an extended period because of population mobility; similarly, a school-based study was impractical because attendance was <50%. Households corresponded to family groupings and were regarded as the primary epidemiological units. In order to increase chances of encountering further cases of ARF, study households were selected because they had members with a known history of ARF or RHD. A household was defined as a single family group that lived in one house or two adjacent houses. Participants were considered to belong to a household if they said they belonged at enrolment and were present on at least two subsequent visits. The number of people who were seen only once in any household, as a ratio of household size, was used as a measure of household turnover. Because of the month-to-month variation in the number of people present at each visit and variation in the number of successful visits (when data and specimens were obtained) for each household, the median number of visits and the consultations per visit was calculated by household and by community.

For the purposes of this study, we have used *emm*ST to denote an *emm* type and *emm* subtype. A household *emm*ST acquisition was defined as the initial recovery of an *emm*ST from any member of a

household. A concurrent acquisition was the finding of more than one person with the same *emm*ST in the household at the time of acquisition. Household persistence was defined as the length of time (months) before an *emm*ST was no longer detected in a household and did not reappear for the remainder of the study period. A secondary event was the recovery of an acquired *emm*ST from another household member at a subsequent visit, acknowledging that this may be due to secondary transmission, re-introduction or previously undetected concurrent acquisition. Community persistence was defined as the time (in months) from first detection of an *emm*ST in study households until no detection for  $\geq 6$  months, or until the end of the observation period.

### Laboratory methods

The methods used for culture and identification of  $\beta$ -haemolytic streptococci have been detailed in a previous report [15]. The procedure for *emm* sequence typing followed that recommended by the Centers for Disease Control and Prevention (CDC) [11] with minor modifications. We used InstaGene™ matrix (Bio-Rad, Hercules, CA, USA) for DNA sample preparation; 20 colonies were harvested directly from culture plates and resuspended in 200  $\mu$ l of the InstaGene matrix suspension. All other steps were according to the manufacturer's instructions. PCR was conducted in 50  $\mu$ l reaction volumes with 5  $\mu$ l of DNA sample, 5  $\mu$ l dNTPs (2 mM), 1  $\mu$ l each of primers 1 and 2 (25  $\mu$ M), 2.5 U *Taq* DNA polymerase, 5  $\mu$ l of 10  $\times$  *Taq* buffer (Qiagen, Valencia, CA, USA),  $\text{sdH}_2\text{O}$  to 50  $\mu$ l. PCR clean-up was done using QIAquick 96 PCR purification kit (Qiagen) according to the manufacturer's instructions, eluting in 60  $\mu$ l  $\text{sdH}_2\text{O}$ .

For sequencing reactions we used the BigDye® Terminator v. 3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) in a reaction volume of 10  $\mu$ l (2  $\mu$ l purified PCR product, 0.5  $\mu$ l primer *emm*seq2, 4  $\mu$ l premix and 3.5  $\mu$ l  $\text{sdH}_2\text{O}$ ). Clean-up was achieved by adding 10  $\mu$ l  $\text{sdH}_2\text{O}$  and using DyeEx96 (Qiagen). The product was then desiccated and sent to a commercial sequencing facility for separation. For sequence analysis, electropherograms were viewed with the Lasergene® SeqMan software v.7.0.0 (DNASTar, Madison, WI, USA) and sequences were blasted against the *Streptococcus pyogenes emm* sequence database on the CDC website [11]. New (novel) *emm* sequences were submitted to the administrator for assignment. *emm* pattern typing of GAS

isolates was done according to the method of Bessen and co-workers [16].

### Data analysis

Epidemiological data were analysed using STATA 8 (Stata Corporation, College Station, TX, USA). The Pearson product-moment correlation coefficient was used to assess correlations. Confidence intervals were calculated using standard methods. Because of differences in surveillance time for the three communities, the variability of household visits and the number of people seen at each household visit, rates were reported per household visit and per consultations when comparing households, and per 100 community consultations when comparing communities.

