AUSTRALIAN GROUP ON ANTIMICROBIAL RESISTANCE

Australian Enterococcus Surveillance Outcome Program (AESOP)

Bloodstream Infection Report

2021 Final Report

Contents

Key findings

Enterococcus species

- Between 1 January to 31 December 2021 a total of 1,297 episodes of enterococcal bacteraemia were reported; the majority (94.4%) of enterococcal bacteraemia episodes were caused by *Enterococcus faecalis* or *Enterococcus faecium.*
- The majority of *E. faecalis* bacteraemias were community-onset (CO) (68.7%), while in *E. faecium* bacteraemias only 32.1% were CO.
- The most frequent source of bacteraemia or clinical manifestation for *E. faecalis* was urinary tract infection (21.8%); for *E. faecium*, it was intra-abdominal infection other than biliary tract (19.3%).
- The combined 30-day all-cause mortality for *E. faecalis* and *E. faecium* was 19.1%.
- There was significant difference in 30-day all-cause mortality between *E. faecalis* (14.5%) and *E. faecium* (25.2%) P <0.01 and between vancomycin-resistant and vancomycin-susceptible *E. faecium* episodes (30.6% and 21.3% respectively) P = 0.03.
- The length of stay in hospital following enterococcal bacteraemia was more than 30 days for 22.7% of patients.
- Of bloodstream infections caused by *E. faecium*, 37.9% were phenotypically vancomycin resistant. There has been a significant decreasing trend in vancomycin resistance in Australia since 2017.
- In 2021, 39.6% of *E. faecium* harboured *vanA* and/or *vanB* genes (*vanA* 14.2%, *vanB* 25.4%). In 2020 35.2% of *E. faecium* harboured *vanA* and/or *vanB* genes.
- Of vancomycin-resistant *E. faecium* (VRE) bacteraemias, 36.4% were due to *vanA*-harbouring isolates. This is the dominant genotype in New South Wales, Queensland and Western Australia.
- There were 73 *E. faecium* multi-locus sequence types (STs), of which ST17, ST1424, ST796, ST78, ST80, ST1421 and ST555 were the most frequently identified.
- *vanA* genes were detected in five STs, and *vanB* genes were detected in 13 STs. The clonal diversity of *E. faecium* harbouring *van* genes varied across Australia.
- In 2021, for rates of resistance to vancomycin in *E. faecium,* compared to the European Antimicrobial Resistance Surveillance Network (EARS-Net) countries, Australia ranked eighth highest. From 2017 to 2020, Australia has ranked first, second, fourth and tenth respectively.

Implications of key findings for health care

When interpreting the Australian Group on Antimicrobial Resistance (AGAR) data, it is important to consider changes in surveillance coverage between 2013 and 2021. AGAR has increased the number of hospitals from 26 in 2013 to 48 in 2021. In addition, the relative distribution of sites has changed with the addition of three more paediatric and/or facilities providing specialist obstetric services, from 2017, and one additional site in 2019, another in 2020 and 2021 and the inclusion of hospitals from north-west regional Western Australia from 2015.

Several themes are discussed below which have implications for the delivery of health care services and the safety of care provided to patients. These have been identified from the analyses of AGAR data.

Changing patterns in *Enterococcus* species

Total numbers of enterococcal bacteraemias identified by AGAR (for hospitals participating in both years) increased in 2021 compared to 2020 from 1,158 vs 1,234 (up 6.6%). The increase was mostly in the number of *E. faecium* (433 vs 492, up 11.1%) rather than *E. faecalis* (642 vs 702, up 5.1%).

The number of VRE isolates increased from 158 in 2020 to 198 in 2021. There was an increase in overall vancomycin resistance rates in *E. faecium* from 32.6% to 37.9%. There was an increase in VRE as a proportion of all enterococcal isolates at 15.3%; it was 12.8% in 2020. The overall contribution of *vanA* and *vanB* genes to VRE varied according to jurisdiction. *vanA*-harbouring types are dominant in New South Wales, Queensland and Western Australia, whilst *vanB*-harbouring types are dominant in Victoria, South Australia, the Northern Territory and Tasmania.

The gradual shift to *vanA*-harbouring *E. faecium* creates the potential for the loss of a valuable treatment choice, namely teicoplanin, which is active only against *vanB*-harbouring types. Optimising all VRE prevention and control mechanisms will be required to respond effectively to resistance in *E. faecium* in Australia.

Epidemiology of clinical manifestations

Urinary tract infection remains the most common manifestation associated with blood stream infection in *E. faecalis* episodes. In 2021, biliary and non-biliary intra-abdominal infections and febrile neutropenia were the most common clinical manifestations associated with *E. faecium*.

Variation across states and territories

Rates of vancomycin resistance in *E. faecium* ranged from 12.7% in Western Australia to 87.5% in the Northern Territory. Teicoplanin resistance ranged from zero in the Northern Territory to 21.2% in New South Wales.

Appropriate adaptation of national treatment guidelines should be considered in order to minimise the use of broad-spectrum antimicrobials whilst balancing delivery of the most appropriate antimicrobial for severe infections.

Variations between hospital and community settings

Enterococcus faecium was more commonly hospital-onset (67.9%) compared to *E. faecalis* (31.3%) hospital-onset. Where susceptibility results were known, vancomycin-resistant *E. faecium* bacteraemia accounted for 5.9% (41/690) of all community-onset enterococcal bacteraemia, compared to 26.3% (157/596) in hospital-onset disease.

These variations have implications for choice of empiric antimicrobial therapy and guidelines in community- versus hospital-onset infections, and accounting for infections in aged care home

residents (which are included in the community-onset group in the AGAR data, but not distinguished as such in this report).

1. Background and objectives

AGAR commenced in 1985 and was established to collect national data on antimicrobial resistance (AMR) in bacteria causing important and life-threatening infections.

AGAR is part of the Antimicrobial Use and Resistance in Australia (AURA) surveillance system funded by the Australian Government Department of Health and Aged Care.

This report on the Australian Enterococcal Surveillance Outcome Program (AESOP) operated by AGAR presents analyses of AMR associated with episodes of bacteraemia (blood stream infection) that were reported by 30 participating Australian public and private laboratories servicing 48 hospitals across Australia in 2021.

AGAR's focus on bacteraemia allows examination of laboratory-confirmed, invasive infections and comparison of rates over time for hospitals, states and territories. AGAR compares Australian data with the European Antimicrobial Resistance Surveillance Network, enabling benchmarking and trend projections. AGAR has collected ongoing data on the prevalence of antimicrobial resistance in Australia over a long period using standardised methods.

The 48 hospitals across Australia that currently contribute to AGAR, including five private hospitals, are listed in Table 1. In 2021, three hospitals, two from Queensland and one from New South Wales were unable to participate due to staff shortages as a result of the COVID-19 pandemic. One new hospital from Victoria contributed data.

Table 1: Hospitals that contributed to AGAR, by state and territory, AGAR, 2021

State or territory	Hospital
New South Wales	Children's Hospital Westmead
	Concord Repatriation General Hospital
	John Hunter Hospital
	Liverpool Hospital
	Nepean Hospital
	Royal North Shore Hospital
	St Vincent's Hospital, Sydney*
	Sydney Children's Hospital
	Westmead Hospital
	Wollongong Hospital
Victoria	Alfred Hospital
	Austin Hospital (Austin Health)
	Monash Children's Hospital†
	Monash Medical Centre (Dandenong Hospital)†
	Monash Medical Centre (Monash Health)
	Royal Melbourne Hospital
	Royal Women's and Children's Hospital
	St Vincent's Hospital*
Queensland	Gold Coast Hospital
	Prince Charles Hospital§
	Princess Alexandra Hospital§
	Royal Brisbane and Women's Hospital
	Greenslopes Private Hospital††
South Australia	Flinders Medical Centre
	Royal Adelaide Hospital
	Women's and Children's Hospital**
Western Australia	Fiona Stanley Hospital
	Joondalup Hospital*
	North-west regional Western Australia (Broome, Carnarvon, Derby, Exmouth, Fitzroy Crossing, Halls Creek, Karratha, Kununurra, Newman, Port Hedland, Wyndham)§§
	Perth Children's Hospital§§
	Royal Perth Hospital##
	Sir Charles Gairdner Hospital
	St John of God Hospital, Murdoch††
Tasmania	Launceston General Hospital
	Royal Hobart Hospital
Northern Territory	Alice Springs Hospital
	Royal Darwin Hospital
Australian Capital Territory	Canberra Hospital

* Public/private hospital
† Microbiology services provided by Monash Medical Centre (Monash Health)
§ Microbiology services provided by Pathology Queensland Central Laboratory
# Microbiology services provided by Sullivan Nicolaides Pathology
** Microbiology services provided by SA Pathology, Royal Adelaide Hospital
†† Private hospital
§§ Microbiology services provided by PathWest Laboratory Medicine WA, Sir Charles Gairdner Hospital
Microbiology services provided by PathWest Laboratory Medicine WA, Fiona Stanley Hospital

1.1. Australian Enterococcal Surveillance Outcome Program

Globally, enterococci are thought to account for approximately 10% of all bacteraemias, and in North America and Europe are the fourth and fifth leading causes of sepsis respectively. [1] [2] In the 1970s healthcare-associated enterococcal infections were primarily due to *Enterococcus faecalis*, however subsequently there has been a steady increase in prevalence of *E. faecium* nosocomial infections.[3-5] Worldwide, the increase in nosocomial *E. faecium* infections has primarily been due to the expansion of polyclonal hospital-adapted clonal complex (CC) 17 isolates. While innately resistant to many classes of antimicrobials, *E. faecium* CC17 has 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 (*E. faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species) pathogens requiring new therapies.[6]

AGAR began surveillance of antimicrobial resistance in *Enterococcus* species in 1995.[7] In 2011, AGAR commenced the Australian Enterococcal Sepsis Outcome Program (AESOP).[8] The term “Sepsis” in the program was changed in 2021 to “Surveillance” to better reflect AGAR’s surveillance of episodes of bacteraemia rather than sepsis.

In order to provide data to support improved antimicrobial prescribing and patient care, 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:

- Assessing susceptibility to ampicillin
- Assessing susceptibility to glycopeptides, and the associated resistance genes
- Monitoring the molecular epidemiology of *E. faecium.*

2. Summary of methods

Forty-eight institutions, in each state and territory of Australia, were enrolled in the 2021 AGAR programs. The AGAR laboratories collected all isolates from unique patient episodes of bacteraemia from 1 January 2021 to 31 December 2021. Approval to conduct the prospective data collection, including de-identified demographic data, was given by the research ethics committees associated with each participating hospital.

In patients with more than one isolate, a new episode was defined as a new positive blood culture more than two weeks after the initial positive culture. An episode was defined as community onset if the first positive blood culture was collected 48 hours or less after admission, and as hospital onset if collected more than 48 hours after admission.

AGAR meets the data security requirements of the AURA surveillance system. These arrangements ensure that data conform to appropriate standards of data management and quality, and that data are used in accordance with appropriate approvals. The Australia Society of Antimicrobials (ASA), as data custodian for AGAR data, is responsible for:

- Approving access to, and use of, AGAR data
- Ensuring that AGAR data are protected from unauthorised access, alteration or loss
- Ensuring compliance with relevant legislation and policies regarding administration, quality assurance, and data access and release.

2.1. Data fields

Laboratory data collected for each episode included an accession number, the date the blood culture was collected, the organism isolated (genus and species), and the antimicrobial susceptibility test results (minimum inhibitory concentrations) for each species. The patient's date of birth, sex and postcode of residence were also provided. If the patient was admitted to hospital, the dates of admission and discharge were recorded. Depending on the level of participation, limited clinical and outcome data were also provided. These included the principal clinical manifestation, device related infection (yes or no) and the outcome (died, all-cause or survived) at seven and 30 days (see Appendix A).

2.2. Species identification

Isolates were identified to species level, if possible, using the routine method for each institution. This included the Vitek® and BD Phoenix™ automated microbiology systems, and if available, matrix assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (Bruker MALDI biotyper® or Vitek® MS).

2.3. Susceptibility testing

Susceptibility testing of isolates is described in Appendix B. The analysis used breakpoints from the Clinical and Laboratory Standards Institute (CLSI) M100–Ed32[9] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) v12.0.[10]

2.4. PCR screening and whole genome sequencing

Whole genome sequencing using the Illumina NextSeq™ 500 platform was performed on all *E. faecium* referred to the Antimicrobial Resistance and Infectious Diseases Research Laboratory (AMRID), Murdoch University, WA. Data were analysed using the Nullarbor bioinformatic pipeline.[11]

2.5. Statistical Analysis

Confidence intervals for proportions, Fisher's exact test for categorical variables, and chi-square test for trend were calculated, if appropriate, using MedCalc for Windows, version 19.7.4 (MedCalc Software, Ostend Belgium).

3. Results

3.1. Isolates recovered

There were 1,297 episodes of enterococcal bacteraemia. *E. faecalis* and *E. faecium* accounted for 94.4% of all enterococcal isolates (Table 2).

