Australian Government
Department of Health

COMMUNICABLE DISEASES INTELLIGENCE

2020 Volume 44

https://doi.org/10.33321/cdi.2020.44.71

Australian Group on Antimicrobial Resistance (AGAR) Australian Staphylococcus aureus Sepsis Outcome Programme (ASSOP) Annual Report 2019

Geoffrey W Coombs, Denise A Daley, Shakeel Mowlaboccus and Stanley Pang, on behalf of the Australian Group on Antimicrobial Resistance

www.health.gov.au/cdi

Communicable Diseases Intelligence
ISSN: 2209-6051 Online

This journal is indexed by Index Medicus and Medline.

Communicable Diseases Network Australia
Communicable Diseases Intelligence contributes to the work of the Communicable Diseases Network Australia.
http://www.health.gov.au/cdna

Communicable Diseases Intelligence (CDI) is a peer-reviewed scientific journal published by the Office of Health Protection, Department of Health. The journal aims to disseminate information on the epidemiology, surveillance, prevention and control of communicable diseases of relevance to Australia.

Website
http://www.health.gov.au/cdi

Contacts
Communicable Diseases Intelligence is produced by:
Health Protection Policy Branch
Office of Health Protection
Australian Government
Department of Health
GPO Box 9848, (MDP 6)
CANBERRA ACT 2601

Email:
cdi.editor@health.gov.au

Submit an Article
You are invited to submit your next communicable disease related article to the Communicable Diseases Intelligence (CDI) for consideration. More information regarding CDI can be found at:
http://health.gov.au/cdi.

Further enquiries should be directed to:
cdi.editor@health.gov.au.

Annual report

Australian Group on Antimicrobial Resistance (AGAR) Australian *Staphylococcus aureus* Sepsis Outcome Programme (ASSOP) Annual Report 2019

Geoffrey W Coombs, Denise A Daley, Shakeel Mowlaboccus and Stanley Pang, on behalf of the Australian Group on Antimicrobial Resistance

Abstract

From 1 January to 31 December 2019, 39 institutions around Australia participated in the Australian *Staphylococcus aureus* Sepsis Outcome Programme (ASSOP). The aim of ASSOP 2019 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 on characterising the molecular epidemiology of the methicillin-resistant isolates. A total of 3,157 *S. aureus* bacteraemia episodes were reported, of which 79.8% were community-onset. 18.5% of *S. aureus* were methicillin resistant. The 30-day all-cause mortality associated with methicillin-resistant SAB was 14.0%, which was not significantly different from the 14.3% mortality associated with methicillin-susceptible SAB ($p = 0.9$). 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, 34% to erythromycin, 13% to tetracycline, 9% to gentamicin and 4% to co-trimoxazole. 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). ST22-IV [2B] (EMRSA-15) is the predominant healthcare-associated clone in Australia. Eighty percent of methicillin-resistant SAB, however, were due to community-associated clones. Although polyclonal, approximately 71.4% of community-associated clones were variously characterised as ST93-IV [2B] (Queensland CA-MRSA), ST5-IV [2B], ST45-V_T [5C2&5], ST1-IV [2B], ST30-IV [2B], ST78-IV [2B] and ST8-IV [2B]. Community-associated MRSA (CA-MRSA), in particular the ST45-V_T [5C2&5] clone, have acquired multiple antimicrobial resistance determinants including ciprofloxacin, erythromycin, clindamycin, gentamicin and tetracycline. The multiresistant ST45-V_T [5C2&5] clone accounted for 12.7% 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 blood stream infections.[1] Although there are a wide variety of manifestations of serious invasive infection caused by *S. aureus,* in the great majority of these cases the organism can be detected in blood cultures. Therefore, *S. aureus* bacteraemia (SAB) is considered a very useful marker for serious invasive infection.[2]

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

The Australian Group on Antimicrobial Resistance (AGAR), a network of laboratories located across Australia, commenced surveillance of antimicrobial resistance in *S. aureus* in 1986.[10] In 2013 AGAR commenced the Australian *Staphylococcus aureus* Sepsis Outcome Programme (ASSOP).[11] The primary objective of ASSOP 2019 was to determine the proportion of SAB isolates demonstrating antimicrobial resistance with particular emphasis on:

1. Assessing susceptibility to methicillin; and

2. Molecular epidemiology of methicillin-resistant *S. aureus* (MRSA).

Methodology

Participants

Thirty-nine laboratories from all Australian states and mainland territories.

Collection period

From 1 January to 31 December 2019, the 39 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. *S. aureus* was identified 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] 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] SCC*mec* was determined using KmerFinder V 3.1[15] and the SCC*mec* database curated from the CGE database.[16, 17]

Chi-square tests for comparison of two proportions and calculation of 95% confidence intervals (95% CI) were performed using MedCalc for Windows, version 12.7 (MedCalc Software, Ostend Belgium).

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

Results

From 1 January to 31 December 2019, a total of 3,157 unique episodes of *S. aureus* bacteraemia were identified. A significant difference ($p < 0.0001$) was seen in patient sex, with 64.7% (2,042) being male (95% CI 63.0–66.3%). The mean age of patients was 58 years, ranging from 0 to 106 years, with a median age of 62 years. Overall 79.8% of episodes (2,519/3,157) were community-onset (95% CI 78.4–81.2%). All-cause mortality at 30 days was 14.3% (95% CI 12.9–15.8%). Methicillin-resistant SAB mortality was 14.0% (95% CI 12.6–15.5%); methicillin-susceptible SAB mortality was 14.3% (95% CI 12.9–15.8%).

