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Australian Group on Antimicrobial Resistance (AGAR) Australian Staphylococcus aureus Sepsis Outcome Programme (ASSOP) Annual Report 2017

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Annual Report

Australian Group on Antimicrobial Resistance (AGAR) Australian *Staphylococcus aureus* Sepsis Outcome Programme (ASSOP) Annual Report 2017

Geoffrey W Coombs, Denise A Daley, Yung Thin Lee, Stanley Pang on behalf of the Australian Group on Antimicrobial Resistance

Abstract

From 1 January to 31 December 2017, 36 institutions around Australia participated in the Australian *Staphylococcus aureus* Sepsis Outcome Programme (ASSOP). The aim of ASSOP 2017 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 methicillin-resistant isolates. A total of 2,515 *S. aureus* bacteraemia episodes were reported, of which 77% were community-onset. Approximately one in five *S. aureus* (19.0%) were methicillin resistant. The 30-day all-cause mortality associated with methicillin-resistant SAB was 18.7% which was significantly higher than the 14.0% mortality associated with methicillin-susceptible SAB. With the exception of the β-lactams and erythromycin, antimicrobial resistance in methicillin-susceptible *S. aureus* was rare. However in addition to the β-lactams approximately 42% of methicillin-resistant *S. aureus* (MRSA) were resistant to erythromycin and ciprofloxacin and approximately 14% resistant to co-trimoxazole, tetracycline and gentamicin. When applying the EUCAST breakpoints teicoplanin resistance was detected in five *S. aureus* isolates. Resistance was not detected for vancomycin and linezolid. Resistance to non-beta-lactam antimicrobials was largely attributable to two healthcare-associated MRSA clones: ST22-IV [2B] (EMRSA-15) and ST239-III [3A] (Aus-2/3 EMRSA). ST22-IV [2B] (EMRSA-15) is the predominant healthcare-associated clone in Australia. Seventy-five percent of methicillin-resistant SAB were due to community-associated clones. Although polyclonal approximately 74% of community-associated clones were characterised as ST93-IV [2B] (Queensland CA-MRSA), ST5-IV [2B], ST45-V_T [5C2&5] and ST1-IV [2B]. CA-MRSA, in particular the ST45-V_T [5C2&5] clone has acquired multiple antimicrobial resistance determinants including ciprofloxacin, erythromycin, clindamycin, gentamicin and tetracycline. ST45-V_T [5C2&5] accounted for 12.8% of CA-MRSA. 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.

Keywords: Australian Group on Antimicrobial Resistance (AGAR); antimicrobial resistance surveillance; *Staphylococcus aureus*, methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), bacteraemia

Background

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

Although prolonged antimicrobial therapy and prompt source control are used to treat SAB,[3] mortality ranges from as low as 2.5% to as high as 40%.[4–6] Mortality rates, however, are known to vary significantly with patient age, clinical manifestation, comorbidities and methicillin resistance.[7,8] A prospective study of SAB conducted in 27 laboratories in Australia and New Zealand found a 30-day all-cause mortality of 20.6%.[9] 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-β-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.[10] In 2013 AGAR commenced the Australian *Staphylococcus aureus* Sepsis Outcome Programme (ASSOP).[11] The primary objective of ASSOP 2017 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-resistant *S. aureus* (MRSA).

Methodology

Participants

Thirty-six laboratories from all eight Australian states and mainland territories.

Collection Period

From 1 January to 31 December 2017, the 36 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 first positive culture were excluded. A new *S. aureus* sepsis episode in the same patient was recorded if it was identified by a culture of blood collected more than 14 days after the last positive culture. Data were collected on age, sex, date of admission and discharge (if admitted), and mortality at 30 days from date of first 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 first positive blood culture(s) in an episode were collected >48 hours after admission.