Table 2: Number of each species recovered, by state and territory, AGAR, 2021

Organism	NSW	Vic	Qld	SA	WA	Tas	NT	ACT	Australia
Enterococcus species	340	362	165	127	182	53	17	51	1,297
*Enterococcus faecalis**	178	170	99	71	107	33	8	36	702
vancomycin resistant, percent	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
vancomycin susceptible, percent	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
*Enterococcus faecium**	146	169	50	55	63	18	8	14	523
vancomycin resistant, percent	31.5	59.8	14.3	34.5	12.7	33.3	87.5	28.6	37.9
vancomycin susceptible, percent	68.5	40.2	85.7	65.5	87.3	66.7	12.5	71.4	62.1
Other enterococcal species	16	23	16	1	12	2	1	1	72
Enterococcus gallinarum	4	8	5	0	4	1	1	0	23
Enterococcus casseliflavus	5	6	2	1	4	1	0	1	20
Enterococcus raffinosus	2	3	2	0	2	0	0	0	9
Enterococcus hirae	1	1	4	0	1	0	0	0	7
Enterococcus avium	0	4	2	0	0	0	0	0	6
Enterococcus durans	2	1	1	0	1	0	0	0	5
Enterococcus mundtii	1	0	0	0	0	0	0	0	1
Enterococcus species	1	0	0	0	0	0	0	0	1

* Vancomycin susceptibilities were not available for three *E. faecalis* and *one E. faecium*

3.2. Place of onset of bacteraemia

A total of 1,288 (99.3%) of patients with enterococcal bacteraemia were admitted to hospital.

Information on place of onset of bacteraemia was available for all *Enterococcus* species episodes (Table 3).

Episodes involving *E. faecalis* and 'other' *Enterococcus* species were predominantly community onset (*E. faecalis* [68.7%, 95% CI: 65.1-72.1] and other *Enterococcus spp.* [63.9%, CI: 51.7-74.9]). However, *E. faecium* episodes were predominantly hospital onset (67.9%; 95% CI: 63.7-71.9). The proportion of *E. faecalis* that were community onset was significantly lower among children (32.2%, 19/59) than adults (72.0%, 463/643) *P* <0.01.

Table 3: Species recovered, by place of onset, AGAR, 2021

Organism	Community onset % (*n*)	Hospital onset % (*n*)	Total, 100%
Enterococcus species	53.7 (696)	46.3 (601)	1,297
Enterococcus faecalis	68.7 (482)	31.3 (220)	702
Vancomycin resistant	–* (0)	–* (0)	0
Vancomycin susceptible	68.7 (480)	31.3 (219)	699
Enterococcus faecium	32.1 (168)	67.9 (355)	523
Vancomycin resistant	20.7 (41)	79.3 (157)	198
Vancomycin susceptible	39.2 (127)	60.8 (197)	324
Other *Enterococcus* species (*n* = 8)	63.9 (46)	36.1 (26)	72

* Insufficient numbers (<10) to calculate percentage

Note: Vancomycin susceptibilities were not available for three *E. faecalis* (two community-onset, one hospital-onset) and one *E. faecium* (hospital onset)

3.3. Onset versus 30-day all-cause mortality

Information on 30-day all-cause mortality, when place of onset was known, was available for 1,088 (83.9%) *Enterococcus* episodes (Table 4).

The 30-day all-cause mortality for *Enterococcus* species was significantly lower among children (3.0% 2/66) compared to adults (20.0%, 204/1,022) ($P < 0.01$). There was a significant difference in the 30-day all-cause mortality between *E. faecium* (25.2% 113/448) and *E. faecalis* (14.5%, 85/586) ($P < 0.01$) and between vancomycin-resistant (30.1%, 57/184) and vancomycin-susceptible (21.3%, 56/263) *E. faecium* episodes ($P = 0.03$).

Table 4: Onset setting and 30-day all-cause mortality (blood culture isolates), AGAR, 2021

Organism	Community onset		Hospital onset		Total	
	Number	Deaths % (*n*)	Number	Deaths % (*n*)	Number	Deaths % (*n*)
Enterococcus species	558	17.2 (96)	530	20.8 (110)	1,088	18.9 (206)
Enterococcus faecalis	392	14.5 (57)	194	14.4 (28)	586	14.5 (85)
Vancomycin resistant	0	–* (0)	0	–* (0)	0	–* (0)
Vancomycin susceptible	390	14.6 (57)	194	14.4 (28)	584	14.6 (85)
Enterococcus faecium	134	25.4 (34)	314	25.2 (79)	448	25.2 (113)
Vancomycin resistant	35	34.3 (12)	149	30.2 (45)	184	31.0 (57)
Vancomycin susceptible	99	22.2 (22)	164	20.7 (34)	263	21.3 (56)
Other enterococcal species (*n* = 8)	32	15.6 (5)	22	13.6 (3)	54	14.8 (8)

* Insufficient numbers (<10) to calculate percentage

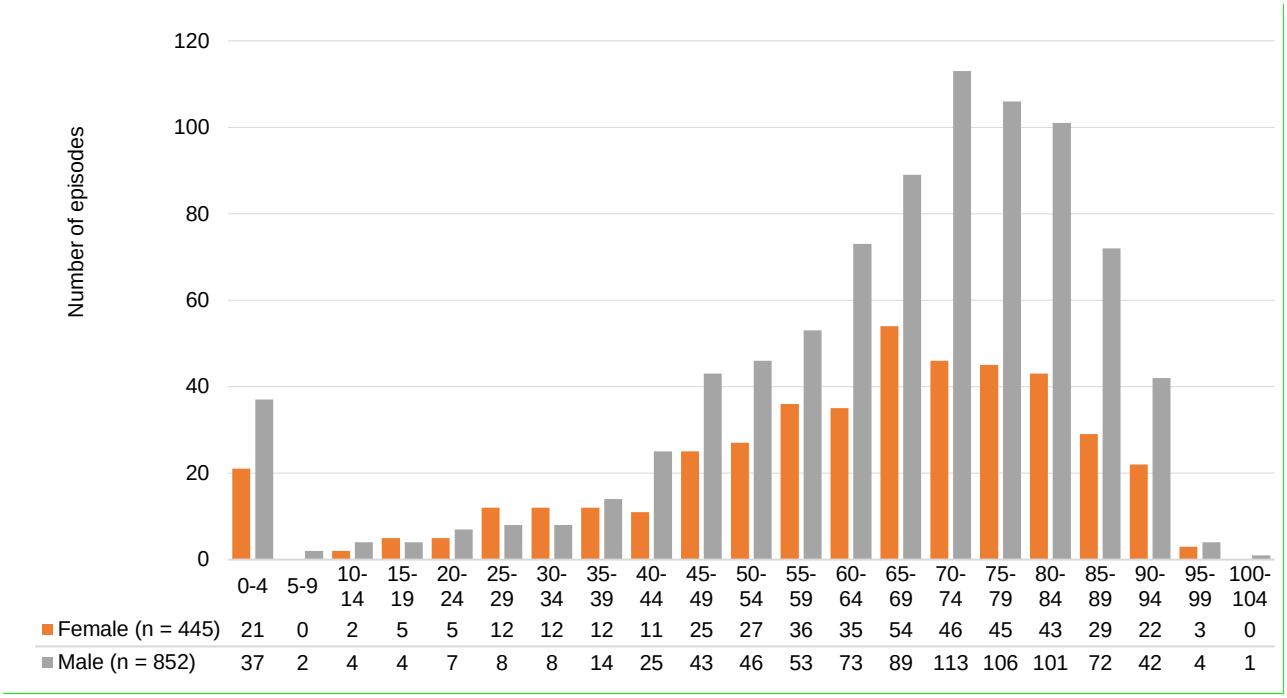
Note: Vancomycin susceptibilities were not available for two *E. faecalis* (community-onset) and one *E. faecium* (hospital-onset).

3.4. Patient age and sex

Age and sex were available for all patients. The proportion of males was 65.7% and females 34.3%.

Increasing age was a surrogate risk factor for bacteraemia (Figure 1); only 11.8% of *Enterococcus* species episodes were in patients aged less than 40 years. The proportion of patients aged 0–19 years was 5.8% (*n* = 75).

Figure 1: Number of episodes of bacteraemia due to *Enterococcus* species, by patient age group and sex, AGAR, 2021.



	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99	100-104
Female (n = 445)	21	0	2	5	5	12	12	12	11	25	27	36	35	54	46	45	43	29	22	3	0
Male (n = 852)	37	2	4	4	7	8	8	14	25	43	46	53	73	89	113	106	101	72	42	4	1

3.5. Principal clinical manifestation

The principal clinical manifestations, which represent the most likely primary site or source for the origin of the blood stream infection, are described below.

The principal clinical manifestation was known for 1,203 (92.8%) patient episodes of enterococcal bacteraemia. Overall, the most frequent principal clinical manifestations were those with urinary tract infection (15.0%), intra-abdominal infection other than biliary tract (14.4%) and biliary tract and those with no identifiable focus (14.1%) (Table 5). There were no significant gender differences in terms of principal clinical manifestation.

Of the hospital-onset episodes where data were available, the most frequent principal clinical manifestations were device related infections without metastatic focus (19.0%) and intra-abdominal infection other than biliary tract (18.1%). Of the community-onset episodes where data were available, the most frequent principal clinical manifestation was urinary tract infection (22.0%) (data not shown).

The principal manifestation was known for 1,133 of the 1,225 (92.5%) *E. faecalis* and *E. faecium* episodes (Table 6). The most common clinical manifestation for *E. faecalis* was urinary tract infection (21.8%), whereas for *E. faecium* it was intra-abdominal infection other than biliary tract (19.3%), febrile neutropenia (19.1%) and biliary tract infection (18.3%). Significant differences were seen between *E. faecalis* and *E. faecium* for a number of clinical manifestations.

Table 5: Principal clinical manifestation for enterococcal bacteraemia, by patient sex, AGAR, 2021

Principal clinical manifestation	Female % (*n*)	Male % (*n*)	Total % (*n*)	Significance*
Urinary tract infection	13.8 (56)	15.7 (125)	15.0 (181)	ns
Intra-abdominal infection other than biliary tract	15.8 (64)	13.7 (109)	14.4 (173)	ns
Biliary tract infection (including cholangitis)	14.8 (60)	13.8 (110)	14.1 (170)	ns
No identifiable focus	14.8 (60)	13.8 (110)	14.1 (170)	ns
Device-related infection without metastatic focus	14.3 (58)	12.3 (98)	13.0 (156)	ns
Febrile neutropenia	9.9 (40)	8.6 (69)	9.1 (109)	ns
Endocarditis left-sided	5.9 (24)	9.0 (72)	8.0 (96)	ns
Other clinical syndrome	4.7 (19)	6.4 (51)	5.8 (70)	ns
Skin and skin structure infection	3.0 (12)	2.9 (23)	2.9 (35)	ns
Osteomyelitis/septic arthritis	1.5 (6)	1.6 (13)	1.6 (19)	ns
Endocarditis right-sided	1.0 (4)	1.0 (8)	1.0 (12)	ns
Device-related infection with metastatic focus	0.5 (2)	1.3 (10)	1.0 (12)	ns
Total	405	798	1,203	

ns = not significant
* Fisher's exact test for difference in principal clinical manifestation and sex

Table 6: Principal clinical manifestation for *Enterococcus faecalis* and *E. faecium* bacteraemia, AGAR, 2021

Principal clinical manifestation	*E. faecalis* % (*n*)	*E. faecium* % (*n*)	Total % (*n*)	Significance*
Urinary tract infection	21.8 (143)	7.1 (34)	15.6 (177)	*P* <0.01
Intra-abdominal infection other than biliary tract	11.0 (72)	19.3 (92)	14.5 (164)	*P* <0.01
No identifiable focus	15.7 (103)	10.9 (52)	13.7 (155)	*P* = 0.02
Device-related infection without metastatic focus	12.5 (82)	14.5 (69)	13.3 (151)	ns
Biliary tract infection (including cholangitis)	8.7 (57)	18.3 (87)	12.7 (144)	*P* <0.01
Febrile neutropenia	1.8 (12)	19.1 (91)	9.1 (103)	*P* <0.01
Endocarditis left-sided	12.6 (83)	2.3 (11)	8.3 (94)	*P* <0.01
Other clinical syndrome	7.8 (51)	4.0 (19)	6.2 (70)	*P* <0.01
Skin and skin structure infection	3.7 (24)	1.9 (9)	2.9 (33)	ns
Osteomyelitis/septic arthritis	2.0 (13)	1.1 (5)	1.6 (18)	ns
Endocarditis right-sided	1.7 (11)	0.2 (1)	1.1 (12)	*P* = 0.02
Device-related infection with metastatic focus	0.9 (6)	1.3 (6)	1.1 (12)	ns
Total	657	476	1,133	

ns = not significant
*Fisher's exact test for difference in principal clinical manifestation between *E. faecalis* and *E. faecium*

3.6. Length of hospital stay following bacteraemic episode

Information on length of hospital stay following bacteraemia was available for 1,204 (92.8%) episodes involving *Enterococcus* species.

Overall, 22.7% of patients remained in hospital for more than 30 days after blood culture collection (Table 7).

