Antimicrobial susceptibility of *Staphylococcus aureus* isolated from hospital inpatients, 2009:

Report from the Australian Group on Antimicrobial Resistance

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Abstract

In 2009, the Australian Group on Antimicrobial Resistance (AGAR) conducted a period-prevalence survey of clinical *Staphylococcus aureus* isolated from hospital inpatients. Thirty medical microbiology laboratories from each state and mainland territory participated. Specimens were collected more than 48 hours post-admission. Isolates were tested by Vitek2® (AST-P579 card) and by Etest for daptomycin. Nationally, the proportion of *S. aureus* that were MRSA was 33.6%, ranging from 27.3% in South Australia to 41.4% in New South Wales/Australian Capital Territory. Resistance to the non-β-lactam antimicrobials was common except for rifampicin, fusidic acid, daptomycin and high-level mupirocin. No resistance was detected for vancomycin, teicoplanin, quinupristin-dalfopristin or linezolid. Resistance in the methicillin susceptible *S. aureus* (MSSA) was rare apart from erythromycin (12%) and absent for vancomycin, teicoplanin, daptomycin, quinupristin-dalfopristin and linezolid. The proportion of methicillin resistant *S. aureus* (MRSA) has remained stable since the first AGAR inpatient survey in 2005 yet during the same time frame resistance to many antimicrobials, in particular tetracycline, trimethoprim-sulphamethoxazole and gentamicin, has significantly decreased. This suggests that non-multi-resistant community-associated MRSA (CA-MRSA) clones are becoming more common in the hospital setting and replacing the long-established multi-resistant clones such as ST239-III (Aus 2/3 EMRSA). Given hospital outbreaks of CA-MRSA are thought to be extremely rare it is most likely that patients colonised at admission with CA-MRSA have become infected with the colonising strain during their hospital stay. *Commun Dis Intell* 2011;35(3):237–243.

Keywords: antibiotic resistance, *Staphylococcus aureus*, nosocomial

Introduction

Staphylococcus aureus is a major pathogen both in the hospital environment and the wider community. It causes a wide variety of infections in man that are associated with considerable morbidity and significant mortality. Manifestations of *S. aureus* infection range from skin and soft tissue infections such as impetigo and furunculosis, to invasive infections such as osteomyelitis, necrotising pneumonia and infective endocarditis. Invasive infections are frequently associated with life-threatening bacteraemia infections. A study of 1,865 cases of *S. aureus* bacteraemia by the Australia New Zealand Cooperative on Staphylococcal Sepsis (ANZCOSS) has shown that all-cause 30-day mortality for *S. aureus* bacteraemia was 20.6%.[1] In Australia, as in most of the world, antimicrobial resistance in *S. aureus* is a major impediment to effective treatment. A subsequent ANZCOSS study of 3,430 bacteraemia cases showed that 30-day mortality varied significantly for isolates with different susceptibility patterns, with mortality increasing as resistance to the number of antimicrobials increased: mortality for methicillin susceptible *S. aureus* (MSSA) was 16.5%, for non-multi-resistant methicillin resistant *S. aureus* (MRSA) 19.4%, for ST22-IV-like MRSA (typically resistant to one or two non-β-lactam antimicrobials) 24.4% and for multi-resistant ST239-III-like MRSA 31.7%.[2]

Strategies exist to combat MRSA causing healthcare associated (HA) infections such as staff and patient screening, contact precautions, patient isolation and decolonisation of positive patients.[3] Although infection control strategies are expensive, the cost per MRSA infection is often more expensive: estimated to be €2, 730 in one Spanish hospital[4] and US$9,275 in a French intensive care unit (ICU).[5] Another effective option available to hospitals is to restrict the use of antimicrobials. A 70% reduction in cephalosporin usage resulted in a 30% reduction in MRSA cases in an Italian ICU despite being offset by increased fluoroquinolone use.[6] The United States of America successfully reduced the HA-MRSA infection rate from 1.4 to 0.6 episodes per 1,000 patient days after fluoroquinolone use was reduced by 34%.[7] An Australian cardiac surgical unit reported no cases of HA-MRSA surgical site infection (SSI) after changing antibiotic prophylaxis protocols from cefazolin to vancomycin and rifampicin. Prior to the intervention more than 50% of the SSIs in the unit were MRSA. The estimated cost saving was AUD$576,655 over the following 12 months based on the reduction of all SSIs.[8] Limited success in reducing MRSA transmission has been achieved through enhanced hand hygiene.[9,10] The Australian Group

for Antimicrobial Resistance (AGAR) has performed antimicrobial resistance period-prevalence surveys in Australia since 1986.[11] Presently, 30 laboratories from all states and mainland territories of Australia contribute to AGAR surveys. Hospital inpatient surveys have been conducted biennially since 2005, alternating with biennial community surveys.[12] The findings of the 2009 AGAR hospital inpatients survey are presented here and results compared to the two previous hospital inpatients surveys.

