

# AUSTRALIAN *STAPHYLOCOCCUS AUREUS* SEPSIS OUTCOME PROGRAMME ANNUAL REPORT, 2013

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## Abstract

From 1 January to 31 December 2013, around Australia 26 institutions around Australia participated in the Australian Staphylococcal Sepsis Outcome Programme (ASSOP). The aim of ASSOP 2013 was to determine the proportion of *Staphylococcus aureus* bacteraemia (SAB) isolates in Australia that are antimicrobial resistant, (with particular emphasis on susceptibility to methicillin) and to characterise the molecular epidemiology of the isolates. Overall 19.1% of the 2,010 SAB episodes were methicillin resistant, which is significantly higher than that reported in most European countries. Although the SAB 30-day all cause mortality appears to be decreasing in Australia, methicillin-resistant SAB associated mortality remains high (20.1%) and was significantly higher than methicillin-sensitive SAB associated mortality (13%) ( $P < 0.0001$ ). With the exception of the  $\beta$ -lactams and erythromycin, antimicrobial resistance in methicillin sensitive *S. aureus* remains rare. However, in addition to the  $\beta$ -lactams, approximately 50% of methicillin-resistant *S. aureus* (MRSA) were resistant to erythromycin and ciprofloxacin and approximately 20% were resistant to cotrimoxazole, tetracycline and gentamicin. Linezolid, daptomycin and teicoplanin resistance was detected in a small number of *S. aureus* isolates. Resistance to vancomycin was not detected. Resistance was largely attributable to 2 healthcare associated MRSA clones; ST22-IV [2B] (EMRSA-15) and ST239-III [3A] (Aus-2/3 EMRSA). ST22-IV [2B] (EMRSA-15) has now become the predominant healthcare associated clone in Australia. Approximately 60% of methicillin-resistant SAB were due to community associated clones. Although polyclonal, almost 50% of community associated clones were characterised as ST93-IV [2B] (Queensland CA-MRSA) and ST1-IV [2B] (WA1). CA-MRSA, in particular the ST45-V [5C2&5] (WA84) clone, has acquired multiple antimicrobial resistance determinants including ciprofloxacin, erythromycin, clindamycin, gentamicin and tetracycline. As CA-MRSA is well established in the Australian community, it is important antimicrobial resistance patterns in community and healthcare associated SAB is monitored as this information will guide therapeutic practices in treating *S. aureus* sepsis. *Commun Dis Intell* 2014;38(4):E309–E319.

**Keywords:** antimicrobial resistance surveillance; *Staphylococcus aureus*, methicillin sensitive, methicillin resistant, bacteraemia

## Introduction

Globally, *Staphylococcus aureus* is one of the most frequent causes of hospital-acquired and community-acquired blood stream infections.<sup>1</sup> Although there are a wide variety of manifestations of serious invasive infection caused by *S. aureus*, the organism can be detected in blood cultures in the majority of cases. Therefore, *S. aureus* bacteraemia (SAB) is considered a very useful marker for serious invasive infection.<sup>2</sup>

Although prolonged antimicrobial therapy and prompt source control are used to treat SAB,<sup>3</sup> mortality ranges from as low as 2.5% to as high as 40%.<sup>4–6</sup> Mortality rates however, are known to vary significantly with patient age, clinical manifestation, co-morbidities and methicillin resistance.<sup>7,8</sup> A recent prospective study of SAB conducted in 27 laboratories in Australia and New Zealand found a 30-day all cause mortality of 20.6%.<sup>9</sup> On univariate analysis, increased mortality was significantly associated with older age, European ethnicity, methicillin resistance, infections not originating from a medical device, sepsis syndrome, pneumonia/empyema and treatment with a glycopeptide or other non- $\beta$ -lactam antibiotic.

The Australian Group on Antimicrobial Resistance (AGAR), a network of laboratories located across Australia, commenced surveillance of antimicrobial resistance in *S. aureus* in 1986.<sup>10</sup> The use of an active surveillance strategy with standard methodology for collection and examination of clinically significant isolates has produced longitudinal data accurately reflecting the changing prevalence of antimicrobial resistance in healthcare-acquired and community-acquired *S. aureus* infections.<sup>11,12</sup> In 2013, AGAR commenced the Australian Staphylococcal Sepsis Outcome Programme (ASSOP). The primary objective of ASSOP 2013 was to determine the proportion of SAB isolates demonstrating antimicrobial resistance with particular emphasis on:

1. assessing susceptibility to methicillin;
2. molecular epidemiology of methicillin susceptible *S. aureus* (MSSA) and methicillin resistant *S. aureus* (MRSA).