Laboratory Testing

Participating laboratories performed antimicrobial susceptibility testing using the Vitek2® (bioMérieux, France) or the Phoenix™ (Becton Dickinson, 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® (bioMérieux, France), matrix-assisted laser desorption ionization (MALDI) 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 Antimicrobial

Resistance and Infectious Diseases (AMRID) Research Laboratory at Murdoch University. Clinical and Laboratory Standards Institute (CLSI)[12] and European Committee on Antimicrobial Susceptibility Testing (EUCAST)[13] breakpoints were utilised for interpretation. Isolates with a resistant or an intermediate category were classified as non-susceptible. Linezolid and daptomycin non-susceptible isolates were retested by Etest® (bioMérieux) using the Mueller-Hinton agar recommended by the manufacturer. *S. aureus* ATCC 29213 was used as the control strain. High level mupirocin resistance was determined by the Phoenix™ or by using a mupirocin 200 µg disk according to CLSI guidelines on all isolates with a mupirocin MIC >8 mg/L by Vitek2®. Multi-resistance was defined as resistance to three or more of the following non-β-lactam antimicrobials: vancomycin, teicoplanin, erythromycin/clindamycin, tetracycline, ciprofloxacin, gentamicin, cotrimoxazole, fusidic acid, rifampicin, high level mupirocin, and linezolid.

Molecular testing was performed by whole genome sequencing (WGS) using the MiSeq platform (Illumina, San Diego, USA). Sequencing results were analysed using the Nullarbor pipeline.[14] The online *spa* typing tool described by Bartels et al.[15] was applied to determine *spa* types. SCC*mec* elements were identified using SCC*mec* sequences described by Monecke et al.[16]

Chi-square tests for comparison of two proportions and calculation of 95% confidence intervals (95%CI) were performed 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 2017, a total of 2,515 unique episodes of *S. aureus* bacteraemia were identified. A significant difference ($p<0.001$) was seen in patient sex with 66.5% (1,673) being male (95% CI 64.6–68.3). The average age of patients was 57 years ranging from 0–101 years with a median age of 62 years. Overall 77.0% (1,936/2,515) of episodes were community onset (95% CI 75.3% – 78.6%). All-cause mortality at 30 days was 14.8% (95% CI 13.3–16.4). Methicillin-resistant SAB mortality was 18.7% (95% CI 14.8–23.1) which was significantly higher than for methicillin-susceptible SAB mortality (14.0%, 95% CI 12.3–15.8) ($p=0.03$).

Methicillin-Susceptible *Staphylococcus aureus* (MSSA) Antimicrobial Susceptibility

Overall 81.0% (2,037) of the 2,515 isolates were methicillin susceptible of which 77.2% (1,572) were penicillin resistant (MIC >0.12 mg/L). However as β-lactamase was detected in 62 phenotypically penicillin susceptible isolates, 80.3% of MSSA were considered penicillin resistant. Apart from erythromycin non-susceptibility (12.4%), resistance to the non-β-lactam antimicrobials amongst MSSA was rare, ranging from 0% to 3.3% (Table 1). There were ten isolates reported by Vitek2® as non-susceptible to daptomycin (MIC >1.0 mg/L). By Etest®, six of the isolates were considered susceptible (MICs 0.38–1.0 mg/L). Four isolates had Etest® MICs of 1.5–2.0 and therefore were considered non-susceptible. Using WGS, daptomycin non-susceptibility in two isolates was due to single point mutations in the *mprF* gene: *mprF*-I420T and *mprF*-L826I. No known single point mutations were identified in two isolates. By Vitek2®, two isolates were linezolid resistant (MIC >4 mg/L). However by Etest®, the isolates had MIC ≤4 mg/L (3.0 mg/L) and were therefore considered linezolid susceptible. When using the EUCAST resistant breakpoint of >2 mg/L, four isolates were teicoplanin resistant (MIC = 4 mg/L). However, using the CLSI resistant breakpoint of >8 mg/L, the isolates were classified as susceptible. All MSSA were vancomycin susceptible. Thirty (1.5%) of 2,035 isolates had high-level mupirocin resistance of which 21 isolates were referred from Queensland. Seventeen of the thirty mupirocin resistant MSSA were also resistant to fusidic acid. Inducible resistance to clindamycin

Table 1: The number and proportion of methicillin-susceptible *Staphylococcus* aureus (MSSA) isolates non-susceptible to penicillin and the non-β-lactam antimicrobials, Australia, 2017

