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Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Surveillance Outcome Program (AESOP)

Bloodstream Infection Annual Report 2021

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

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CDI is produced by the Office of Health Protection and Response, Australian Government Department of Health and Aged Care, GPO Box 9848, (MDP 6) CANBERRA ACT 2601

Email:
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Annual report

Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Surveillance Outcome Program (AESOP)

Bloodstream Infection Annual Report 2021

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

Abstract

From 1 January to 31 December 2021, forty-eight institutions around Australia participated in the Australian Enterococcal Surveillance Outcome Programme (AESOP). The aim of AESOP 2021 was to determine the proportion of enterococcal bacteraemia isolates in Australia that were antimicrobial resistant, and to characterise the molecular epidemiology of the *Enterococcus faecium* isolates. Of the 1,297 unique episodes of enterococcal bacteraemia investigated, 94.4% were caused by either *E. faecalis* (54.1%) or *E. faecium* (40.3%). Ampicillin resistance was detected in one *E. faecalis* isolate and in 89.3% of *E. faecium* isolates. Vancomycin non-susceptibility was not detected in *E. faecalis* but was detected in 37.9% of *E. faecium*. Overall, 39.6% of *E. faecium* harboured the *vanA* and/or *vanB* genes. For the *vanA/vanB* positive *E. faecium* isolates, 35.8% harboured the *vanA* gene and 64.2% the *vanB* gene. Although the percentage of vancomycin-resistant *E. faecium* bacteraemia isolates was significantly lower than that reported in the 2020 AESOP report (presumably due to the COVID-19 elective surgery restrictions placed on hospitals), it remains substantially higher than that recorded in most European countries. Isolates of *E. faecium* consisted of 73 multi-locus sequence types (STs); 77.2% of isolates were classified into seven major STs each containing more than ten isolates. All major STs belonged to clonal cluster (CC) 17, a major hospital-adapted polyclonal *E. faecium* cluster. The major STs (ST17, ST1424, ST796, ST78, ST80, ST1421 and ST555) were found across most regions of Australia. The predominant ST was ST17 which was identified in all regions except the Northern Territory. Overall, 46.5% of isolates belonging to the seven major STs harboured the *vanA* or *vanB* gene. The AESOP 2021 has shown that enterococcal bacteraemia episodes in Australia are frequently caused by polyclonal ampicillin-resistant high-level gentamicin resistant *vanA*- or *vanB*-positive *E. faecium* which have limited treatment options.

Keywords: Australian Group on Antimicrobial Resistance (AGAR); antimicrobial resistance surveillance; *Enterococcus faecium*; *Enterococcus faecalis*; vancomycin resistant enterococci (VRE); bacteraemia

Background

Globally, *Enterococcus* is believed to account for approximately 10% of all bacteraemia cases and is the fourth and fifth leading cause of sepsis in North America and Europe respectively. In the 1970s, healthcare-associated enterococcal infections were primarily due to *Enterococcus faecalis*, but there has been a steady increasing prevalence of *E. faecium* nosocomial infections.[1–3] Worldwide, the increase in nosocomial *E. faecium* infections has primarily been due to

the expansion of polyclonal hospital-adapted clonal complex (CC) 17 strains. While innately resistant to many classes of antibiotics, *E. faecium* has further demonstrated a remarkable capacity to evolve new antimicrobial resistances. In 2009, the Infectious Diseases Society of America highlighted *E. faecium* as one of the key problem bacteria or ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*) requiring new therapies.[4]

The Australian Group on Antimicrobial Resistance (AGAR) is a network of laboratories located across Australia that commenced surveillance of antimicrobial resistance in *Enterococcus* species in 1995.[5] In 2011, AGAR commenced the Australian Enterococcal Sepsis Outcome Programme,[6,7] now known as the Australian Enterococcal Surveillance Outcome Programme (AESOP). The objective of AESOP 2021 was to determine the proportion of *E. faecalis* and *E. faecium* bacteraemia isolates demonstrating antimicrobial resistance, with particular emphasis on:

1. assessing susceptibility to ampicillin;
2. assessing susceptibility to glycopeptides; and
3. the molecular epidemiology of *E. faecium*.

