Global Implications of the Emergence of Community-Associated Methicillin-Resistant Staphylococcus aureus in Indigenous Populations

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The emergence of community-associated methicillin-resistant Staphylococcus aureus (MRSA) in Australia may have been facilitated by conditions in socially disadvantaged populations—particularly, remote Australian Aboriginal communities. The appearance of community-associated MRSA was first noticed in Australia during the early 1980s; subsequently, several genetically diverse strains have independently emerged from geographically distinct regions. Molecular and epidemiological studies support the role of genetic transfer of resistance determinants (SCCmecIV) in this process. Conditions in Aboriginal communities—namely, domestic crowding, poor hygiene, and high rates of scabies, pyoderma, and antibiotic use—have facilitated both the clonal expansion and de novo emergence of strains of community-associated MRSA. Combating the worldwide emergence and spread of community-associated MRSA may require novel community-level control strategies targeted at specific groups, such as remote Indigenous populations.

Community-associated methicillin-resistant Staphylococcus aureus (MRSA) has emerged as a leading cause of skin and soft-tissue infections in many parts of the world. One strain, USA300, now causes up to 70% of skin and soft-tissue infections that present to emergency departments across the United States [1]. Community-associated MRSA emerged in Australia during the early 1980s [2, 3]; in contrast with the United States, there continues to be an increasingly recognized diversity of strains in circulation in Australia [4]. Three previously recognized clonal groups were described from geographically distinct regions, as was a newly documented clonal group apparently unique to tropical northern Australia. The present review describes the emergence of these clonal groups and hypothesizes that conditions in socially disadvantaged populations have facilitated emergence. We follow the story of community-associated MRSA in Australia and discuss the public health implications. Table 1 defines some of the terms used in this review.

Australia has played a significant role in the history of S. aureus epidemiology. In 1952, a pandemic clone of penicillin-resistant S. aureus, termed “phage type 80/81,” was first isolated from neonatal infections in Sydney [5]. Phage type 80/81 subsequently caused severe nosocomial and community infections throughout the developed world during the 1950s and 1960s [6]. This epidemic receded with the introduction of methicillin and related penicillinase-stable antibiotics during the 1960s, only to be replaced by the emergence of MRSA. After sporadic reports of MRSA during the 1960s, an MRSA strain emerged in Melbourne and Sydney hospitals during the late 1970s that subsequently became endemic in Australian and overseas hospitals [7].

In 1980, the appearance of MRSA infections in injection drug users in Detroit heralded the next wave of staphylococcal disease [8]. Unlike patients with health care–associated MRSA, the majority of these patients were young and otherwise healthy and had not been recently hospitalized. These new strains were labeled “community-acquired MRSA.”
Table 1. Glossary of terms used in this review of community-associated methicillin-resistant Staphylococcus aureus (MRSA).

<table>
<thead>
<tr>
<th>Term</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clones and/or strains</td>
<td>Varieties of S. aureus that differ in their basic genetic background, determined by various typing techniques; in Australia, the most common community-associated MRSA clones are WA-MRSA-1 (ST1), Queensland clone (ST93), and the Western Samoan Phage Pattern clone (ST30); in the United States, USA300 is predominant.</td>
</tr>
<tr>
<td>Multilocus sequence type</td>
<td>Strains can be differentiated according to the DNA sequence of 7 housekeeping genes; the sequence is assigned a unique “sequence type”; the genetic relatedness of strains can be inferred, and closely related strains can be grouped together as a clonal complex.</td>
</tr>
<tr>
<td>meca</td>
<td>The gene encoding a modified cell wall component that leads to resistance to methicillin and other β-lactam antibiotics.</td>
</tr>
<tr>
<td>Staphylococcal cassette chromosome (SCC)</td>
<td>The mobile genetic element on which meca resides; there are different types of SCCmec genes (I–V), which vary in size, mobility, and whether other resistance genes are carried; SCCmec can transfer from one staphylococcus to another.</td>
</tr>
<tr>
<td>Community-associated MRSA</td>
<td>Strains of MRSA that are typically not multiresistant to antibiotics and harbor SCCmecIV as the resistance determinant; community-associated MRSA has arisen from the community but now causes infections in hospitals as well as in the community.</td>
</tr>
<tr>
<td>Health care–associated MRSA</td>
<td>Strains of MRSA that are genetically distinct from community-associated MRSA, are multiresistant to antibiotics and usually harbor SCCmecI as the resistance determinant; cause infections almost exclusively in patients with health care contact.</td>
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COMMUNITY-ASSOCIATED MRSA IN AUSTRALIA