## Methods

### Participants

Twenty-six laboratories from all 8 Australian states and territories participated in the program.

### Collection period

From 1 January to 31 December 2013, the 26 laboratories collected all *S. aureus* isolated from blood cultures. *S. aureus* with the same antimicrobial susceptibility profiles isolated from a patient's blood culture within 14 days of the 1st positive culture were excluded. A new *S. aureus* sepsis episode in the same patient was recorded if it was confirmed by a further culture of blood taken more than 14 days after the initial positive culture. Data were collected on age, sex, date of admission and discharge (if admitted), and mortality at 30 days from date of the 1st positive blood culture. To avoid interpretive bias, no attempt was made to assign attributable mortality. Each episode of bacteraemia was designated healthcare onset if the 1st positive blood culture(s) in an episode were collected more than 48 hours after admission.

### Laboratory testing

Participating laboratories performed antimicrobial susceptibility testing using the Vitek2<sup>®</sup> (bioMérieux, France) or the Phoenix<sup>™</sup> (BD, USA) automated microbiology systems according to the manufacturer's instructions. *S. aureus* was identified by morphology and positive results of at least one of the following tests: Vitek MS<sup>®</sup> (bioMérieux, France), matrix-assisted laser desorption ionization biotyper (Bruker Daltonics, Germany), slide coagulase, tube coagulase, 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 (PCR) for the presence of the *nuc* gene may have been performed for confirmation.

Minimum inhibitory concentration (MIC) data and isolates were referred to the Australian Collaborating Centre for *Enterococcus* and *Staphylococcus* Species (ACCESS) Typing and Research. Clinical and Laboratory Standards Institute (CLSI)<sup>13</sup> and European Committee on Antimicrobial Susceptibility Testing (EUCAST)<sup>14</sup> breakpoints were utilised for interpretation. Isolates with a resistant or an intermediate category were classified as non-susceptible. High level mupirocin resistance was determined using a mupirocin 200 µg disk according to CLSI guidelines on all isolates with a mupirocin MIC > 8 by Vitek2<sup>®</sup> or

> 256 by Phoenix<sup>™</sup>.<sup>13</sup> Multi-resistance was defined as resistance to three or more of the following non-β-lactam antimicrobials: vancomycin, teicoplanin, erythromycin, clindamycin, tetracycline, ciprofloxacin, gentamicin, co-trimoxazole, fusidic acid, rifampicin, high level mupirocin, linezolid and daptomycin.

Electrophoresis of chromosomal DNA was performed as previously described, on all MRSA using contour-clamped homogeneous electric field DR III system (Bio-Rad Laboratories Pty Ltd, USA).<sup>15</sup> Chromosomal patterns were examined visually, scanned with Quantity One software (Bio-Rad Laboratories Pty Ltd, USA), and digitally analysed using FPQuest (Applied Maths NV, Belgium). Multilocus sequence typing (MLST) was performed on all unique pulsed-field types as previously described.<sup>16</sup> The sequences were submitted to Multi Locus Sequence Typing via the Internet (<http://www.mlst.net>) where an allelic profile was generated and a sequence type (ST) assigned.

SCC*mec* typing was performed on all MRSA with a unique pulsed-field pattern, using the Clondiag *S. aureus* Genotyping Array Hybridisation Kit (Alere, USA) as previously described.<sup>17</sup>

Detection of Pantone-Valentine leucocidin determinants (PVL) and *mecA* was performed by PCR on all MRSA as previously described.<sup>18, 19</sup>

A chi-square test for comparison of 2 proportions was performed and 95% confidence intervals (95%CI) were determined using MedCalc for Windows, version 12.7 (Medcalc Software, Ostend Belgium).

Approval to conduct the prospective data collection was given by the research ethics committee associated with each participating laboratory.