Antimicrobial	Number Tested	Breakpoint (mg/L)	Non-Susceptible	
			n	%
Penicillin	2,035	>0.12[a]	1,634	80.3
Vancomycin	2,035	>2[a]	0	0.0
Teicoplanin	2,034	>8[b]	0	0.0
		>2[c]	4	0.2
Rifampicin	1,991	>1[b]	8	0.4
		>0.5[c]	9	0.5
Fusidic Acid	2,035	>1[c]	65	3.2
Gentamicin	2,034	>4[b]	15	1.1
		>1[c]	23	0.7
Erythromycin	2,035	>0.5[b]	253	12.4
		>2[c]	216	10.6
Clindamycin	2,034	>0.5[a]	32	1.6
Tetracycline/ Doxycycline	2,029	>4[b]	65	3.2
		>2[c]	66	3.3
Co-trimoxazole	2,033	>2/38[b]	44	2.2
		>4/76[c]	39	1.9
Ciprofloxacin	2,030	>1[a]	53	2.6
Nitrofurantoin	1,922	>32[b]	4	0.2
		>64[c]	0	0
Daptomycin	2,036	>1[a]	4	0.2
Linezolid	2,037	>4[a]	0	0

a CLSI and EUCAST non-susceptible breakpoint

b CLSI non-susceptible breakpoint

c EUCAST non-susceptible breakpoint

was determined by the Vitek2® susceptibility system. Of the 2,218 isolates tested, 14% (311) were erythromycin non-susceptible/clindamycin intermediate/susceptible (CLSI breakpoints) of which 85.2% (265) were classified as having inducible clindamycin resistance. Multi-resistance was uncommon in MSSA (0.5%, 9/1,983).

There were no significant differences in antimicrobial interpretation when CLSI or EUCAST non susceptibility breakpoints were utilised (p>0.05).

MRSA Antimicrobial Susceptibility

The proportion of *S. aureus* that were MRSA was 19.0% (95% CI 17.5–20.6). Of the 478 MRSA identified 418 were cefoxitin screen positive by Vitek2® and 58 had a cefoxitin MIC >4 by Phoenix™. Two isolates were cefoxitin screen

negative but harboured the *mecA* gene. All 478 MRSA isolates were phenotypically penicillin resistant. Amongst the MRSA isolates, non-susceptibility to non-β-lactam antimicrobials was common except for nitrofurantoin, rifampicin and fusidic acid where resistance ranged from 1.1% to 4.0% (Table 2). There were three isolates reported by Vitek2® as non-susceptible to daptomycin (MIC >1.0 mg/L). By Etest®, one of the isolates was considered susceptible (MIC 0.38 mg/L). The remaining two isolates had Etest® MICs of 2.0 mg/L and therefore were considered non-susceptible. Using WGS, daptomycin non-susceptibility was due to single point mutations in the *mprF* gene: *mprF*-L826F and *mprF*-P314S.

When using the EUCAST resistant breakpoint of >2 mg/L, one isolate was teicoplanin resistant (MIC = 8 mg/L). However, using the CLSI resistant breakpoint of >8 mg/L, the isolate was classified as susceptible. Ten (2.1%) of 478 MRSA isolates tested had high-level mupirocin resistance, of which six were from Queensland.

Inducible resistance to clindamycin was determined by the Vitek2® susceptibility system. Of the 415 isolates tested by Vitek2®, 27.7% (115) were erythromycin non-susceptible/clindamycin intermediate/susceptible (CLSI and EUCAST breakpoints) of which 81.7% (94) were classified as having inducible clindamycin resistance.

Multi-resistance was seen in 31.3% of MRSA.

There were no significant differences in interpretation for any drug when CLSI or EUCAST non-susceptibility breakpoints were utilised.

MRSA Molecular Epidemiology

WGS was performed on 96.7% (462/478) of the MRSA. Based on molecular typing, 25.5% (118) and 74.5% (344) of isolates were identified as healthcare-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) clones respectively (Table 3).

Healthcare-associated methicillin-resistant *Staphylococcus aureus*

For the 118 HA-MRSA isolates, 45.8% (54) were epidemiologically classified as hospital-onset and 54.2% (64) were classified as community-onset. Three HA-MRSA clones were identified: 90 isolates of ST22-IV [2B] (EMRSA-15) (19.5% of MRSA typed and 3.6% of *S. aureus*); 25 isolates of ST239-III [3A] (Aus -2/3 EMRSA) (5.4% and 1.0%) and three isolates of ST5-II [2A] (USA100/New York Japan) (0.6% and 0.1%).