Table 7: Length of hospital stay following *Enterococcus* species bacteraemia, by vancomycin resistance and place of onset, AGAR, 2021

Species	Length of stay following bacteraemia				Total
	<7 days % (*n*)	7–14 % days (*n*)	15–30 % days (*n*)	>30 days % (*n*)	
All species	21.8 (262)	28.8 (347)	26.7 (322)	22.7 (273)	1,204
E. faecalis	23.5 (154)	27.2 (178)	25.2 (165)	24.0 (157)	654
Vancomycin resistant	–* (0)	–* (0)	–* (0)	–* (0)	0
Vancomycin susceptible	23.7 (154)	27.0 (176)	25.2 (164)	24.1 (157)	651
E. faecium	18.3 (88)	30.2 (145)	29.8 (143)	21.7 (104)	480
Vancomycin resistant	19.4 (37)	24.6 (47)	31.9 (61)	24.1 (46)	191
Vancomycin susceptible	17.7 (51)	34.0 (98)	28.5 (82)	19.8 (57)	288
Other *Enterococcus* species (*n* = 8)	28.6 (20)	34.3 (24)	20.0 (14)	17.1 (12)	70
Community onset					
E. faecalis	27.6 (123)	30.6 (136)	24.5 (109)	17.3 (77)	445
Vancomycin resistant	–* (0)	–* (0)	–* (0)	–* (0)	0
Vancomycin susceptible	27.8 (123)	30.5 (135)	24.4 (108)	17.4 (77)	443
E. faecium	25.5 (38)	35.6 (53)	24.8 (37)	14.1 (21)	149
Vancomycin resistant	30.0 (12)	25.0 (10)	32.5 (13)	12.5 (5)	40
Vancomycin susceptible	23.9 (26)	39.4 (43)	22.0 (24)	14.7 (16)	109
Hospital onset					
E. faecalis	14.8 (31)	20.1 (42)	26.8 (56)	38.3 (80)	209
Vancomycin resistant	–* (0)	–* (0)	–* (0)	–* (0)	0
Vancomycin susceptible	14.9 (31)	19.7 (41)	26.9 (56)	38.5 (80)	208
E. faecium	15.1 (50)	27.8 (92)	32.0 (106)	25.1 (83)	331
Vancomycin resistant*	16.6 (25)	24.5 (37)	31.8 (48)	27.2 (41)	151
Vancomycin susceptible*	14.0 (25)	30.7 (55)	32.4 (58)	22.9 (41)	179

* Insufficient numbers (<10) to calculate percentage

Note: vancomycin susceptibility not available for three *E. faecalis* (community [2]; hospital onset [1]) and one *E. faecium* (hospital onset).

3.7. Susceptibility testing results

The following sections present the results of susceptibility testing and the findings for antimicrobial resistance by place of onset and multi-drug resistance. Susceptibility testing methods are described in Appendix B.

Percentages of non-susceptibility in national priority indicator species

Overall percentages of resistance or non-susceptibility using both CLSI breakpoints and EUCAST breakpoints are shown in Table 8. Resistance (as defined by EUCAST) by state and territory to glycopeptides in *E. faecium*, and high-level gentamicin resistance in *E. faecalis* is shown in Figure 2. Detailed resistance by state and territory can be found in Appendix C.

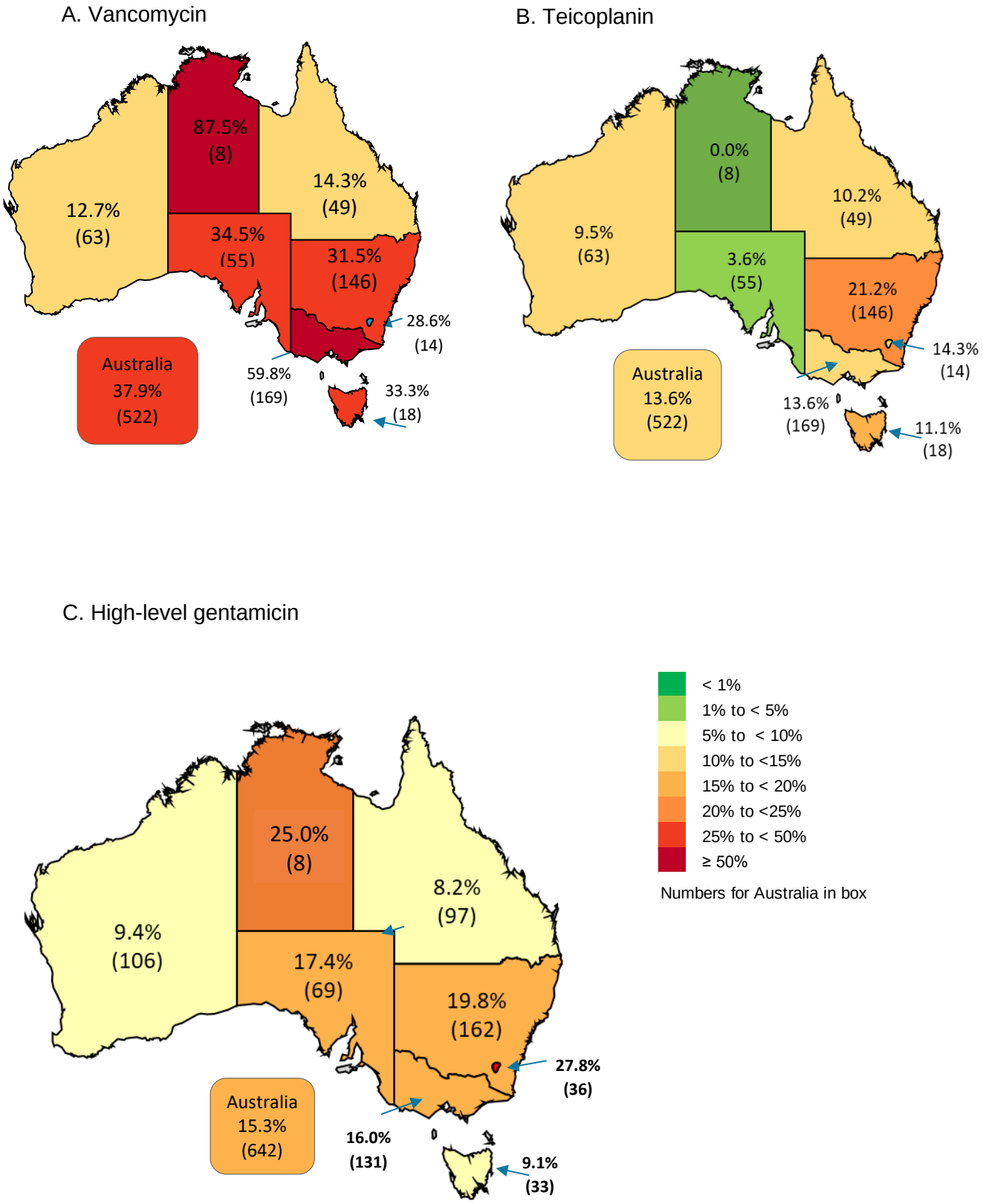
Table 8: Antimicrobial resistances for *E. faecalis* and *E. faecium* (CLSI and EUCAST), AGAR, 2021

Species and antimicrobial	Isolates (n)	CLSI		EUCAST	
		Intermediate % (*n*)	Resistant % (*n*)	Susceptible, increased exposure % (*n*)	Resistant % (*n*)
Enterococcus faecalis					
Ampicillin	698	–*	0.1 (1)	0.0 (0)	0.1 (1)
Benzylpenicillin	587	–*	0.9 (5)	–†	–†
Ciprofloxacin	419	2.4 (10)	5.0 (21)	–*	2.0 (8)§
Daptomycin	650	42.5 (276)	0.3 (2)	–†	–†
Linezolid	697	5.2 (36)	0.3 (2)	–*	0.3 (2)
Teicoplanin	699	0.0 (0)	0.0 (0)	–*	0.1 (1)
Vancomycin	699	0.0 (0)	0.0 (0)	–*	0.0 (0)
Enterococcus faecium					
Ampicillin	521	–*	89.3 (465)	0.0 (0)	89.3 (465)
Benzylpenicillin	436	–*	90.1 (393)	–†	–†
Ciprofloxacin	323	2.8 (9)	88.2 (285)	–*	–#
Linezolid	520	1.3 (7)	0.4 (2)	–*	0.4 (2)
Teicoplanin	522	1.1 (6)	10.3 (54)	–*	13.2 (69)
Vancomycin	522	1.5 (8)	36.4 (190)	–*	37.9 (198)

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; ECOFF = epidemiological cut-off value

* No guidelines for indicated species
† No category defined
§ 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
\# The ciprofloxacin concentration range available on Vitek and Phoenix cards restricts the ability to determine non-wild type (ECOFF 8 mg/L) *E. faecium*

Figure 2: Percentage of *Enterococcus faecium* from patients with bacteraemia with resistance as defined by EUCAST to vancomycin (A) and teicoplanin (B), and *Enterococcus faecalis* with resistance to high-level gentamicin (C), Australia, AGAR, 2021



Antimicrobial resistance by place of onset

Antimicrobial resistances (CLSI and EUCAST) in indicator species by place of onset, if known, are shown in Table 9.

Table 9: Antimicrobial resistances (CLSI, EUCAST), by place of onset, AGAR, 2021

Species and antimicrobial	Community onset					Hospital onset				
	No.	CLSI		EUCAST		No.	CLSI		EUCAST	
		% I	% R	% S-IEI	% R		% I	% R	% S-IE	% R
Enterococcus faecalis										
Ampicillin	479	–*	0.2	0.0	0.2	219	–*	0.0	0.0	0.0
Benzylpenicillin	406	–*	0.2	–†	–†	181	–*	–†	–†	–†
Ciprofloxacin	291	3.1	5.5	–*	1.8§	128	0.8	3.9§	–*	2.4§
Daptomycin	440	41.8	0.2	–†	–†	210	43.8	0.5	–†	–†
Linezolid	478	5.0	0.4	–*	0.4	219	5.5	0.0	–*	0.0
Teicoplanin	480	0.0	0.0	–*	0.2	219	0.0	0.0	–*	0.0
Vancomycin	480	0.0	0.0	–*	0.0	219	0.0	0.0	–*	0.0
Enterococcus faecium										
Ampicillin	167	–*	79.6	0.0	79.6	354	–*	93.8	0.0	93.8
Benzylpenicillin	149	–*	80.5	–†	–†	287	–*	95.1	–†	–†
Ciprofloxacin	109	5.5	77.1	–†	–#	214	1.4	93.9	–†	–#
Linezolid	166	3.0	0.6	–*	0.6	354	0.6	0.3	–*	0.3
Teicoplanin	168	0.6	4.8	–*	5.4	354	1.4	13.0	–*	16.9
Vancomycin	168	0.6	23.8	–*	24.4	354	2.0	42.4	–*	44.4

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; No. = number of isolates; I – Intermediate; R = Resistant; S-IE = susceptible, increased exposure; ECOFF = epidemiological cut-off value

* No guidelines for indicated species
† No category defined
\# The ciprofloxacin epidemiological cut-off value (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
§ The ciprofloxacin concentration range available on Vitek and Phoenix cards restricts the ability to determine non-wild type (ECOFF 8 mg/L) *E. faecium*

3.8. Multi-drug resistance

Enterococci have expected resistant phenotypes to several antimicrobial classes and any additional acquired resistance severely limits the number of treatment options. Range of antimicrobials available on the test panels limits the ability to determine multiple acquired resistances in *E. faecalis* and *E. faecium*. Vancomycin-resistant enterococcus are listed as a serious threat to public health[12] and have been identified as a major AMR threat in Australian healthcare facilities.[13]

3.9. PCR and whole genome sequencing

This section describes the results of the molecular epidemiology of *E. faecium* in the 2021 dataset. The benefits of molecular methods include increased accuracy in detecting the genetic mechanisms for AMR and clarifying the underlining epidemiology.

3.9.1. Molecular epidemiology of *Enterococcus faecium*

van genes

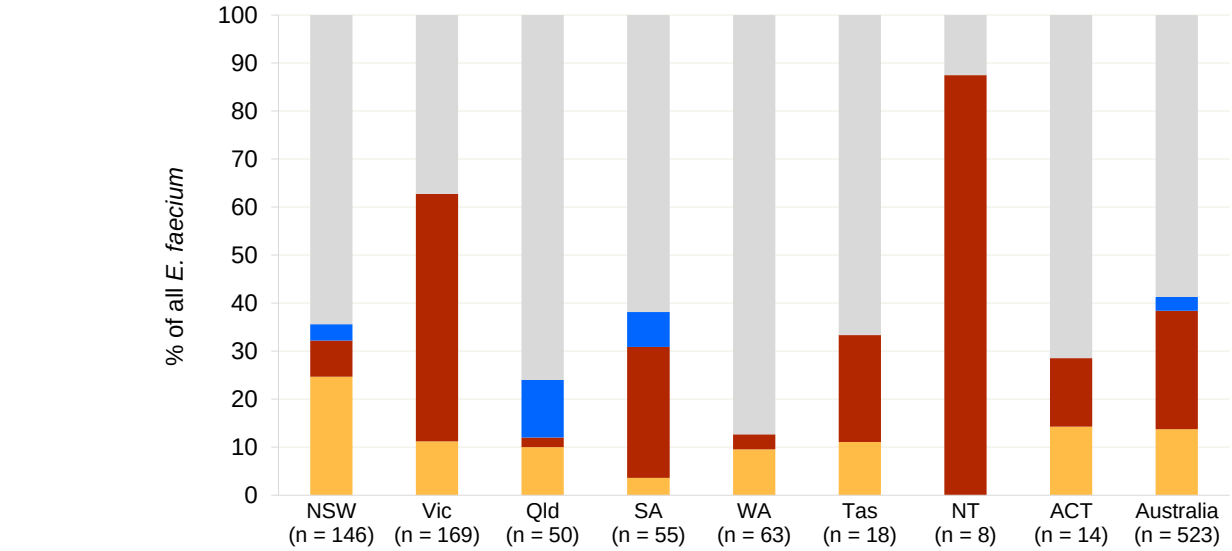
Results of PCR testing for *vanA* and *vanB* genes were available for 508 (97.1%) of the 523 *E. faecium* isolates. *van* genes were detected in 201/508 (39.6%) of *E. faecium*; *vanA* in 72 (14.2%) and *vanB* in 129 (25.4%) (Figure 3).

No *E. faecium* isolates contained both *vanA* and *vanB* genes.

For vancomycin-resistant *E. faecium* (MIC > 4 mg/L), *vanA* was detected in 71/195 (36.4%) and *van B* in 124/195 (63.6%).

In 6/312 (1.9%) of vancomycin-susceptible *E. faecium*, *van* genes were detected: one with *vanA* and 5 with *vanB*. All six isolates had vancomycin MICs ≤ 4 mg/L.