Methodology

Participants

Thirty laboratories servicing 48 institutions from all Australian states and mainland territories.

Collection period

From 1 January to 31 December 2021, the 30 laboratories collected all enterococcal species isolated from blood cultures. Enterococci of the same species and antimicrobial susceptibility profiles isolated from a patient's blood culture within 14 days of the first positive culture were excluded. A new enterococcal bacteraemia episode in the same patient was recorded if it was confirmed by a further culture of blood taken more than 14 days after the initial positive culture. Data were collected on age, sex, dates of admission and discharge (if admitted), and mortality at seven and 30 days from date of blood culture collection. To avoid interpretive bias, no attempt was made to assign attributable mortality. Each episode of bacteraemia was designated as "hospital-onset" if the first positive blood culture(s) in an episode was collected > 48 hours after admission.

Laboratory testing

Enterococcal isolates were identified to the species level by the participating laboratories using matrix-assisted laser desorption ionization (MALDI)—MALDI Biotyper (Bruker Daltonics, USA) or Vitek-MS (bioMérieux, France) or by the Vitek® 2 (bioMérieux). Antimicrobial susceptibility testing was performed using the Vitek® 2 (bioMérieux) or BD Phoenix™ (Becton Dickinson, USA) automated microbiology systems, according to the manufacturer's instructions. 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)[8] and European Committee on Antimicrobial Susceptibility Testing (EUCAST)[9] MIC breakpoints were utilised for interpretation. Linezolid and daptomycin non-susceptible isolates and vancomycin-susceptible isolates which harboured the *vanA* or *vanB* genes were retested by Etest® (bioMérieux) using the Mueller-Hinton agar recommended by the manufacturer. The control strain used was *E. faecalis* ATCC® 29212. Genotyping was performed by whole genome sequencing (WGS) using the NextSeq® 500 platform (Illumina, USA). Sequence reads were analysed using the Nullarbor pipeline.[10]

Confidence intervals for proportions, Fisher's exact test for categorical variables, and

chi-square test for trend were calculated as 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 1,297 unique episodes of enterococcal bacteraemia identified. Although nine *Enterococcus* species were identified, *E. faecalis* and *E. faecium* predominated: 702 isolates (54.1%) were *E. faecalis* and 523 isolates (40.3%) were *E. faecium*. Seventy-two enterococci were identified either as *E. gallinarum* (23 isolates), *E. casseliflavus* (20 isolates), *E. raffinosus* (9 isolates), *E. hirae* (7 isolates), *E. avium* (6 isolates), *E. durans* (5 isolates), *E. mundtii* (1 isolate) or *Enterococcus* sp. [not speciated] (1 isolate).

A significant difference was observed in patient sex ($p < 0.0001$), with 852 (65.7%) being male (95% confidence interval [95% CI]: 62.4–68.9). The average age of patients was 64 years, ranging from 0 to 100 years, with a median age of 69 years. The majority of episodes, 696/1,297 (53.7%) were community-onset (95% CI: 49.9–57.5); however, a significant difference ($p < 0.0001$) in place of onset was observed between *E. faecium* and *E. faecalis*, with only 32.1% (95% CI: 25.2–39.7) of *E. faecium* episodes being community-onset compared to 68.7% (95% CI: 65.1–72.1) for *E. faecalis*. All-cause mortality at 30 days, where outcome was known, was 18.9% (95% CI: 13.8–24.9). There was a significant difference in mortality between *E. faecalis* and *E. faecium* episodes (14.5% vs. 25.2% respectively, $p < 0.01$). There was also a significant difference between vancomycin-susceptible and vancomycin non-susceptible *E. faecium* episodes (21.3% vs 31.0% respectively, $p = 0.03$).

