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## **Australian Group on Antimicrobial Resistance (AGAR) Australian *Staphylococcus aureus* Surveillance Outcome Program (ASSOP)**

Bloodstream Infection Annual Report 2022

Geoffrey W Coombs, Denise A Daley, Princy Shoby, Shakeel Mowlaboccus, on behalf of the Australian Group on Antimicrobial Resistance

# Communicable Diseases Intelligence

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# Australian Group on Antimicrobial Resistance (AGAR) Australian *Staphylococcus aureus* Surveillance Outcome Program (ASSOP)

## Bloodstream Infection Annual Report 2022

Geoffrey W Coombs, Denise A Daley, Princy Shoby, Shakeel Mowlaboccus, on behalf of the Australian Group on Antimicrobial Resistance

### Abstract

From 1 January to 31 December 2022, fifty-five institutions across Australia participated in the Australian *Staphylococcus aureus* Surveillance Outcome Program (ASSOP). The aim of ASSOP 2022 was to determine the proportion of *Staphylococcus aureus* bacteraemia (SAB) isolates in Australia that were antimicrobial resistant, with particular emphasis on susceptibility to methicillin and on characterisation of the molecular epidemiology of the methicillin-resistant isolates. A total of 3,214 SAB episodes were reported, of which 77.5% were community-onset. Overall, 15.0% of *S. aureus* were methicillin resistant. The 30-day all-cause mortality associated with methicillin-resistant SAB was 21.4%, which was significantly different to the 16.8% all-cause mortality associated with methicillin-susceptible SAB ( $p = 0.02$ ). With the exception of the  $\beta$ -lactams and erythromycin, antimicrobial resistance in methicillin-susceptible *S. aureus* was rare. However, in addition to the  $\beta$ -lactams, approximately 31% of methicillin-resistant *S. aureus* (MRSA) were resistant to ciprofloxacin; 30% to erythromycin; 13% to tetracycline; 11% to gentamicin; and 2% to co-trimoxazole. One MRSA isolate, with a daptomycin MIC of 1.5 mg/L, harboured the A302V *mprF* and A23V *cls2* mutations. When applying the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints, teicoplanin resistance was detected in one MRSA isolate. Resistance to vancomycin or linezolid was not detected. Resistance to non- $\beta$ -lactam antimicrobials was largely attributable to the healthcare-associated MRSA (HA-MRSA) clone ST22-IV [2B] (EMRSA-15), and to the community-associated MRSA (CA-MRSA) clone ST45-V [5C2&5] which has acquired resistance to multiple antimicrobials including ciprofloxacin, clindamycin, erythromycin, gentamicin, and tetracycline. The ST22-IV [2B] (EMRSA-15) clone is the predominant HA-MRSA clone in Australia. Nonetheless, 86% of methicillin-resistant SAB episodes were due to CA-MRSA clones. Although polyclonal, approximately 72% of CA-MRSA clones were characterised as ST93-IV [2B] (Queensland clone); ST5-IV [2B]; ST45-V [5C2&5]; ST1-IV [2B]; ST30-IV [2B]; ST97-IV [2B]; ST953-IV [2B]; and ST8-IV [2B]. As CA-MRSA is well established in the Australian community, it is important to monitor antimicrobial resistance patterns in community- and healthcare-associated SAB as this information will guide therapeutic practices in treating *S. aureus* bacteraemia.

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 bloodstream infections.<sup>1</sup> Although there are a wide variety of manifestations of serious invasive infection caused by *S. aureus*, in the majority of cases the organism can be detected in blood cultures. Therefore, *S. aureus* bacteraemia (SAB) is considered a very useful marker for serious invasive infection.<sup>2</sup> In 2009, the Infectious Diseases Society of America highlighted *S. aureus* as one of the key problem bacteria or ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) requiring new therapies.<sup>3</sup>

Although prolonged antimicrobial therapy and prompt source control are used to treat SAB,<sup>4</sup> mortality ranges from as low as 2.5% to as high as 40%.<sup>5–8</sup> Mortality rates, however, are known to vary significantly with patient age, clinical manifestation, comorbidities and methicillin resistance. A 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> In 2013, AGAR commenced the Australian *Staphylococcus aureus* Sepsis Outcome Program, now known as the Australian *Staphylococcus aureus* Surveillance Outcome Program (ASSOP).<sup>11</sup> The primary objective of ASSOP 2022 was to determine the proportion of SAB isolates displaying antimicrobial resistance, with particular emphasis on:

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

## Methodology

### Participants

Thirty-three laboratories servicing 55 institutions from all Australian states and mainland territories.

### Collection period

From 1 January to 31 December 2022, the 33 laboratories collected all *S. aureus* isolated from blood cultures. When isolated from a patient's blood culture within 14 days of the first positive culture, *S. aureus* isolates with the same antimicrobial susceptibility profiles were excluded. A new SAB 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, dates 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 SAB episode was designated health-care onset if the first positive blood culture(s) in the episode were collected > 48 hours after admission.