Figure 3: Vancomycin genotype of *Enterococcus faecium* isolates, by state and territory, and nationally, AGAR, 2021



	NSW (n = 146)	Vic (n = 169)	Qld (n = 50)	SA (n = 55)	WA (n = 63)	Tas (n = 18)	NT (n = 8)	ACT (n = 14)	Australia (n = 523)
not vanA or vanB (n =307)	64.4	37.3	76.0	61.8	87.3	66.7	12.5	71.4	58.7
Not peformed (n = 15)	3.4	0.0	12.0	7.3	0.0	0.0	0.0	0.0	2.9
vanB (n = 129)	7.5	51.5	2.0	27.3	3.2	22.2	87.5	14.3	24.7
vanA (n = 72)	24.7	11.2	10.0	3.6	9.5	11.1	0.0	14.3	13.8

Multi-locus sequence type

Of the 523 *E. faecium* isolates reported, 496 (94.8%) were available for typing by whole genome sequencing (Table 10). Based on the MLST, 73 sequence types (STs) were identified. Overall, 77.2% of *E. faecium* could be characterised into seven major STs (>10 isolates): ST17 (*n* = 124); ST1424 (*n* = 86); ST796 (*n* = 53); ST78 (*n* = 43); ST80 (*n* = 40); ST1421 (*n* = 24) and ST555 (n=13). There were 45 STs with a single isolate.

ST17 was the predominant ST in Queensland, South Australia, Western Australia and Tasmania. ST1424 was the predominant ST in New South Wales and the Australian Capital Territory, ST796 in Victoria and the Northern Territory.

The distribution of vancomycin-resistant *E. faecium* sequence types throughout Australian states and territories is shown in Figure 4.

Table 10: *Enterococcus faecium* MLST, by state and territory, AGAR, 2021

	Percentage, % (*n*)								
MLST	NSW	Vic	QLD	SA	WA	Tas	NT	ACT	Australia
ST17	14.0 (19)	14.4 (24)	58.1 (25)	34.0 (17)	54.1 (33)	29.4 (5)	–* (0)	7.1 (1)	25.0 (124)
ST1424	39.0 (53)	12.0 (20)	4.7 (2)	4.0 (2)	0.0 (0)	17.6 (3)	–* (0)	42.9 (6)	17.3 (86)
ST796	1.5 (2)	24.6 (41)	0.0 (0)	8.0 (4)	0.0 (0)	11.8 (2)	–* (4)	0.0 (0)	10.7 (53)
ST78	3.7 (5)	15.6 (26)	0.0 (0)	14.0 (7)	3.3 (2)	5.9 (1)	–* (0)	14.3 (2)	8.7 (43)
ST80	3.7 (5)	9.6 (16)	16.3 (7)	8.0 (4)	6.6 (4)	5.9 (1)	–* (0)	21.4 (3)	8.1 (40)
ST1421	15.4 (21)	0.6 (1)	2.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	7.1 (1)	4.8 (24)
ST555	0.7 (1)	3.0 (5)	0.0 (0)	6.0 (3)	3.3 (2)	5.9 (1)	–* (1)	0.0 (0)	2.6 (13)
ST789	0.7 (1)	1.2 (2)	0.0 (0)	0.0 (0)	8.2 (5)	0.0 (0)	–* (0)	0.0 (0)	1.6 (8)
ST117	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	9.8 (6)	0.0 (0)	–* (0)	0.0 (0)	1.4 (7)
ST538	4.4 (6)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	1.2 (6)
ST1283	0.7 (1)	0.0 (0)	4.7 (2)	4.0 (2)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	1.0 (5)
ST18	1.5 (2)	1.2 (2)	0.0 (0)	0.0 (0)	1.6 (1)	0.0 (0)	–* (0)	0.0 (0)	1.0 (5)
ST203	0.0 (0)	1.8 (3)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.6 (3)
ST262	1.5 (2)	0.0 (0)	0.0 (0)	2.0 (1)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.6 (3)
ST361	0.7 (1)	0.0 (0)	0.0 (0)	2.0 (1)	0.0 (0)	5.9 (1)	–* (0)	0.0 (0)	0.6 (3)
ST52	0.0 (0)	1.8 (3)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.6 (3)
ST94	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	1.6 (1)	5.9 (1)	–* (0)	0.0 (0)	0.6 (3)
ST1543	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (2)	0.0 (0)	0.4 (2)
ST178	0.7 (1)	0.0 (0)	0.0 (0)	2.0 (1)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.4 (2)
ST2194	1.5 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.4 (2)
ST2195	1.5 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.4 (2)
ST22	0.0 (0)	1.2 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.4 (2)
ST2217	0.0 (0)	1.2 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.4 (2)
ST240	0.0 (0)	0.6 (1)	2.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.4 (2)
ST5	0.0 (0)	0.0 (0)	0.0 (0)	2.0 (1)	1.6 (1)	0.0 (0)	–* (0)	0.0 (0)	0.4 (2)
ST612	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (1)	7.1 (1)	0.4 (2)

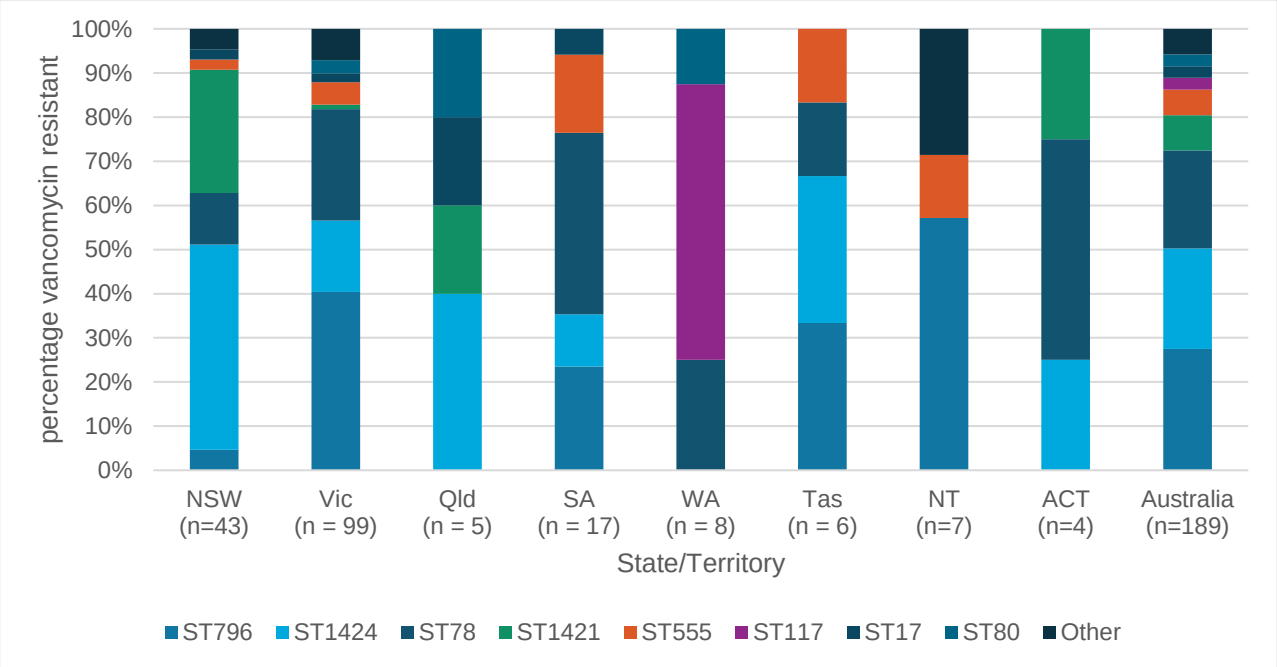
MLST	Percentage, % (*n*)								
	NSW	Vic	QLD	SA	WA	Tas	NT	ACT	Australia
ST648	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	5.9 (1)	–* (0)	0.0 (0)	0.4 (2)
ST761	0.0 (0)	1.2 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.4 (2)
ST1006	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST1044	0.0 (0)	0.0 (0)	0.0 (0)	2.0 (1)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST1052	0.0 (0)	0.0 (0)	0.0 (0)	2.0 (1)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST107	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST1240	0.0 (0)	0.0 (0)	2.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST1258	0.0 (0)	0.0 (0)	2.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST127	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST1445	0.0 (0)	0.0 (0)	0.0 (0)	2.0 (1)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST1755	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST1760	0.0 (0)	0.0 (0)	0.0 (0)	2.0 (1)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST184	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST1926	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST202	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST2048	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST2074	0.0 (0)	0.0 (0)	0.0 (0)	2.0 (1)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST2082	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST2083	0.0 (0)	0.0 (0)	2.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST210	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST2197	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST2199	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST2200	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST2201	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.6 (1)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST2202	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.6 (1)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST2205	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	5.9 (1)	–* (0)	0.0 (0)	0.2 (1)
ST2219	0.0 (0)	0.0 (0)	2.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST2220	0.0 (0)	0.0 (0)	2.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST233	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST25	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST266	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST32	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST39	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST418	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST533	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.6 (1)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST536	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST54	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)

MLST	Percentage, % (*n*)								
	NSW	Vic	QLD	SA	WA	Tas	NT	ACT	Australia
ST598	0.0 (0)	0.0 (0)	0.0 (0)	2.0 (1)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST60	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST640	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST674	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.6 (1)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST855	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.6 (1)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST867	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST874	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.6 (1)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST928	0.0 (0)	0.0 (0)	0.0 (0)	2.0 (1)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST992	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
ST994	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	0.0 (0)	0.2 (1)
Total	**136**	**167**	**43**	**50**	**61**	**17**	**8**	**14**	**496**

MLST = multi-locus sequence type

* Insufficient numbers (<10) to calculate percentage

Figure 4: Distribution of vancomycin-resistant *Enterococcus faecium* sequence types, by state and territory, AGAR, 2021



MLST and *van* genes

The *vanA* gene was detected in five STs; ST17, ST1424, ST80, ST1421 and ST117.

The *vanB* gene was detected in 13 STs: ST17, ST796, ST78, ST80, ST555, ST203, ST1543, ST2217, ST18, ST233, ST538, ST786 and ST2082 (Table 11). No isolate harboured both *vanA* and *vanB* genes.

Table 11: Major *Enterococcus faecium* MLST harbouring *vanA* and/or *vanB* genes, AGAR, 2021

	Percentage* (*n*)				
MLST	***vanA***	***vanB***	***vanA* and *vanB***	***vanA* or *vanB* not detected**	**Total, *n***
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

MLST = multi-locus sequence type

* Percentage of total with *van* genes

3.10. Trend analysis (2013–2021)

Trend data were available for the period 2013 to 2021.

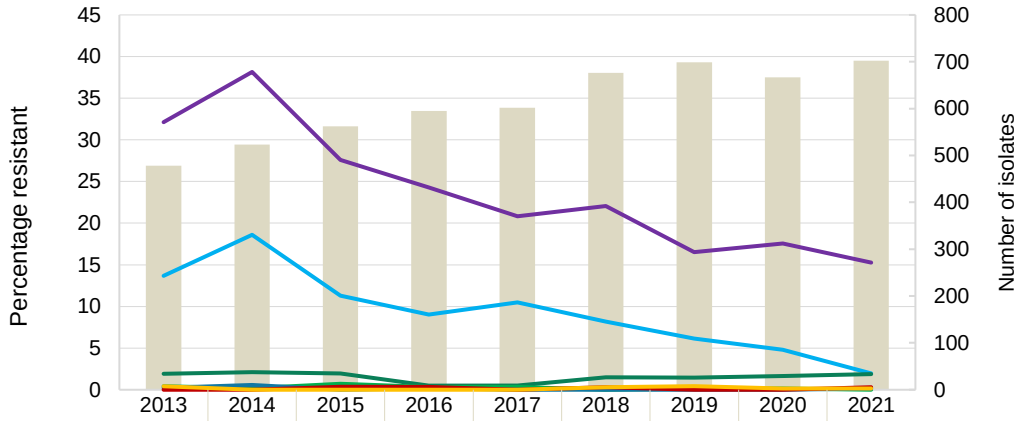
3.10.1. *Enterococcus* species

The 2021 program focused on the proportions of *E. faecium* and *E. faecalis* bacteraemia isolates demonstrating resistance to ampicillin, glycopeptides and other anti-enterococcal agents. Important trends for the period 2013–2021 are described below.

Enterococcus faecalis

National
Resistance (EUCAST) to key antimicrobial agents for *E. faecalis* over the nine-year period 2013 to 2021 is shown in Figure 5. Resistance to ampicillin, vancomycin, teicoplanin and linezolid remains rare. There was a decrease in the proportion of *E. faecalis* with acquired ciprofloxacin resistance in 2021 compared with 2020 (19/397, 4.8% in 2020; 8/408, 2.0% in 2021, *P* = 0.031). In 2021, two linezolid-resistant (both MIC 8.0 mg/L) *E. faecalis* were confirmed from Western Australia and the Australian Capital Territory. The isolate from Western Australia harboured the *optrA* gene. No known mutations or resistance genes could be found in the isolate from the Australian Capital Territory.

