Australian Group on Antimicrobial Resistance (AGAR) Australian *Staphylococcus aureus* Sepsis Outcome Programme (ASSOP) Annual Report 2018

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# Abstract

From 1 January to 31 December 2018, thirty-six institutions around Australia participated in the Australian Staphylococcus aureus Sepsis Outcome Programme (ASSOP). The aim of ASSOP 2018 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 2,673 S. aureus bacteraemia episodes were reported, of which 78.9% were community-onset. A total of 17.4% of S. aureus isolates were methicillin resistant. The 30-day all-cause mortality associated with methicillin-resistant SAB was 17.1% which was not significantly higher than the 13.6% mortality associated with methicillin-susceptible SAB (p = 0.1). 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, 36% to ciprofloxacin and approximately 13% resistant to co-trimoxazole, tetracycline and gentamicin. When applying the EUCAST breakpoints teicoplanin resistance was detected in two 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). The ST22-IV [2B] (EMRSA-15) clone is the predominant healthcare-associated clone in Australia. Seventy-eight percent of methicillin-resistant SAB episodes in 2018 were due to community-associated clones. Although polyclonal, approximately 76.3% of community-associated clones were characterised as ST93-IV [2B] (Queensland CA-MRSA), ST5-IV [2B], ST45-VT [5C2&5], ST1-IV [2B], ST30-IV [2B], ST78-IV [2B] and ST97-IV [2B]. Community-associated MRSA, in particular the ST45-VT [5C2&5] clone, has acquired multiple antimicrobial resistance determinants including ciprofloxacin, erythromycin, clindamycin, gentamicin and tetracycline. The ST45-VT [5C2&5] clone accounted for 11.7% of CA-MRSA. As CA-MRSA is well established in the Australian community, it is important that antimicrobial resistance patterns in community- and healthcare-associated SAB are 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 bloodstream 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 2018 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 2018, 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 hospital-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. Identification of S. aureus was by morphology and by a positive result from at least one of the following tests: Vitek MS® (bioMérieux), matrix-assisted laser desorption ionization (MALDI) biotyper (Bruker Daltonics, USA), 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. The control strain used was S. aureus ATCC 29213. 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, co-trimoxazole, fusidic acid, rifampicin, high-level mupirocin, and linezolid.

Molecular testing was performed by whole genome sequencing (WGS) using the NextSeq platform (Illumina, San Diego, USA). Sequencing results were analysed using the Nullarbor pipeline.14 The spaTyper tool15 was applied to sequence data to determine spa types. SCCmec was determined using KmerFinder V 3.1,16 and using the SCCmec database curated from the CGE database.17,18

Chi-squared 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 2018, a total of 2,673 unique episodes of S. aureus bacteraemia were identified. A significant imbalance (p < 0.0001) was seen in patient sex, with 64.1% (1,713) being male (95% CI 62.3–65.9). The average age of patients was 57 years ranging from 0–100 years with a median age of 61 years. Overall 78.9% (2,108/2,673) of episodes were community onset (95% CI 77.3–80.4). All-cause mortality at 30 days was 14.2% (95% CI 12.7–15.8). Methicillin-resistant SAB mortality was 17.1% (95% CI 13.3–21.4) which was not significantly higher than for methicillin-susceptible SAB mortality (13.6%, 95% CI 12.0–15.3) (p = 0.1).