### Laboratory testing

Participating laboratories performed antimicrobial susceptibility testing using the Vitek2<sup>®</sup> (bioMérieux, France) or the BD Phoenix<sup>™</sup> (Becton Dickinson, USA) automated microbiology systems according to the manufacturer's instructions. Identification of *S. aureus* was achieved by matrix-assisted laser desorption ionization (MALDI) using either the Vitek MS<sup>®</sup> (bioMérieux, France) or the MALDI Biotyper<sup>®</sup> (Bruker Daltonics, Germany). Appropriate growth on chromogenic 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)<sup>12</sup> and European Committee on Antimicrobial Susceptibility Testing (EUCAST)<sup>13</sup> MIC breakpoints were utilised for interpretation. Linezolid and daptomycin non-susceptible isolates were retested by Etest<sup>®</sup> (bioMérieux) using the Mueller-Hinton agar recommended by the manufacturer. The control strain used was *S. aureus* ATCC<sup>®</sup> 29213. High-level mupirocin resistance was determined by the BD Phoenix<sup>™</sup> or by using a mupirocin 200 µg disk according to CLSI guidelines on all isolates with a mupirocin MIC > 8 mg/L by Vitek2<sup>®</sup>. Multi-resistance was defined as resistance to three or more of the following non-β-lactam antimicrobials: ciprofloxacin, co-trimoxazole, erythromycin/clindamycin, fusidic acid, gentamicin, linezolid, high-level mupirocin, rifampicin, tetracycline, teicoplanin, and vancomycin.

Molecular testing was performed by whole genome sequencing (WGS) using the NextSeq 500 platform (Illumina, San Diego, USA). Sequence reads were analysed using the Nullarbor pipeline.<sup>14</sup> The SCC<sub>mec</sub> type was determined using KmerFinder v3.2 and the SCC<sub>mec</sub> database curated from the Center for Genomic Epidemiology database.<sup>15–18</sup>

Confidence intervals for proportions, Fisher's exact test for categorical variables, and chi-square test for trend were calculated, if appropriate, using MedCalc for Windows, version 12.7 (MedCalc Software, 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 2022, there were 3,214 unique episodes of SAB identified. A significant difference ( $p < 0.0001$ ) was observed

in patient sex, with 2,142 (66.6%) being male (95% confidence interval [95% CI] 64.9–68.2). The mean age of patients was 59 years, ranging from 0–101 years, with a median age of 63 years. Overall, 2,491 episodes (77.5%) were community-onset (95% CI: 76.0–78.9). All-cause mortality at 30 days (where known) was 17.5% (95% CI: 16.1–19.0). Methicillin-resistant SAB mortality was 21.4% (95% CI: 17.6–25.7); methicillin-susceptible SAB mortality was 16.8% (95% CI: 15.3–18.4).

### Methicillin-susceptible *Staphylococcus aureus* (MSSA) antimicrobial susceptibility

Overall, 2,733 of the 3,214 isolates (85.0%) were methicillin susceptible. Where results were available, 1,962/2,721 MSSA isolates (72.1%) were penicillin resistant (MIC > 0.12 mg/L). All penicillin-susceptible isolates (MIC ≤ 0.12 mg/L) were tested either by *bla*<sub>Z</sub> PCR or by penicillin disc diffusion (zone-edge test). On testing, a further 74 phenotypically penicillin-susceptible isolates were considered penicillin resistant. Twelve penicillin-susceptible isolates were not available for confirmation. Apart from erythromycin resistance (13.2% and 13.9% using CLSI and EUCAST breakpoints respectively), resistance to the non-β-lactam antimicrobials amongst MSSA was rare (Table 1). There were nine isolates reported by Vitek2<sup>®</sup> as non-susceptible to daptomycin (MIC > 1.0 mg/L). By Etest<sup>®</sup>, eight of these nine isolates were considered daptomycin susceptible (MICs 0.25–1.0 mg/L), whilst the remaining one isolate was unavailable for confirmation.

By Vitek2<sup>®</sup>, three isolates were reported as linezolid resistant (MIC > 4 mg/L). By Etest<sup>®</sup>, the three isolates had a linezolid MIC of 0.75 mg/L and were therefore considered linezolid susceptible. Using EUCAST interpretive criteria, 21 isolates were reported by Vitek2<sup>®</sup> or BD Phoenix<sup>™</sup> as teicoplanin resistant (MIC > 2.0 mg/L). By Etest<sup>®</sup>, all isolates had a teicoplanin MIC ≤ 2.0 mg/L and were therefore considered teicoplanin susceptible. All MSSA were vancomycin susceptible. Overall, 2,098 of the 2,733

**Table 1: The number and proportion of methicillin-susceptible *Staphylococcus aureus* (MSSA) isolates non-susceptible to penicillin and the non-β-lactam antimicrobials, AGAR, 2022**

