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Staphylococcus aureus 'Down Under': contemporary epidemiology of *S. aureus* in Australia, New Zealand, and the South West Pacific

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Abstract

The clinical and molecular epidemiology of *Staphylococcus aureus* disease has changed considerably over the past two decades, particularly with the emergence and spread of community-associated methicillin-resistant *S. aureus* (CA-MRSA) clones. Indeed, some of the first global descriptions of CA-MRSA were from remote indigenous communities in Western Australia, and from Pacific Peoples in New Zealand. The epidemiology of *S. aureus* infections in the South West Pacific has several unique features, largely because of the relative geographical isolation and unique indigenous communities residing in this region. In particular, a number of distinct CA-MRSA clones circulate in Australia and New Zealand, such as sequence type (ST) 93 methicillin-resistant *S. aureus* (MRSA) (Queensland clone) and clonal complex 75 *S. aureus* (*Staphylococcus argenteus*) in Australia, and ST30 MRSA (Southwest Pacific clone) in New Zealand. In addition, there is a disproportionate burden of *S. aureus* disease in indigenous paediatric populations, particularly in remote Aboriginal communities in Australia, and in Pacific Peoples and Maori in New Zealand. In this review, we provide a contemporary overview of the clinical and molecular epidemiology of *S. aureus* disease in the South West Pacific region, with a particular focus on features distinct to this region.

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Introduction

Staphylococcus aureus is a major human pathogen, and infections with *S. aureus* are associated with considerable morbidity and mortality [1–3]. The clinical and molecular epidemiology of *S. aureus* infections has changed dramatically over the past two decades. Remarkably, the first indication of the change to come was a report from Western Australia of the emergence of community-associated methicillin-resistant *S. aureus* (CA-MRSA) causing infections in remote indigenous communities [4]. The emergence and epidemic spread of successful CA-MRSA clones in many parts of the world followed, most notably the USA300 clone in North America [5]. Initial reports of CA-MRSA described several distinct features, including the emergence of these strains in patients without traditional epidemiological risk factors for methicillin-resistant *S. aureus* (MRSA) infection, and low rates of resistance to non-β-lactam antimicrobials. Specifically, patients with CA-MRSA infections were younger, had minimal comorbid illness and lacked prior healthcare contact as compared with patients with infections caused by healthcare-associated MRSA (HA-MRSA) strains [5,6]. More recent studies suggest further changes in the epidemiology of *S. aureus* disease, with the emergence and spread of CA-MRSA clones in the healthcare setting [7]. However, although the changing epidemiology of *S. aureus* disease in North America has been extensively characterized, comparatively little is known about the epidemiology of *S. aureus* disease in the southern hemisphere. It is of note that the relative geographical isolation (both of and within) Australia, New Zealand and the South Pacific (collectively referred to as the South West Pacific) has resulted in the

circulation of a diverse range of *S. aureus* strains [8,9]. Moreover, the epidemiology of *S. aureus* infections in the South West Pacific has distinct socio-demographic features as compared with several other settings, with a disproportionate burden of *S. aureus* disease in unique indigenous populations. This review will describe the contemporary clinical and molecular epidemiology of *S. aureus* disease in the South West Pacific, with a focus on those epidemiological characteristics that are specific to this setting.

Clinical Epidemiology and Demographics of *S. aureus* Disease in the South West Pacific

Skin and soft tissue infections (SSTIs)

The most common clinical manifestation of *S. aureus* disease is SSTI, and, as in other settings [10,11], recent studies have described an increase in the incidence of SSTI in Australia and New Zealand over the past decade [12–15]. For example, one Australian study examined national hospitalization coding data, and observed an increase in the rate of hospital admissions for cutaneous abscesses from 46 per 100 000 population in 1999–2000 to 62 per 100 000 population in 2007–2008, with the highest incidence in the <5-year age group [12]. Utilizing an expanded range of hospital discharge codes, another descriptive study assessed trends in the incidence of serious *S. aureus* disease across the New Zealand population between 2000 and 2011 [15]. These authors observed a significant increase in national rates of hospitalization for *S. aureus* skin infections, from 81 per 100 000 population in 2000 to 140 per 100 000 in 2011 ($p < 0.001$). Similarly, using laboratory-based surveillance, a recent study from Auckland, New Zealand described a significant ($p < 0.001$) increase in non-invasive *S. aureus* infections between 2001 and 2011, largely driven by community-onset methicillin-sensitive *S. aureus* (MSSA) infections [16].

