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

Bloodstream Annual Report 2021

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# Abstract

From 1 January to 31 December 2021, forty-eight institutions around Australia participated in the Australian Staphylococcus aureus Surveillance Outcome Programme (ASSOP). The aim of ASSOP 2021 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 2,928 SAB episodes were reported, of which 78.4% were community-onset. Overall, 16.9% of S. aureus isolates were methicillin resistant. The 30-day all-cause mortality associated with methicillin-resistant SAB was 15.0%, which was not significantly different from the 14.4% all-cause mortality associated with methicillin-susceptible SAB (p = 0.7). 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 36% of methicillin-resistant S. aureus (MRSA) were resistant to ciprofloxacin; 30% to erythromycin; 15% to tetracycline; 16% to gentamicin; and 3% to co-trimoxazole. When applying the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints, teicoplanin resistance was detected in three S. aureus isolates. Resistance to vancomycin or linezolid was not detected. Resistance to non-β-lactam antimicrobials was largely attributable to the healthcare-associated MRSA (HA-MRSA) clone ST22-IV [2B] (EMRSA-15), and the community-associated MRSA (CA-MRSA) clone ST45-V [5C2&5] which has acquired multiple antimicrobial resistance determinants including ciprofloxacin, erythromycin, clindamycin, gentamicin and tetracycline. The ST22-IV [2B] (EMRSA-15) clone is the predominant HA-MRSA clone in Australia. Nonetheless, 85% of methicillin-resistant SAB episodes were due to CA-MRSA clones. Although polyclonal, approximately 68% of CA-MRSA clones were characterised as ST93-IV [2B] (Queensland clone); ST45-V [5C2&5]; ST5-IV [2B]; ST1-IV [2B]; ST30-IV [2B]; and ST97-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.1 Although there are a wide variety of manifestations of serious invasive infection caused by S. aureus, in the 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 In 2009 the Infectious Diseases Society of America highlighted S. aureus as one of the key problem bacteria or ESKAPE pathogens[[1]](#footnote-2) requiring new therapies.3

Although prolonged antimicrobial therapy and prompt source control are used to treat SAB,4 mortality ranges from as low as 2.5% to as high as 40%.5–8 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%.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, now known as the Australian Staphylococcus aureus Surveillance Outcome Programme (ASSOP).11 The primary objective of ASSOP 2021 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 laboratories servicing 48 hospitals from all Australian states and mainland territories.

## Collection period

From 1 January to 31 December 2021, the 30 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 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 Vitek® 2 (bioMérieux, France) or the BD Phoenix™ (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® (bioMérieux, France) or the MALDI Biotyper® (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)12 and European Committee on Antimicrobial Susceptibility Testing (EUCAST)13 MIC breakpoints were utilised for interpretation.Linezolid and daptomycin non-susceptible isolates were retested by Etest® (bioMérieux) using the Mueller-Hinton agar recommended by the manufacturer. The control strain used was S. aureus ATCC® 29213. High-level mupirocin resistance was determined by the BD Phoenix™ or by using a mupirocin 200 μg disk according to CLSI guidelines on all isolates with a mupirocin MIC > 8 mg/L by Vitek® 2. 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, and linezolid.

Molecular testing was performed by whole genome sequencing (WGS) using the NextSeq 500 platform (Illumina, USA). Sequence reads were analysed using the Nullarbor pipeline.14 The SCCmec type was determined using KmerFinder v3.2,15–17 and the SCCmec database curated from the Center for Genomic Epidemiology database.18

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 2021, there were 2,928 unique episodes of SAB identified. A significant difference (p < 0.0001) was observed in patient sex, with 1,937 (66.2%) being male (95% confidence interval [95% CI]: 64.0–68.3). The mean age of patients was 58 years, ranging from 0 to 100 years, with a median age of 62 years. Overall, 2,296 episodes (78.4%) were community-onset (95% CI: 76.7–80.1). All-cause mortality at 30 days (where known) was 14.5% (95% CI: 11.0–18.7). Methicillin-resistant SAB mortality was 15.0% (95% CI: 7.1–26.5); methicillin-susceptible SAB mortality was 14.4% (95% CI: 10.5–19.0).