Antimicrobial	MSSA isolates (n)	CLSI		EUCAST	
		Intermediate % (n)	Resistant % (n)	Susceptible, increased exposure % (n)	Resistant % (n)
Benzylpenicillin	2,721	— <sup>a</sup>	72.1 (1,962)	— <sup>a</sup>	72.1 (1,962)
Benzylpenicillin <sup>b</sup>	2,719	— <sup>a</sup>	74.9 (2,036)	— <sup>a</sup>	74.9 (2,036)
Ciprofloxacin	2,724	0.7 (20)	2.2 (61)	97.0 (2,643)	3.0 (81)
Clindamycin (constitutive)	2,722	0.0 (0)	1.5 (40)	0.0 (0)	1.7 (45)
Clindamycin (inducible + constitutive resistance)	2,722	0.0 (0)	10.8 (293)	0.0 (0)	11.5 (312)
Daptomycin	2,729	0.0 (0) <sup>c</sup>	— <sup>a</sup>	— <sup>a</sup>	0.0 (0)
Erythromycin	2,669	28.2 (753)	13.2 (351)	— <sup>a</sup>	13.9 (370)
Fusidic acid	2,669	— <sup>d</sup>	— <sup>d</sup>	— <sup>a</sup>	2.6 (70)
Gentamicin	2,724	0.8 (23)	0.7 (20)	— <sup>a</sup>	3.5 (94)
Linezolid	2,730	— <sup>a</sup>	0.0 (0)	— <sup>a</sup>	0.0 (0)
Mupirocin (high-level) <sup>e</sup>	2,096	— <sup>a</sup>	1.2 (25)	— <sup>a</sup>	1.2 (25)
Rifampicin	2,721	0.1 (3)	0.3 (7)	— <sup>f</sup>	0.6 (15)
Teicoplanin	2,728	0.0 (0)	0.0 (0)	— <sup>a</sup>	0.0 (0)
Tetracycline/doxycycline <sup>g</sup>	2,720	0.1 (2) <sup>g</sup>	2.7 (74)	— <sup>a</sup>	3.5 (96)
Trimethoprim/sulfamethoxazole	2,723	0.2 (5)	0.3 (8)	0.1 (3)	0.4 (10)
Vancomycin	2,730	0.0 (0)	0.0 (0)	— <sup>a</sup>	0.0 (0)

a No category defined.

b Beta-lactamase adjusted.

c Non-susceptible; resistance not defined (DAP).

d No guidelines for indicated species (FUSc).

e Mupirocin high-level resistance screen.

f The rifampicin concentration range on cards restricts category interpretation to non-resistant or resistant.

g Doxycycline concentration range (Phoenix panel) restricts ability to accurately identify intermediate and resistant category.

MSSA (76.7%) had mupirocin susceptibility testing performed, of which 25 (1.2%) were high-level mupirocin resistant. Eleven of the 25 high-level mupirocin-resistant MSSA isolates were referred from Queensland. The remainder of the isolates were from New South Wales (n = 8), Victoria (n = 3), and South Australia (n = 3). Fourteen of the 25 mupirocin resistant MSSA were also resistant to fusidic acid. Of the 2,722

MSSA isolates tested, 45 (1.7%) were constitutively resistant to clindamycin; however, 312 (11.5%) were classified as having both constitutive and inducible clindamycin resistance. Only 3.9% of MSSA were multi-resistant. By Vitek2<sup>®</sup> or BD Phoenix<sup>™</sup>, fifty-five isolates were reported as non-susceptible to cotrimoxazole.

By disc susceptibility testing, 42/55 (76.4%) were susceptible by both CLSI and EUCAST criteria.

### MRSA antimicrobial susceptibility

The proportion of *S. aureus* that were MRSA was 15.0% (95% CI: 13.8–26.3). Of the 481 MRSA identified, 415 were cefoxitin-screen positive by Vitek2<sup>®</sup> and 66 had a cefoxitin MIC > 4 mg/L by BD Phoenix<sup>™</sup>. All MRSA isolates were penicillin resistant. Amongst the MRSA isolates, resistance to non-β-lactam antimicrobials was common (Table 2). All MRSA were susceptible to vancomycin and linezolid. Two isolates were reported by Vitek2<sup>®</sup> as daptomycin non-susceptible (MIC > 1.0 mg/L). By Etest<sup>®</sup>, one isolate was considered daptomycin susceptible (MIC 0.25 mg/L). The remaining isolate was confirmed as daptomycin non-susceptible by CLSI and daptomycin resistant by EUCAST criteria (MIC 1.5 mg/L). The isolate harboured the known daptomycin resistance A302V *mprF* and A23V *cls2* mutations.

By Vitek2<sup>®</sup>, three isolates were reported as teicoplanin resistant using the EUCAST resistant breakpoint of > 2 mg/L (MIC = 4.0 mg/L). However, using the CLSI resistant breakpoint of > 16 mg/L, the isolates were classified as teicoplanin susceptible. Two of the three isolates were available for testing by Etest<sup>®</sup>: one isolate, with a teicoplanin MIC of 2.0 mg/L, was susceptible by CLSI and EUCAST criteria; one isolate with a teicoplanin MIC of 4.0 mg/L was considered susceptible by CLSI and resistant by EUCAST criteria. Of the 481 MRSA isolates, 346 (71.9%) had mupirocin testing performed. Seven MRSA had high-level mupirocin resistance (2.0%). The isolates were from New South Wales (n = 3), Queensland (n = 3) and Victoria (n = 1).

