

# Staphylococcus aureus and Streptococcus pyogenes in the north: distinctively different

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## ABSTRACT

*Staphylococcus aureus* and *Streptococcus pyogenes* are important contributors to disease in northern Australia. Both are opportunistic pathogens, frequently carried on the skin or in the respiratory tract in the absence of disease. A large proportion of the *S. aureus* strains causing infection in northern Australia possess the Panton Valentine (PVL) toxin, with ST93, ST5, and ST121 being significant. PVL + strains are associated with both community- and healthcare-associated infections, and a large proportion are methicillin-resistant *S. aureus* (MRSA). MRSA strains known to be healthcare associated (ST239 and ST22) are not prevalent. CCI PVL– MRSA continue to cause infections. The diversity of *S. pyogenes* *emm* types in northern Australia is high with skin tropic and non-tropic *emm* types predominating. This contrasts with other parts of Australia where *emm* diversity is lower and rates of pharyngitis higher. The high diversity raises concerns for the likely efficacy of vaccines based on the variable region of the M protein, the nucleotide sequence of which underpins *emm* typing. It is likely that complex interactions occur between these two important bacterial pathogens, and other important skin pathogens in the region such as the scabies mite.

**Keywords:** *emm* typing, M protein, Panton Valentine leucocidin, PVL, pyoderma, rheumatic heart disease, skin infections, *Staphylococcus aureus*, *Streptococcus pyogenes*.

*Staphylococcus aureus* and *Streptococcus pyogenes* are firmicutes, within the Bacillales and Lactobacillales respectively. Both are associated with asymptomatic colonisation but are also human pathogens of global significance, causing a range of infections from superficial to life-threatening invasive disease. They are important causes of skin infections in northern Australia<sup>1</sup> with distinct differences in epidemiology to that seen in other parts of the country.

*S. aureus* has long been one of the most notorious agents of nosocomial infections, but also causes disease in the general community. A dominant concept is the dichotomy between  $\beta$ -lactam resistant (known as methicillin resistant *S. aureus* (MRSA)) and sensitive (methicillin susceptible *S. aureus* (MSSA)) strains. The MRSA phenotype is homoplastic, due to mobility of the *SCCmec* genetic determinant of  $\beta$ -lactam resistance.<sup>2</sup> Also important is the dichotomy between community-associated MRSA (CA-MRSA), and healthcare-associated MRSA (HA-MRSA).<sup>3</sup> HA-MRSA strains are well adapted to the health care environment, are typically multiresistant, and in general do not cause community onset infections. CA-MRSA cause community onset infections, but also now predominate in healthcare facilities. CA-MRSA frequently carry a bacteriophage specifying the pore-forming toxin Panton-Valentine leukocidin (PVL). Phage mobility results in PVL+ CA-MRSA being within several evolutionary lineages, and PVL+ MRSA and MSSA are often closely related. The broad framework for understanding the core genome population structure *S. aureus* is based on 'clonal complexes' (CCs) consisting of closely related sequence types (STs) defined by the multi-locus sequence typing (MLST) scheme.<sup>2</sup>

Australia is similar to rest of the world in that the major HA-MRSA strain for many years was ST239. Recently, ST239 has become less prominent, with the most prevalent lineage now being ST22/CC22 'EMRSA-15'.<sup>4–6</sup> Northern Australia appears to have experienced the steep decline of ST239, but with only limited replacement with ST22.<sup>7,8</sup>

CA-MRSA strains in northern Australia are similar to Australia as a whole, but a contributor to this is expansion of strains originating in remote areas into urban Australia.<sup>4,9,10</sup> The most prominent is ST93. Essentially all ST93 are PVL+ and the strain is regarded as highly virulent. ST93 MRSA and MSSA co-exist. Genomic studies indicate that ST93 arose from a point source/genetic bottleneck in north-western Australia in the 1990s. ST93 is divergent from all other *S. aureus* evolutionary lineages, and the nature of the point source remains enigmatic.<sup>10</sup> Consequently, ST93 does not define an observed CC of a

Received: 28 June 2022

Accepted: 28 August 2022

Published: 20 September 2022

## Cite this:

Holt D and Giffard P (2022)  
*Microbiology Australia*  
43(3), 104–107. doi:[10.1071/MA22034](https://doi.org/10.1071/MA22034)