Methods

Thirty laboratories from all 6 states, the Australian Capital Territory and the Northern Territory participated in the *S. aureus* AGAR survey. From 1 July to 30 November 2009, each laboratory collected up to 100 consecutive *S. aureus* isolates from hospital inpatients (hospital stay > 48 hours at the time of specimen collection). Only 1 isolate per patient was tested. Each *S. aureus* isolate was judged to come from a potentially infected site; specimens received for the purpose of gathering surveillance data were excluded. Hospital laboratories collected only from one institution. The four private laboratories collected from any institution they serviced.

Species identification

S. aureus was identified by morphology and positive results of at least two of the following tests: slide coagulase test, tube coagulase test, appropriate growth on chromogenic agar and demonstration of deoxyribonuclease production. Additional tests such as fermentation of mannitol, growth on mannitol-salt agar or polymerase chain reaction for the presence of the *nuc* gene may have been performed for confirmation.

Susceptibility testing methodology

All isolates were tested using the Vitek2® AST-P579 card. All isolates with a penicillin minimum inhibitory concentration (MIC) of ≤ 0.125 mg/L were screened for the presence of β-lactamase using nitrocefin discs. The MIC to daptomycin was determined using Etest® strips (bioMerieux). Isolates with a daptomycin MIC > 1 mg/L were confirmed by broth microdilution. Results were interpreted for susceptibility according to Clinical Laboratory and Standards Institute breakpoints[13] except for mupirocin and fusidic acid.[14] Isolates with an MIC in the intermediate resistance category have been called resistant in this report.

Statistical analysis

The difference between proportions were tested using Chi-square test with alpha set at the 5% level and Fisher's exact test for 95% confidence limits (GraphPad® Prism Software). Relative risk and 95% confidence intervals (CI) were calculated using VassarStats (http://faculty.vassar.edu).

Results

To ensure institutional anonymity data were combined as follows: New South Wales with the Australian Capital Territory, Tasmania with Victoria, and Queensland with the Northern Territory (Table 1). There were 2,728 isolates included in the survey with the majority (75.6%) contributed by Victoria/Tasmania (26.5%), Queensland/Northern Territory (25.1%) and New South Wales/Australian Capital Territory (24.0%).

Table 1: Isolates by region

Region	Number of institutions	Total	%
NSW/ACT	8	655	24.0
Qld/NT	7	685	25.1
SA	3	282	10.3
Vic/Tas	8	723	26.5
WA	4	383	14.0
Total	30	2,728	100.0

Skin and soft tissue infection (SSTI) specimens contributed the majority (71.2%) of isolates followed by respiratory specimens (17.3%). Blood culture isolates contributed 6.1% of the total with significantly ($P < 0.0001$) more isolates causing non-invasive (91.9%) than invasive (8.1%) infections (Table 2).

The proportion of MRSA was 33.6% (95% CI 31.8%–35.4%) nationally (Table 3), with significantly different ($P < 0.0001$) proportions across Australia ranging from 27.3% (95% CI 22.2%–32.5%) in South Australia to 41.4% (95% CI 37.7%–45.2%) in New South Wales/Australian

Table 2: Source of isolates

Specimen source	n	%
Skin and soft tissue	1,942	71.2
Respiratory	473	17.3
Blood	167	6.1
Urine	93	3.4
Sterile body cavity	52	1.9
Cerebrospinal fluid	1	0.04
Total	2,728	100.0
Invasive	220	8.1
Non-invasive	2,508	91.9

Capital Territory. The proportion of non-invasive *S. aureus* that were MRSA (33.9%) was not significantly higher than for invasive isolates (30.0%) ($P = 0.241$). There were significant differences in the proportion of MRSA isolated in the 5 sources of infection ($P = 0.0002$) with MRSA isolated most commonly from urinary isolates (50.5% of the time) followed by respiratory specimens at 40.2% (Table 4).