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

Overall 81.5% (2,574) of the 3,157 isolates were methicillin susceptible of which 75.1% (1,934) were penicillin resistant (MIC > 0.12 mg/L). However as β-lactamase was detected in 74 phenotypically penicillin susceptible isolates, 78.3% of MSSA were considered penicillin resistant. Nine penicillin-susceptible isolates were not available for β-lactamase testing. Apart from erythromycin resistance (12.8% and 13.5% using CLSI and EUCAST breakpoints respectively), resistance to the non-β-lactam antimicrobials amongst MSSA was rare, ranging from 0% to 3.8% (Table 1). There were five isolates reported by Vitek2® as non-susceptible to daptomycin (MIC > 1.0 mg/L). However by Etest®, four of the isolates were considered daptomycin susceptible (MICs 0.19–1.0 mg/L). The remaining isolate, with an Etest® MIC of 2.0 mg/L, was considered non-susceptible by CLSI and resistant by EUCAST interpretive criteria. By Vitek2®, two isolates were reported as linezolid resistant (MIC > 4 mg/L). However by Etest®, the isolates had MICs of 1.5 and 2.0 mg/L and were therefore considered linezolid susceptible. Using EUCAST interpretive criteria, 28 isolates were reported by Vitek2® as non-susceptible to teicoplanin (MIC 4.0 mg/L). By Etest®, 27 isolates had a teicoplanin MIC of ≤ 2.0 mg/L. One isolate was not available for confirmation. All MSSA were vancomycin susceptible. Twenty-nine (1.1%) of 2,563 isolates had high-level mupirocin resistance, of which 18 isolates were referred from Queensland. Nineteen of the 29 mupirocin-resistant MSSA were also resistant to fusidic acid. Inducible resistance to clindamycin was determined by the Vitek2® susceptibility system. Of the 2,279 isolates tested, 10.4% (237) were erythromycin resistant/clindamycin susceptible (CLSI breakpoints), of which 89.9% (213) were classified as having inducible clindamycin resistance. Multi-resistance was uncommon in MSSA (0.7%, 18/2,553).

Commun Dis Intell (2018) 2020:44(https://doi.org/10.33321/cdi.2020.44.71) Epub 15/09/2020

Table 1: The proportion of methicillin-susceptible *Staphylococcus aureus* (MSSA) isolates non-susceptible to penicillin and the non-β-lactam antimicrobials, Australia, 2019

Antimicrobial	Tested	Breakpoint guideline	Breakpoint (mg/L)[a]			Susceptible	Intermediate	Resistant
			S	I	R	(%)	(%)	(%)
Ciprofloxacin	2,571	CLSI	≤ 1	2	≥ 4	96.7	0.0	3.3
		EUCAST	≤ 0.001	[b]	> 1	0.0	96.7[b]	3.3
Clindamycin	2,552	CLSI	≤ 0.5	1–2	≥ 4	98.2	0.0	1.8
		EUCAST	≤ 0.25	0.5	> 0.5	97.9	0.3	1.8
Cotrimoxazole	2.571	CLSI	≤ 2/38		≥ 4/76	99.7		0.3
		EUCAST	≤ 2/38	4/76	> 4/76	99.7	0.0	0.3
Daptomycin	2,573	CLSI/EUCAST	≤ 1		> 1	100.0		0.0
Erythromycin	2,563	CLSI	≤ 0.5	1–4	≥ 8	57.8	29.4	12.8
		EUCAST	≤ 1	2	> 2	85.4	1.0	13.5
Fusidic Acid	2,554	EUCAST	≤ 1		> 1	97.0		3.0
Gentamicin	2,553	CLSI	≤ 4	8	≥ 16	99.0	0.5	0.5
		EUCAST	≤ 1		> 1	98.3		1.7
High-level Mupirocin	2,563	CLSI/EUCAST	< 256		≥ 256	98.9		1.1
Linezolid	2,572	CLSI	≤ 4		≥ 8	100.0		0.0
		EUCAST	≤ 4		> 4	100.0		0.0
Nitrofurantoin	2,272	CLSI	≤ 32	64	≥ 128	98.8	1.1	0.1
Penicillin[c]	2,565	CLSI/EUCAST	≤ 0.12		≥ 0.25	21.7		78.3
Rifampicin	2,547	CLSI	≤ 1	2	≤ 4	99.6	0.1	0.3
		EUCAST	≤ 0.06	0.12–0.5	> 0.5	33.8	65.8	0.4
Teicoplanin	2,572	CLSI	≤ 8	16	≥ 32	100.0	0.0	0.0
		EUCAST	≤ 2		> 2	99.96	0.0	0.04
Tetracycline/Doxycycline	2,566	CLSI	≤ 4	8	≥ 16	96.5	0.0	3.4
		EUCAST	≤ 1	2	> 2	95.6	0.6	3.8
Vancomycin	2,573	CLSI	≤ 2	4–8	≥ 16	100.0	0.0	0.0
		EUCAST	≤ 2		> 2	100.0	0.0	0.0

a S: susceptible; I: intermediate; R: resistant.
b Susceptible, increased exposure.
c β-lactamase adjusted.

MRSA antimicrobial susceptibility

The proportion of *S. aureus* that were MRSA was 18.5% (95% CI 17.2–19.9%). Of the 583 MRSA identified, 525 were cefoxitin screen positive by Vitek2® and 51 had a cefoxitin MIC > 4 by Phoenix™. The remaining seven were identified as MRSA by *mec*/*nuc* PCR. Eight of the 583 MRSA isolates were phenotypically penicillin susceptible (MIC ≤ 0.125 mg/L), however β-lactamase was detected in all eight. Amongst the MRSA isolates, resistance to non-β-lactam antimicrobials was common, except to rifampicin, nitrofurantoin, cotrimoxazole and fusidic acid where resistance ranged from 1.0% to 6.6% (Table 2). All MRSA were vancomycin susceptible. One isolate was reported by Vitek2® as daptomycin non-susceptible (MIC > 1.0 mg/L). By Etest®, the isolate was considered daptomycin susceptible (MIC 0.125 mg/L).

