ORIGINAL ARTICLE 10.1111/j.1469-0691.2008.02652.x

Nasal carriage of *Staphylococcus aureus*, including community-associated methicillin-resistant strains, in Queensland adults

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Abstract

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections are emerging in southeast Queensland, Australia, but the incidence of carriage of CA-MRSA strains is unknown. The aim of this study was to assess the nasal carriage rate of *S. aureus*, including CA-MRSA strains, in the general adult population of southeast Queensland. 396 patients presenting to general practices in two Brisbane suburbs and 303 volunteers randomly selected from the electoral rolls in the same suburbs completed a medical questionnaire and had nasal swabs performed for *S. aureus*. All isolates of *S. aureus* underwent antibiotic susceptibility testing and single-nucleotide polymorphism (SNP) and binary typing, including determination of Panton–Valentine leukocidin (PVL). The nasal carriage rate of methicillin-susceptible *S. aureus* (MSSA) was 202/699 (28%), a rate similar to that found in other community-based nasal carriage studies. According to multivariate analysis, nasal carriage of *S. aureus* was associated with male sex, young adult age group and Caucasian ethnicity. Only two study isolates (one MSSA and one CA-MRSA) carried PVL. The nasal carriage rate of MRSA was low, at 5/699 (0.7%), and only two study participants (0.3%) had CA-MRSA strains. CA-MRSA is an emerging cause of infection in southeast Queensland, but as yet the incidence of carriage of CA-MRSA in the general community is low.

Keywords: Community-acquired infections, epidemiology, methicillin-resistant *Staphylococcus aureus*, Panton–Valentine leukocidin, staphylococcal infections, *Staphylococcus aureus*, surveillance

Original Submission: 13 March 2008; **Revised Submission:** 26 June 2008; **Accepted:** 8 July 2008

Editor: E. Tacconelli

Clin Microbiol Infect 2009; **15:** 149–155

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Introduction

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is an emerging cause of infection worldwide [1]. In Australia, it was first reported from a small Aboriginal community in 1993 [2], and since then the infection has emerged throughout Australia, with most isolates of CA-MRSA being non-multiresistant (defined as *S. aureus* resistant to two or fewer non-β-lactam antibiotics) (NM-MRSA) [3]. Brisbane, the capital city of the state of Queensland, has the second highest prevalence of CA-MRSA of all the Australian state capital cities, with CA-MRSA strains comprising 13% of clinical isolates of *S. aureus* collected in an outpatient setting in Brisbane in 2004, an increase from 5% in 2000 [3]. The most common clinical manifestation of CA-MRSA infection is skin and soft tissue infection, which occurs in more than 90% of patients [4], but more serious infections, e.g. bacteraemias and necrotizing pneumonias, also occur, particularly in young adults [5]. Many strains of CA-MRSA carry the virulence factor Panton–Valentine leukocidin (PVL), and the incidence of PVL in clinical isolates of *S. aureus* in southeast Queensland is 55% for NM-MRSA and 16% for methicillin-susceptible *S. aureus* (MSSA) [4], a relatively high percentage of PVL carriage for MSSA in comparison to other studies [6]. The most common strain of CA-MRSA in Brisbane is the ST93 Queensland strain (usually PVL-positive), which was first isolated in 2000, but other common strains include the ST30 southwest Pacific strain (usually PVL-positive) and ST1 WA-MRSA-1 (usually PVL-negative) [3,7]. In our recently published clinical study of *S. aureus*, more than half of the NM-MRSA strains were one of these three strains [4].

The most common site for *S. aureus* carriage is the nose [8], and nasal carriage of CA-MRSA strains is associated with a much higher incidence of clinical infection than that of other strains of *S. aureus*. Soldiers who were nasal carriers of CA-MRSA strains had a 38% risk of developing clinical infection with the same strain of *S. aureus* when followed longitudinally over an 8–10-week period, a 10.7-fold greater risk than nasal carriers of MSSA strains [9]. Studies of the carriage rates of CA-MRSA strains in Australia are lacking. Children in a relatively small, predominantly indigenous Queensland community had high rates of both skin infection and nasal carriage of CA-MRSA strains [10]. However, there have been no studies of CA-MRSA carriage performed in the general Australian adult population. The primary aim of this study was to assess the nasal carriage rate of *S. aureus*, including CA-MRSA strains, in adult volunteers in Brisbane. Secondary aims included assessment of the population structure of carriage strains of *S. aureus* and the prevalence of selected virulence factors, including PVL.