## RESULTS

### Household surveillance

Forty-nine households and 1173 people were enrolled. There were 531 household visits and 4842 consultations. Household crowding was extreme in communities 1 and 3 (Table 1). There were limited data from community 2. The median household turnover was 18% [interquartile range (IQR) 10–25] in community 1 and 31% (IQR 25–37) in community 3, although the periods of surveillance differed. Local ceremonial events restricted surveillance in August 2004 and March 2005. Overall prevalence rates for pharyngitis, GAS throat carriage and pyoderma, by community and by age, have been reported elsewhere [1].

### Community dynamics of GAS

In total, 214 throat GAS isolates and 124 skin isolates were *emm* sequence-typed and 43 *emm*ST identified (Table 2). Four novel *emm* subtypes were found, *emm*58.8, *emm*91.1, *emm*99.5 and *emm*100.5. Twelve of 28 *emm*ST (43%) from community 1 were not found in the other communities, as were 1/6 *emm*ST in community 2, and 12/26 (46%) in community 3 (Table 2). Thirteen *emm*ST (*emm* 22, 25, 42, 44/61, 58, 78, 81, 97, 100, 101, 110, 114, stNS544) had been reported from the same region in the mid-1990s [17].

The length of time each *emm*ST was detected in the study population varied greatly. A third of *emm*ST (14/43) appeared, increased in prevalence, peaked and then departed from study households over a period of  $\geq 6$  months. Figure 1 shows this pattern for

Table 1. Comparative population and GAS isolate data from the three study communities

	Community 1	Community 2*	Community 3
No. of months in study	23	12 (1st year)	12 (2nd year)
Approximate community population	2500	800	1800
Households enrolled	18	12	19
Median no. of people per house (IQR)	17 (14–21)	7 (5–9)	14 (10–20)
Median visits per household (IQR)	17.5 (16–19)	6 (4–7)	10 (8–10)
Median consultations per household visit (IQR)	7.9 (7.1–11.5)	3.6 (2.5–5.2)	7.9 (6.2–11.0)
GAS throat isolates per 100 consultations	133 4.4 (95% CI 3.7–5.2)	6 2.0 (95% CI 0.7–4.3)	75 4.9 (95%, CI 3.9–6.1)
GAS skin isolates per 100 consultations	85 2.8 (95% CI 2.2–3.5)	5 1.7 (95% CI 0.5–3.9)	34 2.2 (95% CI 1.5–3.1)

IQR, Interquartile range; CI, confidence interval.

\* Note that there were relatively few GAS isolates from community 2.

community 1. Nine *emmST* (21%) persisted in the community for  $\geq 10$  months. By comparison, 18 *emmST* (42%) were seen at just one community visit, often in several different households, without detectable transmission within study households or to other households. They were not encountered again. The outbreak strain, *emm55*, arrived suddenly, disseminated widely and peaked rapidly. It arrived in community 3 households in February 2005 and was first detected in community 1 households a month later. At both sites, outbreaks of acute post-streptococcal glomerulonephritis (APSGN) followed in its wake [18].

The median time an *emmST* remained detectable in study households at each study site was 5 months (IQR 1–9). For the last 12 months of the study, when communities 1 and 3 could be directly compared, the median number of *emmST* found in the study population at any one time was 6.5 (IQR 4.8–8.3) in community 1 and 4 (IQR 3–7.5) in community 3.

### Household dynamics of GAS

Household acquisition varied widely with a median of 5.5 (IQR 3.7–6.0) new *emmST* per household per year in community 1 and 4.0 (IQR 3.6–6.8) in community 3. These crude rates are based on a median of 97 (IQR 86–140) consultations per house per year in community 1 and 89 consultations (IQR 69–131) in community 3. When rates for individual households were adjusted for the number of visits and the number of consultations, the median household acquisition rate

was 4.9 per household-year (IQR 4.2–9.1) for community 1 and 3.6 (IQR 1.9–7.9) for community 3.