Figure 5: *Enterococcus faecalis*, resistance (EUCAST), Australia, AGAR, 2013–2021



	2013	2014	2015	2016	2017	2018	2019	2020	2021
Number of isolates	478	523	562	595	602	676	699	667	702
Gentamicin (high-level)	32.1	38.2	27.6	24.3	20.8	22.1	16.5	17.6	15.3
Ciprofloxacin (ECOFF)	13.7	18.6	11.3	9.0	10.5	8.2	6.1	4.8	2.0
Nitrofurantoin (ECOFF)	1.9	2.1	2.0	0.5	0.5	1.5	1.4	1.7	1.9
Vancomycin	0.4	0.2	0.7	0.3	0.3	0.0	0.1	0.2	0.0
Ampicillin	0.2	0.6	0.0	0.2	0.0	0.0	0.0	0.0	0.1
Linezolid	0.0	0.0	0.4	0.3	0.0	0.3	0.0	0.0	0.3
Teicoplanin	0.4	0.0	0.0	0.0	0.0	0.3	0.4	0.2	0.1

EUCAST = European Committee on Antimicrobial Susceptibility Testing; ECOFF = epidemiological cut-off values

Notes
1. Percentage resistance determined using EUCAST 2022 breakpoints for all years.
2. Number of contributors per year – 2013 and 2014, n = 27; 2015, n = 35; 2016, n = 33; 2017, n = 35, 2018, n = 38; 2019, n = 41, 2020, n = 42, 2021, n = 41
3. Ciprofloxacin susceptibility data only available for 26/39 (2020) and 25/48 (2021) institutions due to change in Vitek card used.
4. The ciprofloxacin ECOFF (4 mg/L) was used to distinguish between isolates with and without acquired resistance mechanisms, as breakpoints apply to uncomplicated urinary tract infections only.
5. The nitrofurantoin ECOFF (32 mg/L) was used to distinguish between isolates with and without acquired resistance mechanisms, as breakpoints apply to uncomplicated urinary tract infections only.

State and territory

There were no significant changes in antimicrobial resistance among *E. faecalis* in 2021, compared to 2020.

Over the past five years (2017-2021), there was a significant decreasing trend in high-level gentamicin resistance in Queensland (X^2 for linear trend = 9.132, $P < 0.01$), South Australia (X^2 for linear trend = 4.106, $P < 0.04$) and Western Australia (X^2 for linear trend = 7.025, $P < 0.01$) (Table 12).

Table 12: *Enterococcus faecalis*, percentage resistant to gentamicin (high-level) (EUCAST) and number tested, state and territory, AGAR, 2013–2021

	Percentage resistant, (*n*) by year									Trend 2017–2021*
State and territory	2013	2014	2015	2016	2017	2018	2019	2020	2021	
New South Wales	40.0 (85)	42.4 (132)	29.3 (140)	28.2 (149)	16.7 (186)	24.2 (207)	15.3 (215)	19.0 (221)	19.8 (162)	↔
Victoria	34.0 (106)	38.7 (119)	27.4 (106)	22.3 (130)	19.7 (117)	23.1 (117)	22.2 (126)	24.8 (133)	16.0 (131)	↔
Queensland	27.6 (87)	34.3 (102)	25.5 (94)	28.6 (98)	21.2 (99)	16.3 (129)	13.0 (123)	9.3 (97)	8.2 (97)	▼
South Australia	31.6 (19)	35.3 (51)	28.1 (57)	29.4 (51)	35.5 (31)	23.6 (55)	9.4 (64)	13.8 (58)	17.4 (69)	▼
Western Australia	28.2 (71)	28.6 (63)	23.3 (90)	16.1 (87)	22.5 (89)	21.1 (90)	12.8 (78)	15.9 (88)	9.4 (106)	▼
Tasmania	18.2 (11)	30.8 (13)	25.0 (12)	14.8 (27)	19.4 (31)	16.1 (31)	12.2 (41)	7.4 (27)	9.1 (33)	↔
Northern Territory	–† (6)	–† (6)	40.0 (10)	–† (7)	10.0 (10)	18.2 (11)	–† (7)	–† (5)	–† (8)	↔
Australian Capital Territory	30.4 (23)	54.5 (33)	34.3 (35)	22.5 (40)	35.7 (28)	38.5 (26)	44.4 (36)	19.4 (31)	27.8 (36)	–†
Australia	32.1 (408)	38.2 (519)	27.6 (544)	24.3 (589)	20.8 (591)	22.1 (666)	16.5 (690)	17.6 (660)	15.3 (642)	▼

* Chi-square test for trend for past five years (2017–2021), p-value <0.05, decrease ▼; ↔ no significant difference

† Not applicable, insufficient numbers (<10) to calculate percentage

Note: Percentage resistance determined using EUCAST 2022 breakpoints for all years.

Enterococcus faecium

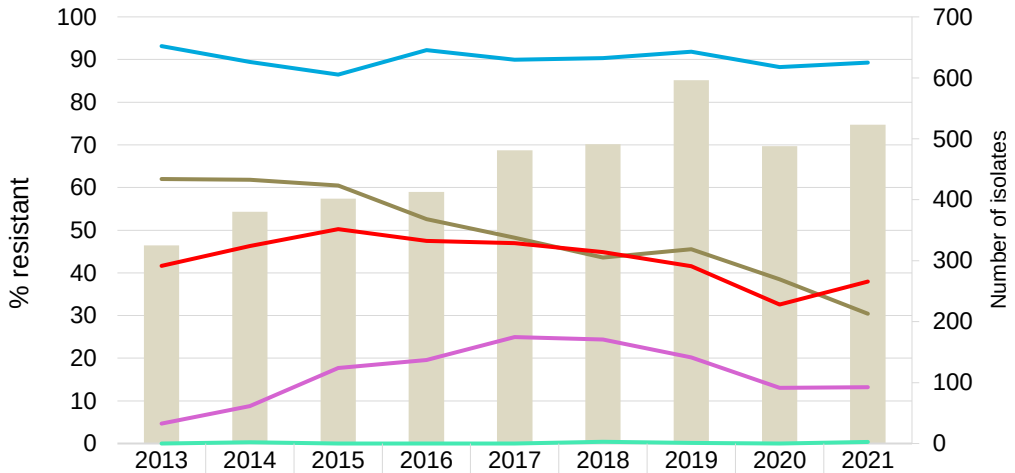
National

The total number of *E. faecium* isolated from patients with bacteraemia increased 7.2% in 2021 compared to 2020 (*n* = 488 in 2020; *n* = 523 in 2021) (Figure 6). There were no significant changes in the proportion of *E. faecium* isolates resistant to vancomycin or teicoplanin.

There was a significant decrease in the proportion of E. faecium isolates resistant to gentamicin (high-level) (184/479, 38.4% in 2020, 146/480, 30.4% in 2021, P < 0.01). The decrease was seen in both vancomycin resistant (63.5% in 2020, 52.0% in 2021), and vancomycin-susceptible (26.4% in 2020, 17.8% in 2021) *E. faecium* (Figure 7).

Two linezolid-resistant *E. faecium* were confirmed in 2021. The G2576T 23S rRNA mutation was detected in one isolate from New South Wales (MIC = 32mg/L). The second isolate from South Australia harboured the *poxtA* gene (MIC = 16 mg/L).

Figure 6: *Enterococcus faecium*, resistance (EUCAST), Australia, AGAR, 2013–2021



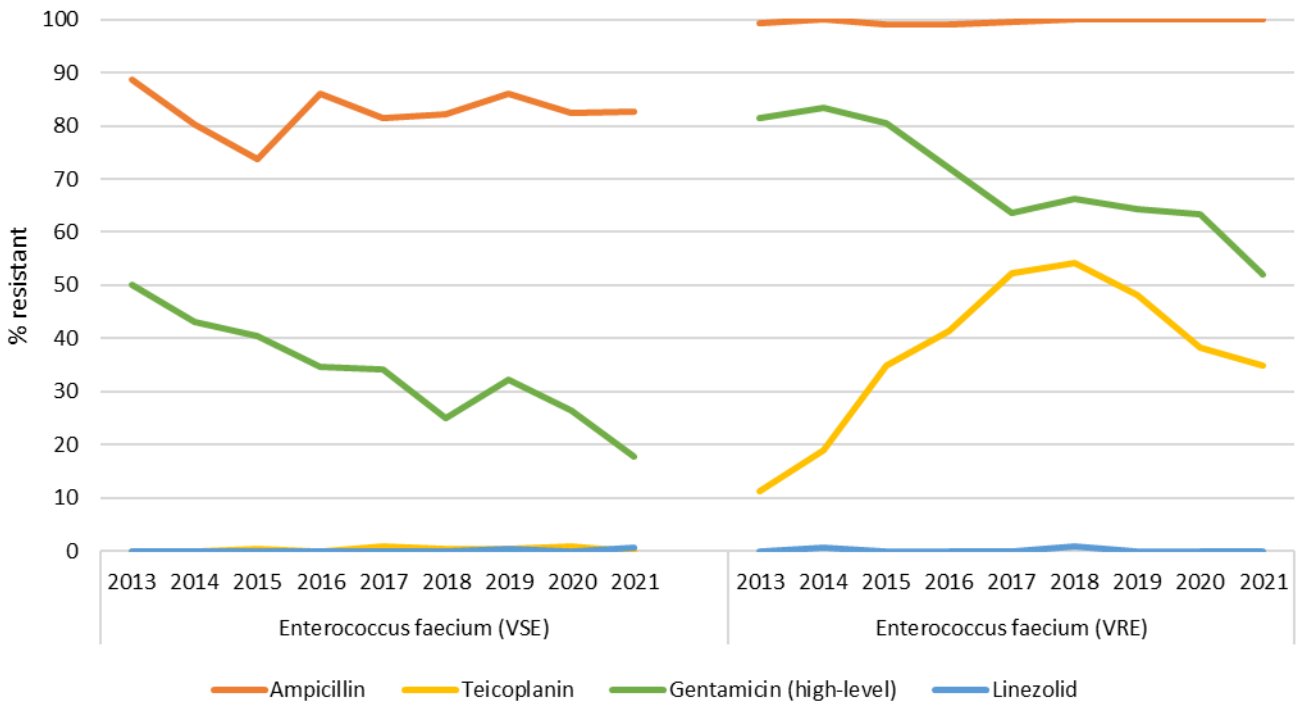
	2013	2014	2015	2016	2017	2018	2019	2020	2021
Number of isolates	325	380	402	413	481	491	596	488	523
Ampicillin	93.1	89.4	86.5	92.2	90.0	90.3	91.9	88.2	89.3
Gentamicin (high-level)	62.0	61.8	60.5	52.6	48.2	43.6	45.5	38.5	30.4
Vancomycin	41.7	46.3	50.2	47.5	47.0	44.9	41.6	32.6	37.9
Teicoplanin	4.7	8.8	17.7	19.6	24.9	24.4	20.2	13.0	13.2
Linezolid	0.0	0.3	0.0	0.0	0.0	0.4	0.2	0.0	0.4

EUCAST = European Committee on Antimicrobial Susceptibility Testing

Notes

1. Percentage resistance determined using EUCAST 2022 breakpoints for all years.
2. Number of contributors per year – 2013 and 2014, n = 27; 2015, n = 35; 2016, n = 33; 2017, n = 35, 2018, n = 38; 2019, n = 41, 2020, n = 42, 2021, n = 41

Figure 7: *Enterococcus faecium,* resistance (EUCAST), by vancomycin susceptibility, Australia, AGAR, 2013–2021



EUCAST = European Committee on Antimicrobial Susceptibility Testing; VSE = vancomycin susceptible *Enterococcus faecium*; VRE = vancomycin resistant *Enterococcus faecium*

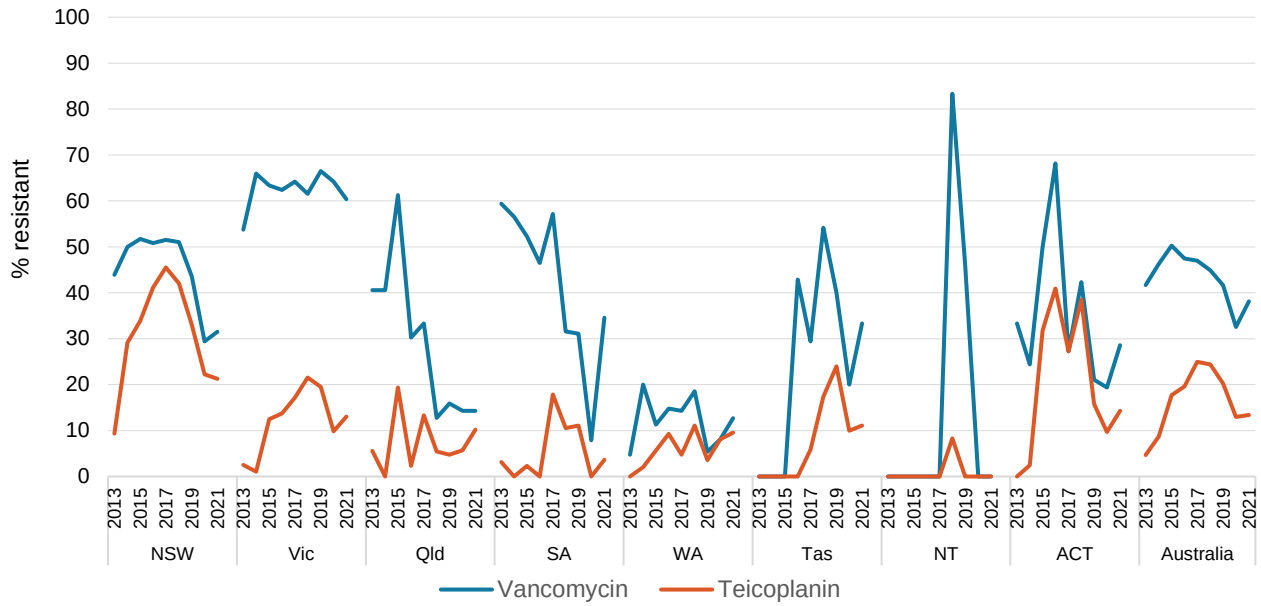
Notes

1. Percentage resistance determined using EUCAST 2022 breakpoints for all years.
2. Number of contributors per year – 2013 and 2014, n = 27; 2015, n = 35; 2016, n = 33; 2017, n = 35, 2018, n = 38; 2019, n = 41, 2020, n = 42, 2021, n = 41

State and territory

The proportion of glycopeptide-resistant *E. faecium* by state and territory is shown in Figure 8. Nationally, the proportion of vancomycin-resistant *E. faecium* increased from 158/485, 32.6% in 2020 to 198/522, 37.9% in 2021. The increase was notable in South Australia (3/38, 7.9% in 2020; 19/55, 34.5% in 2021, P < 0.01). Teicoplanin resistance in *E. faecium* was stable (63/485, 13.0% in 2020 to 69/522, 13.6% in 2021).