Enterococcus faecalis phenotypic susceptibility results

Apart from erythromycin, tetracycline, ciprofloxacin and high-level gentamicin, acquired

Table 1: The number and proportion of *E. faecalis* isolates non-susceptible to ampicillin, penicillin and the non-β-lactam antimicrobials, AGAR, 2021

Species and antimicrobial	Isolates (n)	CLSI[a]		EUCAST[b]	
		Intermediate % (*n*)	Resistant % (*n*)	Susceptible, increased exposure % (*n*)	Resistant % (*n*)
Enterococcus faecalis					
Ampicillin	698	–[c]	0.1 (1)	0.0 (0)	0.1 (1)
Benzylpenicillin	587	–[c]	0.9 (5)	–[d]	–[d]
Ciprofloxacin	419	2.4 (10)	5.0 (21)	–[c]	2.0 (8)[e]
Daptomycin	650	42.5 (276)	0.3 (2)	–[d]	–[d]
Linezolid	697	5.2 (36)	0.3 (2)	–[c]	0.3 (2)
Teicoplanin	699	0.0 (0)	0.0 (0)	–[c]	0.1 (1)
Vancomycin	699	0.0 (0)	0.0 (0)	–[c]	0.0 (0)

a CLSI: Clinical and Laboratory Standards Institute.

b EUCAST: European Committee on Antimicrobial Susceptibility Testing.

c No guidelines for indicated species.

d No category defined.

e The ciprofloxacin ECOFF (4 mg/L, *E. faecalis*) was used to distinguish between isolates with and without acquired resistance mechanisms, as breakpoints apply to uncomplicated urinary tract infections only.

resistance was rare amongst *E. faecalis* isolates (Table 1). Fifty-nine *E. faecalis* isolates (8.4%) were initially reported as linezolid non-susceptible (CLSI breakpoint > 2 mg/L). Two isolates were unavailable for linezolid susceptibility test confirmation. By Etest®, 20 of the 57 referred isolates had a linezolid MIC of ≤ 2 mg/L and were therefore considered linezolid susceptible. Thirty-five isolates with linezolid MICs of 4 mg/L, although intermediate by CLSI criteria, were considered susceptible by EUCAST criteria. Of the remaining two isolates (both linezolid MIC 6.0 mg/L), one isolate harboured the *optrA* gene. No linezolid resistance genes (*cfr*, *cfr(B)*, *optrA*, *poxtA*) nor known mutations in the 23S rRNA were identified in the other isolate.

Nine isolates were initially reported as daptomycin resistant (≥ 8 mg/L) by CLSI criteria. One isolate was unavailable for confirmation. By Etest®, seven of the eight referred isolates had a daptomycin MIC < 8 mg/L. The remaining isolate, with a MIC of 8.0 mg/L, had no known mutations identified.

Enterococcus faecium phenotypic susceptibility results

The majority of *E. faecium* isolates were non-susceptible to multiple antimicrobials including ampicillin, erythromycin, tetracycline, ciprofloxacin, nitrofurantoin and high-level gentamicin (Table 2). Overall, 198 isolates (37.9%) were phenotypically vancomycin non-susceptible (MIC > 4 mg/L). By CLSI and EUCAST criteria respectively, 54 (10.3%) and 69 (13.2%) isolates were teicoplanin non-susceptible. Nineteen isolates (3.6%) were initially reported as linezolid non-susceptible (CLSI breakpoint > 2 mg/L). Two isolates were unavailable for confirmation. By Etest®, nine of the seventeen referred isolates had a linezolid MIC ≤ 2 mg/L and therefore were considered susceptible. Six isolates with a MIC of 4.0 mg/L by Etest®, although intermediate by CLSI criteria, were considered susceptible by EUCAST criteria. Of the remaining two isolates, one (linezolid MIC 24 mg/L) harboured the *poxtA* gene and in the other (linezolid MIC 16 mg/L) the 23S rRNA G2576T mutation was detected.