There was strong correlation between *emmST* acquisition per household year and household size (Pearson correlation coefficient = 0.88,  $P < 0.001$  for community 1, and 0.68,  $P < 0.001$  for community 3), but not between acquisition and household turnover. Six *emmST* were recovered just once (one individual on one occasion), whilst seven *emmST* were recovered from  $\geq 10$  households over the study period and *emm55* was recovered from 22 households.

We documented 216 household *emmST* acquisitions, 141 via the throat, 72 via the skin and three from both sites. However, these are acquisitions of throat carriage compared to acquisitions of skin infection; moreover, every study consultation included a throat swab whereas skin swabs were only taken in the presence of pyoderma. Figure 2 shows that the individuals most likely to be responsible for a household acquisition were in the 5–9 years age group. On 20/216 occasions (9.3%, 95% CI 5.8–14) there was concurrent household acquisition and on 41/216 occasions (19%, 95% CI 13–25) the same *emmST* was recovered from one or more other household members at a subsequent visit (secondary event).

If the first detected acquisition in a household is regarded as the index case, there was no significant difference in secondary events depending on whether initial GAS isolates had come from skin sores or throat. There were 40 instances where we had obtained serial swabs; an individual had an initial negative swab (or no skin swab in the case of

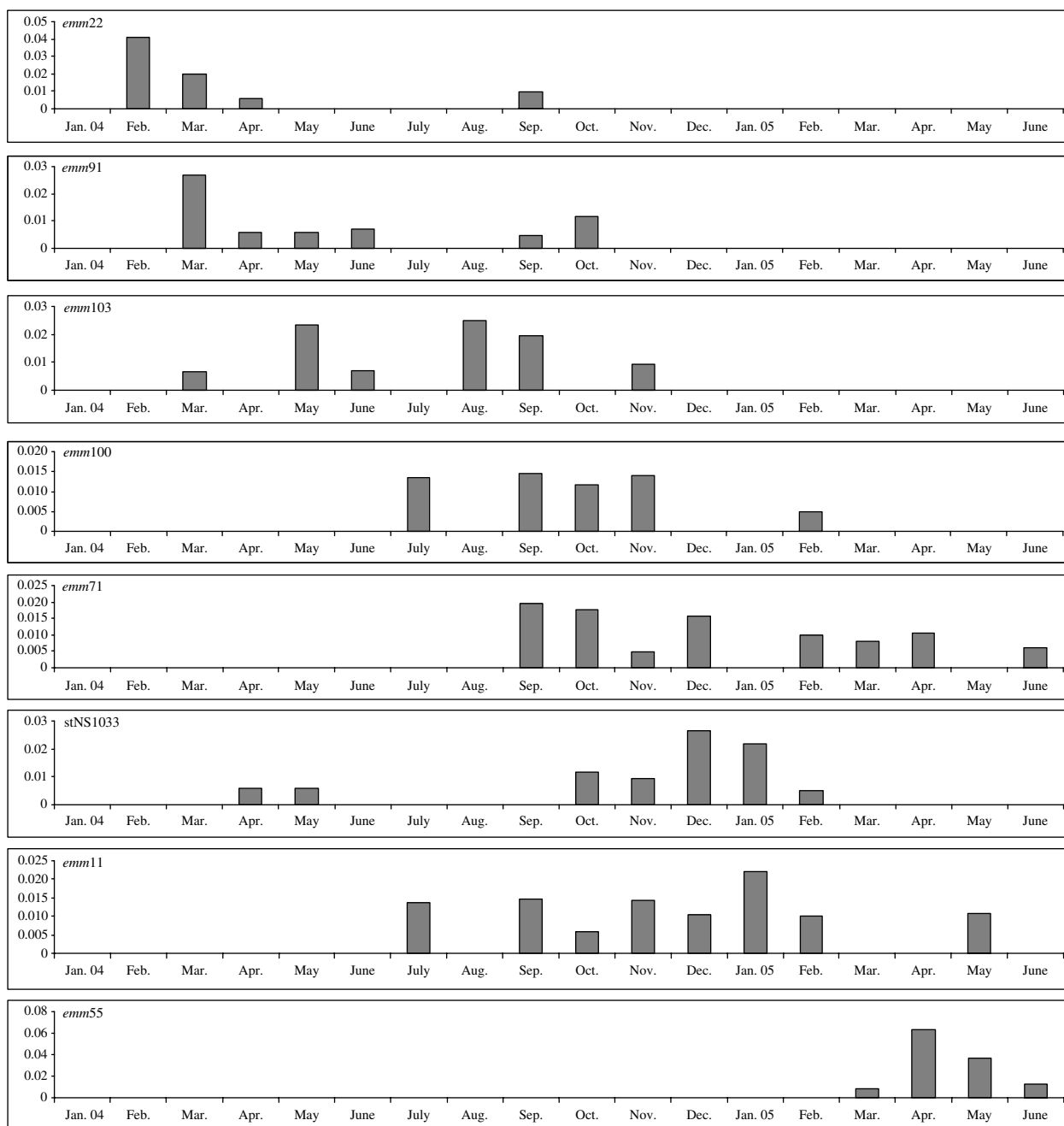
Table 2. *The different emm types and subtypes identified in study households of the three communities*