Community-associated MRSA was initially noticed in Australia during the early 1980s [3, 9], and the first detailed description, in 1989, was of patients from remote Aboriginal communities of Western Australia [2]. After the Western Australian government decided to make MRSA colonization and infection a notifiable disease in 1985 [3], it became apparent that MRSA was increasingly isolated from patients without prior hospital contact. Most of these patients came from remote Aboriginal communities in the Kimberley region (figure 1) in the tropical north of Western Australia. In contrast to previous MRSA strains, the isolates were resistant only to β-lactam antimicrobials, and genetic analysis by PFGE demonstrated a “new” type of MRSA [2]. WA-MRSA, as it became known, spread throughout Western Australia and into major metropolitan centers. Community studies found that 42% of inhabitants of one remote community and 24% of another were colonized with WA-MRSA [10].

Similar strains of non–multiresistant MRSA were also present in the Northern Territory, the jurisdiction adjacent to northern Western Australia. Between 1991 and 1995, infections caused by community-associated strains outnumbered those of health care–associated MRSA at the Royal Darwin Hospital in the tropical Top End of the Northern Territory [11, 12], which suggests that community-associated MRSA was already widespread. The majority of these infections occurred in people from rural and remote indigenous communities.

Although the documentation of community-associated MRSA was more accurate and complete in Western Australia, the incidence of infection during the early 1990s was substantially higher in the Northern Territory. On the basis of population data from the 1996 national census, the incidence of community-associated MRSA isolation in Western Australia [13] from January 1991 through June 1995 was 43 isolations per 100,000 population. The incidence of community-associated MRSA infection in the Top End of the Northern Territory [11] over the same time period was 81 infections per 100,000 population. The true difference in incidence is probably much greater, because notification of infections and colonizations (including screening samples) was mandatory for all Western Australia laboratories, whereas clinical infections at only the Royal Darwin Hospital were included in notification from the Northern Territory. This suggests a possibly earlier emergence of community-associated MRSA in the Northern Territory than in Western Australia, with widespread establishment in the Northern Territory population.

As molecular tools advanced, it became clear that community-associated MRSA was not a “feral descendant” of health care–associated MRSA strains that had escaped into the com-
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rather, the emergence of community-associated MRSA was independent of health care–associated MRSA. Strains of different genetic backgrounds were arising from discrete regions of Australia [15], and all community-associated MRSA strains were different from the traditional health care–associated MRSA strains. Indeed, in contrast to community-associated MRSA, health care–associated MRSA has generally been restricted to a small number of clones that have spread globally with the movement of carrier patients and health staff [16]. Molecular analysis of Northern Territory isolates found them to be genetically distinct from Western Australia strains [15]. It also became evident that WA-MRSA was not simply 1 strain but was at least 5 unrelated strains [17]. In contrast to the clonal transfer of health care–associated MRSA from one colonized or infected patient to another within the hospital setting, often via the hands of health care workers, the picture in Australia indicated multiple independent emergences of community-associated MRSA. The highest rates of notification in Western Australia were from 2 widely separated remote regions—the Kimberley and the more southerly Goldfields [18]. In the Top End of the Northern Territory, Aboriginal people were 13 times more likely than non-Aboriginal people to be infected with community-associated MRSA [11].

In Queensland, on the opposite side of the continent from Western Australia, 2 additional clones were identified: the Western Samoan Phage Pattern (WSPP) clone (ST30), first described in the Pacific Islander population, and the Queensland MRSA clone (ST93), which appeared in both white and Aboriginal populations. The WSPP clone was first documented in Brisbane in 1997 [19]. These isolates were related to a clone causing an epidemic of community-associated MRSA in New Zealand during the mid- to late 1990s [20, 21]. The New Zealand epidemic was centered in areas of Auckland densely populated by Pacific Islanders, and several studies confirmed that Samoans were at highest risk of colonization, infection, and bacteremia with WSPP [22]. Ten isolates from Australia, New Zealand, and Western Samoa were identical by PFGE [21] and supported the postulate that WSPP arrived in Australia via New Zealand during the 1980s and 1990s [19]. Poor living conditions in Samoa were cited as factors leading to the emergence of WSPP, although supportive evidence is scant [21].