Table 2: The number and proportion of *E. faecium* isolates non-susceptible to ampicillin, penicillin and the non-β-lactam antimicrobials, AGAR, 2021

Species and antimicrobial	Isolates (n)	CLSI[a]		EUCAST[b]	
		Intermediate % (*n*)	Resistant % (*n*)	Susceptible, increased exposure % (*n*)	Resistant % (*n*)
Enterococcus faecium					
Ampicillin	521	–[c]	89.3 (465)	0.0 (0)	89.3 (465)
Benzylpenicillin	436	–[c]	90.1 (393)	–[d]	–[d]
Ciprofloxacin	323	2.8 (9)	88.2 (285)	–[c]	–[e]
Linezolid	520	1.3 (7)	0.4 (2)	–[c]	0.4 (2)
Teicoplanin	522	1.1 (6)	10.3 (54)	–[c]	13.2 (69)
Vancomycin	522	1.5 (8)	36.4 (190)	–[c]	37.9 (198)

a CLSI: Clinical and Laboratory Standards Institute.

b EUCAST: European Committee on Antimicrobial Susceptibility Testing.

c No guidelines for indicated species.

d No category defined.

e The ciprofloxacin concentration range available on Vitek and Phoenix cards restricts the ability to determine non-wild type (ECOFF 8 mg/L) *E. faecium*.

Two isolates were initially reported as daptomycin non-susceptible (MICs > 4 mg/L). By Etest®, one isolate had a daptomycin MIC of 4.0 mg/L and was considered susceptible. The other isolate was confirmed as resistant by CLSI criteria (daptomycin MIC 8.0 mg/L) and a L39N mutation was detected in the *liaF* gene.

Genotypic vancomycin susceptibility results

For 336 (47.9%) of the 702 *E. faecalis* isolates, *vanA*/*vanB* polymerase chain reaction (PCR) results were available. No *vanA*/*vanB* genes were detected.

The presence of *vanA*/*vanB* genes was determined by PCR and/or WGS on 508 (97.1%) of the 523 *E. faecium* isolates. Overall, 201 of the 508 isolates (39.6%) harboured a *vanA* and/or *vanB* gene. Of the vancomycin non-susceptible *E. faecium* isolates (Vitek® 2 vancomycin MIC > 4 mg/L), 71 harboured *vanA* and 124 harboured *vanB*. The *vanA* or *vanB* gene was detected in six vancomycin-susceptible *E. faecium* isolates. One isolate, with a vancomycin MIC of ≤ 0.5 mg/L and teicoplanin MIC of 1.0 mg/L, harboured *vanA*. The five *vanB*-positive isolates had vancomycin MICs ranging from ≤ 0.5 mg/L to 3.0 mg/L.

E. faecium molecular epidemiology

Of the 523 episodes, 496 *E. faecium* isolates (94.8%) were available for typing by WGS. The 496 isolates were classified into 73 sequence types (STs), including seven STs with ten or more isolates (Table 3). Of the 66 STs with fewer than ten isolates, 45 STs were each represented by only one isolate. Overall, 383 (77.2%) of the 496 isolates were grouped into the seven major STs. Using eBURST, all major STs were grouped into CC17.

Geographical distribution of the STs varied (Table 3). Among the seven major STs, ST17 (124 isolates) was identified in all regions except the Northern Territory; ST1424 (86 isolates) was identified in all regions except Western Australia and the Northern Territory; ST796 (53 isolates) was identified in all regions except Queensland, Western Australia and the Australian Capital Territory; ST78 (43 isolates) was identified in all regions except Queensland and the Northern Territory; ST80 (40 isolates) was identified in all regions except the Northern Territory; ST1421 (24 isolates) was identified only in New South Wales, Victoria, Queensland and the Australian Capital Territory; and ST555 (13 isolates) was identified in all regions except Queensland and the Australian Capital Territory.

The *vanA* gene was detected in four major STs (69 isolates from ST17, ST1424, ST80 and ST1421) (Table 4).The *vanB* gene was detected in all seven major STs (126 isolates). One minor ST (ST117) harboured *vanA* and eight minor STs (ST18, ST203, ST233, ST538, ST789, ST1543, ST2082 and ST2217) harboured *vanB*.

Discussion

Enterococci are intrinsically resistant to a broad range of antimicrobials including the cephalosporins and sulphonamides. Because of their ability to acquire additional resistance through the transfer of plasmids and transposons and to disseminate easily in the hospital environment, enterococci have become difficult to treat and provide major infection control challenges.

As the AGAR programs are similar to those conducted in Europe, comparison of Australian antimicrobial resistance data with other countries is possible.