## Results

From 1 January to 31 December 2013, 2,010 unique episodes of *S. aureus* bacteraemia were identified. A significant difference ( $P < 0.0001$ ) was seen in patient sex with 65.4% (1,314) being male (95% CI 63.3%–67.5%). The average age of patients was 58 years ranging from 0–102 years with a median age of 62 years. The place of onset was recorded for 1,960 of the 2,010 episodes, of which 71.6% (1,404) were hospital onset (95% CI 69.6%–73.6%). The all cause mortality at 30-days was 14.4% (95% CI 12.8%–16.2%). Methicillin resistant SAB mortality was 20.1% (95% CI 15.9%–24.7%, 67/334), which was significantly higher than methicillin susceptible SAB mortality (13%, 95% CI 11.3%–14.9%, 179/1378,  $P < 0.0001$ ).

### Methicillin susceptible *Staphylococcus aureus* antimicrobial susceptibility

Overall 80.9% (1,626) of the 2,010 isolates were methicillin sensitive of which 79.6% (1,294) were penicillin resistant (MIC > 0.12 mg/L). However, as  $\beta$ -lactamase was detected in 69 phenotypically penicillin susceptible isolates, 83.8% of MSSA were considered penicillin resistant. Apart from erythromycin non-susceptibility (11.0%) resistance to the non- $\beta$ -lactam antimicrobials among MSSA was rare, ranging from 0% to 3.9% (Table 1). A single isolate was linezolid resistant (MIC > 8 mg/L), 5 isolates were non-susceptible to daptomycin (MIC 2–4 mg/L), and using the EUCAST resistant breakpoint of > 2 mg/L 1 isolate was teicoplanin resistant (MIC = 4 mg/L). Vancomycin non-susceptibility was not detected. Twenty (1.2%) of the 1,626 isolates had high level mupirocin resistance of which 16 isolates were referred from Queensland. Inducible resistance to clindamycin was determined by the Vitek2<sup>®</sup> susceptibility system. Of the 1,478 isolates tested, 8.6% (127) were erythromycin non-susceptible/clindamycin intermediate/susceptible (CLSI and EUCAST breakpoints) of which 89.8% (114) were

classified as having inducible clindamycin resistance. Multi-resistance was uncommon in MSSA (1.7%, 28/1626).

There were no significant differences in interpretation for any drug when CLSI or EUCAST non susceptibility breakpoints were utilised ( $P > 0.05$ ).

### Methicillin-resistant *Staphylococcus aureus* antimicrobial susceptibility

The proportion of *S. aureus* that were MRSA was 19.1% (95%CI 17.5%–21.0%). Of the 384 MRSA identified, 97.9% were either ceftioxin screen positive by Vitek2<sup>®</sup> (363/384) or had a ceftioxin MIC > 8 by Phoenix<sup>™</sup> (13/384). Eight isolates that were either ceftioxin screen negative (4/8), or had a ceftioxin MIC  $\leq$  2 mg/L (4/8), were oxacillin resistant (MIC > 2 mg/L) and *mecA* positive by PCR. Although two of the 384 isolates were phenotypically penicillin susceptible, both isolates were  $\beta$ -lactamase positive. Among the MRSA isolates, non-susceptibility to non- $\beta$ -lactam antimicrobials was common except for rifampicin (MIC 2– $\geq$  32 mg/L), fusidic acid (MIC 2 –  $\geq$  32 mg/L), nitrofurantoin (MIC  $\geq$  64 mg/L)

**Table 1: Number and proportion of methicillin sensitive *Staphylococcus aureus* isolates non-susceptible to penicillin and the non- $\beta$ -lactam antimicrobials, Australia, 2013**

Antimicrobial	Tested	Breakpoint (mg/L)	Non-susceptible	
			n	%
Penicillin	1,626	>0.12*	1,342	82.5
Vancomycin	1,626	>2*	0	0.0
Teicoplanin	1,626	>8†	0	0.0
		>2‡	1	<0.1
Rifampicin	1,587	>1†	0	0.0
Fusidic acid	1,480	>1‡	61	3.9
Gentamicin	1,626	>4†	15	0.9
		>1‡	16	1.1
Erythromycin	1,626	>2†	178	11.0
		>1‡	179	11.0
Clindamycin	1,626	>0.5†	39	2.4
		>0.25‡	36	2.4
Tetracycline	1,553	>4†	31	2.0
		>1‡	35	2.3
Co-trimoxazole	1,626	>2/38*	33	2.0
Ciprofloxacin	1,626	>1*	46	2.8
Nitrofurantoin	1,550	>32†	30	1.9
Linezolid	1,626	>4*	1	<0.1
Daptomycin	1,552	>1*	4	0.3

\* Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) non-susceptible breakpoint.