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

Overall, 2,433 of the 2,928 isolates (83.1%) were methicillin susceptible, of which 1,825/2,433 (75.3%) were penicillin resistant (MIC > 0.12 mg/L). All penicillin-susceptible isolates (MIC ≤ 0.12 mg/L) were tested either by blaZ PCR or penicillin disc diffusion (zone-edge test). On testing, a further 65 phenotypically penicillin-susceptible isolates were considered penicillin resistant. Fifty-two penicillin-susceptible isolates were not available for confirmation. Apart from erythromycin resistance (13.0% and 13.5% using CLSI and EUCAST breakpoints respectively), resistance to the non-β-lactam antimicrobials amongst MSSA was rare, ranging from 0% to 2.6% (Table 1). There were six isolates reported by Vitek® 2 as non-susceptible to daptomycin (MIC > 1.0 mg/L). By Etest®, all six isolates were considered daptomycin susceptible (MICs 0.38–1.0 mg/L).

****Table 1: The number and proportion of methicillin-susceptible *Staphylococcus aureus* (MSSA) isolates non-susceptible to penicillin and the non-β-lactam antimicrobials, AGAR, 2021****

|  |  | CLSI | | EUCAST | |
| --- | --- | --- | --- | --- | --- |
| Antimicrobial | Isolates *(n*) | Intermediate % (*n*) | Resistant % (*n*) | Susceptible, increased exposure % (*n*) | Resistant % (*n*) |
| Benzylpenicillin | 2,425 | –a | 75.3 (1,825) | –a | 75.3 (1,825) |
| Benzylpenicillinb | 2,381 | –a | 79.4 (1,890) | –a | 79.4 (1,890) |
| Cefoxitin (methicillin)c | 2,928 | –a | 16.9 (495) | –a | 16.9 (495) |
| Ciprofloxacin | 2,429 | 0.0 (0) | 2.6 (64) | 96.9 (505) | 3.1 (16) |
| Clindamycin (constitutive) | 2,427 | 0.0 (0) | 1.2 (29) | –a | 1.6 (39) |
| Clindamycin (inducible + constitutive resistance) | 2,427 | 0.0 (0) | 10.5 (254) | –a | 11.4 (276) |
| Daptomycin | 2,432 | –a | 0.0 (0)d | –a | 0.0 (0) |
| Erythromycin | 2,428 | 28.7 (697) | 13.0 (315) | 0.5 (12) | 13.5 (328) |
| Fusidic acid | 2,429 | –e | –e | –a | 2.1 (50) |
| Gentamicin | 2,429 | 0.7 (17) | 0.9 (21) | –a | 2.6 (64) |
| Linezolid | 2,432 | –a | 0.0 (0) | –a | 0.0 (0) |
| Mupirocin (high-level)f | 1,849 | –a | 1.2 (22) | –a | 1.2 (22) |
| Rifampicin | 2,426 | 0.1 (2) | 0.1 (3) | –g | 0.2 (6) |
| Teicoplanin | 2,418 | 0.0 (0) | 0.0 (0) | –a | 0.0 (1) |
| Tetracycline/doxycyclineh | 2,429 | 0.1 (3) | 2.2 (54) | 0.5 (13) | 2.4 (59) |
| Trimethoprim/sulfamethoxazole | 2,418 | –a | 0.2 (6) | 0.0 (0) | 0.2 (6) |
| Vancomycin | 2,432 | 0.0 (0) | 0.0 (0) | –a | 0.0 (0) |

a No category defined.

b Beta-lactamase adjusted.

c Resistance as determined by cefoxitin screen (Vitek) or cefoxitin MIC (Phoenix).

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

e No guidelines for indicated species (FUSc).

f Mupirocin.

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

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

By Vitek® 2 or BD PhoenixTM, three isolates were reported as linezolid resistant (MIC > 4 mg/L). One isolate was unavailable for confirmation. By Etest®, the remaining two isolates had a linezolid MIC of 1.5 mg/L and were therefore considered susceptible. Using EUCAST interpretive criteria, 29 isolates were reported by Vitek® 2 as teicoplanin resistant (MIC > 2.0 mg/L). Fourteen isolates were unavailable for confirmation. By Etest®, 14 of the 15 referred isolates had a teicoplanin MIC of ≤ 2.0 mg/L. One isolate with an MIC of 3.0 mg/L was considered resistant. All MSSA were vancomycin susceptible. Only 1,849 of the 2,433 MSSA (76.0%) had mupirocin susceptibility testing performed, of which 22 (1.2%) were high-level mupirocin resistant. Fourteen of the 22 mupirocin resistant MSSA isolates were referred from Queensland; 13 of the 22 isolates were also resistant to fusidic acid. Of the 2,247 isolates tested, 39 (1.6%) were constitutively resistant to clindamycin; however, 276 (11.4%) were classified as having both constitutive and inducible clindamycin resistance. Only 2.5% of MSSA were multi-resistant. By Vitek® 2 or BD PhoenixTM, fifty-two isolates were reported as non-susceptible to cotrimoxazole. Eight isolates were unavailable for confirmation. By disc susceptibility testing, 41/56 (73.2%) were susceptible by both CLSI and EUCAST criteria.