Figure 8: *Enterococcus faecium*, glycopeptide resistance (EUCAST), by state and territory, and nationally, AGAR, 2013–2021



Notes

1. Percentage resistance determined using EUCAST 2022 breakpoints for all years.
2. Number of contributors per year – 2013 and 2014, n = 27; 2015, n = 35; 2016, n = 33; 2017, n = 35, 2018, n = 38; 2019, n = 41, 2020, n = 42, 2021, n = 41
3. Insufficient numbers (< 10) to calculate percentage for Tasmania (2013–2015) and the Northern Territory (2013-2016).

There were significantly decreasing trends in vancomycin resistance in *E. faecium* over the past five years (2017-2021) in New South Wales (X^2 for linear trend = 25.33, $P < 0.01$), South Australia (X^2 for linear trend = 4.691, $P = 0.03$) and Australia overall (X^2 for linear trend = 18.542, $P < 0.01$) (Table 13). Over the same period, teicoplanin resistance in *E. faecium* decreased significantly in New South Wales (X^2 for linear trend = 34.15, $P < 0.01$), Victoria (X^2 for linear trend = 4.561, $P = 0.03$), South Australia (X^2 for linear trend = 7.201, $P = 0.01$) the Australian Capital Territory (X^2 for linear trend = 4.749, $P = 0.03$) and Australia overall (X^2 for linear trend = 38.91, $P < 0.01$) (Table 14).

Table 13: *Enterococcus faecium*, percentage resistant to vancomycin (EUCAST) and number tested, state and territory, AGAR, 2013–2021

State and territory	Percentage resistant, (*n*) by year									Trend 2017–2021*
	2013	2014	2015	2016	2017	2018	2019	2020	2021	
New South Wales	43.9 (107)	50.0 (104)	51.7 (116)	50.8 (124)	51.5 (167)	51.0 (151)	43.5 (209)	29.4 (180)	31.5 (146)	▼
Victoria	53.8 (80)	66.0 (94)	63.3 (120)	62.4 (109)	64.2 (134)	61.5 (130)	66.5 (164)	64.2 (123)	59.8 (169)	↔
Queensland	40.5 (37)	40.5 (37)	61.3 (31)	30.2 (43)	33.3 (45)	12.7 (55)	15.9 (63)	14.3 (35)	14.3 (49)	↔
South Australia	59.4 (32)	56.5 (46)	52.3 (44)	46.5 (43)	57.1 (28)	31.6 (38)	31.1 (45)	7.9 (38)	34.5 (55)	▼
Western Australia	4.8 (42)	20.0 (50)	11.3 (53)	14.8 (54)	14.3 (63)	18.5 (54)	5.4 (56)	8.1 (62)	12.7 (63)	↔
Tasmania	† (5)	† (7)	† (8)	42.9 (14)	29.4 (17)	54.2 (24)	40.0 (25)	20.0 (10)	33.3 (18)	↔
Northern Territory	† (3)	† (1)	† (8)	† (4)	† (5)	83.3 (12)	46.2 (13)	† (6)	† (8)	↔
Australian Capital Territory	33.3 (18)	24.4 (41)	50.0 (22)	68.2 (22)	27.3 (22)	42.3 (26)	21.1 (19)	19.4 (31)	28.6 (14)	↔
Australia	41.7 (324)	46.3 (380)	50.2 (402)	47.5 (413)	47.0 (481)	44.9 (490)	41.6 (594)	32.6 (485)	37.9 (522)	▼

* Chi-square test for trend for past five years (2017–2021), p-value <0.05, decrease ▼; ↔ no significant difference
† Not applicable, insufficient numbers (<10) to calculate percentage

Note: Percentage resistance determined using EUCAST 2022 breakpoints for all years.

Table 14: *Enterococcus faecium*, percentage resistant to teicoplanin (EUCAST) and number tested, state and territory, AGAR, 2013–2021

State and territory	Percentage resistant, (*n*) by year									Trend 2017–2021*
	2013	2014	2015	2016	2017	2018	2019	2020	2021	
New South Wales	9.3 (107)	29.1 (103)	33.9 (115)	41.1 (124)	45.5 (167)	42.0 (150)	33.0 (209)	22.2 (180)	21.2 (146)	▼
Victoria	2.5 (80)	1.1 (94)	12.5 (120)	13.8 (109)	17.2 (134)	21.5 (130)	19.5 (164)	9.5 (122)	12.4 (169)	▼
Queensland	5.6 (36)	0.0 (36)	19.4 (31)	2.3 (43)	13.3 (45)	5.5 (55)	4.8 (63)	5.7 (35)	10.2 (49)	↔
South Australia	3.1 (32)	0.0 (45)	2.3 (44)	0.0 (43)	17.9 (28)	10.5 (38)	11.1 (45)	0.0 (39)	3.6 (55)	▼
Western Australia	0.0 (42)	2.0 (50)	5.7 (53)	9.3 (54)	4.8 (63)	11.1 (54)	3.6 (56)	8.1 (62)	9.5 (63)	↔
Tasmania	† (5)	† (7)	† (8)	0.0 (14)	5.9 (17)	17.4 (23)	24.0 (25)	10.0 (10)	11.1 (18)	↔
Northern Territory	† (3)	† (1)	† (8)	† (4)	† (5)	8.3 (12)	0.0 (13)	† (6)	† (8)	↔
Australian Capital Territory	0.0 (16)	2.4 (41)	31.8 (22)	40.9 (22)	27.3 (22)	38.5 (26)	15.8 (19)	9.7 (31)	14.3 (14)	▼
Australia	4.7 (321)	8.8 (377)	17.7 (401)	19.6 (413)	24.9 (481)	24.4 (488)	20.2 (594)	13.0 (485)	13.2 (522)	▼

* Chi-square test for trend for past five years (2016–2020), p-value <0.05, bold text significant decrease ▼; ↔ no significant difference
† Not applicable, insufficient numbers (<10) to calculate percentage

Note: Percentage resistance determined using EUCAST 2022 breakpoints for all years.

Glycopeptide-resistance and *van* gene trends in *Enterococcus faecium*

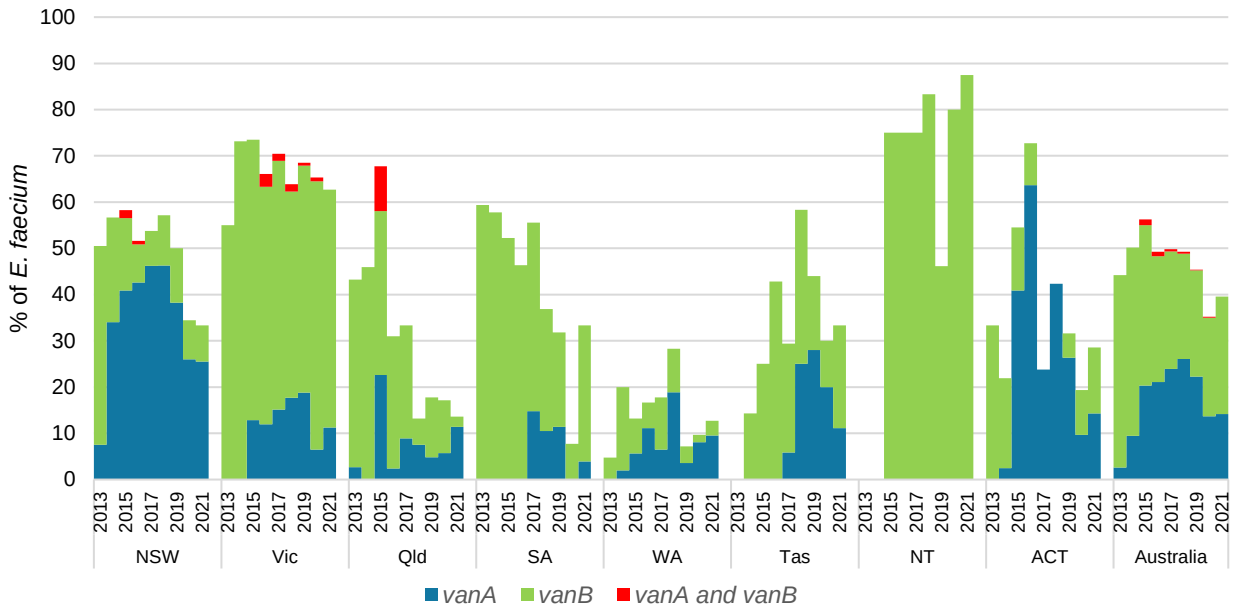
In 2021, glycopeptide resistance was predominantly due to the *vanB* gene. Overall, the proportion of both *vanA* and *vanB E. faecium* in 2021 remained stable compared to 2020.

There was, however, a 3.8-fold increase in *vanB E. faecium* in South Australia in 2021 (3/39, 7.7% in 2020; 15/51, 29.4% in 2021, $P = 0.0154$).

Over the past five-year period (2017-2021) there was a significantly decreasing trend in *vanA* genes in New South Wales (X^2 for linear trend, 25.5517, $P < 0.01$), Victoria (X^2 for linear trend, 4.0233, $P = 0.05$), South Australia (X^2 for linear trend, 5.205, $P = 0.02$), the Australian Capital Territory (X^2 for linear trend, 4.017, $P = 0.05$) and Australia overall, (X^2 for linear trend, 31.2147, $P < 0.01$). Over the same period there was a significant decrease in *van*B genes in Queensland, (X^2 for linear trend, 6.3226, $P = 0.01$, Western Australia, (X^2 for linear trend, 6.4348, $P = 0.01$). There was a significant increase in *vanB* genes in the Australian Capital Territory, (X^2 for linear trend, 5.5848, $P = 0.02$) and in Australia overall, (X^2 for linear trend, 4.957, $P = 0.03$).

There is considerable variation in the proportion of *E. faecium* with *van* genes by state and territory, and the *van* type (Figure 9).

Figure 9: Proportion of *van* genes in *Enterococcus faecium* by state and territory, and nationally, AGAR, 2013–2021



Note: Insufficient number of *E. faecium* isolates (< 10) to calculate percentage for the Northern Territory (2020, 2021).

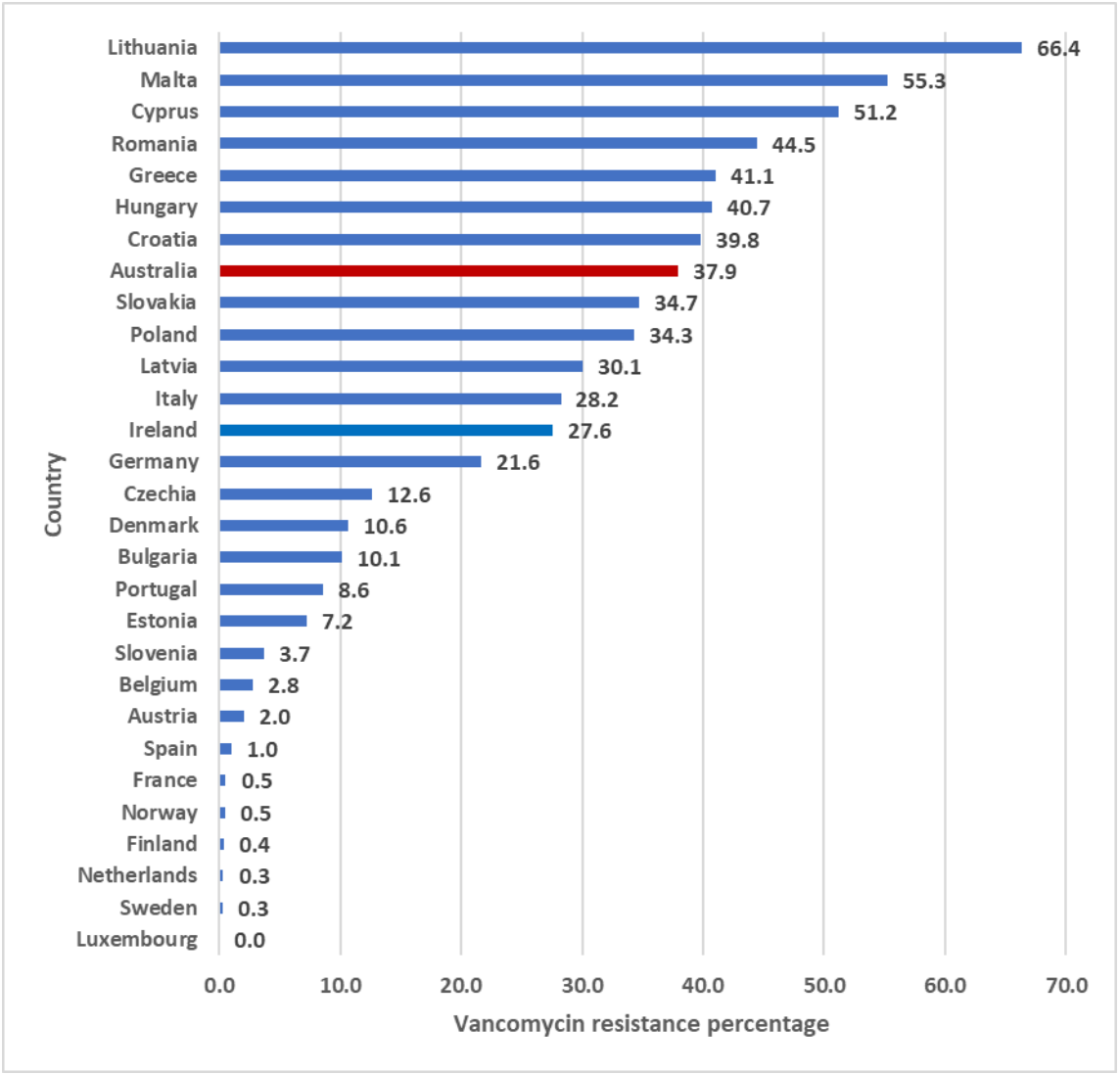
4. International comparisons

Data from AGAR can be compared with data from the European Antimicrobial Resistance Surveillance Network (EARs-Net) program.[15]

EARS-Net is based on routine clinical antimicrobial susceptibility data from local and clinical laboratories reported to ECDC by appointed representatives from the Member States. The data originate form national AMR surveillance initiatives and/or laboratory networks. Only data from invasive isolates (blood and cerebrospinal fluid) are included in EARS-Net.