By Vitek2®, four isolates were linezolid resistant (MIC > 4 mg/L). However by Etest®, the isolates had MIC ≤ 2 mg/L and were therefore considered linezolid susceptible. When using the EUCAST resistant breakpoint of > 2 mg/L, one isolate was teicoplanin resistant (MIC = 4 mg/L). However, using the CLSI resistant breakpoint of > 8 mg/L, the isolate was classified as susceptible. Seven (1.2%) of 578 MRSA isolates tested had high-level mupirocin resistance.

Inducible resistance to clindamycin was determined by the Vitek2® susceptibility system. Of the 527 isolates tested by Vitek2®, 22.2% (117) were erythromycin resistant/clindamycin susceptible (CLSI and EUCAST breakpoints), of which 88.0% (103) were classified as having inducible clindamycin resistance.

Multi-resistance was seen in 12.8% of MRSA (74/577).

MRSA molecular epidemiology

WGS was performed on 93.0% of the MRSA (542/583). Based on molecular typing, 20.1% (109) and 79.9% (433) of isolates were identified as healthcare-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) clones respectively (Table 3).

Healthcare-associated methicillin-resistant *Staphylococcus aureus*

For the 109 HA-MRSA isolates, 30.3% (33) were epidemiologically classified as hospital-onset and 69.7% (76) were classified as community-onset. Three HA-MRSA clones were identified: 89 isolates of ST22-IV [2B] (EMRSA-15) (16.4% of MRSA typed and 2.8% of *S. aureus*); 19 isolates of ST239-III [3A] (Aus – 2/3 EMRSA) (3.5% and 0.6%), and one isolate of ST5-II (NY/Japan) (0.2% and 0.03%).

ST22-IV [2B] (EMRSA-15) was the dominant HA-MRSA clone in Australia, accounting for 81.7% of HA-MRSA, ranging from 0% in the Northern Territory to 100% in Western Australia (Table 4). ST22-IV [2B] (EMRSA-15) is PVL negative, and using CLSI breakpoints, 97.8% and 65.2% were ciprofloxacin and erythromycin non-susceptible respectively. Overall, 30.3% of ST22-IV were hospital-onset.

ST239-III [3A] (Aus-2/3 EMRSA) accounted for 17.4% of HA-MRSA, ranging from 0% in Western Australia and the Northern Territory to 50.0% in Queensland (Table 4). PVL-negative ST239-III [3A] (Aus-2/3 EMRSA) were typically resistant to erythromycin (100%), co-trimoxazole (89.5%), ciprofloxacin (100%), gentamicin (94.7%), tetracycline (100%) and clindamycin (57.9%). Overall, 26.3% of ST239-III were hospital-onset.

Commun Dis Intell (2018) 2020;44(https://doi.org/10.33321/cdi.2020.44.71) Epub 15/09/2020

Table 2: The proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates non-susceptible to penicillin and the non-β-lactam antimicrobials, Australia, 2019

Antimicrobial	Tested	Breakpoint guideline	Breakpoint (mg/L)[a]			Susceptible	Intermediate	Resistant
			S	I	R	(%)	(%)	(%)
Ciprofloxacin	580	CLSI	≤ 1	2	≥ 4	63.3	0.9	35.9
		EUCAST	≤ 0.001	[b]	> 1	0.0	63.3	36.7
Clindamycin	577	CLSI	≤ 0.5	1–2	≥ 4	87.5	0.2	12.3
		EUCAST	≤ 0.25	0.5	> 0.5	87.3	0.2	12.5
Cotrimoxazole	581	CLSI	≤ 2/38		≥ 4/76	95.7	0.3[c]	4.0
		EUCAST	≤ 2/38	4/76	> 4/76	65.7	0.5	3.8
Daptomycin	581	CLSI/EUCAST	≤ 1		> 1	100.0		0.0
Erythromycin	579	CLSI	≤ 0.5	1–4	≥ 8	46.6	19.2	34.2
		EUCAST	≤ 1	2	> 2	62.9	1.4	35.8
Fusidic Acid	577	EUCAST	≤ 1		> 1	93.5		6.6
Gentamicin	575	CLSI	≤ 4	8	≥ 16	88.2	3.1	8.7
		EUCAST	≤ 1		> 1	85.9		14.1
High-level Mupirocin	578	CLSI/EUCAST	< 256		≥ 256	98.8		1.2
Linezolid	582	CLSI	≤ 4		≥ 8	100.0		0.0
		EUCAST	≤ 4		> 4	100.0		0.0
Nitrofurantoin	519	CLSI	≤ 32	64	≥ 128	98.5	1.5	0.0
Penicillin[d]	583	CLSI/EUCAST	≤ 0.12		≥ 0.25	0.0		100.0
Rifampicin	574	CLSI	≤ 1	2	≤ 4	98.8	0.2	1.0
		EUCAST	≤ 0.06	0.12–0.5	> 0.5	27.2	71.6	1.2
Teicoplanin	582	CLSI	≤ 8	16	≥ 32	100.0	0.0	0.0
		EUCAST	≤ 2		> 2	99.8		0.2
Tetracycline/Doxycycline	579	CLSI	≤ 4	8	≥ 16	86.5	0.5	13.0
		EUCAST	≤ 1	2	> 2	85.5	0.5	14.0
Vancomycin	582	CLSI	≤ 2	4–8	≥ 16	100.0	0.0	0.0
		EUCAST	≤ 2		> 2	100.0		0.0

a S: susceptible; I: intermediate; R: resistant.
b Susceptible, increased exposure.
c Intermediate by disc testing
d β-lactamase adjusted.