Of the 479 MRSA isolates tested, 61 (12.7%) and 65 (13.6%) were constitutively resistant to clindamycin by CLSI and EUCAST criteria respectively, whilst 110 (23.0%) and 116 (24.2%) were classified as having both constitutive and inducible clindamycin resistance by CLSI and EUCAST criteria respectively.

By Vitek2<sup>®</sup> or BD Phoenix<sup>™</sup>, 49 MRSA isolates were reported as non-susceptible to cotrimoxazole, 79.6% of which (39/49) were susceptible by disc susceptibility testing using CLSI or EUCAST criteria.

Multi-resistance was identified in 86/477 (18.0%) of MRSA.

### MRSA molecular epidemiology

Whole genome sequencing was performed on 449 of the 481 MRSA isolates (93.3%). Based on molecular typing, 61 (13.6%) and 388 (86.4%) of the isolates were identified as healthcare-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) clones respectively (Table 3).

#### Healthcare-associated MRSA

For the 61 HA-MRSA isolates, 29 (47.5%) episodes were classified as hospital-onset and 32 (52.5%) were classified as community-onset. Based on the multilocus sequence type (MLST) and the SCC $mec$  type, two HA-MRSA clones were identified: 55 isolates of ST22-IV [2B] (EMRSA-15) (12.2% of MRSA typed and 1.7% of *S. aureus*), and six isolates of ST239-III [3A] (Aus-2/3 EMRSA) (1.3% and 0.2%) (Table 3).

The dominant HA-MRSA clone in Australia in 2022 was ST22-IV [2B] (EMRSA-15), accounting for 90.2% of HA-MRSA; it was identified in all states and territories (Table 4). ST22-IV [2B] (EMRSA-15) is Pantone-Valentine leucocidin toxin (PVL) negative and, using EUCAST breakpoints, 98.2% and 50.0% were ciprofloxacin and erythromycin resistant, respectively. Overall, 45.5% of ST22-IV [2B] (EMRSA-15) were hospital-onset.

ST239-III [3A] (Aus-2/3 EMRSA) accounted for 9.8% of HA-MRSA and was identified in New South Wales, Victoria, and the Australian Capital Territory (Table 4). PVL negative, ST239-III [3A] (Aus-2/3 EMRSA) were typically resistant to ciprofloxacin, clindamycin,

**Table 2: The number and proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates non-susceptible to penicillin and the non-β-lactam antimicrobials, AGAR, 2022**

Species and antimicrobial	Isolates (n)	CLSI		EUCAST	
		Intermediate % (n)	Resistant % (n)	Susceptible, increased exposure % (n)	Resistant % (n)
Benzylpenicillin	479	— <sup>a</sup>	100.0 (479)	— <sup>a</sup>	100.0 (479)
Benzylpenicillin <sup>b</sup>	480	— <sup>a</sup>	100.0 (480)	— <sup>a</sup>	100.0 (480)
Ciprofloxacin	479	1.3 (6)	29.4 (141)	69.3 (332)	30.7 (147)
Clindamycin (constitutive)	479	0.0 (0)	12.7 (61)	0.0 (0)	13.6 (65)
Clindamycin (inducible + constitutive resistance)	479	0.0 (0)	23.0 (110)	0.0 (0)	24.2 (116)
Daptomycin	480	0.2 (1) <sup>c</sup>	— <sup>a</sup>	— <sup>a</sup>	0.2 (1)
Erythromycin	478	17.6 (84)	28.7 (137)	— <sup>a</sup>	29.7 (142)
Fusidic acid	478	— <sup>d</sup>	— <sup>d</sup>	— <sup>a</sup>	3.3 (16)
Gentamicin	479	3.3 (16)	5.8 (28)	— <sup>a</sup>	11.3 (54)
Linezolid	480	— <sup>a</sup>	0.0 (0)	— <sup>a</sup>	0.0 (0)
Mupirocin (high-level) <sup>e</sup>	346	— <sup>a</sup>	2.0 (7)	— <sup>a</sup>	2.0 (7)
Rifampicin	479	0.0 (0)	1.0 (5)	— <sup>f</sup>	1.5 (7)
Teicoplanin	478	0.0 (0)	0.0 (0)	— <sup>a</sup>	0.2 (1)
Tetracycline/doxycycline <sup>g</sup>	479	0.0 (0) <sup>g</sup>	10.9 (52)	— <sup>a</sup>	13.2 (63)
Trimethoprim/sulfamethoxazole	478	0.4 (2)	1.7 (8)	0.4 (2)	1.7 (8)
Vancomycin	480	0.0 (0)	0.0 (0)	— <sup>a</sup>	0.0 (0)

a No category defined.

b Beta-lactamase adjusted.

c Non-susceptible; resistance not defined.

d No guidelines for indicated species.

e Mupirocin high-level resistance screen.

f The rifampicin concentration range on some cards restricts category interpretation to non-resistant or resistant.

g Doxycycline concentration range (Phoenix panel) restricts ability to accurately identify intermediate and resistant category.