<i>emmST</i>	Community 1		Community 2		Community 3		Total
	No.	Per 100 consults	No.	Per 100 consults	No.	Per 100 consults	
1					15	0.98	15
11	22	0.73					22
12	1	0.03	3	1.02			4
12.1					1	0.07	1
13L	1	0.03			4	0.26	5
15.1					4	0.26	4
19.4	2	0.07					2
22	13	0.43			2	0.13	15
25.1	2	0.07	1	0.34			3
33	10	0.33			2	0.13	12
42					3	0.20	3
44/61					11	0.72	11
53					2	0.13	2
55	24	0.79			28	1.83	52
56					1	0.07	1
58					1	0.07	1
58.8	8	0.26					8
71	17	0.56			1	0.07	18
75.1	8	0.26					8
76.6	5	0.17			2	0.13	7
77					1	0.07	1
78	4	0.13			7	0.46	11
81.2			1	0.34	2	0.13	3
87	1	0.03			1	0.07	2
91	10	0.33			4	0.26	14
91.1	3	0.10					3
97.1					4	0.26	4
98	4	0.13					4
99.5	6	0.20					6
100	11	0.36			3	0.20	14
100.5	1	0.03					1
101					2	0.13	2
103	15	0.50	2	0.68	1	0.07	18
105	1	0.03					1
110	3	0.10					3
114.2	3	0.10	1	0.34	1	0.07	5
116.1			2	0.68			2
123	7	0.23					7
st2904.1	10	0.33			5	0.33	15
stG653.1	5	0.17			1	0.07	6
stNS1033	17	0.56					17
stNS554	5	0.17					5
Total	219	(7.33)	10	(3.4)	109	(7.17)	338

pyoderma) but was positive the following month and was followed for consecutive months until the swabs were again negative. On 34/40 occasions (85%) the *emmST* was not recovered from the throat swab after a month, in four people (10%), the *emmST* was detected for 2 months. One person had *emm55* isolated for 3 months and another for 4 months. Otherwise, we

were not able to demonstrate prolonged carriage of specific *emmST*. We found no examples of an *emmST* moving from skin to throat and only one example of an *emmST* moving from throat to skin.

There were seven confirmed cases of ARF in study households during the study period and in each case we failed to recover GAS from the throat or skin of

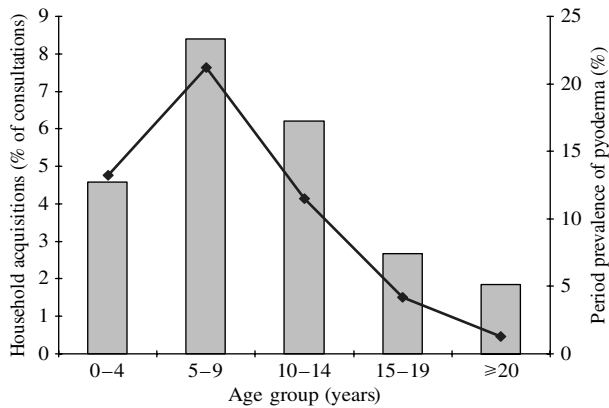


**Fig. 1.** Composite of the eight most common *emm* sequence types for community 1 households. The *x* axis indicates the month and the *y* axis the number of GAS isolates as a proportion of the household consultations for that month.