Table 3: The number and proportion of healthcare-associated and community-associated methicillin-resistant *Staphylococcus aureus*, Australia, 2019 by clone, healthcare and community onset, and Panton-Valentine leucocidin carriage

MLST[a]	Total		Onset				PVL Positive	
			Hospital		Community			
	n	%[b]	n	%[c]	n	%[c]	n	%[c]
Healthcare-associated MRSA								
ST22-IV [2B] (EMRSA-15)	89	16.4%	27	30.3%	62	69.7%	0	0.0
ST239-III [3A] (Aus-2/3)	19	3.5%	5	26.3%	14	73.7%	0	0.0
ST5-II	1	0.2%	1	100.0%			0	0.0
Total HA-MRSA	**109**	**20.1%**	**33**	**30.3%**	**76**	**69.7%**	**0**	**0.0**
Community-associated MRSA								
ST93-IV	132	24.4%	17	12.9%	115	87.1%	126	95.5%
ST5-IV	60	11.1%	13	21.7%	47	78.3%	15	25.0%
ST45-V_T	55	10.1%	18	32.7%	37	67.3%		
ST1-IV	26	4.8%	9	34.6%	17	65.4%		
ST30-IV	14	2.6%	1	7.1%	13	92.9%	14	100.0%
ST78-IV	11	2.0%	2	18.2%	9	81.8%		
ST8-IV	11	2.0%	2	18.2%	9	81.8%	4	36.4%
ST953-IV	10	1.8%	4	40.0%	6	60.0%		
ST22-IV (pvl positive)	8	1.5%	2	25.0%	6	75.0%	8	100.0%
ST97-IV	8	1.5%	3	37.5%	5	62.5%		
ST45-IV	7	1.3%			7	100.0%		
ST6-IV	6	1.1%	2	33.3%	4	66.7%	1	16.7%
ST59-IV	5	0.9%	1	20.0%	4	80.0%		
ST5-V	5	0.9%			5	100.0%		

Commun Dis Intell (2018) 2020;44(https://doi.org/10.33321/cdi.2020.44.71) Epub 15/09/2020

MLST[a]	Total		Onset				PVL Positive	
			Hospital		Community			
	n	%[b]	n	%[c]	n	%[c]	n	%[c]
ST72-IV	5	0.9%	2	40.0%	3	60.0%		
ST872-IV	5	0.9%	1	20.0%	4	80.0%		
ST72-V	4	0.7%	3	75.0%	1	25.0%	1	25.0%
ST88-IV	4	0.7%	1	25.0%	3	75.0%		
ST149-IV	3	0.6%	1	33.3%	2	66.7%		
ST188-IV	3	0.6%	2	66.7%	1	33.3%		
ST5213-IV	3	0.6%			3	100.0%		
ST59-V	3	0.6%	2	66.7%	1	33.3%	1	33.3%
ST1232-V	2	0.4%	1	50.0%	1	50.0%	2	100.0%
ST6142-V	2	0.4%	2	100.0%				
ST6155-IV	2	0.4%			2	100.0%		
ST672-IV	2	0.4%			2	100.0%		
ST772-V	2	0.4%	1	50.0%	1	50.0%	2	100.0%
ST8-V	2	0.4%	2	100.0%				
ST105-II	1	0.2%			1	100.0%		
ST1178-IV	1	0.2%	1	100.0%				
ST1457-IV	1	0.2%			1	100.0%		
ST1524-IV	1	0.2%			1	100.0%	1	100.0%
ST15-IV	1	0.2%			1	100.0%		
ST1814-IV	1	0.2%	1	100.0%				
ST207-IV	1	0.2%	1	100.0%				
ST2112-V	1	0.2%	1	100.0%				

MLST[a]	Total		Onset				PVL Positive	
			Hospital		Community			
	n	%[b]	n	%[c]	n	%[c]	n	%[c]
ST22-V	1	0.2%			1	100.0%		
ST398-V	1	0.2%	1	100.0%				
ST46-VI	1	0.2%			1	100.0%		
ST573-V	1	0.2%			1	100.0%		
ST5-I	1	0.2%			1	100.0%		
ST5-VI	1	0.2%			1	100.0%		
ST5-VIII	1	0.2%	1	100.0%				
ST6144-IV	1	0.2%			1	100.0%		
ST6145-V	1	0.2%	1	100.0%				
ST6146-V	1	0.2%			1	100.0%		
ST6147-V	1	0.2%			1	100.0%	1	100.0%
ST6148-V	1	0.2%			1	100.0%		
ST6149-IV	1	0.2%			1	100.0%		
ST6150-IV	1	0.2%	1	100.0%				
ST6151-IV	1	0.2%			1	100.0%	1	100.0%
ST6152-IV	1	0.2%			1	100.0%	1	100.0%
ST6153-IV	1	0.2%			1	100.0%		
ST6154-IV	1	0.2%	1	100.0%				
ST6156-IV	1	0.2%			1	100.0%		
ST6158-IV	1	0.2%	1	100.0%				
ST6159-IV	1	0.2%			1	100.0%		
ST672-V	1	0.2%			1	100.0%		

MLST[a]	Total		Onset				PVL Positive	
			Hospital		Community			
	n	%[b]	n	%[c]	n	%[c]	n	%[c]
ST789-IV	1	0.2%			1	100.0%		
ST835-IV	1	0.2%			1	100.0%		
ST920-IV	1	0.2%			1	100.0%		
Total CA-MRSA	**433**	**79.9%**	**102**	**23.6%**	**331**	**76.4%**	**178**	**41.1%**

a Multilocus sequence type.
b Percentage of all MRSA typed.
c Percentage of the strain.

Table 4: The number and proportion of healthcare-associated methicillin-resistant *Staphylococcus aureus* (MRSA) multilocus sequence types (MLST), Australia, 2019, by region[a]

MLST	ACT		NSW		NT		Qld		SA		Tas		Vic		WA		Aus	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ST22-IV	6	75.0%	36	87.8%	0		8	50.0%	5	71.4%	5	83.3%	19	90.5%	10	100.0%	89	81.7%
ST239-III	2	25.0%	4	9.8%	0		8	50.0%	2	28.6%	1	16.7%	2	9.5%	0		19	17.4%
ST5-II	0		1	2.4%	0		0		0		0		0		0		1	0.9%
Total	**8**	**100.0%**	**41**	**100.0%**	**0**		**16**	**100.0%**	**7**	**100.0%**	**6**	**100.0%**	**21**	**100.0%**	**10**	**100.0%**	**109**	**100.0%**

a 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.