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

Overall, 82.6% (2,207) of the 2,673 isolates were methicillin susceptible of which 74.7% (1,649) were penicillin resistant (MIC > 0.12 mg/L). However as β-lactamase was detected in 91 phenotypically penicillin-susceptible isolates, 79.0% of MSSA were considered penicillin resistant. Apart from erythromycin non-susceptibility (18.0% and 10.7% using CLSI and EUCAST breakpoints respectively), resistance to the non-β-lactam antimicrobials amongst MSSA was rare, ranging from 0% to 3.2% (Table 1). There were six isolates reported by Vitek2® as non-susceptible to daptomycin (MIC > 1.0 mg/L). By Etest®, five of the isolates were considered susceptible (MICs 0.25–1.0 mg/L). The remaining isolate had an MIC of 2.0 mg/L and was confirmed as non-susceptible, however using WGS no known daptomycin mutations were identified. By Vitek2®, one isolate was linezolid resistant (MIC > 4 mg/L). However by Etest®, the isolate had an MIC ≤ 4 mg/L (2.0 mg/L) and was therefore considered linezolid susceptible. All MSSA were vancomycin and teicoplanin susceptible. Twenty-eight (1.3%) of 2,195 isolates had high-level mupirocin resistance, of which 20 isolates were referred from Queensland. Sixteen of the twenty-eight mupirocin-resistant MSSA were also resistant to fusidic acid. Inducible resistance to clindamycin was determined by the Vitek2® susceptibility system. Of the 1,880 isolates tested, 19.1% (360) were erythromycin non-susceptible / clindamycin susceptible (CLSI breakpoints) of which 51.7% (186) were classified as having inducible clindamycin resistance. Multi-resistance was uncommon in MSSA (1.8%, 38/2,144).

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

****Table 1: The number and proportion of methicillin-susceptible Staphylococcus aureus (MSSA) isolates non-susceptible to penicillin and the non-β-lactam antimicrobials, Australia, 2018****

| Antimicrobial | Number tested | Breakpoint (mg/L) | Non-susceptible |
| --- | --- | --- | --- |
| n | % |
| Penicillina | 2,202 | > 0.12b | 1,740 | 79.0 |
| Vancomycin | 2,206 | > 2b | 0 | 0.0 |
| Teicoplanin | 2,206 | > 8c | 0 | 0.0 |
| > 2d | 0 | 0.0 |
| Rifampicin | 2,200 | > 1c | 7 | 0.3 |
| > 0.5d | 7 | 0.3 |
| Fusidic Acid | 2,202 | > 1d | 71 | 3.2 |
| Gentamicin | 2,202 | > 4c | 15 | 0.7 |
| > 1d | 28 | 1.3 |
| Erythromycin | 2,149 | > 0.5c | 387 | 18.0 |
| > 2d | 231 | 10.7 |
| Clindamycin | 2,201 | > 0.5b | 30 | 1.4 |
| Tetracycline/doxycycline | 2,202 | > 4c | 59 | 2.7 |
| > 2d | 66 | 3.0 |
| Co-trimoxazole | 2,200 | > 2/38c | 66 | 3.0 |
| > 4/76d | 49 | 2.2 |
| Ciprofloxacin | 2,202 | > 1b | 60 | 2.7 |
| Nitrofurantoin | 2,041 | > 32c | 12 | 0.6 |
| Daptomycin | 2,206 | > 1b | 1 | 0.05 |
| Linezolid | 2,206 | > 4b | 0 | 0 |
| High-level mupirocin | 2,144 | > 256c | 28 | 1.3 |

a β-lactamase adjusted

b CLSI and EUCAST non-susceptible breakpoint

c CLSI non-susceptible breakpoint

d EUCAST non-susceptible breakpoint

## MRSA antimicrobial susceptibility

The proportion of S. aureus that were MRSA was 17.4% (95% CI 16.0–18.9). Of the 466 MRSA identified, 404 were cefoxitin screen positive by Vitek2® and 62 had a cefoxitin MIC > 4 mg/L by Phoenix™. Six of the 466 MRSA isolates were phenotypically penicillin susceptible (MIC ≤ 0.125 mg/L), however β-lactamase was detected in all six. Amongst the MRSA isolates, non-susceptibility to non-β-lactam antimicrobials was common except for nitrofurantoin, rifampicin and fusidic acid where resistance ranged from 1.6% to 4.5% (Table 2). All MRSA were vancomycin susceptible. There were nine isolates reported by Vitek2® as non-susceptible to daptomycin (MIC > 1.0 mg/L). One isolate was not available for confirmation. By Etest®, three of the isolates were considered susceptible (MIC 1.0 mg/L). The remaining five isolates had Etest® MICs of 1.5 mg/L (two isolates) and 2.0 mg/L (three isolates) 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-L826F and mprF-S295L. No known daptomycin mutations were found in the other three isolates.