## MRSA antimicrobial susceptibility

The proportion of S. aureus that were MRSA was 16.9% (95% CI: 13.7–20.5). Of the 495 MRSA identified, 438 were cefoxitin-screen positive by Vitek® 2 and 57 had a cefoxitin MIC > 4 mg/L by BD Phoenix™. All MRSA isolates were penicillin resistant. Amongst the MRSA isolates, resistance to non-β-lactam antimicrobials was common, except for rifampicin, cotrimoxazole and fusidic acid where resistance ranged from 0% to 5.5% (Table 2). All MRSA were susceptible to vancomycin and linezolid. Four isolates were reported by Vitek® 2 as daptomycin non-susceptible (MIC > 1.0 mg/L). One isolate was unavailable for confirmation. By Etest®, two of the three isolates were considered daptomycin susceptible (MICs 0.75 and 1.0 mg/L). The remaining isolate was confirmed as non-susceptible by CLSI and resistant by EUCAST criteria (MIC 1.5 mg/L). Polymorphisms in genes encoding mprF, walK, walR, cls, rpoB, rpoC, pgsA and agrA were investigated. No known mutations were detected.

****Table 2: The number and proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates non-susceptible to penicillin and the non-β-lactam antimicrobials, AGAR, 2021****

|  |  | CLSI | | EUCAST | |
| --- | --- | --- | --- | --- | --- |
| Antimicrobial | Isolates (*n*) | Intermediate % (*n*) | Resistant % (*n*) | Susceptible, increased exposure % (*n*) | Resistant % (*n*) |
| Benzylpenicillin | 494 | –a | 100.0 (494) | –a | 100.0 (494) |
| Benzylpenicillinb | 495 | –a | 100.0 (495) | –a | 100.0 (495) |
| Cefoxitin (methicillin)c | 2,928 | –a | 16.9 (495) | –a | 16.9 (495) |
| Ciprofloxacin | 494 | 0.8 (4) | 34.8 (172) | 64.4 (318) | 35.6 (176) |
| Clindamycin (constitutive) | 493 | 0.4 (2) | 7.9 (39) | –a | 9.3 (46) |
| Clindamycin (inducible + constitutive resistance) | 494 | 0.4 (2) | 22.7 (112) | –a | 24.3 (120) |
| Daptomycin | 494 | –a | 0.2 (1)d | –a | 0.2 (1) |
| Erythromycin | 494 | 20.0 (99) | 29.6 (146) | 1.0 (5) | 30.2 (149) |
| Fusidic acid | 495 | –e | –e | –a | 5.5 (27) |
| Gentamicin | 494 | 5.7 (28) | 8.1 (40) | –a | 16.2 (80) |
| Linezolid | 495 | –a | 0.0 (0) | –a | 0.0 (0) |
| Mupirocin (high-level)f | 330 | –a | 0.9 (3) | –a | 0.9 (3) |
| Rifampicin | 494 | 0.0 (0) | 0.4 (2) | –g | 0.8 (4) |
| Teicoplanin | 495 | 0.0 (0) | 0.0 (0) | –a | 0.4 (2) |
| Tetracycline/doxycyclineh | 494 | 0.8 (4) | 12.8 (63) | 1.6 (8) | 14.8 (73) |
| Trimethoprim/sulfamethoxazole | 488 | –a | 2.7 (13) | 0.4 (2) | 2.7 (13) |
| Vancomycin | 495 | 0.0 (0) | 0.0 (0) | –a | 0.0 (0) |

a No category defined.

b Beta-lactamase adjusted.

c Resistance as determined by cefoxitin screen (Vitek) or cefoxitin MIC (Phoenix).

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

e No guidelines for indicated species (FUSc).

f Mupirocin.

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

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

By Vitek® 2, nine isolates were reported as teicoplanin resistant when using the EUCAST resistant breakpoint of > 2 mg/L (MICs = 4.0 mg/L). However, using the CLSI resistant breakpoint of > 8 mg/L, the isolates were classified as susceptible. By Etest®, seven of the nine isolates were considered susceptible (MICs 1.5 and 2.0 mg/L) and the remaining two isolates, each with MIC of 4.0 mg/L, were resistant by EUCAST criteria. Three of 330 MRSA isolates tested (0.9%) had high-level mupirocin resistance.