Community-associated methicillin-resistant *Staphylococcus aureus*

For the 433 CA-MRSA isolates, 23.6% (102) of episodes were epidemiologically classified as hospital-onset and 76.4% (331) were classified as community-onset. Based on the multi locus sequence type and the SCC*mec* type, 61 CA-MRSA clones were identified (Table 3). Overall, 71.4% of CA-MRSA were classified into seven clones each having more than ten isolates: 132 isolates of ST93-IV [2B] (Queensland CA-MRSA) (24.4% of MRSA typed and 4.2% of *S. aureus*); 60 isolates of ST5-IV (11.1% and 1.9%); 55 isolates of ST45-V_T (10.1% and 1.7%); 26 isolates of ST1-IV (4.8% and 0.8%); 14 isolates of ST30-IV (2.6% and 0.4%); 11 isolates of ST78-IV (2.0% and 0.3%) and 11 isolates of ST8-IV (2.0% and 0.3%).

ST93-IV [2B] (Queensland CA-MRSA) accounted for 24.4% of CA-MRSA ranging from 0% in Tasmania and the Australian Capital Territory to 61.1% in the Northern Territory (Table 5). Typically PVL positive, 77.3% (102/132) of ST93-IV [2B] (Queensland CA-MRSA) were resistant to the β-lactams only; most of the remainder were additionally resistant to erythromycin (11.4%, 15/132) or to erythromycin and clindamycin (9.9%, 13/132). Single isolates were resistant to ciprofloxacin and clindamycin. Overall, 87.1% of ST93-IV were community-onset.

ST5-IV accounted for 13.9% of CA-MRSA and was isolated in all regions of Australia, ranging from 4.2% in South Australia to 22.8% in Queensland (Table 5). ST5-IV isolates, of which 25.0% were PVL positive, were typically resistant to the β-lactams only, 61.7% (37/60). Isolates were additionally resistant to erythromycin (15.0%, 9/60); fusidic acid (6.7%, 4/60); co-trimoxazole (3.3%, 2/60); ciprofloxacin (3.3% 2/60); erythromycin and clindamycin (3.3%, 2/60); and single isolates resistant to erythromycin, clindamycin, tetracycline and cotrimoxazole; rifampicin and fusidic acid; ciprofloxacin and gentamicin; and rifampicin. Overall, 78.3% of ST5-IV were community-onset.

ST45-V_T accounted for 12.7% of CA-MRSA and was isolated primarily in New South Wales and Victoria (Table 5). All isolates were PVL negative and were resistant to the β-lactams and ciprofloxacin. Isolates were additionally resistant to erythromycin, gentamicin and tetracycline (16.4%, 9/55); gentamicin and tetracycline (12.7% 7/55); erythromycin, clindamycin and tetracycline (12.7%, 7/55); erythromycin and tetracycline (12.7%, 7/55); tetracycline (7.3%, 4/55); erythromycin, clindamycin, fusidic acid and tetracycline (5.5%, 3/55); gentamicin (5.5%, 3/55); erythromycin, fusidic acid and tetracycline (3.6%, 2/55). Single isolates were resistant to erythromycin, tetracycline and cotrimoxazole; erythromycin and clindamycin; fusidic acid and tetracycline; and fusidic acid. Overall, 67.3% of ST45-V_T were community-onset.

ST1-IV accounted for 6.0% of CA-MRSA and was isolated in all regions of Australia except Tasmania, ranging from 1.6% in Victoria to 30% in the Australian Capital Territory (Table 5). Typically PVL negative, 61.5% of isolates were resistant to the β-lactams only (16/26); other isolates were additionally resistant to fusidic acid (15.4%, 4/26) or to erythromycin and fusidic acid (11.5%, 3/26). Single isolates were resistant to either ciprofloxacin; erythromycin; or erythromycin and clindamycin. Overall, 65.4% of ST1-IV were community-onset.

ST30-IV accounted for 3.2% of CA-MRSA and was isolated in all regions of Australia except the Australian Capital Territory, the Northern Territory, South Australia and Tasmania, ranging from 1.1% in Western Australia to 6.5% in New South Wales (Table 5). All isolates were PVL positive and were typically resistant to the β-lactams only (92.9%, 13/14). A single isolate was resistant to erythromycin and clindamycin. Overall, 92.9% of ST30-IV were community-onset.

ST78-IV accounted for 2.5% of CA-MRSA and was isolated in Western Australia and Victoria (Table 5). All isolates were PVL negative and predominantly resistant to the β-lactams only

Table 5: The number and proportion of the major community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) multilocus sequence types (MLST), Australia (> 10 isolates), 2019, by region[a]

MLST	ACT		NSW		NT		Qld		SA		Tas		Vic		WA		Aus	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ST93-IV			18	14.5%	22	61.1%	32	40.5%	7	29.2%			12	19.0%	41	45.6%	132	30.5%
ST5-IV	2	20.0%	18	14.5%	5	13.9%	18	22.8%	1	4.2%	1	14.3%	6	9.5%	9	10.0%	60	13.9%
ST45-V_T	1	10.0%	37	29.8%					3	12.5%			14	22.2%			55	12.7%
ST1-IV	3	30.0%	6	4.8%	3	8.3%	2	2.5%	4	16.7%			1	1.6%	7	7.8%	26	6.0%
ST30-IV			8	6.5%			1	1.3%					4	6.3%	1	1.1%	14	3.2%
ST78-IV													2	3.2%	9	10.0%	11	2.5%
ST8-IV			4	3.2%			3	3.8%	1	4.2%			2	3.2%	1	1.1%	11	2.5%
Other	4	40.0%	33	26.6%	6	16.7%	23	29.1%	8	33.3%	6	85.7%	22	34.9%	22	24.4%	124	28.6%
Total	**10**	**100.0%**	**124**	**100.0%**	**36**	**100.0%**	**79**	**100.0%**	**24**	**100.0%**	**7**	**100.0%**	**63**	**100.0%**	**90**	**100.0%**	**433**	**100.0%**

a 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.