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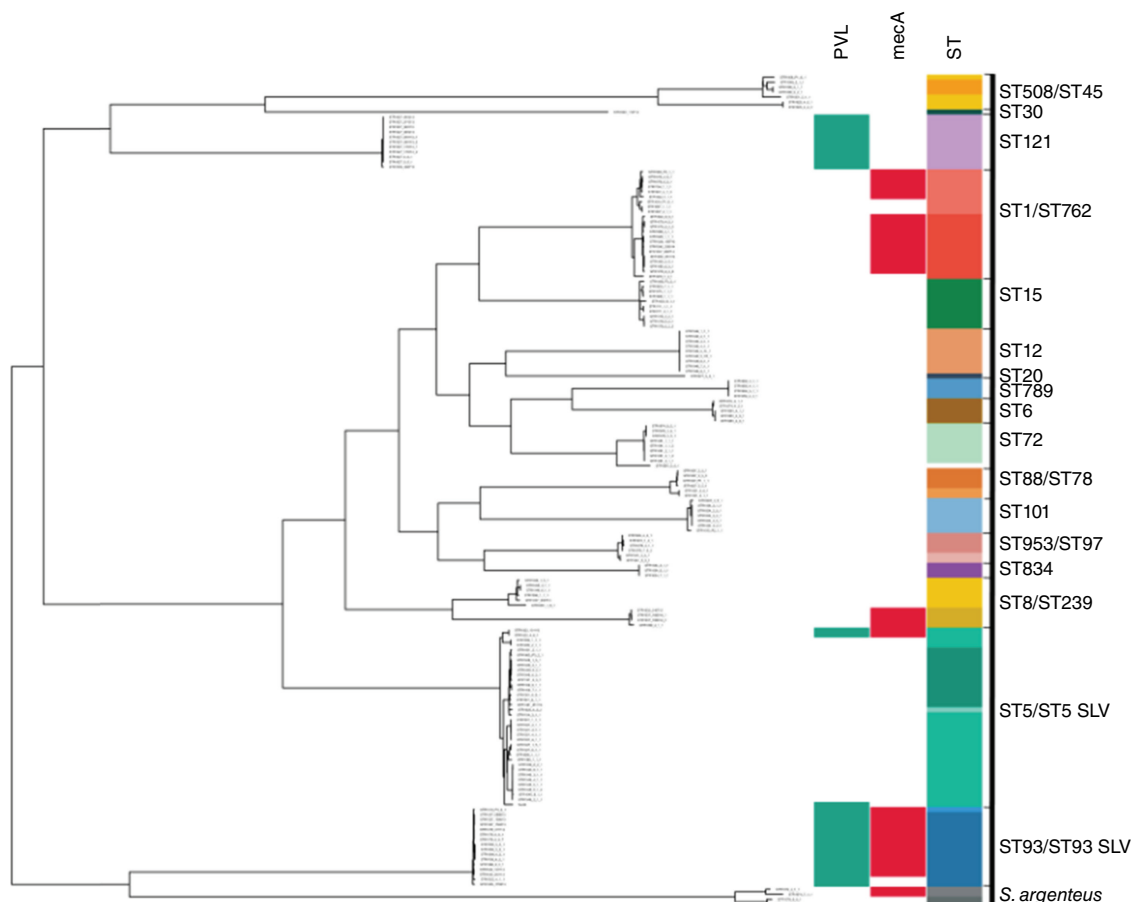
substantial number of related STs. ST93 has disseminated throughout Australia and much of New Zealand<sup>10</sup> and is often isolated from health care facilities as well as the general community.<sup>6</sup> More recent is the emergence of a CC5 PVL+ CA-MRSA strain, also in north-western or northern Australia, and this appears to be in the expansion phase<sup>11</sup> perhaps repeating what was seen with ST93. Other PVL+ strains of current or recent significance in northern Australia include a ST30 MRSA that has long been associated with the Pacific region, and has reduced in prevalence in recent years,<sup>8,12</sup> and ST121 (CC121), which is a PVL+ strain mainly associated with south-east and east Asia, and almost always MSSA.<sup>8,13,14</sup> CA-MRSA strains are not always PVL+. In particular, PVL- CC1 MRSA, often designated as WA-1, has been causing community-acquired infections in north-western Australia for many years.<sup>6,15</sup>