In addition to rising rates of *S. aureus* SSTI, distinct socio-demographic differences have been described for *S. aureus* SSTI in the South West Pacific, with a strikingly disproportionate burden of disease in indigenous communities, particularly in paediatric populations. A recent study of *S. aureus* SSTI in New Zealand children found that Maoris (indigenous New Zealanders) were twice as likely and Pacific Peoples almost three times as likely to be admitted to hospital with *S. aureus* SSTI than European children [14]. Similarly, in Australia, Aboriginal children were 12 times more likely to be hospitalized with skin infections than non-Aboriginal children in Western Australia [17], and Aborigines and Torres Straight Islanders accounted for 37% of cases of infection, predominantly SSTI, in a Queensland study while constituting only 3.6% of the population [18]. The underlying reasons for these notable disparities are unclear, but contributory factors probably include domestic overcrowding, factors related to household hygiene, and delayed or inadequate access to healthcare [13,14,16,17,19].

Data are scarce from regions other than Australia and New Zealand, although a prospective study of skin disease in Fiji [20] found that one-quarter of school-aged children (885/3462; 25.6%) had active impetigo, with *S. aureus* being isolated from 57% (323/563) of swabs.

Invasive *S. aureus* infections

S. aureus causes a spectrum of invasive infections, including osteomyelitis, necrotizing pneumonia, and bloodstream infection. In particular, *S. aureus* bacteraemia (SAB) is associated with considerable morbidity and mortality, with reported global incidence rates varying between 14 and 41 per 100 000 population [2,21], although it should be noted that differences in case ascertainment and study methodology limit comparisons between regions. To date, a number of population-based studies of SAB in Australia, New Zealand and the South Pacific have been performed, with estimated overall annual SAB incidence rates between 11 and 65 per 100 000 population (Table 1). Similarly to *S. aureus* SSTI, significant socio-demographic variation has been described in SAB incidence, with rates being considerably higher in indigenous populations. Notably, in one Australian study from the Northern Territory, SAB incidence in the Aboriginal population was six times higher than in the non-Aboriginal population, with the highest reported SAB incidence rate to date (172 per 100 000 population) [19].

In Australia, concern that healthcare-associated SAB was largely preventable led to the introduction of a national programme to improve the hand hygiene compliance of healthcare workers. Implementation of the programme in 2009–2010 was temporally associated with a reduction in SAB rate [22]. Subsequently, data on rates of SAB associated with Australian public hospitals have become publicly available [23], predominantly as a performance marker for infection control interventions. In 2012–2013, the overall national rate of SAB was 0.9 per 10 000 patient-days, although differences in the range and types of patient treated at each centre are likely to contribute to varying rates between regions. Interestingly, the national reported number of healthcare-associated SAB cases decreased by 8% between 2010–2011 and 2012–2013, a trend also seen in other geographical settings [10,24]. In keeping with these findings, a recent study in Auckland, New Zealand also observed a significant decrease in invasive *S. aureus* infections between 2001 and 2011 [16]. These authors suggested that local measures to improve infection control practices, such as

TABLE 1. Epidemiological studies of *Staphylococcus aureus* bacteraemia (SAB) in Australia and New Zealand

Location [reference]	Time period	Type of study	No. of SAB cases	Age group (s)	Overall SAB incidence (per 100 000 population)	SAB incidence (per 100 000 population) in indigenous populations	Community-onset (%)[a]	Crude 30-day case-fatality ratio (%)	MRSA prevalence (%)
Auckland and Christchurch, NZ [65]	1996–1997	Prospective	424	Adults (≥16 years)	41	Maori, 31; PP, 91	50	19	5
Auckland and Christchurch, NZ [66]	1996–1997	Prospective	125	Children (<16 years)	16.9	NR	70	3	6
Christchurch, NZ [67]	1998–2006	Retrospective	779	Adults and children	21.5	Maori, 17.9; PP, 23.1	64	18	0.4
Australia, multicentre [68]	1999–2002	Retrospective	3192	Adults and children	35	NR	49	21[b]	27
Canberra, Australia [2]	2000–2008	Retrospective	NR	Adults and children	26.3	NR	NR	NR	NR
Alice Springs, Australia [69]	2003–2006	Retrospective	125	Adults and children	NR	160.7[c]	NR	13[d]	21
Northern Territory, Australia [19]	2006–2007	Prospective	110	Adults and children	65	172	NR	NR	25
Suva, Fiji [33]	2006–2007	Retrospective	128	Adults and children	50.1	iTaukei, 66.2	NR	NR	2.3
Australia and NZ, multicentre [70]	2007–2008	Prospective	1994	Adults and children	NR	NR	60.8	20.6[e]	24.1
Australia, multicentre [71]	2007–2010	Prospective	7539	Adults and children	11.2	62.5	60.6	18.1[f]	NR

MRSA, methicillin-resistant *Staphylococcus aureus*; NR, not reported; PP, Pacific Peoples; NZ, New Zealand.
[a]Includes community-onset healthcare-associated cases.
[b]Based on 30-day follow-up of 785 patients at two hospitals.
[c]Reported rate of 8.1 per 100 000 in non-indigenous population.
[d]Based on 90-day follow-up.
[e]Data available for 1865 patients.
[f]Data available for 6916 patients.

improvements in hand hygiene compliance and measures to reduce intravascular device-related infections, may have contributed to this observed decrease [16].