****Table 2: The number and proportion of methicillin-resistant Staphylococcus aureus (MRSA) isolates non-susceptible to penicillin and the non-β-lactam antimicrobials, Australia, 2018****

| Antimicrobial | Number tested | Breakpoint (mg/L) | Non-susceptible (%) |
| --- | --- | --- | --- |
| n | % |
| Penicillin | 466 | > 0.12a | 466 | 100 |
| Vancomycin | 466 | > 2a | 0 | 0 |
| Teicoplanin | 466 | > 8b | 0 | 0 |
| > 2c | 2 | 0.4 |
| Rifampicin | 466 | > 1b | 8 | 1.7 |
| > 0.5c | 8 | 1.7 |
| Fusidic Acid | 464 | > 1c | 21 | 4.5 |
| Gentamicin | 466 | > 4b | 66 | 14.2 |
| > 1c | 72 | 15.5 |
| Erythromycin | 450 | > 0.5b | 190 | 42.2 |
| > 2c | 174 | 38.7 |
| Clindamycin | 465 | > 0.5a | 60 | 12.9 |
| Tetracycline/doxycycline | 466 | > 4b | 65 | 13.9 |
| > 2c | 74 | 15.9 |
| Co-trimoxazole | 464 | > 2/38b | 49 | 10.6 |
| > 4/76c | 49 | 10.6 |
| Ciprofloxacin | 466 | > 1a | 166 | 35.6 |
| Nitrofurantoin | 445 | > 32b | 7 | 1.6 |
| Daptomycin | 466 | > 1a | 5 | 1.1 |
| Linezolid | 466 | > 4a | 0 | 0 |
| High-level mupirocin | 464 | > 256b | 9 | 1.9 |

a CLSI and EUCAST non-susceptible breakpoint

b CLSI non-susceptible breakpoint

c EUCAST non-susceptible breakpoint

By Vitek2®, one isolate was linezolid resistant (MIC > 4 mg/L). However by Etest®, the isolate had an MIC ≤ 4 mg/L (1.0 mg/L) and was therefore considered linezolid susceptible. When using the EUCAST resistant breakpoint of > 2 mg/L, two isolates were teicoplanin resistant (MIC = 4 mg/L). However, using the CLSI resistant breakpoint of > 8 mg/L, the isolates were classified as susceptible. Nine (1.9%) of 464 MRSA isolates tested had high-level mupirocin resistance, of which four were from Queensland.

Inducible resistance to clindamycin was determined by the Vitek2® susceptibility system. Of the 380 isolates tested by Vitek2®, 35.3% (134) were erythromycin non-susceptible / clindamycin susceptible (CLSI and EUCAST breakpoints), of which 61.9% (83) were classified as having inducible clindamycin resistance. Multi-resistance was seen in 40.3% (181/449) 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 96.4% (449/466) of the MRSA. Based on molecular typing, 22.0% (99/449) and 78.0% (350/449) 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, Australia, 2018 by clone, hospital and community onset, and Panton-Valentine leucocidin carriage****