† CLSI non-susceptible breakpoint.

‡ EUCAST non-susceptible breakpoint.

and daptomycin (MIC 2–4 mg/L) where resistance was below 3% nationally (Table 2). Resistance was not detected for vancomycin, teicoplanin or linezolid. Of the 384 MRSA isolates, 1.8% (7/384) had high level mupirocin resistance. Of the 327 isolates tested by Vitek2®, 27.8% (91) were erythromycin non-susceptible/clindamycin intermediate/susceptible (CLSI and EUCAST breakpoints) of which 89.0% (81) were classified as having inducible clindamycin resistance. Multi-resistance was common in MRSA (25.8%, 99/384).

There were no significant differences in interpretation for any drug when CLSI or EUCAST non-susceptibility breakpoints were utilised ( $P > 0.05$ ).

### Methicillin-resistant *Staphylococcus aureus* molecular epidemiology

Of the 384 MRSA identified, 368 were referred to ACCESS Typing and Research for strain characterisation. Based on molecular typing, 41.0% (151) and 59.0% (217) of isolates were classified as healthcare-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) clones respectively (Table 3).

### Healthcare-associated methicillin-resistant *Staphylococcus aureus*

For the 151 HA-MRSA strains, 50.3% (76) were epidemiologically classified as hospital onset (blood culture collected more than 48 hours after admission) and 47.7% (72) were classified as community onset. The date of hospital admission was not available for 3 patients. Three HA-MRSA clones were identified: 88 isolates of ST22-IV [2B] (EMRSA-15) (23.9% of MRSA and 4.4% of *S. aureus*); 59 isolates of ST239-III [3A] (16.0% and 2.9%) and 4 isolates of ST5-II [2A] (USA100/New York Japan MRSA).

ST22-IV [2B] (EMRSA-15) was the dominant HA-MRSA clone in Australia accounting for 58.3% of HA-MRSA, ranging from 42.9% in the Australian Capital Territory to 100% in Tasmania (Table 4). ST22-IV [2B] was typically PVL negative and using CLSI breakpoints, while 100% and 67% were ciprofloxacin and erythromycin resistant respectively.

**Table 2: Number and proportion of methicillin-resistant *Staphylococcus aureus* isolates non-susceptible to penicillin and the non- $\beta$ -lactam antimicrobials, Australia, 2013**

Antimicrobial	Tested	Breakpoint (mg/L)	Non-susceptible	
			n	%
Penicillin	384	>0.12*	381	99.2
Vancomycin	384	>2*	0	0.0
Teicoplanin	384	>8†	0	0.0
		>2‡	0	0.0
Rifampicin	381	>1†	7	1.8
Fusidic acid	327	>1‡	9	2.3
Gentamicin	384	>4†	68	17.7
		>1‡	52	16.0
Erythromycin	384	>2†	192	49.9
		>1‡	192	49.9
Clindamycin	384	>0.5†	84	21.9
		>0.25‡	67	20.5
Tetracycline	363	>4†	63	17.4
		>1‡	79	21.8
Co-trimoxazole	384	>2/38*	71	18.5
Ciprofloxacin	384	>1*	195	50.8
Nitrofurantoin	378	>32†	11	2.9
Linezolid	384	>4*	0	0.0
Daptomycin	362	>1*	4	1.1

\* Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) non-susceptible breakpoint.

† CLSI non-susceptible breakpoint.

‡ EUCAST non-susceptible breakpoint.

**Table 3: Proportion of healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus*, Australia, 2013, by clone, healthcare and community onset, and Panton-Valentine leucocidin carriage**