ST22-IV [2B] (EMRSA-15) was the dominant HA-MRSA clone in Australia accounting for 76% of HA-MRSA ranging from 33.3% in the Northern Territory to 100% in Western Australia and the Australian Capital Territory (Table 4). ST22-IV [2B] (EMRSA-15) is PVL negative and using CLSI breakpoints 96.7% and 46.7% were ciprofloxacin and erythromycin non-susceptible respectively. Overall 42.2% of ST22-IV were hospital-onset.

ST239-III [3A] (Aus-2/3 EMRSA) accounted for 21.2% of HA-MRSA ranging from 0% in Western Australia and the Australian Capital Territory to 66.7% in the Northern Territory (Table 4). PVL negative ST239-III [3A] (Aus-2/3 EMRSA) were typically resistant to erythromycin (100%), co-trimoxazole (92.0%), ciprofloxacin (96.0%), gentamicin (100%), tetracycline (72.0%) and clindamycin (60.0%). Overall 68.08% of ST239-III were hospital-onset.

The three isolates of ST5-II [2A] (USA100/New York Japan) were identified in Queensland and New South Wales (Table 4) and were resistant to the β-lactams. Two of the three isolates were additionally resistant to fusidic acid. All were PVL negative.

Community-associated methicillin-resistant *Staphylococcus aureus*

For the 344 CA-MRSA isolates, 24.4% (84) of episodes were epidemiologically classified as hospital-onset and 75.6% (260) classified as community-onset. Based on the multi

Table 2: The number and proportion of methicillin-resistant Staphylococcus aureus (MRSA) isolates non-susceptible to penicillin and the non-β-lactam antimicrobials, Australia, 2017

Antimicrobial	Number Tested	Breakpoint (mg/L)	Non-Susceptible (%)	
			n	%
Penicillin	478	>0.12[a]	478	100
Vancomycin	478	>2[a]	0	0
Teicoplanin	477	>8[b]	0	0
		>2[c]	1	0.2
Rifampicin	475	>1[b]	9	1.9
		>0.5[c]	9	1.9
Fusidic Acid	477	>1[c]	19	4.0
Gentamicin	477	>4[b]	73	15.3
		>1[c]	79	16.6
Erythromycin	477	>0.5[b]	199	41.7
		>2[c]	197	41.3
Clindamycin	475	>0.5[a]	67	14.1
Tetracycline/ Doxycycline	476	>4[b]	67	14.1
		>2[c]	74	15.5
Co-trimoxazole	475	>2/38[b]	61	12.8
		>4/76[c]	57	12.0
Ciprofloxacin	476	>1[a]	198	41.6
Nitrofurantoin	450	>32[b]	5	1.1
		>64[c]	0	0
Daptomycin	478	>1[a]	2	0.4
Linezolid	478	>4[a]	0	0

a CLSI and EUCAST non-susceptible breakpoint

b CLSI non-susceptible breakpoint

c EUCAST non-susceptible breakpoint

locus sequence type and the *SCCmec* type, 40 CA-MRSA clones were identified (Table 3). Overall, 71.5% of CA-MRSA were classified into five clones each having more than ten isolates: ST93-IV [2B] (Queensland CA-MRSA) (24.5% of MRSA typed and 4.5% of *S. aureus*); ST45-V_T (9.4% and 1.7%); ST5-IV (8.4% and 1.6%); ST1-IV (7.4% and 1.4%); and ST78-IV (3.5% and 0.6%).

ST93-IV [2B] (Queensland CA-MRSA) accounted for 32.8% of CA-MRSA ranging from 0% in Tasmania to 74.4% in the Northern Territory (Table 5). Typically PVL positive, 76.5% (78/102) of ST93-IV [2B] (Queensland CA-MRSA) were resistant to the β-lactams only or additionally resistant to erythromycin (16.8%, 19/113) or erythromycin and clindamycin (3.5%, 4/113). There were two isolates resistant to gentamicin and one isolate resistant to ciprofloxacin. Overall 85.0% of ST93-IV were community-onset.