Of the 493 isolates tested, 39 (7.9%) and 46 (9.3%) were constitutively resistant to clindamycin by CLSI and EUCAST criteria respectively while 112 (22.7%) and 120 (24.3%) were classified as having both constitutive and inducible clindamycin resistance by CLSI and EUCAST criteria respectively.

By Vitek® 2 or BD PhoenixTM, 58 isolates were reported as non-susceptible to cotrimoxazole. Two isolates were unavailable for confirmation. By disc susceptibility testing, 41/56 (73.2%) were susceptible by both CLSI and EUCAST criteria.

Multi-resistance was identified in 21.6% of MRSA.

## MRSA molecular epidemiology

Whole genome sequencing was performed on 472 of the 495 MRSA (95.4%). Based on molecular typing, 71 (15.0%) and 401 (85.0%) of isolates were identified as healthcare-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) clones respectively (Table 3).

****Table 3: Proportion of healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus* (MRSA), AGAR, 2021 by clone, onset, and Panton-Valentine leucocidin (PVL) carriage****

| Clone | Clonal complex | Total, *n* | Community onset, % (*n*)a | Hospital onset, % (*n*)a | PVL positive, % (*n*)a |
| --- | --- | --- | --- | --- | --- |
| **Healthcare-associated** |  |  |  |  |  |
| ST22-IV (EMRSA-15) | 22 | 64 | 68.8 (44) | 31.3 (20) | 0.0 (0) |
| ST239-III (Aus2/3 EMRSA) | 8 | 6 | –b (4) | –b (2) | –b (0) |
| ST5-I (Cordoba) | 5 | 1 | –b (0) | –b (1) | –b (0) |
| **Total HA-MRSA** |  | **71** | **67.6 (48)** | **32.4 (23)** | **0.0 (0)** |
| **Community-associated** |  |  |  |  |  |
| ST93-IV | 93 | 99 | 91.9 (91) | 8.1 (8) | 94.9 (94) |
| ST45-V | 45 | 62 | 80.6 (50) | 19.4 (12) | 0.0 (0) |
| ST5-IV | 5 | 48 | 81.3 (39) | 18.8 (9) | 37.5 (18) |
| ST1-IV | 1 | 28 | 75.0 (21) | 25.0 (7) | 7.1 (2) |
| ST30-IV | 30 | 20 | 85.0 (17) | 15.0 (3) | 80.0 (16) |
| ST97-IV | 97 | 15 | 66.7 (10) | 33.3 (5) | 0.0 (0) |
| ST22-IV | 22 | 9 | –b (5) | –b (4) | –b (9) |
| ST88-IV | 88 | 8 | –b (5) | –b (3) | –b (0) |
| ST59-IV | 59 | 7 | –b (1) | –b (6) | –b (0) |
| ST6-IV | 6 | 7 | –b (6) | –b (1) | –b (3) |
| ST8-IV | 8 | 7 | –b (6) | –b (1) | –b (0) |
| ST953-IV | 97 | 7 | –b (6) | –b (1) | –b (0) |
| ST72-IV | 8 | 5 | –b (4) | –b (1) | –b (0) |
| ST78-IV | 8 | 5 | –b (3) | –b (2) | –b (0) |
| ST188-IV | 188 | 4 | –b (3) | –b (1) | –b (0) |
| ST6145-V | 45 | 4 | –b (3) | –b (1) | –b (0) |
| ST872-IV | 1 | 4 | –b (3) | –b (1) | –b (0) |
| ST5-V | 5 | 3 | –b (2) | –b (1) | –b (0) |
| ST5-VI | 5 | 3 | –b (1) | –b (2) | –b (0) |