Queensland MRSA (ST93) came to prominence when whites...
were also noted to have community-associated MRSA infections [23]. Although the first reported case of fatal necrotizing pneumonia caused by community-associated MRSA in Australia was in a young Aboriginal man, it was initially thought that ST93 was uncommon in Aboriginal populations [24]. Subsequent studies found that 3 of 4 cases of community-associated MRSA bacteremia due to ST93 were in Aboriginal patients [25] and that ST93 was not carried in attendees to urban Brisbane general practices [26] but was carried by 7% of school children in Aboriginal communities [27]. Evidence suggests that the Queensland clone emerged from Aboriginal communities [28, 29].

The most recently described clonal group in Australia, NT-MRSA, was found to predominate in remote Aboriginal communities in the Top End of the Northern Territory. NT-MRSA comprises clonal complex 75 (cc75), which contains ST75. In a longitudinal, community-based study of pyoderma, 71% of community-associated MRSA isolates were cc75 [30]. Although ST75 had been identified in previous Australia-wide surveys of community-associated MRSA [4, 17, 31] and indeed had been labeled as WA-MRSA-8, it was determined that all the isolates were actually from the Northern Territory. Recent typing of the Northern Territory isolates causing infections during 1991 [11] reveals that NT-MRSA was already present at that time (D.C.H., unpublished data). This clone almost certainly emerged from the local Northern Territory population.

MECHANISMS FOR THE EMERGENCE OF COMMUNITY-ASSOCIATED MRSA

Methicillin resistance is mediated by the mecA gene, which is carried on 1 of several types of staphylococcal cassette chromosomes (SCCs), which are mobile genetic elements. Community-associated MRSA typically has type IV SCCmec, which is smaller and more mobile than the types I–III SCCmec seen in health care–associated MRSA [32]. We hypothesize that, in addition to clonal transmission of community-associated MRSA, there is local de novo emergence of new clones of community-associated MRSA when SCCmecIV, or more rarely SCCmecV, is transferred via site-specific integration into already prevalent community strains of methicillin-susceptible S. aureus (MSSA). That is, not only is one clone of community-associated MRSA spreading, but the gene mediating resistance is also repeatedly jumping from one staphylococcus to another—a “gene outbreak.” In addition to a diversity of community-associated MRSA clones arising from geographically distinct regions, we would also expect to find the following: that SCCmecIV-positive and SCCmecIV-negative isolates of the same clone circulate together, that community-associated MRSA and MSSA infections are epidemiologically and clinically similar, that in vivo transfer of SCCmecIV between staphylococcal isolates does occur, and that environmental conditions favoring such transmission are present among populations from which community-associated MRSA has emerged.

Molecular studies that include both MRSA and MSSA strains from confined localities and time spans demonstrate the co-circulation of MSSA and MRSA strains of the same or a similar genetic backbone [30, 33, 34]. It appears that clones of MRSA that harbor SCCmecIV have only lately emerged, suggesting recent and possibly frequent acquisition of SCCmecIV by background MSSA strains [34]. In the Northern Territory community study, cc75 accounted for 25% of all isolates, and within cc75, the ratio of MRSA to MSSA was 2:1 [30]. This clone has not been reported elsewhere to date, and what we have is a prevalent MSSA strain and its direct SCCmecIV-harboring descendant coexisting in an isolated environment.

Early studies of the epidemiology of community-associated MRSA found striking similarities between community-associated MRSA and MSSA infections, leading authors to conclude that “the clinical syndromes associated with S. aureus isolation are independent of methicillin susceptibility” [35 (p. 595), 36]. However, because 1 particular clone of community-associated MRSA—USA300—has become dominant in the United States, slight differences between community-associated MRSA and MSSA infections have emerged [37]. This is likely related to various virulence factors carried by USA300 that have made it such a successful clone. For instance, the presence of arginine catabolic mobile element in USA300 is thought to confer a selective advantage for growth and survival in the host [38]. In contrast, in northern Australia, where no 1 clone has become dominant, we have found no difference with regard to the proportion of skin and soft-tissue infections, need for hospital admission, need for surgery, and length of hospital stay for patients with community-associated MRSA infections, compared with patients with MSSA infections, presenting to the Royal Darwin Hospital [39]. Although USA300, Queensland-MRSA, and the WSPP clone carry the Panton-Valentine leukocidin gene (pvl), NT-MRSA and the original WA-MRSA clones are pvl negative [40]. Most Australian reports of severe community-associated MRSA infections are associated with the Queensland clone [25], which supports the hypothesis that virulence is determined by factors other than the presence of SCCmec. However, pvl has been detected recently in some WA-MRSA strains [4], emphasizing the importance of ongoing clinical and molecular surveillance for changing virulence in community-associated MRSA.