| Strain | Total | Onset | PVL positive |
| --- | --- | --- | --- |
|  | Hospital | Community |  |
|  | n | %a | n | %b | n | %b | n | %b |
| **Healthcare-associated MRSA** |
| ST22-IV [2B] (EMRSA-15) | 81 | 18.0% | 30 | 37.0% | 51 | 63.0% | – | – |
| ST239-III [3A] (Aus-2/3) | 17 | 3.8% | 6 | 35.3% | 11 | 64.7% | – | – |
| ST8-II (Irish EMRSA-1) | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| **Total HA-MRSA** | **99** | **22.0%** | **36** | **36.4%** | **63** | **63.6%** | **0** | **0** |
| **Community-associated MRSA** |
| ST93-IV [2B] (Queensland) | 99 | 22.0% | 11 | 11.1% | 88 | 88.9% | 95 | 96.0% |
| ST5-IV | 44 | 9.8% | 13 | 29.5% | 31 | 70.5% | 14 | 31.8% |
| ST45-VT | 41 | 9.1% | 12 | 29.3% | 29 | 70.7% | – | – |
| ST1-IV | 35 | 7.8% | 6 | 17.1% | 29 | 82.9% | 1 | 2.9% |
| ST30-IV | 21 | 4.7% | 2 | 9.5% | 19 | 90.5% | 17 | 81.0% |
| ST97-IV | 14 | 3.1% | 2 | 14.3% | 12 | 85.7% | – | – |
| ST78-IV | 13 | 2.9% | 3 | 23.1% | 10 | 76.9% | – | – |
| ST5-V | 8 | 1.8% | 1 | 12.5% | 7 | 87.5% | – | – |
| ST8-IV | 8 | 1.8% | – | – | 8 | 100.0% | 5 | 62.5% |
| ST22-IV (PVL positive) | 7 | 1.6% | 1 | 14.3% | 6 | 85.7% | 7 | 100.0% |
| ST872-IV | 7 | 1.6% | 1 | 14.3% | 6 | 85.7% | – | – |
| ST72-IV | 5 | 1.1% | 2 | 40.0% | 3 | 60.0% | – | – |
| ST953-IV | 5 | 1.1% | 3 | 60.0% | 2 | 40.0% | – | – |
| ST45-IV | 3 | 0.7% | 1 | 33.3% | 2 | 66.7% | – | – |
| ST6-IV | 3 | 0.7% | 2 | 66.7% | 1 | 33.3% | – | – |
| ST121-V | 2 | 0.4% | 1 | 50.0% | 1 | 50.0% | – | – |
| ST188-IV | 2 | 0.4% | 1 | 50.0% | 1 | 50.0% | – | – |
| ST2250-IV | 2 | 0.4% | 1 | 50.0% | 1 | 50.0% | – | – |
| ST3628-II | 2 | 0.4% | 1 | 50.0% | 1 | 50.0% | – | – |
| ST59-IV | 2 | 0.4% | 1 | 50.0% | 1 | 50.0% | – | – |
| ST59-V | 2 | 0.4% | – | – | 2 | 100.0% | 2 | 100.0% |
| ST835-I | 2 | 0.4% | 1 | 50.0% | 1 | 50.0% | – | – |
| ST1043-V | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST1224-V | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST1232-V | 1 | 0.2% | – | – | 1 | 100.0% | 1 | 100.0% |
| ST1482-IV | 1 | 0.2% | – | – | 1 | 100.0% | 1 | 100.0% |
| ST149-IV | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST15-IV | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST15-V | 1 | 0.2% | 1 | 100.0% | – | – | – | – |
| ST1649-IV | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST25-II | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST2611-II | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST2625-IV | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST30-V | 1 | 0.2% | – | – | 1 | 100.0% | 1 | 100.0% |
| ST3628-V | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST398-V | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST5008-IV | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST508-IV | 1 | 0.2% | 1 | 100.0% | – | – | 1 | 100.0% |
| ST6-V | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST73-IV | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST834-IV | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST835-IV | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST88-IV | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST923-IV | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| ST97-V | 1 | 0.2% | – | – | 1 | 100.0% | – | – |
| **Total CA-MRSA** | **350** | **78%** | **68** | **19.4%** | **282** | **80.6%** | **145** | **41.4%** |
| **Grand total** | **449** | **100%** | **104** | **23.2%** | **345** | **76.8%** | **145** | **32.3%** |

a Percentage of all MRSA typed

b Percentage of the strain

### Healthcare-associated methicillin-resistant Staphylococcus aureus

For the 99 HA-MRSA isolates, 36.4% (36/99) were epidemiologically classified as hospital-onset and 63.6% (63/99) were classified as community-onset. Three HA-MRSA clones were identified: 81 isolates of ST22-IV [2B] (EMRSA-15) (18% of MRSA typed and 3.0% of S. aureus); 17 isolates of ST239-III [3A] (Aus -2/3 EMRSA) (3.8% and 0.6%), and one isolate of ST8-II (Irish EMRSA-1) (0.2% and 0.04%).