Antimicrobial Resistance Patterns of *S. aureus* in the South West Pacific

A number of national and international surveillance platforms exist for monitoring antimicrobial resistance in *S. aureus* in the South West Pacific. These include: (i) the Regional Resistance Programme, which monitors antimicrobial resistance in 12 Asia-Pacific countries, including Australia and New Zealand [25]; and (ii) systematic national surveillance programmes such as those implemented by the Australian Group on Antimicrobial Resistance (AGAR) and the Institute of Environmental Science and Research in New Zealand [26–28]. Data from such surveys indicate that, as in other settings, antimicrobial resistance patterns in *S. aureus* have changed in the South West Pacific over the past decade, predominantly because of the emergence of CA-MRSA strains. For example, biennial AGAR survey data showed a significant increase in the prevalence of clinical MRSA isolates in outpatients from 11.5% in 2000 to 17.9% in 2012 [28]. In comparison, the proportion of MRSA in *S. aureus* isolates from hospital inpatients remained stable between 2005 (31.9%) and 2011 (30.3%), although there were significant inter-state differences in MRSA prevalence [29]. It is of note that data from these latter surveys showed a decreasing trend in hospital MRSA resistance rates for many non-β-lactam antimicrobials, particularly erythromycin, tetracycline, co-trimoxazole, ciprofloxacin, and gentamicin, suggesting an infiltration of non-multiresistant CA-MRSA clones into the healthcare setting and replacement of previously endemic healthcare-associated clones [28].

Rates of MRSA are lower in New Zealand, with recent aggregate national antimicrobial susceptibility data showing a stable MRSA prevalence of *c.* 10% [30]. As in Australia, rates of resistance in MRSA to many non-β-lactam antimicrobials, specifically erythromycin, clindamycin, and fluoroquinolones, have declined over the past 5 years, again reflecting the emergence of CA-MRSA clones in this setting [42]. Interestingly, however, the rates of fusidic acid resistance in MRSA in New Zealand have increased dramatically, from 12.1% in 2008 to 37.4% in 2012 [30]. This increase is likely to be attributable to the rapid emergence of a sequence type (ST)5 MRSA clone in New Zealand (see below), which typically shows resistance to fusidic acid [31]. Contemporary data on resistance rates in MRSA in Australia and New Zealand are shown in Table 2.

There are few studies on MRSA prevalence from other countries in the South West Pacific. However, one study from Samoa found an MRSA prevalence of 17%, with the majority of MRSA isolates (22/34; 64.7%) being resistant only to β-lactam

TABLE 2. Antimicrobial susceptibility patterns in methicillin-resistant *Staphylococcus aureus* isolates in Australia and New Zealand

	Country [reference]; % resistant (number tested)		
Antimicrobial	Australia—community isolates [28]	Australia—hospital isolates [29]	New Zealand—hospital and community isolates [30]
Clindamycin	13.3 (510)	29.7 (713)	17.4 (7419)
Ciprofloxacin	37.5 (510)	66.9 (713)	24.3 (4923)
Co-trimoxazole	10.2 (510)	30.7 (713)	1.5 (7940)
Erythromycin	39.2 (510)	64.0 (713)	27.1 (7846)
Fusidic acid	5.1 (510)	4.0 (713)	37.4 (4794)
Gentamicin	9.4 (510)	30.4 (713)	4.2 (3687)
Mupirocin	1.6 (510)	1.0 (713)	9.5 (5142)
Tetracycline	14.5 (510)	33.5 (713)	2.4 (7090)

antimicrobials [32]. In addition, a recent study from Fiji [33] found an MRSA prevalence of 6.2% (20/323) in *S. aureus* skin isolates from children, with all 20 isolates being resistant only to β-lactams and no more than one other class of antimicrobial.