Strain	Total		Onset						PVL positive	
	n	%*	n	%†	n	%†	n	%†	n	%†
<b>Healthcare-associated MRSA</b>										
ST22-IV [2B] (EMRSA-15)	88	23.9	38	43.2	49	55.7	1	1.1	0	0.0
ST239-III [3A] (Aus-2/3)	59	16.0	35	59.3	22	37.3	2	3.4	0	0.0
ST5-II [2A] (USA100)	4	1.1	3	75.0	1	25.0	0	0.0	0	0.0
Sub-total	151	41.0	76	50.3	72	47.7	3	2.0	0	0.0
<b>Community-associated MRSA</b>										
ST93-IV [2B] (Queensland)	50	13.6	10	20.0	40	80.0	0	0.0	48	96.0
ST1-IV [2B] (WA1)	45	12.2	17	37.8	28	62.2	0	0.0	4	8.9
ST5-IV [2B] (WA3)	25	6.8	9	36.0	16	64.0	0	0.0	0	0.0
ST78-IV [2B] (WA2)	20	5.4	6	30.0	14	70.0	0	0.0	0	0.0
ST30-IV [2B] (SWP)	18	4.9	7	38.9	11	61.1	0	0.0	14	77.8
ST45-V [5C2&5] (WA84)	17	4.6	4	23.5	13	76.5	0	0.0	0	0.0
ST8-IV [2B] (USA300)	7	1.9	2	28.6	3	42.9	2	28.6	6	85.7
ST73-IV [2B] (WA65)	6	1.6	1	16.7	5	83.3	0	0.0	0	0.0
ST835-IV [2B] (WA48)	4	1.1	1	25.0	3	75.0	0	0.0	0	0.0
ST72-IV [2B] (Korean)	3	0.8	1	33.3	2	66.7	0	0.0	0	0.0
ST953-IV [2B] (WA54)	3	0.8	0	0.0	3	100.0	0	0.0	0	0.0
ST5-IV [2B] (WA121)	2	0.5	0	0.0	2	100.0	0	0.0	2	100.0
ST923-IV [2B] (WA62)	2	0.5	0	0.0	2	100.0	0	0.0	2	100.0
ST5-IV [2B] (WA71)	2	0.5	2	100.0	0	0.0	0	0.0	1	50.0
ST45-V [5C2] (WA4)	1	0.3	1	100.0	0	0.0	0	0.0	0	0.0
ST45-IV [2B] (WA23)	1	0.3	0	0.0	1	100.0	0	0.0	0	0.0
ST6-IV [2B] (WA66)	1	0.3	0	0.0	1	100.0	0	0.0	0	0.0
ST5-V [5C2] (WA90)	1	0.3	0	0.0	1	100.0	0	0.0	0	0.0
ST5-IV [2B] (WA96)	1	0.3	0	0.0	1	100.0	0	0.0	0	0.0
ST8-IV [2B] (WA101)	1	0.3	0	0.0	1	100.0	0	0.0	0	0.0
STnovel-IV [2B] (WA114)	1	0.3	0	0.0	1	100.0	0	0.0	0	0.0
ST5-V [5C2] (WA109)	1	0.3	0	0.0	1	100.0	0	0.0	0	0.0
ST612-IV [2B] (WA20)	1	0.3	0	0.0	1	100.0	0	0.0	0	0.0
ST1-V [5C2]	1	0.3	0	0.0	1	100.0	0	0.0	0	0.0
ST45-V [5C2]	1	0.3	0	0.0	1	100.0	0	0.0	0	0.0
ST59-V [5C2]	1	0.3	0	0.0	1	100.0	0	0.0	0	0.0
ST5-V [5C2]	1	0.3	1	100.0	0	0.0	0	0.0	0	0.0
Sub-total	217	59.0	62	28.6	153	70.5	2	0.9	77	35.5
Total	368	100.0	138	37.5	225	61.1	5	1.4	77	20.9

PVL Panton-Valentine leucocidin.

MRSA Methicillin-resistant *Staphylococcus aureus*.

\* Percentage of all MRSA.

† Percentage of the strain.

ST239-III [3A] (Aus-2/3 EMRSA) accounted for 39.1% of HA-MRSA ranging from 0% in Tasmania to 100% in the Northern Territory (Table 4). PVL negative ST239-III [3A] (Aus-2/3 EMRSA) were typically resistant to erythromycin (100%), co-trimoxazole (100%), ciprofloxacin (97%), gentamicin (97%), tetracycline (84%) and clindamycin (81%).

#### *Community-associated-methicillin-resistant Staphylococcus aureus*

For the 217 CA-MRSA strains, 28.6% (62) of episodes were epidemiologically classified as hospital onset and 70.5% (153) were classified as community onset. The date of hospital admission was not available for 2 patients. Twenty-seven different CA-MRSA clones were identified by pulsed-field gel electrophoresis corresponding to 19 MLST/SCC*mec* clones (Table 3). Overall, 80.7% of CA-MRSA were classified into 6 clones, each having more than 10 isolates (Table 5).