The national proportion of MRSA in 2009 was 33.6%, which was not significantly different from the proportions identified in 2005 or 2007 (31.9% and 32.9% respectively, $P = 0.1823$) and the proportions were stable across all regions (Table 5).

Amongst the MRSA, resistance to the non-β-lactam antimicrobials was common except for fusidic acid, rifampicin, mupirocin and daptomycin where resistance was below 4% (Table 6 and Figure). Resistance was not detected for vancomycin, teicoplanin, quinupristin-dalfopristin or linezolid. Resistance levels varied between regions with New South Wales/Australian Capital Territory having the highest proportions for four of the top 5 antimicrobials for resistance. Compared with New South Wales/Australian Capital Territory, Western Australia had lower levels of resistance by 28 to 53 percentage points (PP) for erythromycin (28 PP), tetracycline (52 PP), trimethoprim-sulphamethoxazole (52 PP), ciprofloxacin (53 PP) and gentamicin (52 PP). For constitutive clindamycin resistance both South Australia and Western Australia had lower rates than the other states. Nearly half of MRSA (446/916, 48.7%) were multi-resistant (resistant to 3 or more non-β-lactams). The proportion of MRSA that

Table 3: Proportion of *Staphylococcus aureus* that were methicillin resistant, 2005 to 2009, by region and source

	All isolates			Invasive*			Non-invasive		
Region	n/N	%	95%CI	n/N	%	95%CI	n/N	%	95%CI
NSW/ACT	271/655	41.4	37.7–45.2	26/65	40.0	29.0–52.1	245/590	41.5	37.6–45.6
Qld/NT	210/685	30.7	27.3–34.2	14/49	28.6	17.9–42.4	196/636	30.8	27.4–34.5
SA	77/282	27.3	22.2–32.5	3/18	16.7	5.8–39.2	74/264	28.0	23.0–33.7
Vic/Tas	250/723	34.6	31.2–38.1	14/57	24.6	15.2–37.1	236/666	35.4	31.9–39.2
WA	108/383	28.2	23.9–32.9	9/31	29.0	16.1–46.6	99/352	28.1	23.7–33.0
Aus	916/2728	33.6	31.8–35.4	66/220	30.0	24.3–36.4	850/2508	33.9	32.1–35.87

* Blood/cerebrospinal fluid/sterile body cavity

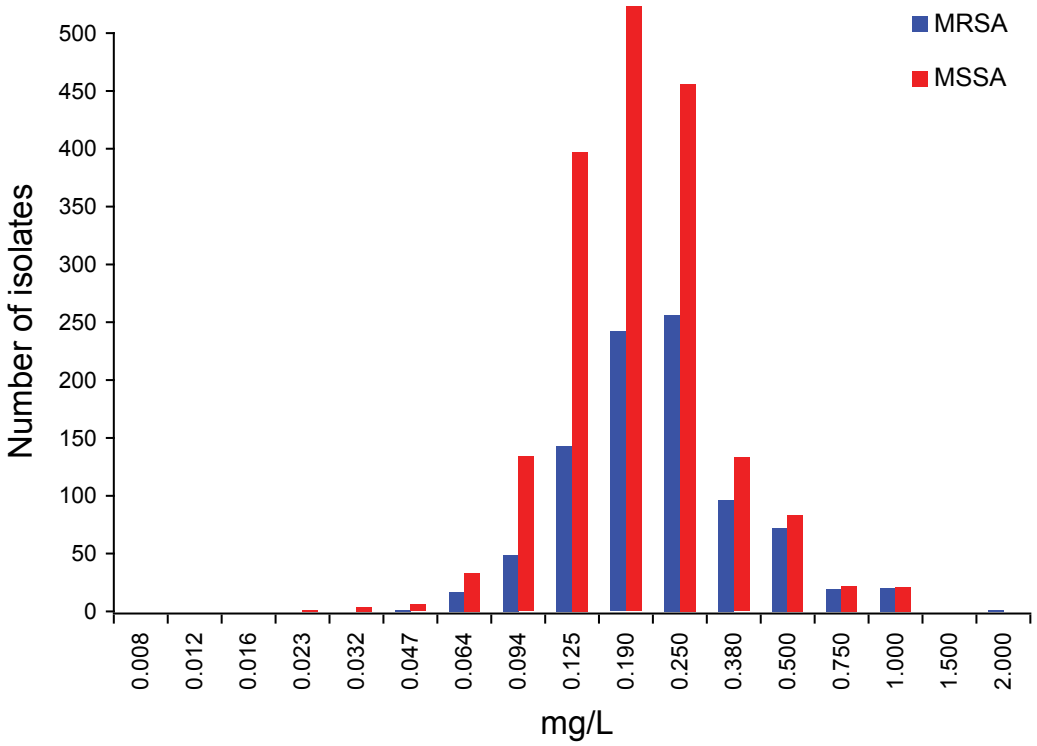
Table 4: Proportion of *Staphylococcus aureus* that were methicillin resistant, by specimen type