**Table 3: Proportion of healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus* (MRSA), AGAR, 2022 by clone, onset, and Panton-Valentine leucocidin (PVL) carriage**

Clone	Clonal complex	Total, <i>n</i>	Community onset, % ( <i>n</i> ) <sup>a</sup>	Hospital onset, % ( <i>n</i> ) <sup>a</sup>	PVL positive, % ( <i>n</i> ) <sup>a</sup>
<b>Healthcare-associated</b>					
ST22-IV (EMRSA-15)	22	55	54.5 (30)	45.5 (25)	0.0 (0)
ST239-III (Aus2/3 EMRSA)	8	6	– <sup>b</sup> (2)	– <sup>b</sup> (4)	– <sup>b</sup> (0)
Total HA-MRSA		61	52.5 (32)	47.5 (29)	0.0 (0)
<b>Community-associated</b>					
ST93-IV	93	104	88.5 (92)	11.5 (12)	99.0 (103)
ST5-IV	5	48	81.3 (39)	18.8 (9)	45.8 (22)
ST45-V	45	38	71.1 (27)	28.9 (11)	0.0 (0)
ST1-IV	1	25	68.0 (17)	32.0 (8)	4.0 (1)
ST30-IV	30	21	85.7 (18)	14.3 (3)	61.9 (13)
ST97-IV	97	21	61.9 (13)	38.1 (8)	0.0 (0)
ST953-IV	97	11	90.9 (10)	9.1 (1)	0.0 (0)
ST8-IV	8	11	81.8 (9)	18.2 (2)	72.7 (8)
ST6-IV	6	8	– <sup>b</sup> (4)	– <sup>b</sup> (4)	– <sup>b</sup> (0)
ST78-IV	78	6	– <sup>b</sup> (4)	– <sup>b</sup> (2)	– <sup>b</sup> (0)
ST5-V	5	6	– <sup>b</sup> (3)	– <sup>b</sup> (3)	– <sup>b</sup> (0)
ST45-IV	45	5	– <sup>b</sup> (2)	– <sup>b</sup> (3)	– <sup>b</sup> (0)
ST872-IV	1	5	– <sup>b</sup> (3)	– <sup>b</sup> (2)	– <sup>b</sup> (0)
ST834-IV	1	4	– <sup>b</sup> (3)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST88-IV	88	4	– <sup>b</sup> (3)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST59-V	59	4	– <sup>b</sup> (4)	– <sup>b</sup> (0)	– <sup>b</sup> (3)
ST22-IV (pvl positive)	22	4	– <sup>b</sup> (4)	– <sup>b</sup> (0)	– <sup>b</sup> (4)
ST1232-V	398	4	– <sup>b</sup> (2)	– <sup>b</sup> (2)	– <sup>b</sup> (4)
ST59-IV	59	3	– <sup>b</sup> (2)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST6151-IV	93	3	– <sup>b</sup> (2)	– <sup>b</sup> (1)	– <sup>b</sup> (3)
ST8430-IV	1	2	– <sup>b</sup> (2)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST3074-IV	5	2	– <sup>b</sup> (1)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST8534-IV	8	2	– <sup>b</sup> (2)	– <sup>b</sup> (0)	– <sup>b</sup> (2)
ST8536-IV	1	2	– <sup>b</sup> (2)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST6959-IV	5	2	– <sup>b</sup> (1)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST398-V	398	2	– <sup>b</sup> (1)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST149-IV	5	2	– <sup>b</sup> (2)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST188-IV	188	2	– <sup>b</sup> (1)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST72-IV	72	2	– <sup>b</sup> (2)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST6145-V	45	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (1)
ST8547-IV	2250	1	– <sup>b</sup> (0)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST8539-IV	30	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (1)
ST6963-IV	22	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST87-IV	59	1	– <sup>b</sup> (0)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST5669-IV	30	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST8537-IV	22	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST7014-V	45	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)

Clone	Clonal complex	Total, <i>n</i>	Community onset, % ( <i>n</i> ) <sup>a</sup>	Hospital onset, % ( <i>n</i> ) <sup>a</sup>	PVL positive, % ( <i>n</i> ) <sup>a</sup>
ST8543-IV	1	1	– <sup>b</sup> (0)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST8-V	8	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST8550-IV	93	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (1)
ST913-IV	913	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST6865-V	5	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST5977-IV	5	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST5213-IV	1	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST1649-IV	6	1	– <sup>b</sup> (0)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST8538-IV	45	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST30-V	30	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST8542-IV	59	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST188-V	188	1	– <sup>b</sup> (0)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST8544-IV	97	1	– <sup>b</sup> (0)	– <sup>b</sup> (1)	– <sup>b</sup> (0)
ST8420-IV	1	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST8548-V	1	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST3628-V	5	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST6607-IV	6	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST8525-V	45	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST672-IV	672	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST8532-IV	22	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST5662-IV	5	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST8533-IV	1	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (1)
ST2250-IV	2250	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST762-IV	1	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST2493-IV	1	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST779-IV	779	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
ST7891-IV	1	1	– <sup>b</sup> (1)	– <sup>b</sup> (0)	– <sup>b</sup> (0)
Total CA-MRSA		388	78.4 (304)	21.6 (84)	42.8 (166)
<b>MRSA typed</b>		<b>449</b>	<b>74.8 (336)</b>	<b>25.2 (113)</b>	<b>37.0 (166)</b>

a Percentage of the clone.