Table 3: Proportion of healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus*, Australia, 2017 by clone, healthcare and community onset, and Panton-Valentine leucocidin carriage

Strain	Total		Onset				PVL Positive	
			Healthcare		Community			
	n	%[a]	n	%[b]	n	%[b]	n	%[b]
Healthcare-associated MRSA								
ST22-IV [2B] (EMRSA-15)	90	19.5	37	41.1	53	58.9	0	0
ST239-III [3A] (Aus-2/3)	25	5.4	17	68	8	32	0	0
ST5-II (NY/Japan/USA100 variant)	3	0.6	0	100	3	100	0	0
Total HA-MRSA	118	25.5	54	45.8	64	54.2	0	0
Community-associated MRSA								
ST93-IV [2B] (Queensland)	113	24.5	17	15	96	85	106	93.8
ST45-VT	44	9.5	17	38.6	27	61.4	15	34.1
ST5-IV	39	8.4	13	33.3	26	66.7	9	23.1
ST1-IV	34	7.4	8	23.5	26	76.5	1	2.9
ST78-IV	16	3.5	3	18.8	13	81.3	2	12.5
ST30-IV	10	2.2	1	10	9	90	7	70
ST8-IV	10	2.2	2	20	8	80	10	100
ST5-Vt	8	1.7	2	25	6	75	0	0
ST97-IV	8	1.7	2	25	6	75	0	0
ST6-IV	7	1.5	2	28.6	5	71.4	4	57.1
ST953-IV	6	1.3	2	33.3	4	66.7	0	0
ST22-IV	4	0.9	1	25	3	75	4	100
ST188-IV	4	0.9	3	75	1	25	0	0
ST59-VT	4	0.9	1	25	3	75	4	100

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Strain	Total		Onset				PVL Positive	
			Healthcare		Community			
	n	%[a]	n	%[b]	n	%[b]	n	%[b]
ST672-VT	4	0.9	1	25	3	75	0	0
ST45-IV	3	0.6	2	66.7	1	33.3	2	66.7
ST872-IV	3	0.6	1	33.3	2	66.7	0	0
ST6slv-VT	2	0.4	0	0	2	100	0	0
ST72-IV	2	0.4	0	0	2	100	2	100
ST73-IV	2	0.4	0	0	2	100	0	0
ST835 –no CCR genes	2	0.4	0	0	2	100	0	0
ST1232-VT	1	0.2	0	0	1	100	1	100
ST1568-VI	1	0.2	0	0	1	100	0	0
ST1649-IV	1	0.2	0	0	1	100	0	0
ST1850-IV	1	0.2	0	0	1	100	0	0
ST1-V	1	0.2	1	100	0	0	0	0
ST218-IV	1	0.2	0	0	1	100	0	0
ST2250-IV	1	0.2	1	100	0	0	0	0
ST2371-IV	1	0.2	0	0	1	100	1	100
ST3349-III	1	0.2	1	100	0	0	0	0
ST398-V	1	0.2	0	0	1	100	0	0
ST573-V	1	0.2	0	0	1	100	0	0
ST59-IV	1	0.2	0	0	1	100	1	100
ST72dlv-IV	1	0.2	0	0	1	100	1	100
ST72-IV	1	0.2	1	100	0	0	0	0
ST772-VT	1	0.2	1	100	0	0	1	100

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Strain	Total		Onset				PVL Positive	
			Healthcare		Community			
	n	%[a]	n	%[b]	n	%[b]	n	%[b]
ST834-IV	1	0.2	0	0	1	0	0	0
ST835-I	1	0.2	0	0	1	0	0	0
ST835-V	1	0.2	1	100	0	0	0	0
ST88-IV	1	0.2	0	0	1	100	0	0
Total CA-MRSA	344	74.5	84	24.4	260	75.6	171	49.7
Grand Total	462	18.4	138	29.9	324	70.1	171	49.7

a Percentage of all MRSA typed
b Percentage of the strain

Table 4: The number and proportion of healthcare-associated methicillin-resistant *Staphylococcus aureus* (MRSA) multilocus sequence types, Australia, 2017, by region

Type	ACT		NSW		NT		Qld		SA		Tas		Vic		WA		Aus	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ST22-IV	2	100	42	71.2	1	33.3	4	50.0	14	82.4	5	83.3	13	92.9	9	100	90	76.3
ST239-III			16	27.1	2	66.7	2	25.0	3	17.6	1	16.7	1	7.1			25	21.2
ST5-II			1	1.7			2	25.0									3	2.5
Total	2	100	59	100	3	100	8	100	17	100	6	100	14	100	9	100	118	100

ACT = Australian Capital Territory; NSW = New South Wales; NT = Northern Territory; Qld = Queensland; SA = South Australia; Tas = Tasmania; Vic = Victoria; WA = Western Australia; Aus = Australia