Evidence of the in vivo transfer of SCCmecIV to an MSSA strain was elegantly provided by Wielders et al. [41], when they described a patient in whom initially an MSSA and then an MRSA were isolated. The isolates were identical except for the presence of mecA, and the mecA was identical to that excised from a Staphylococcus epidermidis isolate from the same patient.
It appeared that the MSSA had acquired mecA from the *S. epidermidis* to become MRSA.

**COMMON FACTORS IN GROUPS AT HIGH RISK FOR COMMUNITY-ASSOCIATED MRSA**

Populations at high risk for community-associated MRSA outbreaks include sporting teams [42], incarcerated persons [43], the military [44], children in day care facilities [45], men who have sex with men [46], and indigenous communities across the world [36, 47, 48]. A study of community-associated MRSA infections in an American football team found that infections developed at turf abrasion sites and in players who had more frequent skin contact with other players. Hygiene practices were suboptimal, and antibiotic use was much higher among team players than among the general population [42]. Investigations of outbreaks in jails in the United States identified poor hygiene practices, close contact with MRSA-infected inmates, and poor access to medical care as risk factors for community-associated MRSA infection [43].

Indigenous populations often live in remote and isolated settings, although there are crowded living conditions within communities. As has been the case in Australia, community-associated MRSA appears to have emerged from these settings. In remote Alaskan villages, outbreaks of community-associated MRSA skin and soft-tissue infections were associated with prior antibiotic use and use of communal saunas from which community-associated MRSA was recovered [47, 48]. An epidemic of community-associated MRSA occurred in an American Indian rural community with crowded housing conditions, poor access to health care, and high rates of skin disease, which led the authors to comment that “community-associated MRSA may be found in ever-increasing numbers in other communities of low socioeconomic status” [36, p. 1204] and that “rural communities are not sheltered” [36, p. 1205]. We contend that not only are such communities “not sheltered,” but that in fact they may be the milieu from which community-associated MRSA is emerging and subsequently spreading to the wider population.

**FACTORS CONTRIBUTING TO THE EMERGENCE OF COMMUNITY-ASSOCIATED MRSA FROM AUSTRALIAN ABORIGINAL COMMUNITIES**

Risk factors for emergence and transmission of community-associated MRSA—namely, crowding, poor hygiene, skin infections, and antibiotic use—are highly prevalent in Australian Aboriginal communities [49]. Crowding is most severe in the Northern Territory, with reports of a mean of 3.4 persons per bedroom in one study [50] and up to 7.5 per bedroom in another [51]. Water supplies are deficient and unreliable [52], and >60% of households were found to have no or poorly functioning facilities for either washing children, washing clothes, or removing feces [50]. Although it is difficult to make causative links between independent factors, it is likely that domestic crowding, poor hygiene, and associated sociodemographic factors contribute to extremely high rates of scabies and impetigo in Aboriginal communities [49, 50].

The prevalence of scabies is 25% in adults and 65% in children in some Northern Territory Aboriginal communities [53], and by age 1 year, 63% and 69% of all children in the community have presented with scabies and skin sores, respectively, to community clinics [54]. The prevalence of impetigo among children (<15 years of age) has been up to 70% [53], but we more recently observed an overall prevalence of 20% [51]. Group A streptococcus has previously been the primary pathogen, found in >80% of pyoderma lesions [49], but the pattern appears to be changing in the Northern Territory. In a more recent study, *S. aureus* was recovered from 57% of pyoderma lesions, and group A streptococcus was recovered from 29% of lesions (usually with *S. aureus*) [51]. It is not clear why the microbiological epidemiology is changing, but with the emergence of community-associated MRSA, intramuscular benzathine penicillin may no longer be the most appropriate antibiotic for the treatment of skin sores in these communities. The ongoing heavy burden of staphylococcal skin infection in crowded settings is likely to be associated with high rates of antibiotic use and to facilitate person-to-person transmission of community-associated MRSA and the transfer of SCC*
mec*IV into resident MSSA strains.