that person in the 2 months prior to presentation of the illness. In four cases this was because the person was absent from the household at the critical visits. We recovered 29 isolates of GAS from other household members in the 2 months prior to the person presenting with ARF, the month of presentation and 2 months following presentation (Table 3). They represented 15 different *emmST*.

#### Age and *emmST* and *emm* pattern-type distribution

There were no detectable differences in rates of common *emmST* with age. The proportion of pattern type D decreased with age, from 44% of isolates in the 0–4 years age group to 25% in those aged  $\geq 15$  years, presumably in relation to the declining prevalence of pyoderma (Fig. 3). Pattern types A–C were more



**Fig. 2.** Age group of the individuals responsible for household introduction of new GAS *emmST* into the household as a proportion of consultations in that age group (□) compared to the reported period prevalence of pyoderma in those age groups (◆◆) [1].

common in the early teenage years. The outbreak of *emm55* (pattern type A–C) mainly affected the 10–14 years age group, involving 10.3% of that population, compared to 3.4% of 0–4 years age group, 7.4% of the 5–9 years age group and 1% of people aged  $\geq 15$  years.

## DISCUSSION

A key finding of this study was the diversity of *emmST* within households and across the region. There were 43 different *emmST* overall with multiple *emmST* being present in the study population at any one time. In the second year of the study alone, 38 separate *emmST* were detected in a total study population of just over 1000 people. Except for 15 isolates of *emm1* in community 3, classic rheumatogenic *emm* types were few. In this regard, the status of *emm11* is unclear; it was detected in the household of the first case of ARF reported in this study (Table 3). This *emmST* has *emm* pattern type E and is serum opacity factor (SOF) positive, characteristics unlike other rheumatogenic types. Yet M serotype 11 was recovered from the throats of a number of people with ARF in Trinidad in the 1970s [5]. Subsequently, it found its way onto at least one published list of rheumatogenic GAS serotypes [19] but has not been universally accepted as such [20].

Marked *emmST* diversity was found in a previous study of an Aboriginal island community [17] and has been reported from populations in Ethiopia, Brazil, Thailand and India where rates of ARF and/or RHD

are relatively high [21–24]. Moderate diversity has also been reported from Japan and Italy where the rates of RHD are low [25, 26]. Contrasting reports from temperate climate regions include a large study of Pittsburgh schoolchildren that detected only 13 different *emmST* over a 4-year period [4] and only 22 *emmST* were identified in a 2-year study of 202 families in Melbourne [27]. The number of different *emmST* seen in any one year in Salt Lake City (population 180 000), where there has been enhanced surveillance, is usually  $< 20$  [28].

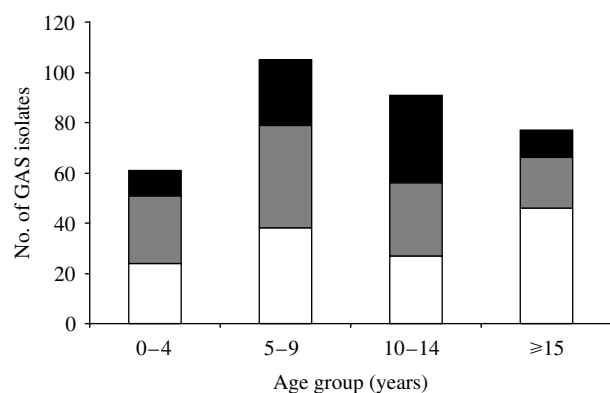
It would be of no surprise to find that genetic diversity is greatest where the community burden of GAS is high and co-infection with multiple M types or *emmST* is common. Horizontal gene transfer appears to be the primary mechanism [29]. GAS are polylysogenic – they contain multiple prophage elements – accounting for most of the variability between strains, perhaps including factors that determine rheumatogenicity. Type-specific immune responses to epitopes of M protein put *emm* genes under selective pressure. Thus, diversity is likely to be greatest, with new types emerging more rapidly, where the burden of colonization and infection is highest. This has ominous implications for multivalent vaccine development, particularly for those based on M protein determinants; only 103/338 (30%) of GAS isolates, and 11/43 (26%) of the *emmST* in this study would have been covered by the proposed 26-valent vaccine [30]. This also includes 72/214 (34%) of GAS throat isolates.