b Insufficient numbers (<10) to calculate percentage.

cotrimoxazole, erythromycin, gentamicin, and tetracycline. Four of the six ST239-III [3A] (Aus-2/3 EMRSA) were hospital-onset.

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

For the 388 CA-MRSA isolates, 84 episodes (21.6%) were classified as hospital-onset and 304 (78.4%) as community-onset. Based on the MLST and the SCCmec type, 64 CA-MRSA clones were identified (Table 3). Overall, 71.9% of CA-MRSA were classified into eight clones

each represented by ten or more isolates: 104 isolates of ST93-IV [2B] (Queensland clone) (23.2% of MRSA typed and 3.2% of *S. aureus*); 48 isolates of ST5-IV [2B] (10.7% and 1.5%); 38 isolates of ST45-V [5C2&5] (8.5% and 1.2%); 25 isolates of ST1-IV [2B] (5.6% and 0.8%); 21 isolates of ST30-IV [2B] (4.7% and 0.7%); 21 isolates of ST97-IV [2B] (4.7% and 0.7%); 11 isolates of ST953-IV [2B] (2.4% and 0.3%), and 11 isolates of ST8-IV [2B] 2.4% and 0.3%.

ST93-IV [2B] (Queensland clone) accounted for 26.8% of CA-MRSA, ranging from 0% in

**Table 4: The number and proportion of healthcare-associated methicillin-resistant *Staphylococcus aureus* (MRSA) clones, AGAR, 2022, by state and territory.**

Clone	Percentage (n) <sup>a</sup>								
	ACT	NSW	NT	Qld	SA	Tas.	Vic	WA	Australia
ST22-IV (EMRSA-15)	– <sup>b</sup> (2)	86.2 (25)	– <sup>b</sup> (2)	– <sup>b</sup> (2)	100.0 (11)	– <sup>b</sup> (1)	90.9 (10)	– <sup>b</sup> (2)	90.2 (55)
ST239-III (Aus2/3 EMRSA)	– <sup>b</sup> (1)	13.8 (4)	– <sup>b</sup> (0)	– <sup>b</sup> (0)	0.0 (0)	– <sup>b</sup> (0)	9.1 (1)	– <sup>b</sup> (0)	9.8 (6)
<b>Total</b>	3	29	2	2	11	1	11	2	61

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

b Insufficient numbers (<10) to calculate percentage.

Tasmania to 60.5% of CA-MRSA in the Northern Territory (Table 5). Typically PVL positive, 88.5% of ST93-IV [2B] were community-onset.

ST5-IV [2B] accounted for 12.4% of CA-MRSA and was isolated in all regions of Australia except the Australian Capital Territory (Table 5). All ST5-IV [2B] were PVL negative and 81.3% of ST5-IV [2B] were community-onset.

ST45-V [5C2&5] accounted for 9.8% of CA-MRSA and was isolated primarily in New South Wales and Victoria (Table 5). Of the ST45-V [5C2&5] isolates, 47.4% were PVL positive and 71.1% were community-onset.

ST1-IV [2B] accounted for 6.4% of CA-MRSA and was isolated in all regions of Australia except Victoria, the Northern Territory and the Australian Capital Territory (Table 5). Of the ST1-IV [2B] isolates, 8.0% were PVL positive and 68.0% were community-onset.

ST30-IV [2B] accounted for 5.4% of CA-MRSA and was isolated in all regions of Australia except Tasmania and the Northern Territory (Table 5). Of the ST30-IV [2B] isolates, 76.2% were PVL positive and 85.7% were community-onset.

ST97-IV [2B] accounted for 5.4% of CA-MRSA and was isolated in all regions except South

Australia and the Northern Territory (Table 5). All ST97-IV [2B] isolates were PVL negative and 61.9% of ST97-IV [2B] were community-onset.

ST953-IV [2B] accounted for 2.8% of CA-MRSA and was only isolated in Western Australia (Table 5). Overall 81.8% of ST953-IV [2B] were PVL positive and 90.9% were community-onset.

ST8-IV [2B] accounted for 2.8% of CA-MRSA and was only isolated in New South Wales, Victoria and Queensland. All ST8-IV [2B] were PVL negative and 81.8% were community-onset.

Overall, 67.9% of CA-MRSA were non-multi-resistant, including 57.5% of isolates resistant to the  $\beta$ -lactams only. A significant increase ( $p < 0.0001$ ) was observed in multi-resistant CA-MRSA isolates in ASSOP 2022 (32.1%) from 9.2% in ASSOP 2013. Multi-resistance was primarily due to the ST45-V [5C2&5] clone.