ST93-IV [2B] (Queensland CA-MRSA) accounted for 23.0% of CA-MRSA, ranging from 15.4% in Western Australia to 100% in Tasmania (Table 5). PVL positive ST93-IV [2B] (Queensland CA-MRSA) was typically resistant to the  $\beta$ -lactams only (77.1%, 37/48) or additionally resistant to erythromycin (10.4%, 5/48). Four isolates were resistant to erythromycin and clindamycin. A single isolate was non-susceptible to ciprofloxacin with an MIC of 2 mg/L. One isolate exhibited high-level mupirocin resistance.

ST1-IV [2B] (WA1) accounted for 20.7% of CA-MRSA, ranging from 0% in the Australian Capital Territory and Tasmania to 26.9% in Western Australia (Table 5). Typically PVL negative, 66.7% of isolates were resistant to the  $\beta$ -lactams only (30/45) or additionally resistant to erythromycin (8.9%, 4/45) or fusidic acid (6.7%, 3/45) or both (2.2%, 1/45). Four isolates were non-susceptible to ciprofloxacin and additionally resistant to erythromycin and clindamycin (1); erythromycin, gentamicin, daptomycin and tetracycline (1); erythromycin, fusidic acid, and co-trimoxazole (1); or erythromycin, clindamycin and nitrofurantoin (1). Single isolates were non-susceptible to nitrofurantoin; or resistant to gentamicin; gentamicin, erythromycin and high-level mupirocin; erythromycin or fusidic acid; and tetracycline.

ST5-IV [2B] (WA3) accounted for 11.5% of CA-MRSA ranging from 0% in the Australian Capital Territory and Tasmania to 17.9% in South Australia (Table 5). PVL negative ST5-IV [2B] (WA3) was typically resistant to the  $\beta$ -lactams only (44%, 11/25) or additionally resistant to erythromycin (20%, 5/25). Three isolates were non-susceptible

to ciprofloxacin including one isolate additionally resistant to erythromycin and clindamycin. Two isolates exhibited high-level mupirocin resistance. Two isolates were resistant to erythromycin and clindamycin. Single isolates were resistant to erythromycin and co-trimoxazole, or rifampicin.

ST78-IV [2B] (WA2), PVL negative, accounted for 9.2% of CA-MRSA and was isolated predominately in Western Australia (Table 5). Isolates were resistant to the  $\beta$ -lactams only (50%, 10/20) or additionally resistant to erythromycin (45%, 9/20). One isolate was additionally resistant to erythromycin and clindamycin.

ST30-IV [2B] (SWP CA-MRSA) and ST45-V [5C2&5] (WA84) accounted for 8.3% and 7.8% of CA-MRSA respectively and were isolated primarily in the eastern regions of Australia (Table 5). Typically PVL positive, ST30-IV [2B] (SWP CA-MRSA) was typically resistant to the  $\beta$ -lactams only (50%, 9/18). Isolates were additionally non-susceptible to nitrofurantoin (6 isolates); resistant to cotrimoxazole (1); erythromycin (1); clindamycin (1); tetracycline and nitrofurantoin (1); or clindamycin, fusidic acid, nitrofurantoin and high-level mupirocin (1). All PVL negative ST45-V [5C2&5] (WA84) isolates were resistant to the  $\beta$ -lactams and ciprofloxacin. Isolates were additionally resistant to erythromycin and tetracycline (2 isolates); erythromycin, gentamicin and tetracycline (2); erythromycin and clindamycin (2); erythromycin (1); erythromycin and gentamicin (1); erythromycin, clindamycin and tetracycline (1); erythromycin, clindamycin and gentamicin (1); or erythromycin, clindamycin, gentamicin and tetracycline (1).

Overall 90.8% of CA-MRSA were non-multi-resistant and 51.6% were resistant to the  $\beta$ -lactams only. However, 20 CA-MRSA isolates were multi-resistant.

#### **Panton-Valentine leucocidin**

Overall 20.9% (77) of MRSA were PVL positive, all were CA-MRSA (Table 3). PVL positive CA-MRSA clones included the international CA-MRSA clone ST8-IV [2B] USA300.