Materials and Methods

The study was performed in volunteer adult populations (aged 18 years or older) in two Brisbane suburbs, Inala and Carindale, between July 2005 and March 2006. These suburbs were chosen because Inala has large populations of Aboriginal and Torres Strait Islanders and Polynesians [11], two ethnic groups known to have a high rate of CA-MRSA infections [7,12], whereas Carindale, in contrast, does not. Three hundred and ninety-six patients who presented with non-infectious conditions to a general practice in each suburb completed a one-page medical questionnaire and had swabs taken from the anterior nares, which were used to culture for *S. aureus* on horse blood agar. Three hundred and three volunteers randomly selected from the Australian electoral roll for the suburbs of Inala and Carindale completed a similar questionnaire and underwent nasal swabbing. All participants were assessed as to the presence or absence of healthcare-associated risk factors. These were defined as hospitalization, surgery, dialysis, residence in a long-term-care facility (nursing home, hostel or prison) or employment in a healthcare occupation in the previous 12 months, known MRSA infection or colonization in the last 12 months, or the presence of a permanent indwelling catheter or percutaneous or invasive medical device (e.g. tracheostomy tube, gastrostomy tube, Foley catheter) at the time of culture [13]. CA-MRSA was defined as MRSA isolated from patients without the above-mentioned healthcare-associated risk factors. The study was performed prior to the proposed new definition of CA-MRSA by Millar *et al.* [14], but the definition of CA-MRSA that was used meets all of the proposed mandatory criteria.

All isolates of *S. aureus* were tested for antibiotic susceptibility using Vitek 2 (bioMerieux-Vitek, Hazelwood, MO, USA). NM-MRSA was defined as MRSA resistant to two or fewer non-β-lactam antibiotics [3]. Mupirocin susceptibility was tested by disk diffusion using a CLSI inoculum, with interpretation of disk zones based on the criteria of Finlay *et al.* [15,16]. The identity of isolates was determined by real-time PCR assays for *mec* and *nuc*, and kinetic PCR for single-nucleotide polymorphism (SNP) genotyping was conducted using Sybr Green (Invitrogen Life Technologies, Carlsbad, CA, USA), as described by Huygens *et al.* [17]. The method uses a set of eight SNPs (*arcC210, tpi241/3*, *arcC162*, *gmk318*, *pta294*, *tpi36*, *pta383*) derived from the multilocus sequence typing (MLST) database that is highly predictive of major clonal complexes (CCs) or sequence types (STs) [17,18]. The relationship of SNP profiles to the population structure of *S. aureus* as defined by MLST is available at http://www.ihbi.qut.edu.au/research/cells_tissue/phil_giffard/. The identity of ST93 was confirmed using a specific SNP, *aroE252*. Isolates were tested for the PVL genes by real-time PCR as described previously [17]. MLST was performed on selected isolates as specified by Enright *et al.* [19]. Isolates that underwent MLST were those that did not fit a specific CC or ST on SNP typing, comprising <1% of the *S. aureus* isolates that we have typed [17]. Additionally, the prevalence of CCs and singletons among these carriage strains of MSSA was compared with that among clinical strains of MSSA from a clinical cohort study of *S. aureus* infection conducted in the same region from June 2004 to February 2005 [4] (Table 4).

Statistical computations of CIs for proportions and of ORs for groups of subjects were performed using the VassarStats website (http://faculty.vassar.edu/lowry/VassarStats.html). Probabilities were calculated using the Yates chi-squared and the Fisher exact tests. Unconditional logistic regression analysis of potentially predictive variables was undertaken with EPI INFO version 3.4 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA).