ST22-IV [2B] (EMRSA-15) was the dominant HA-MRSA clone in Australia accounting for 81.8% of HA-MRSA ranging from 0% in the Northern Territory to 100% in Tasmania (Table 4). The ST22-IV [2B] (EMRSA-15) clone is Panton-Valentine leucocidin (PVL) negative and using CLSI breakpoints 96.3% and 59.7% were ciprofloxacin and erythromycin non-susceptible respectively. Overall 37.0% of ST22-IV were hospital-onset.

****Table 4: The number and proportion of healthcare-associated methicillin-resistant Staphylococcus aureus (MRSA) multilocus sequence types, Australia, 2018, by region****

| Type | ACT | NSW | NT | Qld | SA | Tas | Vic | WA | Aus |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| ST22-IV | 3 | 75.0% | 35 | 79.5% | – | – | 5 | 50% | 9 | 90.0% | 6 | 100.0% | 15 | 93.8% | 8 | 100.0% | 81 | 81.8% |
| ST239-III | – | – | 9 | 20.5% | 1 | 100.0% | 5 | 50% | 1 | 10.0% | – | – | 1 | 6.3% | – | – | 17 | 17.2% |
| ST8-II | 1 | 25.0% | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 1 | 1.0% |
| **Total** | **4** | **100.0%** | **44** | **100.0%** | **1** | **100.0%** | **10** | **100.0%** | **10** | **100.0%** | **6** | **100.0%** | **16** | **100.0%** | **8** | **100.0%** | **99** | **100.0%** |

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

ST239-III [3A] (Aus-2/3 EMRSA) accounted for 17.2% of HA-MRSA ranging from 0% in Western Australia, Tasmania and the Australian Capital Territory to 50.0% in the Northern Territory (Table 4). The PVL-negative ST239-III [3A] (Aus-2/3 EMRSA) isolates were typically resistant to erythromycin (100%), co-trimoxazole (94.1%), ciprofloxacin (100%), gentamicin (100%), tetracycline (81.3%) and clindamycin (75.0%). Overall 35.3% of ST239-III were hospital-onset.

### Community-associated methicillin-resistant Staphylococcus aureus

For the 350 CA-MRSA isolates, 19.4% (68) of episodes were epidemiologically classified as hospital-onset and 80.6% (282) classified as community-onset. Based on the multilocus sequence type and the SCCmec type, 45 CA-MRSA clones were identified (Table 3). Overall, 76.3% of CA-MRSA were classified into seven clones each having more than ten isolates: 99 isolates of ST93-IV [2B] (Queensland CA-MRSA) (22% of MRSA typed and 3.7% of S. aureus); 44 isolates of ST5-IV (9.8% and 1.6%); 41 isolates of ST45-VT (9.1% and 1.5%); 35 isolates of ST1-IV (7.8% and 1.3%); 21 isolates of ST30-IV (4.7% and 0.8%); 14 isolates of ST97-IV (3.1% and 0.5%) and 13 isolates of ST78-IV (2.9% and 0.5%).

ST93-IV [2B] (Queensland CA-MRSA) accounted for 28.3% of CA-MRSA, ranging from 0% in Tasmania to 67.9% in the Northern Territory (Table 5). Typically PVL positive, 76.8% (76/99) of ST93-IV [2B] (Queensland CA-MRSA) were resistant to the β-lactams only, other isolates were additionally resistant to erythromycin (5.1%, 5/99) or erythromycin and clindamycin (2.0%, 2/99). There were two isolates resistant to erythromycin and ciprofloxacin. Overall 88.9% of ST93-IV were community-onset.