Another finding of this study was the presence of 13 *emmST* that were previously reported in the Top End more than a decade ago, none known to be a classic rheumatogenic type. The persistently high rates of skin infection in the region suggest that skin-tropic strains are continuously cycling through these communities. Shulman and others have proposed that the decline in the incidence of ARF in the United States was related to the replacement of rheumatogenic strains by non-rheumatogenic strains [31]. Yet in the study communities with sustained high rates of ARF, persistence of recognized throat-tropic *emmST* or rheumatogenic types has not been demonstrated, and ARF outbreaks have never been reported. The incidence of ARF does not even vary with season [14]. This raises the possibility that rheumatogenic determinants, some perhaps independent of M protein, could circulate in settings highly conducive to phage-mediated lateral gene transfer between streptococcal strains [29].

Table 3. *GAS emmST recovered from other household members of the seven people in the study who had ARF; emmST recovered during the month of presentation and 2 months either side*

ARF case no.	- 2 months	- 1 month	ARF presentation month	+1 month	+ 2 months
1	<i>stNS1033</i> <i>11</i> (two) (22)*	<i>stNS554</i> <i>91-1</i> (21)	<i>11</i>  (10)	—  (24)	<i>st2904.1</i>  (22)
2	— (0)	— (15)	— (18)	— (8)	<i>StNS1033</i> (15)
3	<i>25-1</i>  (8)	<i>22</i> (×2)  (9)	<i>22</i>  (16)	—  (14)	<i>98</i> <i>103</i> (two) (18)
4	<i>78</i> <i>71</i> (8)	<i>9</i>  (9)	— <i>9</i> (9)	— <i>2</i> (2)	—  (10)
5	— (9)	— (9)	<i>100</i> (7)	— (0)	<i>22</i> (14)
6	<i>stNS1033</i> (three) <i>11</i> (two) <i>76-6</i> (14)	<i>stNS1033</i>  (14)	<i>76-6</i>  (24)	—  (1)	—  (16)
7	<i>91</i> (15)	<i>33</i> (10)	— (1)	— (22)	— (14)

\* The number of household consultations at each visit is shown in parentheses.



**Fig. 3.** The relationship between *emm* pattern type and age: *emm* pattern-type D is relatively more common in the younger age groups and decreases with age whilst patterns A–C were more common in the early teenage years. These data include the outbreak strain *emm55* that made up 63% of all throat types (*emm* pattern types A–C). ■, Throat tropic A–C; ▒, skin tropic D; □, skin and throat tropic E.

We distinguished four basic epidemiological patterns although there was a degree of overlap. They included a group of *emmST* that appeared to move sequentially through the community over a 3- to

6-month period, *emmST* that persisted for a long period of time, often more than a year, and *emmST* that made brief single-month cameo appearances. The fourth pattern was an outbreak. It is difficult to determine the extent to which these patterns are due to properties of the organisms, the environment or the host response.