Results

Enrolments included 396 participants from general medical practices (199 from Carindale Medical Centre and 197 from Inala Health Centre General Practice) and 303 from the electoral roll (153 from Carindale and 150 from Inala), a total of 699 participants. Demographics of participants are presented in Table 1. The age range of participants was 18–96 years, with a median age of 53 years; 293 (42%) of the subjects

TABLE 1. Demographic and clinical features of study participants and their relationship to *Staphylococcus aureus* nasal carriage rate

Participant group	Number	Number with positive nasal swab for *S. aureus*	Proportion of participants with *S. aureus* nasal carriage (%)	95% CI (low)	95% CI (high)	OR	p (two-tailed)
All participants	699	202	28.9	25.7	32.4	–	–
General practice participants	396	106	26.8	22.7	31.3	0.78	0.178
Electoral roll participants	303	96	31.7	26.7	37.1	–	–
Caucasian ethnicity	572	180	31.5	27.8	35.4	2.14	0.006
Aboriginal/Torres Strait Islander ethnicity	102	18	17.6	11.5	26.2	–	–
Other ethnicity	25	4	16.0	6.4	34.7	–	–
Male	293	102	34.8	29.6	40.4	1.63	0.004
Female	406	100	24.6	20.7	29.1		
Age 18–39 years	192	66	34.4	28	41.4	1.17[a]	0.470
Age 40–59 years	239	74	31.0	25.4	37.1		
Age >59 years	268	62	23.1	18.5	28.5	1.74[b]	0.009
Subjects without healthcare risk factors[c]	418	121	29.0	24.8	33.5	1.01	1
Subjects with healthcare risk factors[c]	281	81	28.8	23.9	34.4		
Subjects from Inala[d]	347	86	24.8	20.5	29.6	0.67	0.02
Subjects from Carindale[e]	352	116	33.0	28.3	38.0		
Antibiotics in last 12 months (self-reported)	268	72	26.9	21.9	32.5	0.85	0.39
No antibiotics in last 12 months (self-reported)	431	130	30.2	26.0	34.7		
Boils or other skin infections in last 12 months	50	13	26.0	15.9	39.6	0.86	0.75
No boils or other skin infections in last 12 months	649	189	29.1	25.8	32.7		

[a]40–59 vs. 18–39 years.
[b]>59 vs. 18–39 years.
[c]Defined as hospitalization, surgery, dialysis, healthcare occupation or residence in a long-term-care facility (nursing home, hostel, or prison) in the previous 12 months, or the presence of a permanent indwelling catheter or percutaneous medical device.
[d]Median weekly income per inhabitant US$150 (Source: 2001 Australian population census, Australian Bureau of Statistics, http://www.censusdata.abs.gov.au).
[e]Median weekly income per inhabitant US$380 (Source: 2001 Australian population census, Australian Bureau of Statistics, http://www.censusdata.abs.gov.au).

were male. The ethnicities of participants were as follows: 572 Caucasian (82%), 13 Asian (2%), 102 Aboriginal/Torres Strait Islander (15%), and four Polynesian/Maori (0.6%). Four hundred and eighteen participants (60%) were assessed as having no healthcare risk factors.

The results of univariate analysis of the factors associated with *S. aureus* nasal carriage are shown in Table 1. Overall, 202 (28.9%) of the subjects were *S. aureus* carriers. The carriage rate was lower in females (24.6%) than in males (34.8%, OR 1.63, p 0.004). The carriage rate progressively declined with increasing age, with young adults (18–39 years) having a significantly higher carriage rate than those aged 59 years or older (34.4% vs. 23.1%; OR 1.74, p 0.009). There were no significant differences in carriage rates between electoral roll participants and general practice participants, and no differences between those with and those without healthcare risk factors. A history of either antibiotic exposure or boils or other skin infections within the last 12 months did not significantly affect carriage rates. Participants from Inala, a relatively economically impoverished Brisbane suburb (median weekly income per inhabitant of US$150), had a significantly lower rate of nasal carriage than those from Carindale, a suburb with a higher median weekly income of US$380 (24.8% vs. 33.0%; OR 0.67, p 0.02). The carriage rate among Aboriginal/Torres Strait Islanders was 17.6%, significantly lower than that among Caucasians (31.5%; OR 2.14, p 0.006).