In the 2021 European Centre for Disease Prevention and Control (ECDC) enterococci surveillance program, the European Union/European Economic Area (EU/EEA) population-weighted mean percentage of *E. faecium* resistant to vancomycin was 14.3% (95% CI: 14.1–14.6).[11] The 2020 national percentages ranged from 0.0% in Luxembourg to 66.4% in Lithuania.[i]

i https:// http://atlas.ecdc.europa.eu/public/index.aspx.

Table 3: The number and proportion of major *Enterococcus faecium* sequence types, AGAR, 2021, by state and territory

	Percentage, % (*n*)[a]								
MLST[b]	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Australia
ST17	7.1 (1)	14.0 (19)	–[c] (0)	58.1 (25)	34.0 (17)	29.4 (5)	14.4 (24)	54.1 (33)	25.0 (124)
ST1424[d]	42.9 (6)	39.0 (53)	–[c] (0)	4.7 (2)	4.0 (2)	17.6 (3)	12.0 (20)	0.0 (0)	17.3 (86)
ST796	0.0 (0)	1.5 (2)	–[c] (4)	0.0 (0)	8.0 (4)	11.8 (2)	24.6 (41)	0.0 (0)	10.7 (53)
ST78	14.3 (2)	3.7 (5)	–[c] (0)	0.0 (0)	14.0 (7)	5.9 (1)	15.6 (26)	3.3 (2)	8.7 (43)
ST80	21.4 (3)	3.7 (5)	–[c] (0)	16.3 (7)	8.0 (4)	5.9 (1)	9.6 (16)	6.6 (4)	8.1 (40)
ST1421[d]	7.1 (1)	15.4 (21)	–[c] (0)	2.3 (1)	0.0 (0)	0.0 (0)	0.6 (1)	0.0 (0)	4.8 (24)
ST555	0.0 (0)	0.7 (1)	–[c] (1)	0.0 (0)	6.0 (3)	5.9 (1)	3.0 (5)	3.3 (2)	2.6 (13)
Other types (n = 66)	7.1 (1)	22.1 (30)	–[c] (3)	18.6 (8)	26.0 (13)	23.5 (4)	20.4 (34)	32.8 (20)	22.8 (113)
Total	**14**	**136**	**8**	**43**	**50**	**17**	**167**	**61**	**496**

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 MLST: multi-locus sequence type.

c Insufficient numbers (< 10) to calculate percentage.

d *pstS*-null.

Table 4: The number and proportion of major *Enterococcus faecium* sequence types harbouring *vanA/B* genes, AGAR, 2021

MLST[b]	Percentage[a] (*n*)				Total, n
	vanA	*vanB*	*vanA* and *vanB*	*vanA* or *vanB* not detected	
ST17	1.6 (2)	4.0 (5)	0.0 (0)	94.4 (117)	124
ST1424	51.2 (44)	0.0 (0)	0.0 (0)	48.8 (42)	86
ST796	0.0 (0)	100.0 (53)	0.0 (0)	0.0 (0)	53
ST78	0.0 (0)	100.0 (43)	0.0 (0)	0.0 (0)	43
ST80	7.5 (3)	5.0 (2)	0.0 (0)	87.5 (35)	40
ST1421	62.5 (15)	0.0 (0)	0.0 (0)	37.5 (9)	24
ST555	0.0 (0)	84.6 (11)	0.0 (0)	15.4 (2)	13
Other types (n =66)	4.4 (5)	10.6 (12)	0.0 (0)	85.0 (96)	113
Total	13.9 (69)	25.4 (126)	0.0 (0)	60.7 (301)	496

a Percentage of total with *van* genes.

b MLST: multi-locus sequence type.

