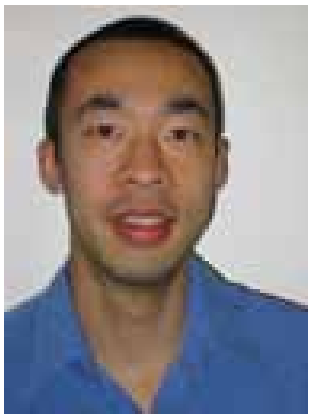
CA-MRSA: emerging remotely



Steven YC Tong [1, 2], *Philip M Giffard* [1] & *Deborah C Holt* [1]

[1] Menzies School of Health Research, Charles Darwin University Darwin NT
[2] Royal Darwin Hospital Darwin NT
[1] Menzies School of Health Research
PO Box 41096
Casuarina NT 0811
Tel (08) 8922 7917
Fax (08) 8927 5187
Email
Steven.tong@menzies.edu.au

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) was first described in remote Indigenous populations in Australia over 20 years ago. The burden of staphylococcal disease, including *S. aureus* bacteraemia, disproportionately affects Indigenous populations and is likely related to socio-economic disadvantage. Factors such as domestic crowding, poor hygiene and high rates of scabies, skin sores and antibiotic use contribute to the transmission and emergence of CA-MRSA. Studies focusing on two clones, sequence type (ST) 93 and clonal complex (CC) 75, provide supportive evidence for the emergence of methicillin-resistance in Indigenous communities.

Despite the initial report of CA-MRSA originating from remote Indigenous communities in the Kimberley region of Western Australia [1], the burden of staphylococcal disease and the emergence of CA-MRSA in Indigenous communities has been underappreciated. CA-MRSA has been present in the Northern Territory (NT) and Western Australia (WA) from at least the late 1980s [2, 3]. Between 1991 and 1995, isolations of CA-MRSA in the NT already outnumbered isolations of hospital-associated MRSA [4]. The highest incidence of MRSA notifications during the 1990s in WA were consistently from the remote Kimberley and Goldfield regions [5].

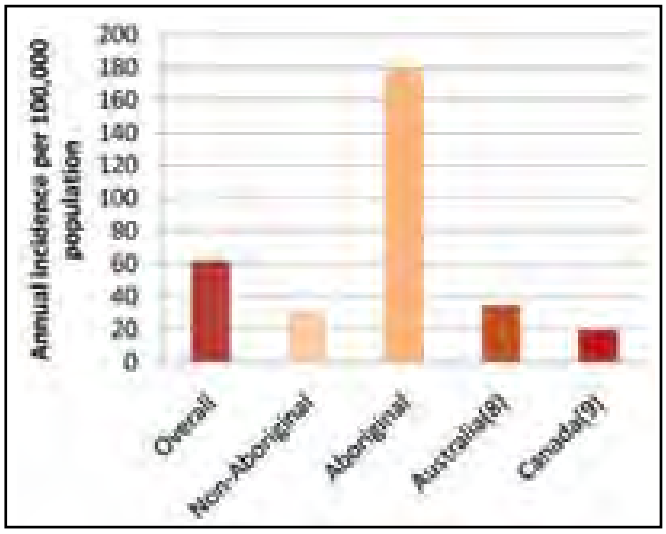


Figure 1: Annual incidence of *Staphylococcus aureus* bacteraemia in the Top End and comparative rates for Australia and Canada (references in brackets).

More recent studies have revealed the burden of disease due to *S. aureus* and CA-MRSA continues to be high in Indigenous communities. Pyoderma was found in 38% of children in three remote Top End communities with *S. aureus* recovered from 59% of pyoderma lesions and methicillin-resistance detected in 23% of these isolates [6]. The annual incidence of *S. aureus* bacteraemia in the Top End Indigenous population is 172 cases per 100,000, while the incidence in the non-Indigenous population of 30 cases per 100,000 (rate ratio 5.8 [95% confidence interval, 3.8-8.9]) is similar to that of the rest of Australia [7] (Figure 1 [8, 9]). This difference in the incidence rates of *S. aureus* bacteraemia demonstrates that the health disparity between Indigenous and non-Indigenous Australians includes the burden of staphylococcal disease.