The resistance profiles of the eight predominant CA-MRSA clones are shown in Table 6.

**Table 5: The number and proportion of the major community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) clones (> 10 isolates), AGAR, by state and territory and Panton-Valentine leucocidin (PVL) carriage, 2022**

Clone	Percentage (n) <sup>a</sup>								
	ACT	NSW	NT	Qld	SA	Tas.	Vic.	WA	Australia
ST93-IV (Qld CA-MRSA)	– <sup>b</sup> (2)	15.4 (21)	60.5 (23)	37.3 (19)	42.3 (11)	0.0 (0)	20.0 (11)	24.6 (17)	26.8 (104)
Number PVL positive	2	21	23	19	10	0	11	17	103
Number PVL negative	0	0	0	0	1	0	0	0	1
ST5-IV	0.0 (0)	7.4 (10)	26.3 (10)	9.8 (5)	15.4 (4)	– <sup>b</sup> (1)	7.3 (4)	20.3 (14)	12.4 (48)
Number PVL positive	0	0	8	0	2	0	1	11	22
Number PVL negative	0	10	2	5	2	1	3	3	26
ST45-V	– <sup>b</sup> (1)	20.6 (28)	2.6 (1)	2.0 (1)	0.0 (0)	0.0 (0)	12.7 (7)	0.0 (0)	9.8 (38)
Number PVL positive	0	0	0	0	0	0	0	0	0
Number PVL negative	1	28	1	1	0	0	7	0	38
ST1-IV	0.0 (0)	6.6 (9)	0.0 (0)	5.9 (3)	11.5 (3)	– <sup>b</sup> (1)	0.0 (0)	13.0 (9)	6.4 (25)
Number PVL positive	0	1	0	0	0	0	0	0	1
Number PVL negative	0	8	0	3	3	1	0	9	24
ST30-IV	– <sup>b</sup> (1)	8.8 (12)	0.0 (0)	3.9 (2)	3.8 (1)	0.0 (0)	7.3 (4)	1.4 (1)	5.4 (21)
Number PVL positive	1	7	0	1	1	0	2	1	13
Number PVL negative	0	5	0	1	0	0	2	0	8
ST97-IV	– <sup>b</sup> (1)	6.6 (9)	0.0 (0)	9.8 (5)	0.0 (0)	– <sup>b</sup> (1)	3.6 (2)	4.3 (3)	5.4 (21)
Number PVL positive	0	0	0	0	0	0	0	0	0
Number PVL negative	1	9	0	5	0	1	2	3	21
ST953-IV	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	15.9 (11)	2.8 (11)
Number PVL positive	0	0	0	0	0	0	0	0	0
Number PVL negative	0	0	0	0	0	0	0	11	11
ST8-IV	0.0 (0)	5.9 (8)	0.0 (0)	2.0 (1)	0.0 (0)	0.0 (0)	3.6 (2)	0.0 (0)	2.8 (11)
Number PVL positive	0	5	0	1	0	0	2	0	8
Number PVL negative	0	3	0	0	0	0	0	0	3
Other clones (n = 56)	– <sup>b</sup> (1)	28.7 (39)	10.5 (4)	29.4 (15)	26.9 (7)	– <sup>b</sup> (4)	45.5 (25)	20.3 (14)	28.1 (109)
Number PVL positive	0	4	0	4	1	0	8	2	19
Number PVL negative	1	35	4	11	6	4	17	12	90
<b>Total</b>	<b>6</b>	<b>136</b>	<b>38</b>	<b>51</b>	<b>26</b>	<b>7</b>	<b>55</b>	<b>69</b>	<b>388</b>
PVL positive	3	38	31	25	14	0	24	31	166
PVL negative	3	98	7	26	12	7	31	38	222

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

b Insufficient numbers (<10) to calculate percentage.

**Table 6: Resistance combinations for the most predominant community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) clones, AGAR, 2022<sup>a</sup>**

Resistance pattern <sup>b</sup>	ST93-IV	ST22-IV	ST5-IV	ST45-V	ST1-IV	ST30-IV	ST97-IV	ST953-IV	ST8-IV
<b>Single resistance</b>									
β-lactams only	41		22		10	11	4	4	3
<b>Resistance to methicillin and one antimicrobial</b>									
Cip		20		1				2	2
Clin					1				
Ery	1		2				3		
Fus			1			1	1		
Rif							2		
Tet	1								
<b>Resistance to methicillin and two antimicrobials</b>									
CipGen		1							
CipTet		1		1					
ClinTet								1	
EryCip		3			1				
EryClin	12		1		2	1	1		
<b>Resistance to methicillin and three antimicrobials</b>									
CipTetGen				5					
CipRifFus				1					
CipSxtGen		1							
EryClinTet					1	1			
EryClinCip		7	1	1					
EryCipTet				1					
<b>Resistance to methicillin and four antimicrobials</b>									
EryCipTetGen				1					
EryClinCipGen				1					
EryClinCipTet		1		2					
<b>Resistance to methicillin and five antimicrobials</b>									
EryClinCipTetFus				1					
ErylcrCipTetGen				4					
<b>Resistance to methicillin and six antimicrobials</b>									
ErylcrTetGenRifFus									1
<b>Total</b>	55	34	27	19	15	14	11	7	6

a Only data from isolates tested against all antimicrobial groups were included (n = 188).

b Cip: ciprofloxacin; Clin: clindamycin; Ery: erythromycin; Fus: fusidic acid; Gen: gentamicin; Rif: rifampicin; Sxt: cotrimoxazole; Tet: tetracycline; Tei: teicoplanin.