In AESOP 2021, a total of 40.3% of enterococcal bacteraemia episodes were due to *E. faecium*, of which 37.9% (95% CI: 33.7–42.2) were phenotypically vancomycin non-susceptible by Vitek® 2 or BD Phoenix™. However, 39.6% of *E. faecium* isolates tested (201/508) harboured a *vanA/vanB* gene, of which 35.8% were *vanA*-positive. Overall, 72 *E. faecium* isolates (14.2%) harboured the *vanA* gene. Prior to the 2021 AESOP, we have reported a significant increase in *vanA*-positive *E. faecium* in Australia, from 6% in 2013 to 22.3% in 2019.[12–18] The decrease in *vanA*-positive *E. faecium* in 2020 and 2021 (13.7% and 14.2% respectively)[19] was primarily due to a decrease in ST1421 and ST1424 isolates. The majority of *E. faecium* isolates were non-susceptible to multiple antimicrobials including ampicillin, erythromycin, tetracycline, ciprofloxacin and high-level gentamicin. The 2021 AESOP survey confirms that the incidence of vancomycin-resistant *E. faecium* bacteraemia in Australia continues to be a significant problem.

Five (3.9%) of the 129 *vanB*-positive *E. faecium* and one (1.4%) of the 72 *vanA*-positive *E. faecium* isolates had a vancomycin MIC at or below the CLSI and the EUCAST susceptible breakpoint (≤ 4 mg/L) and therefore would not have been identified using routine phenotypic antimicrobial susceptibility methods.

By WGS, *E. faecium* was shown to be polyclonal, consistent with the known plasticity of the enterococcal genome. The seven major *E. faecium* STs form part of CC17, a global hospital-derived lineage that has successfully adapted to hospital environments. CC17 is characteristically ampicillin- and quinolone-resistant and subsequent acquisition of *vanA*- or *vanB*- containing transposons by horizontal transfer in CC17 clones has resulted in multi-resistant enterococci with pandemic potential.

In AESOP 2021, seven *E. faecium* STs predominated: ST17 (of which 1.6% of isolates harboured *vanA*, 4.0% *vanB* genes); ST1424 (51.2% *vanA*, 0% *vanB)*; ST796 (100% *vanB)*; ST78 (100% *vanB*), ST80 (7.5% *vanA,* 5.0% *vanB*); ST1421 (62.5% *vanA,* 0% *vanB*) and ST555 (0% *vanA,* 84.6% *vanB*).

Conclusions

The AESOP 2021 study has shown that, although predominately caused by *E. faecalis,* enterococcal bacteraemia in Australia is frequently caused by ampicillin-resistant, high-level gentamicin-resistant vancomycin-resistant *E. faecium*. Furthermore the percentage of *E. faecium* bacteraemia isolates resistant to vancomycin in Australia (37.9%) remains significantly higher than that seen in most European countries. In addition to being a significant cause of healthcare-associated sepsis, the emergence of multiple multi-resistant hospital-adapted *E. faecium* strains has become a major infection control issue in Australian hospitals. Ongoing studies on the enterococcal genome will contribute to our understanding of the rapid and ongoing evolution of enterococci in the hospital environment and will assist in preventing their nosocomial transmission.

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Members of the AGAR in 2021 were:

Australian Capital Territory

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New South Wales

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Monica Lahra and Peter Huntington, Sydney Children's Hospital

Alison Kesson and Andrew Jarrett, Children's Hospital Westmead

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Northern Territory

Rob Baird and Jann Hennessy, Royal Darwin Hospital

James McLeod, Alice Springs Hospital

Queensland

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, Pathology Queensland Prince Charles Hospital

Naomi Runnegar and Joel Douglas, Pathology Queensland Princess Alexandra Hospital

Jennifer Robson and Marianne Allen, Sullivan Nicolaides Pathology, Greenslopes 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 Brooke Wooley, Launceston General Hospital

Victoria

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Katherine Bond and Rose Cotronei, Royal Melbourne Hospital

Western Australia

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 Foster, Australian Clinical Laboratories, St John of God Hospital, Murdoch

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

Christopher Blyth, Perth Children's Hospital

Author Details

Prof. Geoffrey W Coombs,[1,2,3]

Ms Denise A Daley,[2,3]

Ms Princy Shoby,[1]

Dr Shakeel Mowlaboccus,[1,2]

on behalf of the Australian Group on Antimicrobial Resistance

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

Telephone: +61 8 6152 2397

Email: g.coombs@murdoch.edu.au

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