Australia ranks in the top third in rates of resistance to vancomycin in *E. faecium* compared to the thirty participating European countries (Figure 10), ranking eighth. In 2020, 2019, 2018 and 2017 Australia ranked tenth, fourth, second and first respectively.

Figure 10: Comparison of *Enterococcus faecium* rates of resistance to vancomycin in Australia and European countries, blood culture isolates, AGAR, 2021



EU/EEA = European Union (EU) and European Economic Area (EEA) countries population-weighted mean percentages

Source: EARS-Net (Europe)[15, 16, 19]

5. Limitations of the study

Although this study is considered comprehensive in its coverage of Australia, and the methods follow international standards, the data and their interpretation have a number of limitations:

- The data are not denominator controlled, and there is currently no consensus on an appropriate denominator for such surveys; hospital size, patient throughput, patient complexity and local antibiotic use patterns all influence the types of resistance that are likely to be observed.
- Although data have been collected from 48 large hospitals across Australia, it is not yet clear how representative the sample is of Australia as a whole, because the proportion of the population that is served by the laboratories that participate in AGAR is not accurately known. Further, it is likely that the proportion of the population served differs in each state and territory
- Concentration ranges of some antimicrobial agents in both the Vitek® and Phoenix™ cards limit the ability to accurately identify ‘susceptible’ for some combinations of antimicrobial agents and species.
- Data are classified into hospital- and community-onset infections; healthcare-associated community-onset infections may be included in the community-onset group.

6. Discussion and conclusions

AGAR data show that in 2021 episodes of enterococcal bacteraemia in Australia had their onset overwhelmingly in the community. For the AESOP, the most frequent predisposing clinical manifestations were urinary tract infection, biliary tract and intra-abdominal infection. However, episodes where there was no identifiable focus also contributed to high proportions of presentations for enterococcal bacteraemia overall.

E. faecium bacteraemia has significant clinical consequences and resource implications, due to increased length of hospital stay. Bacteraemia episodes contributed to increased length of hospital stay; the average length of stay in all Australian public hospitals in 2018–2019 was 5.5 days.[17] Thirty-day all-cause mortality due to *E. faecium* in 2021 was 25.2% (CO, 25.4%; HO, 25.2%); there was a significant difference in 30-day all-cause mortality between vancomycin-susceptible and resistant episodes (21.3% and 30.6% respectively *P*=0.03)

In the 2021 survey, 39.6% of *E. faecium* harboured *vanA* or *vanB* genes; in 2020 it was 35.2%. Vancomycin, which until recently was the mainstay of therapy for *E. faecium*, can no longer be recommended empirically; agents with less certain efficacy such as linezolid are the alternative.

For almost two decades, and unlike in most other countries where vancomycin resistance is a problem, vancomycin resistance in Australia has been dominated by the *vanB* genotype. However, in the 2018 survey, 48.8% of vancomycin-resistant *E. faecium* bacteraemias were due to *vanA*; increasing from 6.1% in 2013. Since 2017, *vanA* genotype has remained around 50% (2018, 52.7%, 2019, 48.2%), in 2020 it fell to 36.3%, it was 35.8% in 2021. In the 2021 survey 35.8% of *E. faecium* bacteraemia harboured the *vanA* gene. This type of vancomycin resistance has emerged rapidly in the past seven years, particularly in New South Wales, Queensland and Western Australia, where it is now the dominant genotype. This in turn has reduced the overall teicoplanin susceptibility of *E. faecium* in Australia.

The percentage of *E. faecium* bacteraemia isolates that are resistant to vancomycin in Australia is significantly higher than that seen in almost all European countries. In 2021, the European Union/European Economic Area (EU/EEA) population-weighted mean percentage was 10.2%. Australia ranks in the top third in rates of resistance to vancomycin in *E. faecium* (37.9%) compared to all European countries, ranking eighth highest. In 2020 it was ranked tenth highest; and in 2019, fourth highest.[15, 18, 19]

Although infection prevention and control strategies are essential for control of this organism, many antimicrobials have been implicated in the development of vancomycin non-susceptible *E. faecium.* Vancomycin, used commonly as an empiric therapeutic choice for MRSA, and other broad-spectrum antibiotics which select for enterococci due to intrinsic resistance, especially the third-generation cephalosporins, are widely used in Australia.

It should be noted that outbreaks of multi-drug resistant organisms occur in hospitals and other institutional care settings, and substantial transmission occurs before invasive blood stream infections develop. AGAR data may therefore underestimate local or regional spread of multidrug-resistant organisms and may not assist with early detection of sentinel resistances. AGAR bacteraemia data need to be assessed with other sources of information to provide broader insights into antimicrobial resistance in Australia. The AURA Surveillance System enables these assessments via Australian Passive AMR Surveillance (APAS) and National Alert System for Critical Antimicrobial Resistances (CARAlert) data, which complement AGAR data.

It is clear that AGAR surveillance remains core to Australia's response to the problem of increasing AMR. AGAR data contribute to understanding AMR in Australian human health settings, and to informing the national response to AMR.

Abbreviations

Abbreviation	Term
AGAR	Australian Group on Antimicrobial Resistance
AMR	Antimicrobial resistance
APAS	Australian Passive AMR Surveillance
ASA	Australian Society of Antimicrobials
AURA	Antimicrobial Use and Resistance in Australia
CARAlert	National Alert System for Critical Antimicrobial Resistance
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
CO	Community-onset
ECOFF	Epidemiological cut-off value
EUCAST	European Committee on Antimicrobial Susceptibility Testing
HO	Hospital-onset
MDR	Multi-drug resistant
MIC	Minimum inhibitory concentration
MLST	Multi-locus sequence type
PCR	Polymerase chain reaction
WGS	Whole genome sequencing
WHO	World Health Organization

Acknowledgements

Participating members of AGAR:

Institution	AGAR members
Alfred Hospital, Vic	Adam Jenney and Jacqueline Williams
Alice Springs Hospital, NT	James McLeod
Austin Hospital, Vic	Marcel Leroi and Elizabeth Grabsch
Canberra Hospital, ACT	Peter Collignon and Susan Bradbury
Children's Hospital Westmead, NSW	Alison Kesson and Andrew Jarrett
Concord Hospital, NSW	Thomas Gottlieb and John Huynh
John Hunter Hospital, NSW	Hemalatha Varadhan and Bree Harris
Joondalup Hospital, WA	Shalinie Perera and Ian Meyer
Launceston General Hospital, Tas	Pankaja Kalukottege and Kathy Wilcox
Liverpool Hospital, NSW	Michael Maley and Helen Ziochos
Monash Children's Hospital, Vic	Tony Korman and Despina Kotsanas
Monash Health (Dandenong Hospital), Vic	Tony Korman and Kathryn Cisera
Monash Health (Monash Medical Centre), Vic	Tony Korman and Despina Kotsanas
Nepean Hospital, NSW	James Branley and Linda Douglass
Pathology Queensland Central Laboratory, Qld	Graeme Nimmo and Narelle George
Pathology Queensland Gold Coast University Hospital, Qld	Petra Derrington and Cheryl Curtis
Pathology Queensland Prince Charles Hospital, Qld	Robert Horvath and Laura Martin
Pathology Queensland Princess Alexandra Hospital, Qld	Naomi Runnegar and Joel Douglas
PathWest Laboratory Medicine – north-west regional WA	Michael Leung
PathWest Laboratory Medicine – WA, Fiona Stanley Hospital	Denise Daley
PathWest Laboratory Medicine – WA, Perth Children's Hospital	Christopher Blyth
PathWest Laboratory Medicine – WA, Queen Elizabeth II Hospital	Ronan Murray and Jacinta Bowman
PathWest Laboratory Medicine – WA, Royal Perth Hospital	Owen Robinson and Geoffrey Coombs
Royal Darwin Hospital, NT	Rob Baird and Jann Hennessy
Royal Hobart Hospital, Tas	Louise Cooley and David Jones
Royal Melbourne Hospital	Katherine Bond and Rose Cotronei
Royal North Shore Hospital, NSW	Angela Wong
Royal Women's Hospital, Vic	Andrew Daley and Gena Gonis
SA Pathology, Flinders Medical Centre, SA	Kelly Papanaoum and Xiao Chen,
SA Pathology, Royal Adelaide Hospital, SA	Morgyn Warner and Kija Smith
SA Pathology, Women's and Children's Hospital, SA	Morgyn Warner and Kija Smith
St John of God Hospital, Murdoch, WA	Sudha Pottumarthy-Boddu and Jacqueline Foster
St Vincent's Hospital, Melbourne, Vic	Amy Crowe and Lisa Brenton
St Vincent's Hospital, Sydney, NSW	David Lorenz
Sullivan Nicolaides Pathology, Qld	Jennifer Robson and Marianne Allen
Sydney Children's Hospital, NSW	Monica Lahra and Peter Huntington
Westmead Hospital, NSW	Jon Iredell and Andrew Ginn
Wollongong Hospital, NSW	Peter Newton and Melissa Hoddle

Reference laboratories

AGAR also gratefully acknowledges Dr Shakeel Mowlaboccus and Mrs Princy Shoby at the Antimicrobial Resistance and Infectious Disease Research Laboratory, Murdoch University, Western Australia for performing the whole genome sequencing on the *E. faecium* isolates.

Funding

AGAR also gratefully acknowledges the Australian Government Department of Health and Aged Care for funding the AGAR Surveillance Outcome Programs.

References

1. Diekema DJ, Hsueh PR, Mendes RE, Pfaller MA, Rolston KV, Sader HS, et al. The Microbiology of Bloodstream Infection: 20-Year Trends from the SENTRY Antimicrobial Surveillance Program. Antimicrob Agents Chemother. 2019;63(7).
2. Pinholt M, Ostergaard C, Arpi M, Bruun NE, Schonheyder HC, Gradel KO, et al. Incidence, clinical characteristics and 30-day mortality of enterococcal bacteraemia in Denmark 2006-2009: a population-based cohort study. Clin Microbiol Infect. 2014;20(2):145-151.
3. Murray BE. The life and times of the Enterococcus. Clin Microbiol Rev. 1990;3(1):46-65.
4. Simonsen GS, Smabrekke L, Monnet DL, Sorensen TL, Moller JK, Kristinsson KG, et al. Prevalence of resistance to ampicillin, gentamicin and vancomycin in *Enterococcus faecalis* and *Enterococcus faecium* isolates from clinical specimens and use of antimicrobials in five Nordic hospitals. J Antimicrob Chemother. 2003;51(2):323-331.
5. Treitman AN, Yarnold PR, Warren J, Noskin GA. Emerging incidence of *Enterococcus faecium* among hospital isolates (1993 to 2002). J Clin Microbiol. 2005;43(1):462-463.
6. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(1):1-12.
7. Christiansen KJ, Turnidge JD, Bell JM, George NM, Pearson JC, Australian Group on Antimicrobial Resistance. Prevalence of antimicrobial resistance in Enterococcus isolates in Australia, 2005: report from the Australian Group on Antimicrobial Resistance. Commun Dis Intell Q Rep. 2007;31(4):392-397.
8. Coombs GW, Daley D, Pearson JC, Ingram PR. A change in the molecular epidemiology of vancomycin resistant enterococci in Western Australia. Pathology. 2014;46(1):73-75.
9. CLSI. Performance standards for antimicrobial susceptibility testing. 32nd ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2022.
10. European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 12.0, valid from 2022-01-01. 2022.
11. Seemann T, Goncalves da Silva A, Bulach DM, Schultz MB, Kwong JC, Howden BP. *Nullarbor* Github. [Internet] 2020 Available from: https://github.com/tseemann/nullarbor.
12. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. Atlanta, GA: CDC, 2019.
13. Williamson DA, Howden BP, Paterson DL. The risk of resistance: what are the major antimicrobial resistance threats facing Australia? Med J Aust. 2019;211(3):103-105 e101.
14. Coombs GW, Daley DA, Lee YT, Pang S, Bell JM, Turnidge JD, et al. Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Sepsis Outcome Programme(AESOP) Annual Report 2015. Commun Dis Intell (2018). 2018;42.
15. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net) - annual epidemiological report 2019. [Internet] Stockholm: ECDC; 2020 [updated 18 Nov 2020] Available from: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2019.
16. European Centre for Disease Prevention and Control. Additional tables - antimicrobialresistance in the EU/EEA 2019. [Internet] Stockholm: ECDC; 2020 [updated 18 Nov 2020] Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Additional-tables-EUEEA-population-weighted-mean-2019.pdf.
17. Australian Institute of Health and Welfare. Australia's hospitals at a glance 2018–19. Cat. no. HSE 247. Canberra: AIHW, 2020 16 Sep 2020. Report No.
18. WHO Regional Office for Europe/European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2022 – 2020
19. European Centre for Disease Prevention and Control. Data from the ECDC Surveillance Atlas - Antimicrobial resistance. [Internet] Stockholm: ECDC; 2021 [updated 18 Nov 2021] Available from: https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc.