## **Discussion**

The Australian Group on Antimicrobial Resistance Targeted Resistance Surveillance program (AGAR-TRS) collects data on antimicrobial resistance, focussing on bloodstream infections caused by *S. aureus*, *Enterococcus* and *Enterobacteriaceae*. All data being collected in the AGAR-TRS programs are generated as part of routine patient care in Australia with most being available through labo-

**Table 4: Number and proportion of healthcare-associated methicillin-resistant Staphylococcus aureus multilocus sequence types, Australia, 2013, by state or territory**

Type	ACT		NSW		NT		Qld		SA		Tas.		Vic.		WA		Aus.	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ST22-IV [2B] (EMRSA-15)	3	42.9	35	56.5	0	0.0	14	70.0	13	81.3	1	100.0	14	45.2	8	88.9	88	58.3
ST239-III (3A) (Aus-2/3 EMRSA)	4	47.1	26	41.9	5	100.0	6	30.0	3	18.7	0	0.0	14	45.2	1	11.1	59	39.1
ST5-II [2A] (USA100)	0	0.0	1	1.6	0	0.0	0	0.0	0	0.0	0	0.0	3	9.6	0	0.0	4	2.6
Total	7	100.0	62	100.0	5	100.0	20	100.0	16	100.0	1	100.0	31	100.0	9	100.0	151	100.0

**Table 5: Number and proportion of the major community-associated methicillin-resistant Staphylococcus aureus multilocus sequence types, Australia (> 10 isolates), 2013, by state or territory**

Type	ACT		NSW		NT		Qld		SA		Tas.		Vic.		WA		Aus.	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ST93-IV [2B] (Qld)	1	25.0	10	30.3	9	47.4	8	17.1	9	32.1	1	100.0	4	12.1	8	15.4	50	23.0
ST1-IV [2B] (WA1)	0	0.0	4	12.1	4	21.1	12	25.5	5	17.9	0	0.0	6	18.2	14	26.9	45	20.7
ST5-IV [2B] (WA3)	0	0.0	2	6.1	1	5.3	6	12.8	5	17.9	0	0.0	3	9.1	8	15.4	25	11.5
ST78-IV [2B] (WA2)	0	0.0	1	3.0	0	0.0	1	2.1	2	7.1	0	0.0	1	3.0	15	28.8	20	9.2
ST30-IV [2B] (SWP)	0	0.0	3	9.1	3	15.8	6	12.8	2	7.1	0	0.0	3	9.1	1	1.9	18	8.3
ST45-V [5C2&5] (WA84)	2	50.0	6	18.2	0	0.0	0	0.0	1	3.6	0	0.0	8	24.2	0	0.0	17	7.8
Other	1	25.0	7	21.2	2	10.5	14	29.7	4	14.3	0	0.0	8	24.2	6	11.5	42	19.4
Total	4	100.0	33	100.0	19	100.0	47	100.0	28	100.0	1	100.0	33	100.0	52	100.0	217	100.0

ratory and hospital bed management information systems. Isolates are referred to a central laboratory where strain and antimicrobial resistance determinant characterisation is performed. As the programs are similar to those conducted in Europe, comparison of Australian antimicrobial resistance data with other countries is possible.<sup>20</sup>

In the 2012 European Centre for Disease Prevention and Control and Prevention SAB surveillance program, the European Union/European Economic Area (EU/EEA) population-weighted mean percentage of *S. aureus* resistant to methicillin was 17.8%, ranging from 0.7% in Sweden to 53.9% in Romania.<sup>21</sup> In ASSOP 2013, 19.1% (95% CI 17.5%–21.0%) of the 2,010 SAB episodes were methicillin resistant. Five European countries reported a similar percentage to Australia, including Bulgaria (19.8%; 95% CI, 15%–26%), Croatia (22%, 95% CI 18%–26%), France (19.2%, 95% CI 18%–20%), Ireland (22.6%, 95% CI 20%–25%) and Slovakia (21.7%, 95% CI 18%–26%). However, for 16 of the 30 European countries (primarily northern Europe countries including Germany and the United Kingdom) the percentage of SAB isolates resistant to methicillin was less than that reported in ASSOP 2013. Similar to Europe, which has seen the EU/EEA population-weighted mean percentage decrease significantly from 23.2% in 2009 to 17.8% in 2012, the percentage of methicillin resistant SAB in Australia has decreased from 23.8% (95% CI 21.4%–26.4%) in 2007 to 19.1% (95% CI 17.5%–21.0%) in 2013 ( $P < 0.0001$ ).<sup>20</sup> The decrease in methicillin resistant SAB is consistent with what has been reported elsewhere<sup>21,22</sup> and is believed to be attributed to the implementation of antimicrobial stewardship and a package of improved infection control procedures including hand hygiene, MRSA screening and decolonisation, patient isolation and infection prevention care bundles.<sup>23–27</sup> However, unlike Europe, Australia has a high prevalence of CA-MRSA and so further reduction in the proportion of SAB due to MRSA may prove problematic.