Molecular Epidemiology of *S. aureus* in the South West Pacific

The relative geographical isolation and distinct indigenous communities residing within the South West Pacific have contributed to the diverse nature of circulating *S. aureus* strains in this region. Indeed, the earliest reported CA-MRSA infections, caused by an ST8 CA-MRSA strain, were from indigenous communities in the remote Kimberly region in Western Australia [4]. Similarly, reports in the mid-1990s from New Zealand suggested that an ST30 MRSA clone (colloquially known as the 'South West Pacific' clone) was responsible for an increasing number of community-associated infections in Pacific peoples [34,35]. This section will review the major contemporary *S. aureus* clones in the South West Pacific, with a specific focus on clones distinct to each geographical setting. The standard nomenclature of multilocus ST (MLST) and SCC*mec* typing will be used to describe MRSA clones (for example, ST5-IV refers to an ST5 strain containing the type IV SCC*mec* element).

Australia

Since 2008, the predominant CA-MRSA clone in Australia has been the ST93-IV Queensland clone [36]. First identified in 2000 in a study in Ipswich in southeast Queensland [37], this clone harbours the *lukF-PV/lukS-PV* (Panton–Valentine leukocidin (PVL)) genes, is typically susceptible to non-β-lactam antimicrobials, and has successfully spread throughout Australia. A singleton by MLST, ST93-IV is associated with both skin infections and severe invasive infections, such as necrotizing pneumonia and osteomyelitis [38]. Interestingly, there have been recent reports describing the emergence and transmission of this clone in other parts of the world, largely facilitated by international travel [39,40]. Genomic analysis of nationally representative ST93 isolates has revealed genetic diversity within the ST93 clone [41,42], and more recent phylogenetic data suggest that this clone emerged in Western Australia in the 1970s, and acquired the mobile SCC*mec*-IV on at least two occasions in the mid-1990s [43]. It is of note that, despite a lack of known virulence-associated determinants as compared with other CA-MRSA clones, a representative ST93 strain (JKD6159) was shown to be significantly more virulent than other CA-MRSA clones (including USA300) in murine models of skin infection and systemic sepsis [44]. The exact mechanism(s) for this increased virulence potential is unclear, although recent data suggest that increased production of exotoxins, particularly α-haemolysin and phenol-soluble modulin α3, may have partially contributed to this observation [43,45].

Another distinct clone that has emerged as a major cause of community-onset *S. aureus* infections in Australia, specifically in indigenous populations in the Northern Territory, is clonal complex (CC)75 *S. aureus*. In one recent study, CC75 accounted for 8% of all MSSA isolates and 69% of MRSA isolates recovered from skin lesions in Aboriginal children in the Northern Territory, although it was rarely isolated from patients with hospital-onset infections [46]. Phenotypically, strains from this lineage are typically non-pigmented, and genomic analysis of a representative CC75 strain (MSHR1132) showed that this strain lacked an operon encoding the carotenoid pigment staphyloxanthin [9]. Another key distinguishing genomic feature of this clone is the marked genetic divergence from other *S. aureus* lineages, with *c.* 10% nucleotide diversity from other *S. aureus* lineages [9]. The differential phylogeny of CC75 has led to the suggestion that this clone be renamed as a separate species, *Staphylococcus argenteus* [9,46].

A number of other CA-MRSA clones are known to circulate in Australia, with the six most common identified in an AGAR survey in 2012 being (in decreasing order of prevalence): ST93-IV, ST30-IV, ST1-IV, ST45-IV, ST78-IV, and ST5-IV [36]. In contrast to the diverse nature of CA-MRSA clones, circulating HA-MRSA clones in Australia are more restricted: ST239-III (also known as 'Aus2/3 EMRSA') has been endemic in eastern Australia since the late 1970s [47,48], and was the dominant HA-MRSA clone until recently, when it was replaced by ST22-IV (also known as 'EMRSA-15') [29]. The latter first appeared in 2000, probably because of importation by

overseas healthcare workers [49]. Of concern is the recent identification of PVL-positive ST22-IV as the cause of a nosocomial outbreak in a neonatal intensive-care unit in Sydney [50]. PVL-positive ST22-IV has successfully disseminated in both hospitals and the community in India [51], and there are reports of outbreaks in both Europe and Japan [52].