Table 5: The number and proportion of the major community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) multilocus sequence types, Australia (>10 isolates), 2017, by region

Type	ACT		NSW		NT		Qld		SA		Tas		Vic		WA		Aus	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ST93-IV	2	28.6	15	20.5	29	74.4	27	37.5	3	17.6			9	19.1	29	32.6	113	32.8
ST45-Vt	1	14.3	29	39.7			1	1.4	1	5.9			11	23.4	1	1.2	44	12.8
ST5-IV			5	6.8	4	10.3	13	18.1	3	17.6			4	8.5	10	11.6	39	11.3
ST1-IV	2	28.6	1	1.4	3	7.7	8	11.1	3	17.6	3	100	2	4.3	12	14.0	34	9.9
ST78-IV			1	1.4			1	1.4	2	11.8			1	2.1	11	12.8	16	4.7
Other	2	28.6	22	30.1	3	7.7	22	7.7	5	29.4			20	42.6	24	27.9	98	28.5
Total	7	100	73	100	39	100	72	100	17	100	3	100	47	100	86	100	344	100

ACT = Australian Capital Territory; NSW = New South Wales; NT = Northern Territory; Qld = Queensland; SA = South Australia; Tas = Tasmania; Vic = Victoria; WA = Western Australia; Aus = Australia

ST45-V_T accounted for 12.8% of CA-MRSA and was isolated primarily in New South Wales and Victoria (Table 5). All isolates were PVL negative and were resistant to the β-lactams. Isolates were additionally non-susceptible to ciprofloxacin, erythromycin, gentamicin and tetracycline (37.2%, 16/43); ciprofloxacin, gentamicin and tetracycline (16.3%, 7/43); ciprofloxacin, erythromycin and gentamicin (11.6%, 5/43); ciprofloxacin, erythromycin and tetracycline (9.3%, 4/43); ciprofloxacin (7.0% 3/43); ciprofloxacin and erythromycin (4.7%, 2/43). Single isolates were resistant to either ciprofloxacin and gentamicin; ciprofloxacin and rifampicin; ciprofloxacin and tetracycline; ciprofloxacin, tetracycline and fusidic acid; ciprofloxacin, erythromycin, tetracycline and co-trimoxazole; or ciprofloxacin, erythromycin, tetracycline and high-level mupirocin. Overall 61.4% of ST45-V_T were community-onset.

ST5-IV accounted for 11.3% of CA-MRSA and was isolated in all regions of Australia except the Australian Capital Territory ranging from 0% to 18.1% in Queensland (Table 5). ST5-IV, of which 23% were PVL positive, was typically resistant to the β-lactams only 43.6% (17/39); to β-lactams and co-trimoxazole (30.8%, 12/39); or additionally resistant to either erythromycin; fusidic acid; high-level mupirocin; or gentamicin and high-level mupirocin. Overall 66.7% of ST5-IV were community-onset.

ST1-IV accounted for 9.9% of CA-MRSA ranging from 1.4% in New South Wales to 100% in Tasmania (Table 5). Typically PVL negative, 48.4% of isolates were resistant to the β-lactams only (15/31) or additionally resistant to erythromycin (25.8%, 8/31); fusidic acid (9.7%, 3/31); erythromycin and fusidic acid (6.5%, 2/31). Single isolates were resistant to either ciprofloxacin; erythromycin and tetracycline; or gentamicin and high-level mupirocin. Overall 76.5% of ST1-IV were community-onset.

ST78-IV accounted for 4.7% of CA-MRSA and was predominantly isolated in Western Australia (Table 5). Isolates were resistant to the β-lactams and erythromycin (87.5%, 14/16); one isolate resistant to the β-lactams only; and one isolate additionally resistant to high-level mupirocin. Overall 81.3% of ST78-IV were community-onset.

Overall 85.3% of CA-MRSA were non-multiresistant including 43.5% resistant to the β-lactams only. However 50 (14.7%) CA-MRSA isolates were multi-resistant, a significant increase from ASSOP 2016 (7.7%, p=0.01).[17] Multi-resistance was primarily due to the ST45-V_T clone.

Panton-Valentine leucocidin: Overall 171 (37.0%) MRSA were PVL positive, including 49.7% of CA-MRSA (Table 3).