(72.7%, 8/11). Three isolates were also resistant to erythromycin (27.3%). Overall, 81.8% of ST78-IV were community-onset.

ST8-IV accounted for 2.5% of CA-MRSA and was isolated all regions except the Australian Capital Territory, the Northern Territory and Tasmania ranging from 1.1% in Western Australia to 4.2% in South Australia (Table 5). 36.4% of ST8-IV were PVL positive. Two isolates were resistant to the β-lactams only. Isolates were additionally resistant to ciprofloxacin (27.3%, 3/11); ciprofloxacin and erythromycin (18.2%, 2/11) and single isolates resistant to ciprofloxacin, erythromycin, clindamycin and cotrimoxazole; ciprofloxacin and tetracycline; and erythromycin. Overall, 81.8% of ST8-IV were community-onset.

Overall, 88.5% of CA-MRSA were non-multi-resistant, including 55.2% of CA-MRSA isolates which were resistant to the β-lactams only. A substantial increase was seen in multi-resistant CA-MRSA isolates in ASSOP 2019 (13.7%), from 9.2% in ASSOP 2013.[11] Multi-resistance was primarily due to the ST45-V_T clone.

Panton-Valentine leucocidin

Overall, 178 MRSA (32.8%) 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 *Enterobacteriaceae*. 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 is performed. As the programmes are similar to those conducted in Europe,[18] comparison of Australia antimicrobial resistance data with other countries is possible.

In ASSOP 2019, 18.5% (95% CI 17.2–19.9%) of the 3,157 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.[18]

In Europe, the EU/EEA population-weighted mean percentage has significantly decreased from 23.2% in 2009 to 16.4% in 2018. A decrease in methicillin-resistant SAB has been reported in several parts of the world[19,20] and is believed to be due to the implementation of antimicrobial stewardship and a package of improved infection control procedures including hand hygiene, MRSA screening and decolonisation, patient isolation and infection prevention care bundles.[21–25] The percentage of methicillin-resistant SAB in Australia however has remained stable over the seven years of ASSOP ranging from 19.1% in 2013 to 18.5% in 2019. In Australia, although we have not seen a significant change in the percentage of methicillin-resistant SAB overall, we have observed significant decreases in HA-MRSA from 41.0% to 20.1% of all MRSA ($p < 0.0001$), and in hospital-onset MRSA from 38.0% to 24.9% of MRSA ($p < 0.0001$) over the seven ASSOP surveys.[11,26–30]

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 2019, the all-cause mortality at 30 days was 14.3% (95% CI 12.9–15.8%). Methicillin-resistant SAB mortality was 14.0% (95% CI 12.6–15.5%); methicillin-susceptible SAB mortality was 14.3% (95% CI 12.9–15.8%).

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 20% of isolates were resistant to erythromycin and ciprofloxacin and approximately 2% resistant to co-trimoxazole, tetracycline and gentamicin. Resistance was

largely attributable to two healthcare-associated MRSA clones, ST22-IV [2B] (EMRSA-15), which is typically ciprofloxacin and erythromycin resistant, and ST239-III [3A] (Aus-2/3 EMRSA) which is typically erythromycin, clindamycin, ciprofloxacin, co-trimoxazole, tetracycline and gentamicin resistant. 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 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 2019 approximately 16% of MRSA were characterised as ST22-IV [2B] (EMRSA-15). CA-MRSA, in particular the ST45-V_T clone (10.1% 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 resistant when EUCAST criteria were applied. One isolate was non-susceptible to daptomycin by CLSI and EUCAST interpretive criteria.

Approximately 23.6% 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 2019 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 2019 has demonstrated that antimicrobial resistance in SAB in Australia continues to be a serious problem and continues to be associated with a high mortality. This may be due, in part, to the prevalence of methicillin-resistant SAB in Australia, which is higher than most EU/EEA countries. Consequently, MRSA must remain a public health priority, and continuous surveillance of SAB and its outcomes and the implementation of comprehensive MRSA strategies targeting hospitals and long-term care facilities are essential.

Acknowledgments

This study was funded by a grant from the Australian Commission on Safety and Quality in Health Care.

Members of the AGAR in 2019 were:

Australian Capital Territory

Peter Collignon and Susan Bradbury, The Canberra Hospital

New South Wales

Thomas Gottlieb and John Huynh, Concord Hospital

James Branley and Linda Douglass, Nepean Hospital

Angela Wong, Royal North Shore Hospital

Sebastiaan van Hal and Alicia Beukers, Royal Prince Alfred Hospital

Jon Iredell and Andrew Ginn, Westmead Hospital

Rod Givney and Bree Harris, John Hunter Hospital

Peter Newton and Melissa Hoddle, Wollongong Hospital

Jock Harkness and David Lorenz, St Vincent's Hospital

Michael Maley and Helen Ziochos, Liverpool Hospital

Monica Lahra and Peter Huntington, Sydney Children's Hospital

Northern Territory

Rob Baird and Jann Hennessy, Royal Darwin Hospital

James McLeod, Alice Springs Hospital

Queensland

Enzo Binotto and Bronwyn Thomsett, Pathology Queensland Cairns Base Hospital

Graeme Nimmo and Narelle George, Pathology Queensland Central Laboratory, Royal Brisbane and Women's Hospital

Petra Derrington and Cheryl Curtis, Pathology Queensland Gold Coast Hospital

Robert Horvath and Laura Martin, Pathology Queensland Prince Charles Hospital

Naomi Runnegar and Joel Douglas, Pathology Queensland Princess Alexandra Hospital