| ST149-IV | 5 | 2 | –b (1) | –b (1) | –b (2) |
| ST2250-IV | 2250 | 2 | –b (2) | –b (0) | –b (0) |
| ST45-IV | 45 | 2 | –b (1) | –b (1) | –b (0) |
| ST59-V | 59 | 2 | –b (1) | –b (1) | –b (0) |
| ST5-unk | 5 | 2 | –b (1) | –b (1) | –b (0) |
| ST7696-V | 45 | 2 | –b (2) | –b (0) | –b (0) |
| ST7709-IV | 97 | 2 | –b (2) | –b (0) | –b (0) |
| ST8-novel | 8 | 2 | –b (2) | –b (0) | –b (0) |
| ST121-V | 121 | 1 | –b (1) | –b (0) | –b (0) |
| ST1232-V | 398 | 1 | –b (1) | –b (0) | –b (0) |
| ST1524-IV | 5 | 1 | –b (1) | –b (0) | –b (1) |
| ST188-V | 188 | 1 | –b (0) | –b (1) | –b (0) |
| ST1-novel | 1 | 1 | –b (1) | –b (0) | –b (0) |
| ST2048-IV | 395 | 1 | –b (0) | –b (1) | –b (0) |
| ST2884-V | 88 | 1 | –b (1) | –b (0) | –b (0) |
| ST3628-V | 5 | 1 | –b (1) | –b (0) | –b (1) |
| ST3921-IV | 30 | 1 | –b (1) | –b (0) | –b (0) |
| ST398-V | 398 | 1 | –b (1) | –b (0) | –b (0) |
| ST4301-IV | 22 | 1 | –b (1) | –b (0) | –b (0) |
| ST508-IV | 45 | 1 | –b (0) | –b (1) | –b (0) |
| ST5213-IV | 1 | 1 | –b (0) | –b (1) | –b (0) |
| ST5662-IV | 5 | 1 | –b (1) | –b (0) | –b (0) |
| ST6149-IV | 97 | 1 | –b (1) | –b (0) | –b (1) |
| ST6151-IV | 93 | 1 | –b (1) | –b (0) | –b (0) |
| ST672-V | 672 | 1 | –b (1) | –b (0) | –b (1) |
| ST6963-IV | 22 | 1 | –b (1) | –b (0) | –b (0) |
| ST72-V | 8 | 1 | –b (1) | –b (0) | –b (0) |
| ST73-IV | 5 | 1 | –b (1) | –b (0) | –b (0) |
| ST7684-IV | 6 | 1 | –b (0) | –b (1) | –b (1) |
| ST7685-V | Singleton | 1 | –b (1) | –b (0) | –b (0) |
| ST7697-IV | 5 | 1 | –b (1) | –b (0) | –b (1) |
| ST7698-IV | 5 | 1 | –b (1) | –b (0) | –b (0) |
| ST7699-V | 45 | 1 | –b (1) | –b (0) | –b (0) |
| ST7700-IV | 1 | 1 | –b (0) | –b (1) | –b (1) |
| ST7701-IV | 5 | 1 | –b (1) | –b (0) | –b (0) |
| ST7702-IV | 1 | 1 | –b (0) | –b (1) | –b (0) |
| ST7703-IV | 1 | 1 | –b (1) | –b (0) | –b (0) |
| ST7704-novel | 398 | 1 | –b (1) | –b (0) | –b (0) |
| ST7705-IV | 22 | 1 | –b (1) | –b (0) | –b (0) |
| ST7706-IV | 398 | 1 | –b (1) | –b (0) | –b (0) |
| ST7707-IV | 1 | 1 | –b (0) | –b (1) | –b (0) |
| ST7708-IV | 93 | 1 | –b (1) | –b (0) | –b (0) |
| ST7711-IV | 1 | 1 | –b (1) | –b (0) | –b (1) |
| ST7-IV | 7 | 1 | –b (1) | –b (0) | –b (0) |
| ST80-IV | 80 | 1 | –b (0) | –b (1) | –b (0) |
| ST834-IV | Singleton | 1 | –b (1) | –b (0) | –b (0) |
| ST87-IV | 59 | 1 | –b (1) | –b (0) | –b (0) |
| ST88-novel | 88 | 1 | –b (1) | –b (0) | –b (0) |
| **Total CA-MRSA** |  | **401** | **79.6 (319)** | **20.4 (82)** | **37.9 (152)** |
| MRSA typed |  | 472 | 77.8 (367) | 22.2 (105) | 32.2 (152) |