	All isolates		
Source of infection	n/N	%	95%CI
Skin and soft tissue	613/1,942	31.6	29.5–33.7
Respiratory	190/473	40.2	35.9–44.7
Blood/cerebrospinal fluid	57/168	33.9	27.2–41.4
Urine	47/93	50.5	40.6–60.5
Sterile body cavity	9/52	17.3	9.4–29.7

Table 5: Proportion of *Staphylococcus aureus* that were methicillin-resistant *Staphylococcus aureus*, 2005 to 2009

	Methicillin-resistant *Staphylococcus aureus*					
	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus
2005	43.4	26.7	24.7	31.6	22.5	31.9
2007	41.3	31.0	27.2	33.3	19.0	32.9
2009	41.4	30.7	27.3	34.6	28.2	33.6
X^2 for trend	0.6683	2.565	0.5669	1.419	3.452	1.779
P	0.4136	0.1093	0.4515	0.2336	0.0632	0.1823

Figure: Daptomycin minimum inhibitory concentration (susceptible MIC ≤ 1 mg/L)



were multi-resistant ranged from 11.1% in Western Australia to 59.4% in New South Wales/Australian Capital Territory (data not shown).

Some significant improvements in resistance to the non-β-lactams have occurred since the first AGAR hospital inpatients survey in 2005. Nationally, resistance has decreased to erythromycin (80.0% in 2005 to 70.9% in 2009, $P < 0.0001$), clindamycin (44.2% to 35.0%, $P < 0.0001$), tetracycline (59.4% to 45.1%, $P < 0.0001$), trimethoprim-sulphamethoxazole (60.3% to 41.6%, $P < 0.0001$), ciprofloxacin (76.8% to 71.2%, $P = 0.0052$), gentamicin (60.6% to 43.7%, $P < 0.0001$) and rifampicin (5.2% to 3.3%, $P = 0.048$) while resistance has remained stable to fusidic acid (4.3% to 3.1%, $P = 0.1621$) and high-level mupirocin (0.6% to 0.7%, $P = 0.979$). The national decreases in resistance may primarily be the result of significant regional decreases in New South Wales/Australian Capital Territory and Victoria/Tasmania particularly for erythromycin, tetracycline, trimethoprim-

Table 6: MSRA: Number and proportion resistant to the non-β-lactam antimicrobials, Australia, by region

	NSW/ACT (n=271)		Qld/NT (n=210)		SA n=77)		Vic/Tas (n=250)		WA (n=108)		Aus (n=916)		Difference across regions	
Drug	n	%	n	%	n	%	n	%	n	%	n	%	X^2	*P*
Erythromycin	212	78.2	141	67.1	56	72.7	186	74.4	54	50.0	649	70.9	32.93	<0.0001
Clindamycin*	138	50.9	79	37.6	9	11.7	84	33.6	11	10.2	321	35.0	78.63	<0.0001
Tetracycline	150	55.4	105	50.0	36	46.8	119	47.6	3	2.8	413	45.1	92.39	<0.0001
Trimethoprim-sulphamethoxazole	147	54.2	90	42.9	28	36.4	114	45.6	2	1.9	381	41.6	90.72	<0.0001
Ciprofloxacin	225	83.0	127	60.5	53	68.8	215	86.0	32	29.6	652	71.2	148.1	<0.0001
Gentamicin	150	55.4	103	49.1	33	42.9	111	44.4	3	2.8	400	43.7	90.99	<0.0001
Fusidic acid	4	1.5	11	5.2	3	3.9	7	2.8	3	2.8	28	3.1	5.924	0.2049
Rifampicin	2	0.7	16	7.6	0	0.0	10	4.0	2	1.9	30	3.3	19.21	0.0007
Mupirocin†	2	0.7	2	1.0	0	0.0	1	0.4	1	0.9	6	0.7	0.6890	0.9527