The zoonotic potential of MRSA has been noted for horses, pigs, cows, and domestic pets [55-58]. Poor dog health and dog overpopulation are major problems in many Aboriginal communities, and dogs are an intriguing potential contributor to community-associated MRSA emergence. One community study found a median of 3 (and up to 17) dogs per household, and it was common for dogs to have open wounds [59]. The probable transmission of community-associated MRSA between dogs and humans, in both directions, has been documented elsewhere [58] and would seem to be even more likely in Aboriginal communities. An additional consideration is that dogs are also colonized with other staphylococcal species, including *Staphylococcus sciuri* [60]. The *S. sciuri* genome contains an *mecA* homologue that is thought to possibly be the evolutionary precursor of *mecA* now found in MRSA [32]. Therefore, it is possible, not only that antibiotic pressure and overcrowding is amplifying the transmission of community-associated MRSA strains in both dogs and humans, but that community-associated MRSA origins may relate to non-*S. aureus* staphylococcal species in dogs.

**WHAT CAN WE DO?**

There is a rising prevalence of community-associated MRSA infections worldwide, and evidence is accumulating that com-
munity-associated MRSA is not simply replacing MSSA but is adding to the overall burden of staphylococcal disease [61, 62]. Community-associated MRSA strains also cause health care–associated and nosocomial MRSA infections; people who are colonized on hospital admission can serve as a source of transmission within the hospital environment [10, 63–67]. This was recognized in early community-associated MRSA reports from the Northern Territory [12]. Of concern, clones in Australia are beginning to acquire more virulence and antibiotic resistance determinants [4]. Furthermore, if there is truly ongoing acquisition of SCCmecIV by local MSSA strains, we are likely to see increasing de novo emergence of community-associated MRSA in community settings. Combating the emergence and spread of community-associated MRSA may require novel infection-control strategies targeted at specific groups at the community level.

The role of subpopulations acting as the foci for the emergence and amplification of infectious diseases has been long recognized with sexually transmitted and vector-borne diseases [68]. “Core transmitters” with crusted scabies have also been identified as important in driving the ongoing scabies outbreaks in remote Aboriginal communities, which in turn underlie high rates of pyoderma [49]. There is growing appreciation of the importance of such “core groups” in the epidemiology of antimicrobial-resistant pathogens, including community-associated MRSA [69–71]. In the United States, large jails housing up to 20,000 inmates have been identified as likely foci for the amplification and subsequent spread of community-associated MRSA into the wider community [44, 70, 72]. Public health interventions directed at these “superspreader institutions” are predicted to have a disproportionate effect on controlling the epidemic of community-associated MRSA [69]. Authorities in the United States have produced guidelines aimed at reducing the transmission of community-associated MRSA within prisons, the military, and the general population [44, 73]. One correctional facility in Texas has demonstrated significant reductions in community-associated MRSA infections through improvements in screening for and care of skin infections, personal hygiene, and antibiotic therapy [74].

Although Australia’s health care system ranks high internationally, the health inequalities between Aboriginal and non-Aboriginal Australians are well documented. A considerable increase in resources is required to enable remote Aboriginal communities to meet published recommendations for control of community-associated MRSA. It could be that we are paying a heavy microbiological price for the neglect of Aboriginal housing and health hardware needs in remote communities over the past 2 decades. Improving living conditions for Aboriginal Australians should reduce rates of skin infection, and, if our hypothesis is correct, public health strategies targeted at screening for and appropriate treatment of skin infections should slow the emergence of new community-associated MRSA strains. Clinical trials are required to determine whether the current recommendation of intramuscular benzathine penicillin is still the most appropriate antibiotic for treatment of impetigo in remote Aboriginal communities. Despite appropriate calls for accelerated development of new antibiotics to treat resistant organisms [75], we must bear in mind that the unfettered use of antimicrobial agents in disadvantaged communities without addressing underlying socioeconomic conditions is likely to further promote the emergence of microbial resistance.

Acknowledgments

Financial support. Australian National Health and Medical Research Council, Australian National Heart Foundation, and Cooperative Research Centre for Aboriginal Health.

Potential conflicts of interest. All authors: no conflicts.

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