Jennifer Robson and Georgia Peachey, Sullivan Nicolaides Pathology, Greenslopes Hospital

Clare Nourse, Queensland Children's Hospital

South Australia

Kelly Papanaoum and Xiao Ming Chen, SA Pathology, Flinders Medical Centre

Morgyn Warner and Kija Smith, SA Pathology, Royal Adelaide Hospital and Women's and Children's Hospital

Tasmania

Louise Cooley and David Jones, Royal Hobart Hospital

Pankaja Kalukottege and Kathy Wilcox, Launceston General Hospital

Victoria

Denis Spelman and Jacqueline Williams, The Alfred Hospital

Marcel Leroi and Elizabeth Grabsch, Austin Health

Tony Korman and Despina Kotsanas, Monash Medical Centre and Monash Children's Hospital

Tony Korman and Kathryn Cisera, Dandenong Hospital

Andrew Daley and Gena Gonis, Royal Women's and Children's Hospital

Mary Jo Waters and Lisa Brenton, St Vincent's Hospital

Western Australia

David McGechie and Denise Daley, PathWest Laboratory Medicine, WA Fiona Stanley Hospital

Ronan Murray and Jacinta Bowman, PathWest Laboratory Medicine, WA Sir Charles Gairdner Hospital

Michael Leung, PathWest Laboratory Medicine, Northwest WA

Owen Robinson and Geoffrey Coombs, PathWest Laboratory Medicine, WA Royal Perth Hospital

Sudha Pottumarthy-Boddu and Jacqueline Schuster, Australian Clinical Laboratories, St John of God Hospital, Murdoch

Shalinie Perera and Ian Meyer, Western Diagnostic Pathology, Joondalup Hospital

Christopher Blyth, PathWest Laboratory Medicine, Perth Children's Hospital

Author Details

Prof Geoffrey W Coombs,[1,2]
Ms Denise A Daley,[2,3]
Dr Shakeel Mowlaboccus,[1]
Dr Stanley Pang,[1,2]

on behalf of the Australian Group on Antimicrobial Resistance

1. Antimicrobial Resistance and Infectious Disease (AMRID) Research Laboratory, Murdoch University, Murdoch, Western Australia, Australia

2. Department of Microbiology, PathWest Laboratory Medicine-WA, Fiona Stanley Hospital, Murdoch, Western Australia, Australia

3. Australian Group on Antimicrobial Resistance, Fiona Stanley Hospital, Murdoch, Western Australia, Australia

Corresponding Author

Prof Geoffrey Coombs
Antimicrobial Resistance and Infectious Disease (AMRID) Research Laboratory, Murdoch University, Murdoch, Western Australia, Australia
Telephone: +61 8 6152 2397
Email: g.coombs@murdoch.edu.au

References

1. Laupland KB. Incidence of bloodstream infection: a review of population-based studies. *Clin Microbiol Infect*. 2013;19(6):492–500.

2. Johnson AP, Pearson A, Duckworth G. Surveillance and epidemiology of MRSA bacteraemia in the UK. *J Antimicrob Chemother*. 2005;56(3):455–62.

3. Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, Kirby A, Tilley R, Török ME et al. Clinical management of *Staphylococcus aureus* bacteraemia. *Lancet Infect Dis*. 2011;11(3):208–22.

4. Collignon P, Nimmo GR, Gottlieb T, Gosbell IB for the Australian Group on Antimicrobial Resistance. *Staphylococcus aureus* bacteremia, Australia. *Emerg Infect Dis*. 2005;11(4):554–61.

5. Frederiksen MS, Espersen F, Frimodt-Møller N, Jensen AG, Larsen AR, Pallesen LV et al. Changing epidemiology of pediatric *Staphylococcus aureus* bacteremia in Denmark from 1971 through 2000. *Pediatr Infect Dis J*. 2007;26:398–405.

6. Benfield T, Espersen F, Frimodt-Møller N, Jensen AG, Larsen AR, Pallesen LV et al. Increasing incidence but decreasing in-hospital mortality of adult *Staphylococcus aureus* bacteraemia between 1981 and 2000. *Clin Microbiol Infect*. 2007;13(3):257–63.

7. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in *Staphylococcus aureus* bacteremia. *Clin Microbiol Rev*. 2012;25(2):362–86.

8. Kaasch AJ, Barlow G, Edgeworth JD, Fowler VG Jr, Hellmich M, Hopkins S et al. *Staphylococcus aureus* bloodstream infection: a pooled analysis of five prospective, observational studies. *J Infect*. 2014;68(3):242–51.

9. Turnidge JD, Kotsanas D, Munckhof W, Roberts S, Bennett CM, Nimmo GR et al. *Staphylococcus aureus* bacteraemia: a major cause of mortality in Australia and New Zealand. *Med J Aust*. 2009;191(7):368–73.

10. Nimmo GR, Bell JM, Collignon PJ for the Australian Group on Antimicrobial Resistance. Fifteen years of surveillance by the Australian Group for Antimicrobial Resistance (AGAR). *Commun Dis Intell Q Rep*. 2003;27(Suppl):S47–54.

11. Coombs GW, Nimmo GR, Daly DA, Le TT, Pearson JC, Tan HL et al. Australian *Staphy-*

lococcus aureus Sepsis Outcome Programme annual report, 2013. *Commun Dis Intell Q Rep*. 2014;38(4):E309–19.

12. Clinical and Laboratory Standards Institute (CLSI). M100. Performance standards for antimicrobial susceptibility testing; 30th Edition. Villanova, PA, USA, January 2020.

13. The European Committee on Antimicrobial Susceptibility Testing (EUCAST). *Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0*. Basel: EUCAST; 2020. Available from: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_10.0_Breakpoint_Tables.pdf.

14. Seemann T, Goncalves da Silva A, Bulach DM, Schultz MB, Kwong JC, Howden BP. Nullarbor. San Francisco; Github. [Accessed: 03 June 2016.] Available from: https://github.com/tseemann/nullarbor.