* Constitutive resistance

† High-level resistance

Table 8: MSSA: Number and proportion resistant to penicillin and the non-β-lactam antimicrobials, Australian, by region

Drug	NSW/ACT (n=384)		Qld/NT (n=475)		SA (n=205)		Vic/Tas (n=473)		WA (n=275)		Aus (n=1812)		Difference across regions	
	n	%	n	%	n	%	n	%	n	%	n	%	X^2	*P*
Penicillin	330	85.9	411	86.5	180	87.8	421	89.0	230	83.6	1,572	86.8	4.856	0.3024
Erythromycin	50	13.0	68	14.3	18	8.8	52	11.0	30	10.9	218	12.0	5.553	0.2351
Clindamycin*	12	3.1	5	1.1	2	1.0	5	1.1	1	0.4	25	1.4	11.66	0.0200
Tetracycline	22	5.7	4	0.8	8	3.9	8	1.7	9	3.3	51	2.8	21.96	0.0002
Trimethoprim-sulphamethoxazole	14	3.6	5	1.1	5	2.4	11	2.3	0	0.0	35	1.9	13.98	0.0074
Ciprofloxacin	12	3.1	4	0.8	4	2.0	10	2.1	10	3.6	40	2.2	8.282	0.0818
Gentamicin	10	2.6	2	0.4	1	0.5	9	1.9	0	0.0	22	1.2	14.83	0.0051
Fusidic acid	11	2.9	19	4.0	9	4.4	16	3.4	12	4.4	67	3.7	1.621	0.8050
Rifampicin	1	0.3	1	0.2	0	0.0	1	0.2	0	0.0	3	0.2	1.123	0.8906
Mupirocin†	0	0.0	7	1.5	0	0.0	3	0.6	1	0.4	11	0.6	9.763	0.0446

* Constitutive resistance

† High-level resistance

sulphamethoxazole and gentamicin. Significant falls in rifampicin resistance occurred in Queensland/ Northern Territory and South Australia.

In 2009, as in past AGAR hospital isolates surveys, increasing age was a risk factor for methicillin resistance (Table 7). Of 2,728 *S. aureus* isolates, 916 were MSRA (34%). Inpatients 41 years and older were 1.6 times more likely (RR 1.6, 95% CI 1.4–1.9) to have an MRSA not MSSA infection compared with younger patients.

Resistance to the non-β-lactams amongst methicillin susceptible *S. aureus* (MSSA) was rare apart from erythromycin (12.0% nationally) (Table 8). Resistance was not detected for vancomycin, teicoplanin, quinupristin-dalfopristin, daptomycin or linezolid. Multi-resistance was uncommon in MSSA (31/1812, 1.7%).

Nationally, there were no significant changes in the trends for resistance for MSSA in any of the antimicrobials tested. In Victoria/Tasmania, there was a significant increase in resistance in penicillin by 7 PP between 2005 and 2009 (82.0% and 89.0% respectively, $P = 0.0022$). Changes occurred in resistance patterns for tetracycline with a 3 PP decrease in resistance from 2005 and 2009 in Victoria/ Tasmania (5.1% and 1.7% respectively, $P = 0.0051$) and an increase by 3 PP for tetracycline resistance in Western Australia (0.0% to 3.3% respectively, $P = 0.0045$).

Table 7: Age by methicillin susceptibility of *Staphylococcus aureus*

Age (years)	MRSA		Total tested
	n	%	
0–1	18	2.0	184
2–16	20	2.2	95
17–40	108	11.8	360
41–61	214	23.4	621
62–101	556	60.7	1,468
Total	916	100.0	2,728

Discussion

This survey demonstrates that MRSA remains a significant burden in Australian hospitals. However, the trend data generated may have some limitations. The mix of laboratories has altered over time with one fewer New South Wales and one fewer South Australian laboratory participating in the 2009 survey compared with the 2005 survey. However, an analysis of results of the 28 laboratories that participated in all surveys gave similar results with no changes to the statistical significance of the antimicrobial resistance trends in MRSA or MSSA either regionally or nationally.