a Percentage of the clone.

b Insufficient numbers (<10) to calculate percentage.

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

For the 71 HA-MRSA isolates, 23 (32.4%) were classified as hospital-onset and 48 (67.6%) were classified as community-onset. Based on the multilocus sequence type (MLST) and the SCCmec type, three HA-MRSA clones were identified: 64 isolates of ST22-IV [2B] (EMRSA-15) (13.6 % of MRSA typed and 2.2% of S. aureus); six isolates of ST239-III [3A] (Aus-2/3 EMRSA) (1.3% and 0.2%), and one isolate of ST5-I [1B] (Cordoba strain) (Table 3).

The dominant HA-MRSA clone in Australia in 2021 was ST22-IV [2B] (EMRSA-15), accounting for 90.1% of HA-MRSA; it was identified in all states and territories (Table 4). ST22-IV [2B] (EMRSA-15) is Panton-Valentine Leucocidin toxin (PVL) negative and, using CLSI breakpoints, 95.3% and 59.4% were ciprofloxacin and erythromycin non-susceptible respectively. Overall, 31.3% of ST22-IV [2B] (EMRSA-15) were hospital-onset.

ST239-III [3A] (Aus-2/3 EMRSA) accounted for 8.5% of HA-MRSA and was only identified in New South Wales and South Australia (Table 4). PVL negative ST239-III [3A] (Aus-2/3 EMRSA) were typically resistant to erythromycin (100%); cotrimoxazole (100%); ciprofloxacin (100%); gentamicin (100%); tetracycline (100%); and clindamycin (66.7%). Overall, 33.3% of ST239-III [3A] (Aus-2/3 EMRSA) were hospital-onset.

****Table 4: The number and proportion of healthcare-associated methicillin-resistant *Staphylococcus aureus* (MRSA) clones, AGAR, 2021, by state and territory****

|  | Percentage (n)a | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Clone | ACT | NSW | NT | Qld | SA | Tas. | Vic. | WA | Australia |
| ST22-IV (EMRSA-15) | –b (3) | 79.3 (23) | –b (2) | –b (2) | –b (5) | –b (2) | 100.0 (17) | 100.0 (10) | 90.1 (64) |
| ST239-III (Aus2/3 EMRSA) | –b (0) | 17.2 (5) | –b (0) | –b (0) | –b (1) | –b (0) | 0.0 (0) | 0.0 (0) | 8.5 (6) |
| ST5-1 (Cordoba) | –b (0) | 3.4 (1) | –b (0) | –b (0) | –b (0) | –b (0) | 0.0 (0) | 0.0 (0) | 1.4 (1) |
| **Total** | **3** | **29** | **2** | **2** | **6** | **2** | **17** | **10** | **71** |

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.

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

For the 401 CA-MRSA isolates, 82 episodes (20.4%) were classified as hospital-onset and 319 (79.6%) as community-onset. Based on the MLST and the SCCmec type, 67 CA-MRSA clones were identified (Table 3). Overall, 67.8% of CA-MRSA were classified into six clones each having ten or more isolates: 99 isolates of ST93-IV [2B] (Queensland clone) (24.7% of MRSA typed and 3.4% of S. aureus); 62 isolates of ST45-V [5C2&5] (15.5% and 2.1%); 48 isolates of ST5-IV [2B] (12.0% and 1.7%); 28 isolates of ST1-IV [2B] (7.0% and 1.0%); 20 isolates of ST30-IV [2B] (5.0% and 0.7%) and 15 isolates of ST97-IV [2B] (3.7% and 0.5%).

ST93-IV [2B] (Queensland CA-MRSA) accounted for 24.7% of CA-MRSA, ranging from 0% in Tasmania to 60.6% in the Northern Territory (Table 5). Typically PVL positive, 91.9% of ST93-IV [2B] were community-onset.

****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, 2021****

|  | Percentage (*n*)a | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Clone | ACT | NSW | NT | Qld | SA | Tas. | Vic. | WA | Australia |
| ST93-IV (Qld CA-MRSA) | 9.1 (1) | 10.4 (12) | 60.6 (20) | 30.5 (18) | 23.5 (8) | –b (0) | 12.7 (7) | 37.9 (33) | 24.7 (99) |
| Number PVL positive | 0 | 12 | 20 | 17 | 7 | 0 | 7 | 31 | 94 |
| Number PVL negative | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 2 | 5 |
| ST45-V | 36.4 (4) | 31.3 (36) | 0.0 (0) | 5.1 (3) | 2.9 (1) | –b (0) | 29.1 (16) | 2.3 (2) | 15.5 (62) |
| Number PVL positive | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Number PVL negative | 4 | 36 | 0 | 3 | 1 | 0 | 16 | 2 | 62 |
| ST5-IV | 0.0 (0) | 7.0 (8) | 15.2 (5) | 16.9 (10) | 8.8 (3) | –b (3) | 7.3 (4) | 17.2 (15) | 12.0 (48) |
| Number PVL positive | 0 | 0 | 3 | 0 | 1 | 2 | 2 | 10 | 18 |
| Number PVL negative | 0 | 8 | 2 | 10 | 2 | 1 | 2 | 5 | 30 |
| ST1-IV | 9.1 (1) | 7.0 (8) | 6.1 (2) | 10.2 (6) | 14.7 (5) | –b (2) | 1.8 (1) | 3.4 (3) | 7.0 (28) |
| Number PVL positive | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 2 |
| Number PVL negative | 1 | 8 | 2 | 4 | 5 | 2 | 1 | 3 | 26 |
| ST30-IV | 0.0 (0) | 8.7 (10) | 0.0 (0) | 3.4 (2) | 0.0 (0) | –b (1) | 7.3 (4) | 3.4 (3) | 5.0 (20) |
| Number PVL positive | 0 | 9 | 0 | 1 | 0 | 1 | 3 | 2 | 16 |
| Number PVL negative | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 4 |
| ST97-IV | 0.0 (0) | 6.1 (7) | 0.0 (0) | 5.1 (3) | 0.0 (0) | –b (0) | 7.3 (4) | 1.1 (1) | 3.7 (15) |
| Number PVL positive | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Number PVL negative | 0 | 7 | 0 | 3 | 0 | 0 | 4 | 1 | 15 |
| Other clones (n = 61) | 45.5 (5) | 29.6 (34) | 18.2 (6) | 28.8 (17) | 50.0 (17) | –b (1) | 34.5 (19) | 34.5 (30) | 32.2 (129) |
| Number PVL positive | 1 | 5 | 1 | 4 | 4 | 0 | 6 | 1 | 22 |
| Number PVL negative | 4 | 29 | 5 | 13 | 13 | 1 | 13 | 29 | 107 |
| **Total** | **11** | **115** | **33** | **59** | **34** | **7** | **55** | **87** | **401** |
| PVL positive | 1 | 26 | 24 | 24 | 12 | 3 | 18 | 44 | 152 |
| PVL negative | 10 | 89 | 9 | 35 | 22 | 4 | 37 | 43 | 249 |