We recently reported a multi-year longitudinal genomics-based study of *S. aureus* in Top End dialysis clinic clients, staff, and researcher.<sup>8</sup> The objective was identification of reservoirs underpinning infection. The genetic nature of the recovered isolates are largely consistent with other studies and provide 'in miniature' a picture of *S. aureus* epidemiology in the Top End (Fig. 1). The infections were nearly all 'skin and soft tissue', with a large proportion caused by the PVL+ MRSA (ST93 and ST5), PVL+ MSSA (ST121), and PVL- MRSA (ST762 (CC1)). Strikingly, asymptomatic carriage of the PVL+ strains was vanishingly rare. In contrast, the PVL- MRSA strains were associated with both carriage and

infection, and putative transmission from carriage to infection was identified. ST762 is single locus variant of ST1. ST762 isolates are very rare in the MLST database but were prevalent in the STARRS isolates, and putatively transmitted from carriage to infection. These are potentially WA-1 or similar. The STARRS PVL- MSSA isolates largely reflect CCs found globally. They were stably carried, largely in the nasal cavity, are under-represented in the infection isolates, and the only putative transmission events identified were 'carriage to carriage'. HA-MRSA were rare, with ST239 represented by one carriage and one clinical isolate. No ST22 isolates were recovered.

It is of interest that the species *Staphylococcus argenteus* was first identified during a survey of *S. aureus* carriage and infections in a remote community in the Northern Territory. The species is now known to be globally distributed, with similar pathogenic properties and potential to acquire antimicrobial resistance as *S. aureus*.<sup>16</sup> It is one of five known species in the '*S. aureus* complex' with the others being *S. aureus*, *Staphylococcus schweitzeri*, *Staphylococcus singaporensis*, and *Staphylococcus roterodami*. In general, these newly defined species appear rare in humans, and in the case of *S. schweitzeri* are overwhelmingly associated with non-human animals. In the STARRS study a small minority of the carriage isolates and none of the clinical isolates were *S. argenteus*.<sup>8</sup> The current clinical impact of *S. argenteus* in northern Australia is unclear.

*Streptococcus pyogenes* (Group A streptococci (GAS)) are  $\beta$ -haemolytic, pyogenic organisms which cause a range



**Fig. 1.** *Staphylococcus aureus* sequence types (STs) recovered from carriage and infection in a study of transmission in dialysis clients in northern Australia. Maximum parsimony tree based on 20 651 orthologous SNPs generated from genome sequence alignment with *S. aureus* isolate Mu50. Reproduced from Holt et al.<sup>8</sup> (CC BY 4.0).

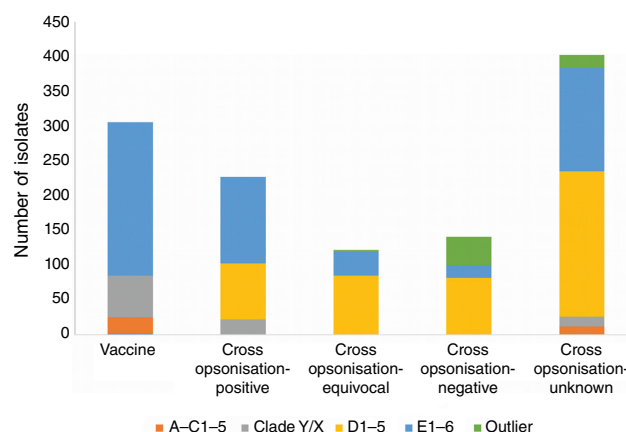
of infections from pyoderma and pharyngitis, to invasive diseases including necrotising fasciitis and toxic shock syndrome. Importantly, autoimmune responses post-infection can lead to significant sequelae including acute rheumatic fever (ARF), rheumatic heart disease (RHD), and acute post-streptococcal glomerulonephritis (ASPGN). It has long been recognised that the burden of ARF and RHD in northern Australia is among the highest reported in the world.<sup>17</sup>

The N-terminal region of the surface streptococcal M protein is highly variable and has been the basis of both serotyping and genetic typing methods. *emm* typing has classically been the main approach to genetic typing and involves sequence analysis of the region of the *emm* gene encoding the variable N-terminal region. Further analysis combining *emm* sequence type with other information including the arrangement of *emm* and *emm*-like genes, defines *emm* pattern types. Population based studies have indicated that *emm* patterns A–C show throat tropism, *emm* pattern D shows skin tropism, while *emm* pattern E does not appear to have a predilection for either site. Over 200 *emm* sequence types have been defined that correlate well with the *emm* patterns.<sup>18</sup>