****Table 5: The number and proportion of the major community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) multilocus sequence types, Australia
(> 10 isolates), 2018, by region****

| Type | ACT | NSW | NT | Qld | SA | Tas | Vic | WA | Aus |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| ST93-IV | 1 | 14.3% | 15 | 18.3% | 19 | 67.9% | 17 | 26.2% | 13 | 46.4% | – | – | 6 | 15.0% | 28 | 29.8% | 99 | 28.5% |
| ST5-IV | – | – | 7 | 7.3% | 3 | 10.7% | 14 | 21.5% | 2 | 7.1% | – | – | 4 | 7.5% | 14 | 13.8% | 44 | 11.8% |
| ST45-V | 2 | 28.6% | 26 | 31.7% | 1 | 3.6% | 1 | 1.5% | 3 | 10.7% | – | – | 7 | 17.5% | 1 | 1.1% | 41 | 11.8% |
| ST1-IV | – | – | 5 | 6.1% | 2 | 7.1% | 5 | 7.7% | 4 | 14.3% | 3 | 100.0% | 5 | 12.5% | 11 | 11.7% | 35 | 10.1% |
| ST30-IV | – | – | 5 | 6.1% | – | – | 9 | 13.8% | 1 | 3.6% | – | – | 1 | 2.5% | 5 | 5.3% | 21 | 6.1% |
| ST97-IV | 1 | 14.3% | 3 | 3.7% | – | – | 7 | 10.8% | – | – | – | – | 1 | 2.5% | 2 | 2.1% | 14 | 4.0% |
| ST78-IV | – | – | 3 | 3.7% | – | – | – | – | – | – | – | – | – | – | 10 | 10.6% | 13 | 3.7% |
| Other | 3 | 42.9% | 19 | 23.2% | 3 | 10.7% | 12 | 18.5% | 5 | 17.9% | – | – | 17 | 42.5% | 24 | 25.5% | 83 | 23.9% |
| **Total** | **7** | **100.0%** | **83** | **100.0%** | **28** | **100.0%** | **65** | **100.0%** | **28** | **100.0%** | **3** | **100.0%** | **41** | **100.0%** | **95** | **100.0%** | **350** | **100.0%** |

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

ST5-IV accounted for 12.6% of CA-MRSA and was isolated in all regions of Australia except the Australian Capital Territory and Tasmania, ranging from 7.1% in South Australia to 21.5% in Queensland (Table 5). The ST5-IV isolates, of which 31.8% were PVL positive, were typically resistant to the β-lactams only, 34% (15/44). Isolates were additionally resistant to co-trimoxazole 20.5%, (9/44); erythromycin 13.6% (6/44), fusidic acid 9.1% (4/44) erythromycin and co-trimoxazole (6.8%, 3/44); erythromycin and high-level mupirocin (4.5%, 2/44); and single isolates resistant to ciprofloxacin, erythromycin and high-level mupirocin; gentamicin and high-level mupirocin; erythromycin and tetracycline; and ciprofloxacin and erythromycin. Overall 70.7% of ST5-IV were community-onset.

ST45-VT accounted for 11.7% of CA-MRSA and was isolated primarily in New South Wales (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 (34.1%, 14/41); ciprofloxacin, gentamicin and tetracycline (14.6% 6/41); ciprofloxacin, erythromycin and gentamicin (14.6%, 6/41); ciprofloxacin, erythromycin and tetracycline (7.3%, 3/41); ciprofloxacin and tetracycline (4.9%, 2/41) and erythromycin (4.9%, 2/41). Single isolates were non-susceptible to ciprofloxacin, erythromycin, fusidic acid and tetracycline; ciprofloxacin, erythromycin, tetracycline and co-trimoxazole; ciprofloxacin, fusidic acid and co-trimoxazole; erythromycin, gentamicin and tetracycline; ciprofloxacin and gentamicin; and ciprofloxacin and erythromycin. Overall 70.7% of ST45-VT were community-onset.

ST1-IV accounted for 10.0% of CA-MRSA and was isolated in all regions of Australia except the Australian Capital Territory, ranging from 6.1% in New South Wales to 100% in Tasmania (Table 5). Typically PVL negative, 65.7% of isolates were resistant to the β-lactams only (23/35). Other isolates were additionally resistant to erythromycin (17.1%, 6/35); and erythromycin and fusidic acid (5.7%, 2/35). Single isolates were resistant to either ciprofloxacin; ciprofloxacin and co-trimoxazole; or gentamicin. Overall 82.9% of ST1-IV were community-onset.