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.

ST45-V [5C2&5] accounted for 15.5% of CA-MRSA and was isolated primarily in New South Wales and Victoria (Table 5). All isolates were PVL negative. Overall, 80.6% of ST45-V [5C2&5] were community-onset.

ST5-IV [2B] accounted for 12.0% of CA-MRSA and was isolated in all regions of Australia except the Australian Capital Territory, ranging from 7.0% in New South Wales to 17.2% in Western Australia (Table 5). Overall, 37.5% of ST5-IV [2B] were PVL positive and 81.3% of ST5-IV [2B] were community-onset.

ST1-IV [2B] accounted for 7.0% of CA-MRSA and was isolated in all regions of Australia, ranging from 1.8% in Victoria to 14.7% in South Australia (Table 5). Overall, 7.1% of ST1-IV [2B] were PVL positive and 75.9% of ST1-IV [2B] were community-onset.

ST30-IV [2B] accounted for 5.0% of CA-MRSA and was isolated in all regions of Australia except South Australia, the Northern Territory and the Australian Capital Territory, ranging from 3.4% in Queensland and Western Australia to 8.7% in New South Wales (Table 5). Overall, 80.0% of ST30-IV [2B] were PVL positive and 85.0% of ST30-IV [2B] were community-onset.

ST97-IV [2B] accounted for 3.7% of CA-MRSA and was isolated in all regions except South Australia, Tasmania, the Northern Territory and the Australian Capital Territory, ranging from 1.1% in Western Australia to 7.3% in Victoria (Table 5). All isolates of ST97-IV [2B] were PVL negative and 66.7% of ST97-IV [2B] were community-onset.

Overall, 65.1% of CA-MRSA were non-multi-resistant, including 52.9% isolates resistant to the β-lactams only. A significant increase was seen in multi-resistant CA-MRSA isolates in ASSOP 2021 (34.9%) from 9.2% in ASSOP 2013.11 Multi-resistance was primarily due to the ST45-V [5C2&5] clone.

Resistance profiles for the six predominant CA-MRSA clones are shown in Table 6.