New Zealand and Polynesia

For almost two decades, the predominant CA-MRSA clone in New Zealand has been the South West Pacific ST30-IV clone [53]. First isolated in the Auckland community in 1992 from individuals who had contact with Western Samoa [34], this clone emerged throughout the mid-1990s and early 2000s to become the major cause of CA-MRSA infections throughout New Zealand, and it has subsequently been reported from several other regions, including Europe and North America [54]. Interestingly, a study of *S. aureus* skin isolates from Samoa in 2007 [32] found that ST30-IV constituted only 12% (4/34) of MRSA, with the three most common MRSA clones being ST8-IV (USA300) (13/34; 29%), ST93-IV (Queensland clone) (9/34; 26%), and ST1-IV MRSA (9/34; 26%). Like other CA-MRSA clones, ST30-IV harbours the *lukF-PV/lukS-PV* genes and is predominantly associated with skin infections in otherwise healthy individuals, although recent data suggest that ST30-IV is also responsible for a sizeable proportion of MRSA infections in patients with prior healthcare exposure [55]. Recent phylogenomic analysis suggests that South West Pacific ST30-IV may have emerged independently from an ancestral CC30 clone in 1967, although this study did not include isolates from New Zealand or Samoa [56].

Since 2005, an ST5-IV clone has rapidly displaced ST30-IV as the predominant CA-MRSA clone in New Zealand, accounting for approximately half of all MRSA in a national period-prevalence survey in 2012 [26]. Although the underlying reasons for the rapid and sustained emergence of this clone are unclear, it is noteworthy that this clone typically shows resistance to fusidic acid, and, in New Zealand, fusidic acid is the recommended topical antimicrobial agent for the treatment of impetigo [57]. Indeed, recent data suggest that community prescriptions for fusidic acid have increased significantly in New Zealand over the past decade (Williamson DA, in submission).

There are few data on the molecular epidemiology of *S. aureus* infections from other regions in the South West Pacific, although a recent study from Fiji [33] found that CC1 MRSA accounted for all community MRSA isolates, and that the most common MRSA types in the hospital setting were ST239-III (14/36; 39%), CC1 (15/36; 42%), CC30 (5/36; 14%), CC59 (1/36; 3%), and CC101 (1/36; 3%).

MSSA clones

Despite the majority of *S. aureus* disease in Australia and New Zealand being caused by MSSA, relatively little is known about the molecular epidemiology and population structure of MSSA circulating in either country. However, a recent study of community-onset *S. aureus* disease in Auckland children identified three predominant MSSA clones—CC1, CC121, and CC30—that, together, accounted for approximately two-thirds of MSSA isolates [58]. It is of note that the prevalence of *lukF-PV/lukS-PV* genes in MSSA isolates was 56%, a rate higher than that reported in a previous New Zealand study, which detected the *lukF-PV/lukS-PV* genes in 37% of disease-causing MSSA isolates [59]. In a recent Australian study on community-onset *S. aureus* infections presenting to general practices in south-eastern Australia [60], the MSSA population consisted of 25 different strains, with the *lukF-PV/lukS-PV* genes being detected in at least four clonal clusters and in one singleton (CC1, CC20, CC121, CC30, and ST93). Three of the PVL-positive lineages (CC1, CC30, and ST93) were also identified in the CA-MRSA population. Among a collection of 105 MSSA isolates in Fiji, a diverse range of CCs were detected, with the most common being CC5, CC7, CC14, CC75, and CC121 [33].

Emerging MRSA clones in Australia and New Zealand

Over the past decade, a number of notable overseas CA-MRSA clones have been detected in both Australia and New Zealand. These include ST8-IV (USA300) [36,55], ST59-V ('Taiwan CA-MRSA'), and ST772-V ('Bengal Bay clone') [36,55]. In addition, a recent New Zealand study described the isolation of CC398 MRSA from nine patients [61] with two distinct clusters: one attributable to CC398 isolates harbouring *lukF-PV/lukS-PV* genes and associated with travel to South-east Asia; and the other attributable to a 'PVL-negative' ST398 strain similar to the European livestock-associated CC398 lineage [62]. PVL-negative CC398 MRSA has recently been reported from an individual in Australia [63], and has also been detected in an Australian swine herd [64].

Conclusions

In summary, the clinical and molecular epidemiology of *S. aureus* disease in the South West Pacific has changed considerably over the past two decades. Important limitations of this review include the paucity of data available from South West Pacific regions other than Australia and New Zealand, and the comparative lack of data on the molecular epidemiology of MSSA. Notable features include the emergence and dissemination of distinct CA-MRSA clones, particularly ST93-IV and CC75

in Australia, and ST30-IV and fusidic acid-resistant ST5 in New Zealand. Moreover, international travel has facilitated both the exportation of these clones to other settings, and the importation of overseas MRSA clones into this relatively isolated region. Of most concern, however, are observations of increasing rates of *S. aureus* SSTI in both Australia and New Zealand, particularly in indigenous paediatric populations. Future work should aim to understand the factors driving this trend, in order to inform specific strategies designed to reduce the burden of staphylococcal disease in this region.

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Transparency Declaration

The authors declare no conflict of interests.

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