Discussion

The AGAR surveillance programmes collect data on antimicrobial resistance, focussing on bloodstream infections caused by *S. aureus*, *Enterococcus* and *Enterobacteriaceae*. All data collected in the AGAR programs are generated as part of routine patient care in Australia, with most available through laboratory and hospital bed management information systems. Isolates are referred to a central laboratory where strain and antimicrobial resistance determinant characterisation is performed. As the programmes are similar to those conducted in Europe,[18] comparison of Australia antimicrobial resistance data with other countries is possible.

In ASSOP 2017, 19.0% (95% CI 17.5–20.6) of the 2,515 SAB episodes were methicillin resistant. In the 2017 European Centre for Disease Prevention and Control and Prevention (ECDC) SAB surveillance program, the European Union/European Economic Area (EU/EEA) population-weighted mean percentage of *S. aureus* resistant to methicillin was 16.9% (95% CI 17–17), ranging from 1.0% (95% CI 1–2) in Norway to 44.4% (95% CI 40–49) in Romania.[18]

Europe has seen the EU/EEA population-weighted mean percentage has significantly decreased from 23.2% in 2009 to 16.9% in 2017. The percentage of methicillin-resistant SAB in

Australia however has remained stable over the five years of ASSOP ranging from 19.1% in 2013 to 19.0% in 2017.

A decrease in methicillin-resistant SAB is consistent has been reported in several parts of the world[19,20] and is believed to be due 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.[21–25] In Australia although we have not seen a decrease in MRSA bacteraemia we have observed significant decreases in HA-MRSA from 41.0% to 25.5% (p<0.001) and hospital-onset MRSA from 38.0% to 29.9% (p=0.02) over the five ASSOP surveys.[11,17,26,27] Over the same time period we have observed a significant increase in CA-MRSA from 59.0% to 74.5% (p<0.001) and community-onset MRSA from 61.1% to 70.1% (p=0.008).

Because of the increased burden of CA-MRSA bacteraemia in Australia a significant reduction in the overall proportion of SAB due to MRSA may prove problematic.

In ASSOP 2017 the all-cause mortality at 30-days was 14.8% (95% CI 13.3–16.4). In comparison, the 2008 Australian New Zealand Cooperative on Outcomes in Staphylococcal Sepsis (ANZCOSS) reported a significantly higher figure of 20.6% (95% CI 18.8–22.5, p<0.001), and when adjusted for Australian institutions only was 25.9% (personal communication). MRSA-associated SAB mortality remains high (18.7%, 95% CI 14.8–23.1) and was significantly higher than MSSA-associated SAB mortality (14.0%, 95% CI 12.3–15.8), p=0.03.

With the exception of the β-lactams and erythromycin, antimicrobial resistance in MSSA remains rare. However for MRSA in addition to the β-lactams, approximately 25% of isolates were resistant to erythromycin and ciprofloxacin and approximately 5% resistant to co-trimoxazole, tetracycline and gentamicin. Resistance was largely attributable to two 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. From the early 1980s until recently the multi-resistant ST239-III [3A] (Aus-2/3 EMRSA) has been the dominant HA-MRSA clone in Australian hospitals. However, ST22-IV [2B] (EMRSA-15) has replaced ST239-III [3A] (Aus-2/3 EMRSA) as the most prevalent HA-MRSA isolated from clinical specimens and this change has occurred throughout most of the country.[28] In ASSOP 2017 approximately 20% of MRSA were characterised as ST22-IV [2B] (EMRSA-15). CA-MRSA, in particular the ST45-V_T clone (9.5% of MRSA), has acquired multiple antimicrobial resistance determinants including ciprofloxacin, erythromycin, clindamycin, gentamicin and tetracycline.

Resistance was not detected for vancomycin, linezolid or teicoplanin when CLSI interpretive criteria were applied. However five isolates were teicoplanin non-susceptible when EUCAST criteria were applied. There were six isolates resistant to daptomycin by both CLSI and EUCAST criteria.

Approximately 24.4% of SAB caused by CA-MRSA were healthcare-onset. Transmission of CA-MRSA in Australian hospitals is thought to be rare.[29,30] It is likely that many of the healthcare onset CA-MRSA SAB infections reported in ASSOP 2017 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) 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 2017 has demonstrated antimicrobial resistance in SAB in Australia continues to be 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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