However, Indigenous ethnicity itself does not appear to explain this difference. Notably, there was a strong correlation between incident isolation of *S. aureus* and measures of socio-economic disadvantage and remoteness in the Top End [7]. A case-control study comparing CA-MRSA with MSSA found that rather than Indigenous ethnicity, female sex (adjusted OR 1.5) and remote residence (aOR 1.8) were associated with CA-MRSA on multivariate logistic analysis [7]. It is likely that factors in remote Indigenous communities, such as domestic crowding, poor hygiene and high rates of scabies, skin sores and antibiotic use, contribute to the transmission and emergence of CA-MRSA [10]. A possible explanation for the association of CA-MRSA with female sex is that children have a particularly high prevalence of skin disease and it is women who provide most of the childcare.

Two *S. aureus* lineages, ST93 and CC75, are of particular interest and provide insight into the emergence of CA-MRSA from Indigenous populations. ST93, known as the Queensland clone, was first described in a Caucasian group of patients in

Queensland [11]. Subsequent studies, though, have led to the conclusion that it has probably emerged from Indigenous communities [12]. ST93 harbours Panton-Valentine leukocidin, a pore-forming toxin linked to severe disease manifestations [13]. Of concern, it is also the most rapidly expanding clone of CA-MRSA in Australia [14, 15]. The spread of ST93-MRSA had been thought to be due to a rapid clonal expansion following a recent single instance of acquisition of SCC*mec,* the mobile genetic element which mediates methicillin-resistance [16]. However, analysis of the *spa* gene, a hypervariable repeat region of the genome, has demonstrated diversity of *spa* types in both ST93-MSSA and ST93-MRSA isolates from the Top End [17]. This diversity within ST93-MRSA is not consistent with an explosive clonal expansion. Rather, the data support an early acquisition of SCC*mec* with subsequent rearrangements of the *spa* sequence or multiple, independent acquisitions of SCC*mec.* Therefore, there is a reasonable likelihood that there is ongoing emergence of ST93-MRSA from circulating ST93-MSSA strains in Indigenous communities.

In contrast to the geographic expansion of ST93 within Australia, CC75 has only been isolated from the Top End to date. CC75 is the dominant strain of CA-MRSA in Top End communities, where 71% of CA-MRSA strains recovered from pyoderma lesions were CC75 [6]. CC75 is of great interest in that phenotypically it resembles *S. aureus,* but phylogenetic analysis indicates significant genotypic divergence from the rest of *S. aureus* [18, 19]. Analysis of the MLST loci revealed remarkable diversity within CC75 isolates, even when isolated from within the same small human population in the NT [18]. It appears that CC75 is not a clone of *S. aureus* but a distinct taxon in its own right. Whether CC75 should be formally reclassified is problematic, given the lack of a diagnostic phenotype, but the phylogenetic justification for reclassification is strong. Both CC75-MRSA and CC75-MSSA were found to co-circulate with evidence of multiple acquisition events of SCC*mec* by CC75-MSSA [6]. Thus, this is an example of ancient MSSA strains and their direct SCC*mec*-harbouring descendents coexisting in an isolated environment where there are many factors present to drive the emergence of resistance.

Most *S. aureus* collections originate from affluent regions of the world and our knowledge of the population structure of *S. aureus* is therefore skewed. Remarkably, CC75 has recently also been found in Cambodia and possibly Malaysia and Indonesia [19]. It is fascinating to speculate that this highly divergent lineage of *S. aureus,* which has been found in neglected human populations in terms of staphylococcal research, may be associated with population movements in the Asia-Pacific region. Strikingly, within Australia, CC75 appears only to be found in the Top End, where the Indigenous population is unique in that it had contact with Maccassan traders in historical times.

In summary, in northern Australia, both the conserved and radiating ST93 and the diverse, divergent and endemic CC75, have likely been subject to multiple introductions of SCC*mec.* Further research into the population structures of CC75 and ST93 are likely to provide ongoing insights into the emergence of methicillin-resistance in community strains of *S. aureus.* This understanding should fuel the need to address issues of socio-economic disadvantage in Indigenous communities, to reduce the impact of staphylococcal disease and the emergence of resistance.