Throat acquisition of an M type or *emmST*, and its persistence, is not necessarily determined by type-specific antibodies to M protein [32–34], yet type-specific immunity does protect against disease [35]. Type-specific immunity is also highly variable from individual to individual, both in strength of response and duration, and is not necessarily determined by the severity of the original infection [36]. As distinct from reports elsewhere [4, 7], detection of each *emmST* in the throat was almost always brief, a paradoxical finding in view of the rates of ARF. This finding could be due to limitations of data collection. It could also be hypothesized that type-specific immunity leads to low rates of persistence in individuals with greater persistence in the community due to constant replenishment of the non-immune pool through population mobility. Similarly, a persistently high community



turnover of *emmST* could modify the risk of an ARF outbreak. Additional facets of the host response that limit carriage could include non-type-specific immunity, such as to C5a peptidase and the hyaluronic acid capsule.

The pattern of sequential M type (or *emmST*) replacement (shown in Fig. 1), has been demonstrated elsewhere [4, 7, 14]. Similarly, strains that make a brief appearance and vanish again are well known; their contribution to disease burden is unclear, although they contribute to genetic diversity. Some GAS strains have an enhanced ability to disseminate and cause disease, as demonstrated by the dramatic arrival and dissemination of *emm55*. This pattern has previously been reported in the Top End and other parts of the world [37].

The household holds the key to the epidemiology of GAS. This was demonstrated in two classic studies of the 1960s [38, 39]. Levine and co-workers cultured the throats of all people who presented with a respiratory illness on an airforce base in Maine, USA; if a  $\beta$ -haemolytic streptococcus was recovered, patients were divided into those with GAS and those who were GAS-negative (some presumably having GCS/GGS) [39]. They then cultured the throats of family contacts living on the base and found that 48% of 244 child contacts (aged 5–9 years) of elementary school-children with GAS also harboured GAS compared to 2% of 115 child contacts of GAS-negative children ( $P < 0.002$ ). On 72% of occasions (range 47–80%), the GAS-positive patients and their culture-positive contacts shared the same M serotype. The percentage of positive family contacts was also higher in larger families. The authors concluded that transmission of GAS ‘requires a fairly direct and close degree of contact between carriers and potential susceptibles, and that in our society the major locus of this combination of persons and the environment is the home’.

In our study, household acquisition and spread was highly variable; nevertheless, we could not conclude that GAS from pyoderma were more likely to be transmitted than those from the throat. However, if an individual introduced an *emmST* to a household, there was a 1 in 5 chance of a secondary event at a subsequent visit. In contrast, in a study of GAS pharyngitis in Melbourne families, a primary case was followed by at least one secondary case in 43% of families [27] and the mean time to detection of a secondary case was 8 days. In our study, household visits were usually a month apart; as such we may have missed a substantial proportion of secondary

transmissions. In their landmark study of GAS carriage and pharyngitis in Cleveland families, Dingle and co-workers found that household acquisition of an M serotype most commonly came through a child aged <6 years [38]. This corresponds to the findings of our study, and also corresponds with the peak age group (5–9 years) of pyoderma in our study population. In the Cleveland study, if the index case had pharyngitis, then 25% of other household members acquired the same organism, with illness being more likely in younger children. If the index case had no illness, the secondary carrier rate was 9%. In some households the *emmST* persisted for many months, sometimes years.

It has been proposed that the distribution of *emmST* is determined by age, reflecting exposure to, and acquisition of, immunity to common *emmST* [40]. Whilst we did not find a clear age-dependent relationship with individual *emmST*, we did demonstrate a decline in the proportion of skin types with age that probably reflects rates of pyoderma. It is not clear how much of that decline is due to acquisition of immunity or a reduction in other predisposing factors such as scabies and local trauma.

This study shows that the epidemiology of GAS in remote Aboriginal communities is a remarkably dynamic process with great *emmST* diversity, a multiplicity of *emmST* present in the community at any one time, high household acquisition and secondary event rates and a relatively short detection time. Four different epidemiological patterns were recognized at the community level. Classic rheumatogenic GAS types were largely absent and symptomatic pharyngitis was rare. The hypothesis that skin infection plays a role in the pathogenesis of ARF in remote Aboriginal communities has yet to be proven. In the meantime, inadequate health awareness, crowded household conditions and population mobility are likely to be some of the driving forces behind GAS dissemination and diversity within the region.

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## DECLARATION OF INTEREST

None.

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