For 2009, the national proportion of *S. aureus* that were MRSA was 33.6%, which was similar to the proportion in 2005 (31.9%, $P = 0.19$) and 2007 (32.9%, $P = 0.18$). Yet, differences between regions were significant with New South Wales/Australian Capital Territory having a higher proportion than other regions. Approximately a third of blood/CSF and skin and soft tissue *S. aureus* infections were methicillin resistant. The proportion for respiratory and urine specimens was higher with half of all

S. aureus isolated from urines having methicillin resistance. The overall proportion of MRSA in invasive (mainly bacteraemia) isolates was similar to that of non-invasive isolates (30.0% and 33.9% respectively, $P = 0.2724$). The high proportion of MRSA in invasive isolates is of concern as MRSA bacteraemia is associated with increased mortality compared with MSSA.[15,16] Direct comparison with prevalence in other countries is difficult due to methodological differences. For example, the European surveillance system reports the proportion of MRSA in bacteraemia isolates in both inpatients and outpatients. Amongst 198 continuous contributing laboratories in 22 European countries the proportion of MRSA compared with MSSA significantly decreased from 2002 to 2009. Targeted MRSA public health initiatives in several countries was cited as a possible cause of this decline. The overall proportion of MRSA in Europe in 2009 varied markedly from less than 1% in Iceland and Norway to 58% in Malta.[17] The Netherlands and the Scandinavian countries have been consistently able to keep MRSA at very low levels in their hospitals over long periods.

Amongst the MRSA in this study, more that 70% were resistant to erythromycin and ciprofloxacin, and more than 40% were resistant to tetracycline, trimethoprim-sulphamethoxazole and gentamicin. Regional differences were again common and this was due to the different MRSA clones circulating in Australia. In the 1980s and 1990s multi-resistant strains (later typed as ST239-III or Aus2/3 EMRSA) became epidemic in the eastern Australian states with some spread to hospitals in South Australia, the Northern Territory and Tasmania.[18]

In 1982, a state-wide MRSA policy was introduced in Western Australia with the aim of preventing these strains from becoming established in Western Australia hospitals. As a result, MRSA with tetracycline, trimethoprim-sulphamethoxazole and gentamicin resistance (characteristic of ST239-III) are rare in Western Australia—less than 3% in this survey. Erythromycin and ciprofloxacin resistance was more widespread in this survey with at least 30% of MRSA with this profile in any region. Erythromycin and ciprofloxacin resistance is common in ST239-III strains but is also characteristic of ST22-IV (EMRSA-15). ST22-IV is a common healthcare-associated MRSA (HA-MRSA) in Australia and is found in all regions.[19,20] Resistance was not detected for vancomycin, teicoplanin, quinupristin-dalfopristin or linezolid. Compared with previous AGAR hospital inpatient surveys in 2005 and 2007, the proportion of MRSA resistant to erythromycin, clindamycin, tetracycline, trimethoprim-sulphamethoxazole, ciprofloxacin, gentamicin and rifampicin has decreased nationally, lead by significant decreases in New South Wales/Australian Capital Territory and Victoria/Tasmania, whilst the proportion of *S. aureus* that are MRSA has remained stable in all regions and nationally. This finding suggests that non-multi-resistant community strains of MRSA are becoming more common in Australian hospitals at the expense of the long-established multi-resistant ST239-III.

Given reports of outbreaks of CA-MRSA in Australian hospitals are thought to be rare,[21,22] it is likely that many infections in hospital inpatients are caused by the patients' own colonising strains acquired prior to admission. It appears that current infection control procedures are successful in preventing their spread. Although at present in Australia there is no evidence of increasing resistance in local CA-MRSA,[23] data from the United States of America show that previously non-multi-resistant CA-MRSA can acquire multiple resistances over time.[24] With community clones such as the Queensland clone (ST93-IV), South Western Pacific (ST30-IV) and WA 1 (ST1-IV) well established in Australia,[12,25] it is important to monitor susceptibility patterns to MRSA over time as this information will guide therapeutic practices. In addition to this threat, virulent multi-resistant overseas CA-MRSA have recently been isolated in Australia[26] and only time will tell if these difficult to treat clones become established in the Australian community or healthcare institutions.

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