References

1. Udo, E.E. *et al.* (1993) Genetic analysis of community isolates of methicillin-resistant *Staphylococcus aureus* in Western Australia. *J. Hosp. Infect.* 25, 97-108.
2. Riley, T.V. and Rouse, I.L. (1995) Methicillin-resistant *Staphylococcus aureus* in Western Australia, 1983-1992. *J. Hosp. Infect.* 29, 177-188.
3. Pearman, J.W. *et al.* (1985) Control of methicillin-resistant *Staphylococcus aureus* (MRSA) in an Australian metropolitan teaching hospital complex. *Med. J. Aust.* 142, 103-108.
4. Maguire, G.P. *et al.* (1996) Emerging epidemic of community-acquired methicillin-resistant *Staphylococcus aureus* infection in the Northern Territory. *Med. J. Aust.* 164, 721-723.
5. Dailey, L. *et al.* (2005) Methicillin-resistant *Staphylococcus aureus,* Western Australia. *Emerg. Infect. Dis.* 11, 1584-1590.
6. McDonald, M. *et al.* (2006) Use of a single-nucleotide polymorphism genotyping system to demonstrate the unique epidemiology of methicillin-resistant *Staphylococcus aureus* in remote Aboriginal communities. *J. Clin. Microbiol.* 44, 3720-3727.
7. Tong, S.Y. *et al.* (2009) Community-associated strains of methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *S. aureus* in Indigenous northern Australia: epidemiology and outcomes. *J. Infect. Dis.* 199, 1461-1470.
8. Collignon, P. *et al.* (2005) *Staphylococcus aureus* bacteremia, Australia. *Emerg. Infect. Dis.* 11, 554-561.
9. Laupland, K.B. *et al.* (2008) *Staphylococcus aureus* bloodstream infections: risk factors, outcomes and the influence of methicillin resistance in Calgary, Canada, 2000-2006. *J. Infect. Dis.* 198, 336-343
10. Tong, S.Y. *et al.* (2008) Global implications of the emergence of community-associated, methicillin-resistant *Staphylococcus aureus* in Indigenous populations. *Clin. Infect. Dis.* 46, 1871-1878.
11. Munckhof, W.J. *et al.* (2003) Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection in Queensland, Australia. *Int. J. Infect. Dis.* 7, 259-267.
12. Vlack, S. *et al.* (2006) Carriage of methicillin-resistant *Staphylococcus aureus* in a Queensland Indigenous community. *Med. J. Aust.* 184, 556-559.
13. Peleg, A.Y. *et al.* (2005) Life-threatening, community-acquired methicillin-resistant *Staphylococcus aureus* infection in Australia. *Eur. J. Clin. Microbiol. Infect. Dis.* 24, 384-387.
14. Nimmo, G.R. *et al.* (2006) Methicillin-resistant *Staphylococcus aureus* in the Australian community: an evolving epidemic. *Med. J. Aust.* 184, 384-388.
15. Coombs, G. *et al.* (2009) Prevalence of MRSA strains among *Staphylococcus aureus* isolated from outpatients, 2006: Report from the Australian Group for Antimicrobial Resistance. *Commun. Dis. Intell.* 33, 10-20.
16. Munckhof, W.J. *et al.* (2008) Methicillin-susceptible, non-multiresistant methicillin-resistant and multiresistant methicillin-resistant *Staphylococcus aureus* infections: a clinical, epidemiological and microbiological comparative study. *Eur. J. Clin. Microbiol. Infect. Dis.* 27, 355-364.
17. Tong, S.Y. *et al.* (2009) High-resolution melting analysis of the *spa* locus reveals significant diversity within sequence type 93 methicillin-resistant *Staphylococcus aureus* from northern Australia. *Clin. Microbiol. Infect.* (in press).
18. Ng, J.W. *et al.* (2009) Phylogenetically distinct *Staphylococcus aureus* lineage prevalent among Indigenous communities in northern Australia. *J. Clin. Microbiol.* 47, 2295-2300.
19. Ruimy, R. *et al.* (2009) Comparisons between geographically diverse samples of carried *Staphylococcus aureus. J. Bacteriol.* 191, 5577-5583.

Steven Tong is an infectious diseases physician at the Royal Darwin Hospital, who is currently investigating the clinical and molecular epidemiology of *Staphylococcus aureus* in the Top End of northern Australia as part of his PhD, based at the Menzies School of Health Research.

Phil Giffard is the Head of Laboratory Science at the Menzies School of Health Research and an Adjunct Professor in the School of Life Sciences at Queensland University of Technology (QUT). His career has included post-doctoral studies on the oral streptococci at the Institute of Dental Research and 15 years as a microbiology academic and CRC for Diagnostics researcher at QUT. Phil has long-standing research interests in microbial genotyping technology and associated bioinformatic methods and the molecular biology of the lactic acid bacteria.

Deborah Holt is a molecular biologist based at the Menzies School of Health Research, with a specific interest in gene discovery. Her work is focused on skin pathogens of importance in Aboriginal communities, particularly the genetic epidemiology and pathogenesis of scabies.