****Table 6: Resistance combinations for the most predominant CA-MRSA clones,a AGAR, 2021****

| Resistance patternb | ST93-IV | ST45-V | ST5-IV | ST1-IV | ST30-IV | ST97-IV |
| --- | --- | --- | --- | --- | --- | --- |
| **Single resistance** |  |  |  |  |  |  |
| β-lactams only | 85 |  | 29 | 16 | 19 | 13 |
| **Resistance to methicillin and one antimicrobial** |  |  |  |  |  |  |
| Cip |  | 8 |  |  | 1 |  |
| Dap |  |  |  | 1 |  |  |
| Ery |  |  | 1 | 1 |  | 2 |
| Fus |  |  | 2 | 3 |  |  |
| Sxt |  |  | 1 |  |  |  |
| Tet |  |  |  | 1 |  |  |
| Tei |  |  | 1 |  |  |  |
| **Resistance to methicillin and two antimicrobials** |  |  |  |  |  |  |
| CipFus |  | 1 |  |  |  |  |
| CipGen |  | 4 |  |  |  |  |
| CipTet |  | 7 |  |  |  |  |
| Ery Tet |  |  | 1 | 1 |  |  |
| EryCip |  | 1 | 1 | 1 |  |  |
| EryClin | 13 |  | 8 |  |  |  |
| **Resistance to methicillin and three antimicrobials** |  |  |  |  |  |  |
| CipTetGen |  | 14 |  |  |  |  |
| EryCipGen |  | 1 |  |  |  |  |
| EryClinFus |  |  | 1 | 3 |  |  |
| EryClinTet |  |  | 1 | 1 |  |  |
| EryClinCip |  | 1 | 1 |  |  |  |
| **Resistance to methicillin and four antimicrobials** |  |  |  |  |  |  |
| CipTetGenFus |  | 1 |  |  |  |  |
| CipTetGenRif |  | 1 |  |  |  |  |
| EryClinSxtCip |  |  | 1 |  |  |  |
| EryClinCipTet |  | 6 |  |  |  |  |
| **Resistance to methicillin and five antimicrobials** |  |  |  |  |  |  |
| EryClinCipTetGen |  | 15 |  |  |  |  |
| **Total** | **98** | **60** | **48** | **28** | **20** | **15** |

a Note: Only data from isolates tested against all antimicrobial groups were included (n =269).

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

## Panton-Valentine leucocidin

Overall, 152 MRSA (32.2%) were PVL positive. All were CA-MRSA (Table 3).

# Discussion

The AGAR surveillance programmes collect data on antimicrobial resistance, focussing on bloodstream infections caused by S. aureus, Enterococcus and gram-negative bacilli including the Enterobacterales, Pseudomonas aeruginosa and Acinetobacter species. All data collected in the AGAR programmes 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 is performed. As the programmes are similar to those conducted in Europe,19 comparison of Australian antimicrobial resistance data with other countries is possible.

In ASSOP 2021, methicillin resistance was found in 16.9% (95% CI: 13.7–20.5) of the 2,928 SAB episodes. In the 2021 European Centre for Disease Prevention and Control (ECDC) SAB surveillance programme, the European Union/European Economic Area (EU/EEA) population-weighted mean percentage of S. aureus resistant to methicillin was 14.3% (95% CI: 14.1–14.6), ranging from 0.9% (95% CI: 0.5–1.5) in Norway to 42.9% (95% CI: 35.5–50.5) in Cyprus.19

In Europe, the EU/EEA population-weighted mean percentage has significantly decreased from 23.2% in 2009 to 14.3% in 2021. A decrease in methicillin-resistant SAB has been reported in several parts of the world,20,21 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.22–26 The percentage of methicillin-resistant SAB in Australia, however, has not decreased significantly over the nine years of ASSOP, ranging from 18.8% in 2013 to 17.2% in 2021 (Χ2 for linear trend = 2.46; p = 0.11).[[2]](#footnote-3) Nonetheless, while a significant decrease in MRSA bacteraemia has not been seen in Australia, significant decreases in HA-MRSA from 41.0% to 15.0% (p < 0.0001) and in hospital-onset MRSA from 38.0% to 21.6% (p < 0.0001) have been observed over the nine ASSOP surveys.11,27–33 Over the same time period, significant increases in CA-MRSA from 59.0% to 85.0% (p < 0.0001) and in community-onset MRSA from 61.1% to 78.4% (p < 0.0001) 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 2021, the all-cause mortality at 30 days was 14.5% (95% CI: 11.0–18.7). No significant difference in mortality was observed between methicillin-resistant SAB and methicillin-susceptible SAB (p = 0.8).

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 30% of isolates were resistant to erythromycin; 35% to ciprofloxacin; 15% to tetracycline; and 16% 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 2021, 13.6% of MRSA were characterised as ST22-IV [2B] (EMRSA-15).

In ASSOP 2021, ST93-IV [2B] (Queensland clone) remained the predominant CA-MRSA clone (24.7% of CA-MRSA) in Australia. CA-MRSA, in particular the ST45-V [5C2&5] clone (13.1% of MRSA), has acquired multiple antimicrobial resistance determinants including ciprofloxacin, erythromycin, clindamycin, gentamicin and tetracycline.

Approximately 20.4% of SAB caused by CA-MRSA was hospital-onset. As transmission of CA-MRSA in Australian hospitals is thought to be rare,34,35 it is likely that many of the hospital-onset CA-MRSA SAB infections reported in ASSOP 2021 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 2021 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 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 strategies targeting hospitals and long-term care facilities are essential.

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1. ESKAPE: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species. [↑](#footnote-ref-2)
2. Rates include only those laboratories that participated in all years 2013–2021. [↑](#footnote-ref-3)