In the temperate regions of Australia the molecular epidemiology of *S. pyogenes* is similar to that of other developed countries, where throat tropic *emm* types dominate and more restricted *emm* diversity is observed.<sup>19</sup> However, in northern Australia, the prevalence of *S. pyogenes* pyoderma is high, while pharyngitis is low compared with other areas of the country.<sup>20</sup> The *emm* types belonging to the skin tropic *emm* pattern D and non-tropic *emm* pattern E predominate.<sup>21</sup> Outbreaks of invasive disease related to a subset of *emm* types are seen on a background of high diversity and rapid turnover in the circulating *emm* types.<sup>22–25</sup> While novel *emm* sequence types have been found in remote communities in northern Australia, the overall diversity does not seem to be the result of local diversification but rather the circulating population represents a large subset of known global *S. pyogenes* diversity.<sup>26,27</sup> The pattern seen in northern Australia is consistent with what is seen in developing countries,<sup>19</sup> as well as in Indigenous populations in other developed countries such as New Zealand where the burden of ARF and RHD is similarly high.<sup>17,28,29</sup> In these regions, skin and throat tropic *emm* types co-exist, increasing the total diversity of circulating *emm* types.

The variable N-terminal region of the M protein is considered a useful vaccine target due to its immunogenic epitopes and low propensity to induce antibodies which cross react with human tissues. However, the high diversity of *emm* types in northern Australia and developing regions creates concerns for the likely efficacy of such vaccines in these areas.<sup>21</sup> An *emm* cluster system has been developed which is an elaboration of the *emm* typing scheme and is based on the surface exposed portion of the M protein and its binding capacity with six human serum proteins, and *emm* cluster can be inferred from the *emm* type.<sup>30</sup> This can serve as a resource for vaccine development as cross-opsonisation experiments have demonstrated cross-protection between some *emm* types.<sup>30</sup>

A 30mer M protein vaccine which has reached human trials is largely based on *emm* types prevalent in North America and Europe. It contains only a single *emm* pattern D sequence, which did not demonstrate a high proportion of cross protection for other pattern D *emm* types.<sup>30</sup> A study examining over 1700



**Fig. 2.** *emm* clusters and vaccine coverage of skin and soft tissue isolates recovered from northern Australia from 1987 to 2008. Reproduced from Giffard et al.<sup>21</sup> (CC BY 4.0).

isolates from northern Australia collected over more than 20 years demonstrated that over 50% of the isolates were cluster D or outlier *emm* types. Based on the cross-opsonisation data,<sup>30</sup> the 30mer vaccine may not provide good protection against these isolates. In addition, poor coverage of the 30mer vaccine against APSGN associated strains such as *emm*55 is predicted<sup>21</sup> (Fig. 2). Broader protection may be elicited by the 26mer precursor of the 30mer vaccine, which contained two additional cluster D4 *emm* types that are prevalent in northern Australia, or by utilising a combination vaccine approach.<sup>21</sup> Alternatively, other vaccine strategies targeting more conserved regions of the M protein and non-M protein targets<sup>29</sup> may prove more effective in regions with high *emm* diversity.

*S. aureus* and *S. pyogenes* are significant pathogens causing substantial health impacts from acute infections and their serious sequelae. In northern Australia, rates of skin infections are high and there are likely complex interactions with other skin pathogens such as the scabies mite *Sarcoptes scabiei* and the dermatophyte *Trichophyton rubrum*.<sup>1</sup> *S. aureus* and *S. pyogenes* are commonly both recovered from impetigo lesions,<sup>31,32</sup> and *S. pyogenes* is more likely to be recovered from impetigo lesions if scabies infection is also present.<sup>31,32</sup> This dynamic creates particular challenges for public health programs targeting skin health in this region.<sup>1</sup>

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**Data availability.** Data sharing is not applicable as no new data were generated or analysed during this study.

**Conflicts of interest.** The authors declare no conflicts of interest.

**Declaration of funding.** This work did not receive any specific funding.

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