Table 2 shows the results of the multivariate logistic regression analysis for the association of *S. aureus* carriage and the variables age group, ethnicity, sex and location (suburb). This confirmed the univariate analysis results showing that nasal *S. aureus* carriage was associated with young adult age group, Caucasian ethnicity (as compared to Aboriginal/Torres Strait Islander ethnicity) and male sex, and that this

TABLE 2. Unconditional multivariate logistic regression of the association of *Staphylococcus aureus* nasal carriage with the variables age group, ethnicity, sex and suburb

Variable	OR	95% CI	Standard error	*Z*-statistic	p-Value
Age group (18–39 years vs. >59 years)	2.5170	1.5863–3.9938	0.2355	3.9189	0.0001
Age group (40–59 years vs. >59 years)	1.6536	1.0941–2.4993	0.2107	2.3869	0.0170
Ethnicity (Caucasian vs. Aboriginal/Torres St Islander)	2.6338	1.4082–4.9262	0.3195	3.0315	0.0024
Ethnicity (other vs. Aboriginal/Torres St Islander)	0.9681	0.2863–3.2743	0.6217	–0.0521	0.9585
Male	1.8069	1.2812–2.5481	0.1754	3.3729	0.0007
Location (suburb of Inala vs. suburb of Carindale)	0.8836	0.6058–1.2889	0.1926	–0.6422	0.5207

was independent of the other variables. Although, according to univariate analysis, there was a higher rate of nasal carriage of *S. aureus* in the suburb of Carindale than in the more economically impoverished suburb of Inala, patients from Inala were older and were also much more likely to be of Aboriginal/Torres Strait ethnicity. Hence, according to multivariate analysis, there were no significant differences between the two suburbs after the factors of age and ethnicity were taken into account.

One hundred and ninety-one of the 202 isolates of *S. aureus* were available for genotyping, and were divided into 18 SNP profiles corresponding to 16 CCs or STs (some CCs correspond to more than one SNP profile) (Table 3). All five MRSA isolates were non-multiresistant, and had SNP profiles corresponding to CC5 (two isolates), CC509 (two isolates) and ST93 (one isolate). Two isolates of NM-MRSA were community-associated (ST93 and CC5), and three were isolated from participants with healthcare risk factors (CC5 and two isolates of CC509). The ST93 NM-MRSA isolate was positive for PVL, which is characteristic of the Queensland clone of CA-MRSA [1,5]. The only other PVL-positive isolate of *S. aureus* in the study was methicillin-susceptible and also corresponded to ST93. Both PVL-positive isolates were from Aborigines. Only one MRSA isolate (profile CGATTACA, CC5) was resistant to a non-β-lactam (erythromycin). All isolates of *S. aureus* in this study were mupirocin-susceptible.

TABLE 3. Single-nucleotide polymorphism (SNP) genotyping profiles and multilocus sequence typing correlations of 186 methicillin-susceptible *Staphylococcus aureus* (MSSA) and five methicillin-resistant *S. aureus* (MRSA) nasal carriage isolates

SNP profile	Correlation	*mecA*	*pvl*	Number with profile	
				MSSA	NM-MRSA
CGAATCCA	CC45	–	–	1	
CGATAACA	CC5	–	–	26	
CGATAACT	CC1	–	–	5	
CGATTACA	CC5	–	–	34	
CGATTACA	CC5	+	–		2
CGATTACT	CC20	–	–	4	
CGATTCCA	CC72	–	–	1	
CGGATCCA	CC45	–	–	20	
CGGTAACA	CC25	–	–	1	
CGGTTACA	CC22	–	–	3	
CGGTTCCA	CC509	–	–	5	
CGGTTCCA	CC509	+	–		2
TGATAACA	CC8	–	–	1	
TGATAACT	CC9	–	–	1	
TGATACCA	CC8	–	–	11	
TGATTACA	CC78	–	–	22	
TGATTACT	CC1	–	–	6	
TGATTCCA	ST629	–	–	8	
TGGATCCA	CC30	–	–	36	
TGGTTCTA	ST93	–	+	1	
TGGTTCTA	ST93	+	+		1

NM-MRSA, non-multiresistant *S. aureus*; CC, clonal complex; ST, sequence type.