In ASSOP 2013, the all cause mortality at 30-days was 14.4% (95% CI 12.8%–16.2%). In comparison, the 2008 Australian New Zealand Cooperative on Outcome in Staphylococcal Sepsis reported a significantly higher figure of 20.6% (95% CI 18.8%–22.5%,  $P < 0.0001$ ), and when adjusted for Australian institutions only was 25.9% (personal communication). Although the SAB 30-day mortality appears to be falling in Australia, MRSA-associated SAB mortality remains high (20.1%, 95% CI, 15.9%–24.7%, 67/334) and was significantly higher than MSSA-associated SAB mortality (13%, 95% CI 11.3%–14.9%, 179/1378,  $P < 0.0001$ ). Although it has recently been shown that invasive MRSA infection may be more life-threatening,

partially because of the inferior efficacy of the standard treatment, vancomycin,<sup>9</sup> the emergence of hyper-virulent multi-resistant CA-MRSA clones such as ST93-IV [2B] (Queensland CA-MRSA) causing healthcare-associated SAB is of concern.<sup>30</sup>

With the exception of the  $\beta$ -lactams and erythromycin, antimicrobial resistance in MSSA remains rare. However, in addition to the  $\beta$ -lactams, approximately 50% of MRSA were resistant to erythromycin and ciprofloxacin and approximately 20% were resistant to co-trimoxazole, tetracycline and gentamicin. Resistance was largely attributable to 2 healthcare associated MRSA clones, ST22-IV [2B] (EMRSA-15), which is typically ciprofloxacin and erythromycin resistant, and ST239-III [3A] (Aus-2/3 EMRSA) which is typically erythromycin, clindamycin, ciprofloxacin, co-trimoxazole, tetracycline and gentamicin resistant. Since the early 1980s the multi-resistant ST239-III [3A] (Aus-2/3 EMRSA) was the dominant HA-MRSA clone in Australian hospitals. However, ST22-IV [2B] (EMRSA-15) has recently replaced it as the most prevalent HA-MRSA isolated from clinical specimens and this change has occurred throughout the country.<sup>31</sup> In the current survey, ST239-III [3A] was the only HA-MRSA clone in the Northern Territory. In ASSOP 2013, approximately 24% of MRSA were characterised as ST22-IV [2B] (EMRSA-15). CA-MRSA, in particular the ST45-V [5C2&5] (WA84) clone, has acquired multiple antimicrobial resistance determinants including ciprofloxacin, erythromycin, clindamycin, gentamicin and tetracycline. Linezolid, daptomycin and teicoplanin resistance was detected in a small number of *S. aureus* isolates. Resistance was not detected for vancomycin.

Approximately 30% of SAB caused by CA-MRSA were healthcare onset cases. Although in several parts of the United States of America the CA-MRSA clone USA300 has replaced the HA-MRSA clone ST5-II [2A] (USA100) as a cause of healthcare associated MRSA infection,<sup>28</sup> transmission of CA-MRSA in Australian hospitals is thought to be rare.<sup>33,34</sup> Consequently, it is likely that many of the healthcare onset CA-MRSA SAB infections reported in ASSOP 2013 were caused by the patient's own colonising strains acquired prior to admission. In Australia, CA-MRSA clones such as PVL-positive ST93-IV [2B] (Queensland CA-MRSA) and PVL-negative ST1-IV [2B] (WA1) are well established in the community and therefore it is important to monitor antimicrobial resistance patterns in both community and healthcare associated SAB as this information will guide therapeutic practices in treating *S. aureus* sepsis.

In conclusion, ASSOP 2013 has demonstrated that antimicrobial resistance in SAB in Australia is a

significant problem and continues to be associated with a high mortality. This may be due, in part, to the high prevalence of methicillin resistant SAB in Australia, which is significantly higher than most EU/EEA countries. Consequently, MRSA must remain a public health priority and continuous surveillance of SAB and its outcomes and the implementation of comprehensive MRSA strategies targeting hospitals and long-term care facilities are essential.

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