15. Clausen PTLC. Aarestrup FM, Lund O. Rapid and precise alignment of raw reads against redundant databases with KMA. *BMC Bioinformatics*. 2018;19(1):307.

16. International Working Group on The Classification of Staphylococcal Cassette Chromosome Elements (IWG-SCC). Classification of staphylococcal cassette chromosome mec (SCC*mec*): guidelines for reporting novel SCC*mec* elements. *Antimicrob Agents Chemother*. 2009;53(12):4961–7.

17. Kondo Y, Ito T, Ma XX, Watanabe S, Kreiswirth BN, Etienne J et al. Combination of multiplex PCRs for staphylococcal cassette chromosome *mec* type assignment: rapid identification system for *mec*, *ccr* and major difference in junkyard regions. *Antimicrob Agents Chemother*. 2007;51(1):264–74.

18. European Centre for Disease Prevention and Control (ECDC). Surveillance of antimicrobial resistance in Europe 2018. [Internet.] Solna: ECDC; 2019. Available from: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2018.

19. Johnson AP, Davies J, Guy R, Abernethy J, Sheridan E, Pearson A et al. Mandatory surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia in England: the first 10 years. *J Antimicrob Chemother*. 2012;67(4):802–9.

20. de Kraker ME, Davey PG, Grundmann H, BURDEN study group. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med*. 2011;8(10):e1001104.

21. Johnson PD, Martin R, Burrell LJ, Grabsch EA, Kirsa SW, O'Keeffe J et al. Efficacy of an alcohol/chlorhexidine hand hygiene program in a hospital with high rates of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection. *Med J Aust*. 2005;183(10):509–14.

22. Vos MC, Behrendt MD, Melles DC, Mollema FP, de Groot W, Parlevliet G et al. 5 years of experience implementing a methicillin-resistant *Staphylococcus aureus* search and destroy policy at the largest university medical center in the Netherlands. *Infect Control Hosp Epidemiol*. 2009;30(10):977–84.

23. Grayson ML, Jarvie LJ, Martin R, Johnson PD, Jodoin ME, McMullan C et al. Significant reductions in methicillin-resistant *Staphylococcus aureus* bacteraemia and clinical isolates associated with a multisite, hand hygiene culture-change program and subsequent successful statewide roll-out. *Med J Aust*. 2008;188(11):633–40.

24. Kim YC, Kim MH, Song JE, Ahn JY, Oh DH, Kweon OM et al. Trend of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in an institution with a high rate of MRSA after the reinforcement of antibiotic stewardship and hand hygiene. *Am J Infect*

Control. 2013;41(5):e39–43.

25. Lawes T, Edwards B, López-Lozano JM, Gould I. Trends in *Staphylococcus aureus* bacteraemia and impacts of infection control practices including universal MRSA admission screening in a hospital in Scotland, 2006–2010: retrospective cohort study and time-series intervention analysis. *BMJ Open*. 2012;2(3). pii: e000797.

26. Coombs GW, Daley DA, Thin Lee Y, Pearson JC, Robinson JO, Nimmo GR et al. Australian Group on Antimicrobial Resistance Australian *Staphylococcus aureus* Sepsis Outcome Programme annual report, 2014. *Commun Dis Intell Q Rep*. 2016;40(2):E244–54.

27. Coombs GW, Daley DA, Lee YT, Pang S for the Australian Group on Antimicrobial Resistance. Australian Group on Antimicrobial Resistance (AGAR) Australian *Staphylococcus aureus* Sepsis Outcome Programme (ASSOP) annual report 2016. *Commun Dis Intell (2018)*. 2018;42. pii: S2209-6051(18)00021-0.

28. Coombs GW, Daley DA, Lee YT, Pang S, Bell JM, Turnidge JD et al. Australian Group on Antimicrobial Resistance (AGAR) Australian *Staphylococcus aureus* Sepsis Outcome Programme (ASSOP) Annual Report 2015. *Commun Dis Intell(2018)*. 2018;42. pii: S2209-6051(18)00016-7.

29. Coombs GW, Daley DA, Lee YT, Pang S. Australian Group on Antimicrobial Resistance (AGAR) Australian *Staphylococcus aureus* Sepsis Outcome Programme (ASSOP) annual report 2017. *Commun Dis Intell (2018)*. 2019;43. doi: https://doi.org/10.33321/cdi.2019.43.43.

30. Coombs GW, Daley DA, Mowlaboccus S, Lee YT, Pang S; Australian Group on Antimicrobial Resistance.Australian Group on Antimicrobial Resistance (AGAR) Australian *Staphylococcus aureus* Sepsis Outcome Programme (ASSOP) annual report 2018. *Commun Dis Intell (2018)*. 2020;44. doi: https://doi.org/10.33321/cdi.2020.44.18.

31. Coombs GW, Pearson JC, Nimmo GR, Collignon PJ, Bell JM, McLaws ML et al. Antimicrobial susceptibility of *Staphylococcus aureus* and molecular epidemiology of methicillin-resistant *S. aureus* isolated from Australian hospital inpatients: Report from the Australian Group on Antimicrobial Resistance 2011 *Staphylococcus aureus* Surveillance Programme. *J Glob Antimicrob Resist*. 2013;1(3):149–56.

32. O'Brien FG, Pearman JW, Gracey M, Riley TV, Grubb WB. Community strain of methicillin-resistant *Staphylococcus aureus* involved in a hospital outbreak. *J Clin Microbiol*. 1999;37(9):2858–62.

33. Schlebusch S, Price GR, Hinds S, Nourse C, Schooneveldt JM, Tilse MH et al. First outbreak of PVL-positive nonmultiresistant MRSA in a neonatal ICU in Australia: comparison of MALDI-TOF and SNP-plus-binary gene typing. *Eur J Clin Microbiol Infect Dis*. 2010;29(10):1311–4.