TABLE 4. Comparison of distribution of clonal complexes (CCs) and sequence types (STs) in clinical and nasal carriage isolates of *Staphylococcus aureus*

Clone	Carriage *S. aureus* cohort (%) (*n* = 186)	Clinical *S. aureus* cohort (%) (*n* = 168)[a]	OR	p-Value
CC30	36 (19.4)	16 (9.5)	0.4	0.01[b]
CC45	21 (11.3)	12 (7.1)	0.4	0.07[b]
CC15	26 (14.0)	12 (7.1)	0.5	0.06[b]
CC78	22 (11.8)	17 (10.1)	0.8	0.7[b]
CC8	12 (6.5)	11 (6.5)	1.0	0.9[b]
CC5	34 (18.3)	31 (18.5)	1.0	0.9[b]
CC1	11 (5.9)	17 (10.1)	1.8	0.2[b]
ST93	1 (0.5)	10 (6.0)	11.7	0.004[c]
Other	23 (12.4)	45 (26.8)	–	–

[a]This was a study of clinical isolates of *S. aureus* performed in the same geographical region [4].
[b]Yates chi-squared test.
[c]Fisher exact two-tailed test.

Two MRSA isolates from Caucasians aged 55 and 85 years, living at the same Inala address, belonged to SNP profile CGGTTCCA. None of the strains of *S. aureus* associated with this SNP profile in Australia had previously been noted to be methicillin-resistant [16,19]. MLST of these isolates revealed two new STs, which varied at one locus, new (ST12-like): 1, 3, 1, 8, 11, new (5-like), new (11-like), and new (ST12-like): 1, new (3-like), 1, 8, 11, new (5-like), new (11-like).

Table 4 shows a comparison of the 186 MSSA genotypes from this nasal carriage study with MSSA genotypes of 168 isolates associated with clinical infections in adults from a study also conducted in southeast Queensland [4]. CC30 was significantly over-represented among nasal carriage isolates, whereas ST93 was significantly under-represented. CC15 and CC45 were also over-represented among carriage isolates, but neither was statistically significant. If healthcare-associated strains were excluded by removing clinical isolates from patients admitted to hospital for more than 48 h, the significant differences were maintained for CC30 and ST93, but not for CC15 (data not shown).

PVL was detected in only one of 186 MSSA isolates and one of five NM-MRSA isolates, both belonging to ST93. This is in marked contrast to the prevalence of 16% in MSSA and of 55% in NM-MRSA as seen in the clinical cohort [4].

Discussion

The nasal carriage rate of MRSA in volunteers from two Brisbane suburbs is currently low, at 5/699 (0.7%), and only

two study participants (0.3%) had CA-MRSA nasal carriage. This low prevalence of nasal carriage contrasts with a 13% prevalence of CA-MRSA in the same region in clinical isolates, more than 90% of which were from adults [3]. Children are known to have a high incidence of CA-MRSA infections [5], but the present study did not include children, primarily because only adults are listed on the electoral roll and, for the general practice component of the study, it was difficult to recruit children. The unexpectedly low carriage rate of the predominant clone of CA-MRSA that causes clinical infections in Brisbane, the ST93 PVL-positive Queensland clone, is particularly noteworthy [3,4]. There are several possible explanations for the discrepancy between the carriage rate and clinical prevalence of CA-MRSA in this region. The first is that the epidemiology of CA-MRSA strains may be different to that of other strains of *S. aureus*. The most important reservoir of *S. aureus* carriage is the nasopharynx [8], but perhaps this is not the case for CA-MRSA strains [20]. Other sites that could be important reservoirs of CA-MRSA carriage include the gastrointestinal tract [21], and household pets are also important reservoirs [22]. Another study showed that the throat was an important site of MRSA carriage [23], although the majority of patients in this study had healthcare-associated strains of MRSA. An alternative explanation for the relatively low carriage rates of CA-MRSA strains, as compared to MSSA strains, is the higher likelihood of progression to clinical disease with CA-MRSA strains, resulting in earlier antibiotic treatment and eradication. This is supported by a study showing that soldiers who were nasal carriers of CA-MRSA strains, who were followed longitudinally over an 8–10-week period, had a 10.7-fold greater risk of clinical infection than nasal carriers of MSSA strains [9].