ST30-IV accounted for 6.0% of CA-MRSA and was isolated in all regions of Australia except the Australian Capital Territory, the Northern Territory and Tasmania, ranging from 2.5% in Victoria to 13.8% in Queensland (Table 5). ST30-IV isolates, of which 81.0% were PVL positive, were typically resistant to the β-lactams only (85.7%, 18/21). Single isolates were resistant to either erythromycin; ciprofloxacin; or gentamicin, rifampicin and tetracycline. Overall 90.5% of ST30-IV were community-onset.

ST97-IV accounted for 4.0% of CA-MRSA and was isolated in all regions of Australia except the Northern Territory, South Australia and Tasmania, ranging from 2.1% in Western Australia to 14.3% in the Australian Capital Territory (Table 5). Typically PVL negative, 64.3% of isolates were resistant to the β-lactams only (9/14). Other isolates were additionally resistant to erythromycin (25.8%, 3/14). Single isolates were resistant to erythromycin, fusidic acid and co-trimoxazole or co-trimoxazole alone. Overall 85.7% of ST97-IV were community-onset.

ST78-IV accounted for 3.7% of CA-MRSA and was predominantly isolated in Western Australia (Table 5). Isolates were resistant to the β-lactams and erythromycin (87.5%, 9/13); two isolates resistant to the β-lactams only; one isolate additionally resistant to ciprofloxacin and one to tetracycline. Overall 76.9% of ST78-IV were community-onset.

Overall 84.7% of CA-MRSA were non-multiresistant including 50.4% resistant to the β-lactams only. A substantial increase was seen in multi-resistant CA-MRSA isolates in ASSOP 2018 (15.3%), from 9.2% in ASSOP 2013.11 Multi-resistance was primarily due to the ST45-VT clone.

## Panton-Valentine leucocidin

Overall 145 (31.6%) of MRSA were PVL positive, all of which 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 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,19 comparison of Australia’s antimicrobial resistance data with other countries is possible.

In ASSOP 2018, 17.4% (95% CI 16.0–18.9) of the 2,673 SAB episodes were methicillin resistant. In the 2018 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 16.4% (95% CI 16–17), ranging from 0% (95% CI 0–4) in Iceland to 43% (95% CI 39–49) in Romania.20

Europe has seen the EU/EEA population-weighted mean percentage decrease markedly from 23.2% in 2009 to 16.4% in 2018. The percentage of methicillin-resistant SAB in Australia however has remained stable over the previous five years of ASSOP ranging from 19.1% in 2013 to 19.0% in 2017 with a non-significant reduction 17.4% in 2018.

A decrease in methicillin-resistant SAB has been reported in several parts of the world20,21 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 In Australia, although we have not seen a significant decrease in MRSA bacteraemia, we have observed significant decreases in HA-MRSA from 41.0% to 23.2% (p < 0.0001) and hospital-onset MRSA from 38.0% to 22.2% (*p* < 0.0001) over the six ASSOP surveys.11,27,28,29,30

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 2018, the all-cause mortality at 30 days was 14.2% (95% CI 12.7–15.8). The MRSA-associated SAB mortality was 17.1% (95% CI 15.5–18.8), which was not significantly higher (p = 0.1) than the MSSA-associated SAB mortality (13.6%, 95% CI 12.2–15.1).

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% 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. In the early 1980s, 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 that 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.31 In ASSOP 2018 approximately 18% of MRSA were characterised as ST22-IV [2B] (EMRSA-15). Community-associated MRSA, in particular the ST45-VT clone (9.1% 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 two isolates were teicoplanin non-susceptible when EUCAST criteria were applied. There were six isolates resistant to daptomycin by both CLSI and EUCAST criteria.

Approximately 14.8% of SAB caused by CA-MRSA were hospital-onset. Transmission of CA-MRSA in Australian hospitals is thought to be rare.32,33 It is likely that many of the hospital-onset CA-MRSA SAB infections reported in ASSOP 2018 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 2018 has demonstrated that antimicrobial resistance in SAB in Australia continues to be a major 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 notably higher than in 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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