20. Australian Institute of Health and Welfare. Australia's hospitals at a glance 2018–19. Cat. no. HSE 247. Canberra: AIHW, 2020.

Appendix A. Study design

Forty-eight institutions participated in the 2021 survey, 42 adult and six children's hospitals. All states and territories were represented. The hospital peer group/type[20] represented were:

Principal referral hospitals (*n* = 25)
Public acute group A hospitals (*n* = 4)
Children's hospitals (*n* = 5)
Combined Women's and children's hospitals (*n* = 1)
Private acute group A hospitals (*n* = 2)
Regional and district hospitals from north-west regional Western Australia (*n* = 11)

- Public acute group C hospitals (*n* = 6)
- Public acute group D hospitals (*n* = 5)

The 30 laboratories that serviced the hospitals participating in AGAR collected all isolates from different patient episodes of enterococcal bacteraemia. In patients with more than one isolate, a new episode was defined as a new positive blood culture more than two weeks after the initial positive culture.

An episode was defined as community onset if the first positive blood culture was collected ≤48 hours after admission, and as hospital onset if collected >48 hours after admission.

All laboratories that participated in AGAR obtained basic laboratory information for each patient episode plus varying demographic information, depending on the level at which they are enrolled in the program. There are two levels of enrolment: Bronze and Silver (Tables A1). At Bronze level, participating laboratories provided date of collection, date of birth, sex, postcode and admission date. At Silver level, participating laboratories provided discharge date, device-related infection, principal clinical manifestation, outcome at seven and 30 days, and date of death if appropriate.

Table A1: Level of AESOP participation of laboratories that contributed data on enterococcal bacteraemia, by state and territory, 2021

State or territory	Number of institutions	Level of participation	
		Bronze	Silver
New South Wales	10	1	9
Victoria	8	0	8
Queensland	5	0	5
South Australia	3	0	3
Western Australia	17*	2	15
Tasmania	2	0	2
Northern Territory	2	1	1
Australian Capital Territory	1	0	1
Total	48	4	44

*includes 11 regional and district hospitals in north Western Australia

Appendix B. Methods

Species identification

Isolates were identified using the routine methods for each institution. These included the Vitek® and Phoenix™ automated microbiology systems, and, if available, mass spectrometry (MALDI - TOF).

Susceptibility testing

Testing was performed using two commercial semi-automated methods: Vitek 2 (bioMérieux) (*n* = 27) and Phoenix (BD) (*n* = 3), which are calibrated to the ISO (International Organization for Standardization) reference standard method of broth microdilution. Commercially available Vitek 2 (AST-P612, AST-P643, or AST-P656) or Phoenix (PMIC-84) cards were used by all participants throughout the survey period.

The CLSI M100[9] and the EUCAST v12.0[10] breakpoints from January 2022 were used in the analysis.

Additional tests performed on *E*. faecalis and *E. faecium* include:

- E-test MIC if:
  - Linezolid MIC >4 mg/L, or if MIC not provided
  - Daptomycin MIC > 4 mg/L
  - Vancomycin and teicoplanin if MIC not provided or discrepant with *van* gene
  - Ampicillin > 8 mg/L (*E. faecalis*) or ampicillin ≤ 4 mg/L (*E. faecium*), or if MIC not provided
- *van* gene PCR on *E. faecalis*, if not provided:
  - Vancomycin MIC > 4 mg/L or teicoplanin > 2 mg/L, or vancomycin or teicoplanin MIC not provided.

Clinical and outcome data

Device related infection

Device-related bacteraemia is defined as a bacteraemia derived from central (which includes portacaths, PICC lines) or peripheral (venous and arterial) intravascular devices, from catheter-associated urinary tract infection (including nephrostomy tubes and stents), or ventilator-associated respiratory tract infection or bacteraemias associated with biliary stents.

Principal clinical manifestation

For AESOP surveys, the principal clinical manifestation for each patient episode is categorised as:

- Biliary tract infection (including cholangitis)
- Device-related infection with metastatic focus
- Device-related infection without metastatic focus
- Endocarditis Left-sided
- Endocarditis Right-sided
- Febrile neutropenia
- Intra-abdominal infection other than biliary tract
- No identifiable focus
- Osteomyelitis/septic arthritis
- Other clinical syndrome
- Skin and skin structure infection
- Urinary tract infection

Length of hospital stay following bacteraemia
Length of hospital stay following bacteraemia is calculated from the date of blood culture collection to patient discharge or death.

All-cause mortality
All-cause mortality refers to outcome (died, survived, unknown) at 7- and 30-days from blood culture date of collection.

Antimicrobials tested

The antimicrobials tested are shown in Table B1.

Table B1: Antimicrobials on susceptibility testing cards and interpretive guidelines for CLSI and EUCAST

Antimicrobial agent	Breakpoint (mg/L)						
	CLSI M100*				EUCAST v12.0†		
	S	SDD	I	R	S, SD	S, IE	R
Benzylpenicillin							
Enterococcus spp.	≤8		–§	≥16	–#	–#	–#
Amoxicillin–clavulanic acid							
Enterococcus spp.	–#		–#	–#	≤4**	8**	>8**
Ampicillin							
Enterococcus spp.	≤8		–§	≥16	≤4	8	>8
Ciprofloxacin							
Enterococcus spp. ‡‡	≤1		2	≥4	≤4‡	–‡	>4‡
E. faecalis (ECOFF) ‡					≤4	–§	>4
E. faecium (ECOFF) ‡					≤8	–§	>8
Daptomycin							
Enterococcus faecium		≤4	–	≥8	–#	–#	–#
Enterococcus spp. other than *E. faecium*	≤2		4	≥8	–#	–#	–#
Doxycycline (Phoenix card)							
Enterococcus spp.	≤4		8	≥16	–#	–#	–#
Erythromycin							
Enterococcus spp.	≤0.5		1–4	≥8	–#	–#	–#
Imipenem (Phoenix card)							
Enterococcus spp.	–#		–#	–#	≤0.001	0.002–4	>4
Linezolid							
Enterococcus spp.	≤2		4	≥8	≤4	–§	>4
Nitrofurantoin							
Enterococcus spp.	≤32		64	≥128	–#	–#	–#
Rifampicin							
Enterococcus spp.	≤1		2	≥4	–#	–#	–#
Teicoplanin							
Enterococcus spp.	≤8		16	≥32	≤2	–§	>2
Tetracycline							
Enterococcus spp.	≤4		8	≥16	–#	–#	–#
Vancomycin							
Enterococcus spp.	≤4		8–16	≥32	≤4	–§	>4

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; I = intermediate (CLSI); R = resistant; S = susceptible (CLSI); S, IE = susceptible, increased exposure (EUCAST); S, SD = sensitive, standard dosing (EUCAST); SDD = sensitive dose dependent (CLSI); ECOFF = epidemiological cut-off value

* The breakpoints selected to identify resistance are described in the *Performance Standards for Antimicrobial Susceptibility Testing. 32nd ed. CLSI supplement* M100, 2022

† EUCAST breakpoint tables for interpretation of MICs and zone diameters, version 12.0, 2022 (www.eucast.org)

§ No category defined

No guidelines for indicated species

** For susceptibility testing purposes, EUCAST fixes the concentration of clavulanate at 2 mg/L, rather than the 2:1 ratio used in CLSI guidelines
‡ The ciprofloxacin concentration range on the Phoenix™ card restricts the ability to categorise *Enterococcus spp.*
§§ Breakpoints apply to *E. faecalis* only

Molecular confirmation of resistance

For *E. faecium* WGS was performed by the Antimicrobial Resistance Infectious Diseases (AMRID) Research Laboratory at Murdoch University using the Illumina NextSeq™ 500 platform. The Nullarbor bioinformatic pipeline[11] was used to identify the multi-locus sequence type and *van* gene.

Quality control

Quality control strains used were those recommended by CLSI and EUCAST standards.

Data validation

Various checks were made to ensure that the data were valid. These included:

- Null values in the mandatory fields
- Missing MIC data
- Patient age if ≥100 or <0 days
- Confirm dates when:
  - Specimen collected after patient discharged or died
  - Patient discharged or died before admitted
  - Patient admitted before born
  - Patient admitted more than two days after specimen collected
  - Patient admitted more than six months before specimen collected

Appendix C. Susceptibility to antimicrobial agents

Overall percentages of resistance or non-susceptibility for *E. faecium* and *E. faecalis* are shown in Table C1. For some antimicrobials, the concentration range tested did not distinguish between intermediate susceptibility (I) and resistant (R), and the term non-susceptible (NS) was used to describe these isolates.

Table C1: Susceptibility (CLSI and EUCAST) to antimicrobial agents in *E. faecium* and *E. faecalis* by state and territory, 2021

Antimicrobial agent and species	Category*	CLSI and EUCAST percentage susceptibility at indicated category								
		NSW	Vic	Qld	SA	WA	Tas	NT	ACT	Australia
Ampicillin										
Enterococcus faecalis	n	177	169	98	70	107	33	8	36	698
	%R	0.6, 0.6	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	n/a	0.0, 0.0	0.1, 0.1
Enterococcus faecium	n	129	153	46	46	56	13	8	14	465
	%R	89.0, 89.0	90.5, 90.5	93.9, 93.9	83.6, 83.6	88.9, 88.9	72.2, 72.2	n/a	100.0, 100.0	89.3, 89.3
Benzylpenicillin										
Enterococcus faecalis	n	163	96	97	68	106	13	8	36	587
	%R	1.8, –†	0.0, –†	0.0, –†	0.0, –†	1.9, –†	0.0, –†	n/a	0.0, –†	0.9, –†
Enterococcus faecium	n	139	100	49	53	62	10	8	14	435
	%R	91.4, –†	89.0, –†	93.9, –†	83.0, –†	91.9, –†	70.0, –†	n/a	100.0, –†	90.1, –†
Ciprofloxacin										
Enterococcus faecalis	n	109	140	0	43	106	13	8	0	419
	%R/ECOFF§	9.2, 1.0	2.1, 1.4	n/a	4.7, 0.0	5.7, 4.7	0.0, 0.0	n/a	n/a	5.0, 2.0
Enterococcus faecium	n	96	121	1	24	62	10	8	0	322
	%R/ECOFF§	88.5, n/a	90.1, n/a	n/a	79.2, n/a	90.3, n/a	n/a	n/a	n/a	88.2, n/a
Daptomycin										
Enterococcus faecalis	n	175	169	96	47	106	13	8	36	650
	%R	0.6, –†	0.0, –†	1.0, –†	0.0, –†	0.0, –†	0.0, –†	n/a	0.0, –†	0.3, –†
Enterococcus faecium	n	34	0	0	24	3	0	0	0	61
	%R	0.0, –†	n/a	n/a	4.2, –†	n/a	n/a	n/a	n/a	1.6, –†
Linezolid										
Enterococcus faecalis	n	176	169	98	70	107	33	8	36	697
	%R	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.9, 0.9	0.0, 0.0	n/a	2.8, 2.8	0.3, 0.3
Enterococcus faecium	n	144	169	49	55	63	18	8	14	520
	%R	0.7, 0.7	0.0, 0.0	0.0, 0.0	1.8, 1.8	0.0, 0.0	0.0, 0.0	n/a	0.0, 0.0	0.4, 0.4
Teicoplanin										
Enterococcus faecalis	n	178	169	98	70	107	33	8	36	699
	%R	0.0, 0.6	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	n/a	0.0, 0.0	0.0, 0.1

Antimicrobial agent and species	Category*	CLSI and EUCAST percentage susceptibility at indicated category								
		NSW	Vic	Qld	SA	WA	Tas	NT	ACT	Australia
Enterococcus faecium	n	146	169	49	55	63	18	8	14	522
	%R	17.8, 21.2	7.7, 13.6	10.2, 10.2	3.6, 3.6	7.9, 9.5	5.6, 11.1	n/a	14.3, 14.3	10.3, 13.6
Tetracycline/doxycycline**										
Enterococcus faecalis	n	123	97	75	45	106	13	8	0	467
	%NS	61.0, –†	68.0, –†	64.0, –†	66.7, –†	65.1, –†	92.3, –†	n/a	n/a	65.1, –†
Enterococcus faecium	n	114	100	46	24	62	10	8	0	364
	%NS	64.0, –†	80.0, –†	89.1, –†	45.8, –†	69.4, –†	40.0, –†	n/a	n/a	71.2, –†
Vancomycin										
Enterococcus faecalis	n	178	169	98	70	107	33	8	36	699
	%R	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	n/a	0.0, 0.0	0.0, 0.0
Enterococcus faecium	n	146	169	49	55	63	18	8	14	522
	%R	28.8, 31.5	57.4, 59.8	14.3, 14.3	34.5, 34.5	12.7, 12.7	33.3, 33.3	n/a	28.6, 28.6	36.4, 37.9

CLSI = Clinical and Laboratory Standards Institute; ECOFF = epidemiological cut-off value; EUCAST = European Committee on Antimicrobial Susceptibility Testing; I = intermediate (CLSI) or susceptible, increased exposure (EUCAST); n/a = insufficient numbers (<10) to calculate; NS = intermediate plus resistant; R = resistant; SDD = sensitive dose dependent (CLSI)

* Category analysed for each organism. If different for CLSI and EUCAST, they are separated by a comma.

† No breakpoints defined for indicated species

§ 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

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

** The doxycycline concentration range available on the Phoenix card used restricts the ability to accurately identify intermediate and resistant (CLSI) categories for enterococci