The nasal carriage rate of all strains of *S. aureus* (methicillin-susceptible and methicillin-resistant) in this community-based adult study was 202/699 (28.9%), a rate similar to that found in other community-based studies [24,25]. Carriage rates were significantly lower in women and in older adult age groups, and these findings confirm others [8,26,27]. This study also revealed that carriage rates were lower in Aboriginal/Torres Strait Islanders, and others have found that people with non-Caucasian ethnicities, e.g. Mexicans, Hispanics and New Guinea Highlanders, have lower rates of *S. aureus* nasal carriage than do Caucasians [26,28].

The study showed that baseline resistance to mupirocin of nasal isolates is negligible in a community without significant pre-exposure to mupirocin. In Australia, nasal mupirocin ointment is not approved for Pharmaceutical Benefits Schedule funding (a national scheme that subsidises the cost of medically prescribed drugs), and topical mupirocin ointment has a restricted Pharmaceutical Benefits Schedule listing. Hence, use of mupirocin nasal ointment is rare in a community setting. The finding of negligible baseline mupirocin resistance was gratifying, as mupirocin is recommended as part of the eradication therapy for recurrent staphylococcal skin infection, particularly for the newly emerging CA-MRSA strains [29].

Only one of 186 carriage isolates of MSSA in this study had detectable PVL. Clinical MSSA isolates in the same geographical region have a much higher incidence of PVL, with a recent study showing a 16% PVL detection rate in MSSA [4]. This is in keeping with the findings of a Dutch cohort study [30]. There was also differential prevalence of CC30, CC45, CC15 and ST93 in carriage and in clinical isolates. Over-representation of CC45 among carriage isolates has been reported previously [30,31]. However, the under-representation of CC30 was unexpected, as it has previously been reported as being over-represented in invasive strains [31]. This discrepancy may be explained in part by the inclusion of non-invasive infections in the present clinical collection. ST93 is a strain unique to Australia, with a high prevalence of PVL gene carriage [3,4]. Its under-representation among carriage isolates is striking. Another study found that CA-MRSA carriage isolates have much lower rates of PVL carriage than do clinical CA-MRSA isolates, although strain types of CA-MRSA differed greatly between clinical and carriage isolates [32]. At face value, these findings support the hypothesis that clinical strains of *S. aureus* are more virulent than carriage strains, by virtue of possessing virulence factors such as PVL. However, *S. aureus* is highly clonal, and horizontal spread of a wide variety of accessory genes is well described. Therefore, confounding cannot be discounted. It should also be mentioned that the role of PVL in the virulence of staphylococcal infection is controversial and has recently been questioned [33].

This study shows that, despite the emergence of CA-MRSA infection as a cause of significant morbidity and mortality in southeast Queensland, the incidence of nasal carriage of CA-MRSA strains in the general community is low. Further studies in other populations are planned, to assess the relative importance of nasal carriage of CA-MRSA strains as compared to other carriage sites.

Acknowledgements

We thank N. Whitby and her staff at Carindale Medical Centre and F. de Looze and N. Hayman and their staff at Inala Health Centre General Practice for allowing us to perform the study. N. Underwood of Infection Management Service,

Princess Alexandra Hospital and University of Queensland medical students H. Gilchrist and A. Michael recruited the participants, assisted with completion of patient questionnaires, and performed nasal swabbing. Limited electoral roll data were obtained with permission of the Electoral Commissioner, and the study was endorsed by the Inala Elders Aboriginal and Torres Strait Islander Corporation. The study was approved by the Princess Alexandra Hospital Research and Ethics Committee. Part of this work was presented at the Australian Society for Antimicrobials annual scientific meeting in Melbourne in February 2007 and at the Australian Society for Infectious Diseases annual scientific meeting in Queensland in April 2008.

Transparency Declaration

This study was funded by the Communicable Diseases Unit, Queensland Health. The authors do not report any relationships (commercial or otherwise) which might constitute dual or conflicting interests.

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