## Panton-Valentine leucocidin

Overall 166 (37.0%) of MRSA were PVL positive. All were CA-MRSA (Table 3).

## Discussion

The AGAR surveillance programs collect data on antimicrobial resistance, focussing on bloodstream infections caused by *S. aureus*, *Enterococcus* and gram-negative bacilli including the *Enterobacteriales*, *Pseudomonas aeruginosa* and *Acinetobacter* species. All data collected in the AGAR programs are generated as part of routine patient care in Australia, with most data available through laboratory and hospital bed management information systems. Isolates are referred to a central laboratory where strain and antimicrobial resistance determinant characterisation are performed. As the programs are similar to those conducted in Europe, comparison of Australian antimicrobial resistance data with other countries is possible.<sup>19,20</sup>

In ASSOP 2022, methicillin resistance was found in 15.0% (95% CI: 13.8–26.3) of the 3,214 SAB episodes. In the 2021 European Centre for Disease Prevention and Control (ECDC) SAB surveillance program, methicillin resistance ranged from 0.9% (95% CI: 0.5–1.5) in Norway to 42.9% (95% CI: 35.5–50.5) in Cyprus.<sup>21</sup>

A decrease in methicillin-resistant SAB has been reported in several parts of the world,<sup>22,23</sup> 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.<sup>24–27</sup> The percentage of methicillin-resistant SAB in Australia has decreased significantly over the ten years of ASSOP, ranging from 18.5% in 2013 to 15.1% in 2022 ( $X^2$  for linear trend = 12.993;  $p = 0.0003$ ).<sup>i</sup> There have also been significant decreases in HA-MRSA from 41.0% to 13.6% ( $p < 0.0001$ ) and

in hospital-onset MRSA from 38.0% to 24.5% ( $p < 0.0001$ ) over the ten ASSOP surveys.<sup>11,28–35</sup> Over the same time period, significant increases in CA-MRSA from 59.0% to 85.0% ( $p < 0.01$ ) and in community-onset MRSA from 61.1% to 75.5% ( $p < 0.01$ ) have been observed. 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 2022, the all-cause mortality at 30 days was 17.5% (95% CI: 16.7–19.0). A significant difference in mortality was observed between methicillin-resistant SAB (21.4%) and methicillin-susceptible SAB (16.8%) ( $p = 0.02$ ).

With the exception of the  $\beta$ -lactams and erythromycin, antimicrobial resistance in MSSA remains rare. However, for MRSA, in addition to the  $\beta$ -lactams, approximately 31% of isolates were resistant to ciprofloxacin; 30% to erythromycin; 13% to tetracycline; and 11% to gentamicin. Antimicrobial resistance was identified in the two predominant HA-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, cotrimoxazole, tetracycline and gentamicin resistant. In the early 1980s, the multi-resistant ST239-III [3A] (Aus-2/3 EMRSA) was the dominant HA-MRSA clone in Australian hospitals. However, in 2013, the first ASSOP survey showed ST22-IV [2B] (EMRSA-15) was replacing ST239-III [3A] (Aus-2/3 EMRSA) as the most prevalent HA-MRSA, and this change has occurred throughout most of the country. In ASSOP 2022, 12.2% of MRSA were characterised as ST22-IV [2B] (EMRSA-15), and 1.3% as ST293-III [3A].

In ASSOP 2022, ST93-IV [2B] (Queensland clone) remained the predominant CA-MRSA clone (26.8% of CA-MRSA) in Australia. CA-MRSA, in particular the ST45-V [5C2&5] clone (8.5% of MRSA), has acquired multiple

i Rates include only those laboratories that participated in all years 2013–2022.

antimicrobial resistance determinants including resistance to ciprofloxacin, erythromycin, clindamycin, gentamicin and tetracycline.

Approximately 21.6% of SAB caused by CA-MRSA was hospital-onset. As transmission of CA-MRSA in Australian hospitals is thought to be rare,<sup>36,37</sup> it is likely that many of the hospital-onset CA-MRSA SAB infections reported in ASSOP 2022 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 clone) 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 2022 has demonstrated antimicrobial resistance in SAB in Australia continues to be a significant problem and is associated with a high mortality. This may be due, in part, to the high prevalence of community-associated methicillin-resistant SAB in Australia, which is higher than in most EU/EEA countries. Consequently, MRSA must remain a public health priority; continuous surveillance of SAB and its outcomes, and the implementation of comprehensive MRSA management strategies targeting hospitals and long-term care facilities are essential.

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