Australian Government
Department of Health

AGAR

AUSTRALIAN GROUP ON ANTIMICROBIAL RESISTANCE

Australian Enterococcus Sepsis Outcome Report

2021 Draft Final Report

Contents

Key findings

Enterococcus species

- 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 *E. faecium*
- The majority of *E. faecalis* bacteraemias were community-onset (CO) (68.7%), while in *E. faecium* bacteraemias only 31.3% were CO
- The most frequent source of sepsis 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%; the 30-day all-cause mortality for *E. faecium* bacteraemia was higher, particularly in vancomycin-resistant isolates (28.0%)
- There was significant difference in 30-day all-cause mortality between *E. faecalis* (14.5%) and *E. faecium* (25.2%) $P<0.01$. There was no significant difference between vancomycin-resistant and vancomycin-susceptible *E. faecium* episodes
- The length of stay following enterococcal bacteraemia was more than 30 days for 22.8% of patients
- Of bloodstream infections caused by *E. faecium*, 33.5% were phenotypically vancomycin resistant. In *E. faecium* isolates received to date, 42.8% of *E. faecium* harboured *vanA* and/or *vanB* genes (*vanA* 15.1%, *vanB* 27.7%).
- Of vancomycin-resistant *E. faecium* (VRE) bacteraemias, 34.1% were due to *vanA*-harbouring isolates. This is the dominant genotype in New South Wales, Queensland and Western Australia)
- Of the isolates sequenced to date, there were 54 *E. faecium* multi-locus sequence types (STs), of which ST17, ST1424, ST796, ST78, ST80 and ST1421 were the most frequently identified
- *vanA* genes were detected in five STs, and *vanB* genes were detected in 10 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 third. In 2020, Australia ranked 10th

Implications of key findings for health care

When interpreting AGAR data, it is important to consider changes in surveillance coverage between 2013 and 2021. AGAR has increased the number of laboratories 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 and another in 2020 and the inclusion of hospitals from north-west regional Western Australia from 2015.

Several themes, which have implications for the delivery of health care services and the safety of care provided patients, have been identified from the analyses of AGAR data.

Changing patterns in *Enterococcus* species

Total numbers of enterococcal bacteraemias identified by AGAR, excluding those from two institutions that contributed in 2020 or 2021 only, increased in 2021 compared to 2020 from 1,230 to 1,297 (5.3%). The increase was mostly in the number of *E. faecium* (443 to 523, 16.5%) rather than *E. faecalis* (642 to 702, 8.9%).

The number of VRE isolates increased by 10.2%; 175 in 2021, compared to 158 in 2020. There was an increase in overall vancomycin resistance rates in *E. faecium* from 32.6% to 33.9%. There was an increase in VRE as a proportion of all enterococcal isolates at 13.7%; 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

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 10.6% in Queensland to 54.5% in Victoria. Teicoplanin resistance ranged from zero in the Northern Territory to 19.7% 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 (67.9%) was more commonly hospital-onset than *E. faecalis* (31.3%). Vancomycin-resistant *E. faecium* bacteraemia accounted for 5.7% (37/641) of all community-onset enterococcal bacteraemia, compared to 24.0% (138/575) 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

This report on the Enterococcal sepsis outcome program operated by the Australian Group on Antimicrobial Resistance (AGAR) presents analyses of antimicrobial resistance (AMR) associated with episodes of bacteraemia (blood stream infection) that were reported by 48 participating Australian public and private laboratories 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 institutions across Australia that contributed to AGAR in 2021 are listed in Table 1.

Historically, the main focus of AGAR was antimicrobial resistance in *Staphylococcus aureus*. The scope broadened over time to include studies on *Escherichia coli, Enterobacter species, Klebsiella species, Haemophilus influenzae, Streptococcus pneumoniae* and *Enterococcus* species.

AGAR publishes detailed annual reports on each program on its website (www.agargroup.org.au), and also in the Communicable Diseases Intelligence (CDI) journal.

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 Sepsis 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 (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, P. 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]

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 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, and the outcome (died, all-cause or survived) at seven and 30 days.

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–A32[9] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) v12.0.[10]

2.4. PCR screening and whole genome sequencing

All *E. faecium* were subjected to whole genome sequencing using the Illumina NextSeq™ 500 platform. 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	Total
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	0.2
vancomycin susceptible, percent	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	99.8
Enterococcus faecium	146	168	49	55	62	18	8	14	520
vancomycin resistant, percent	25.3	54.5	10.6	35.2	11.3	27.8	87.5	28.6	33.9
vancomycin susceptible, percent	74.7	45.5	89.4	64.8	88.7	72.2	12.5	71.4	66.1
Other enterococcal species	16	23	16	1	12	2	1	1	72
Enterococcus gallinarum	4	8	5		4	1	1		23
Enterococcus casseliflavus	5	6	2	1	4	1		1	20
Enterococcus raffinosus	2	3	2		2				9
Enterococcus hirae	1	1	4		1				7
Enterococcus avium		4	2						6
Enterococcus durans	2	1	1		1				5
Enterococcus mundtii	1								1
Enterococcus species	1								1

* Vancomycin susceptibility was not available for four *E. faecium* (one each from Vic and SA, and two from Qld) and six *E. faecalis* (one each from Vic and Qld and four from SA)

3.2. Place of onset of bacteraemia

Almost all patients with bacteraemia were admitted to hospital (1,288, 99.3% *Enterococcus* species).

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 (68.7%, 95% CI: 62.1-72.1 for *E. faecalis*). However, *E. faecium* episodes were predominantly hospital-onset (68.1%; 95% CI: 63.9-72.1). The proportion of *E. faecalis* that were community-onset was lower among children (31.0%, 18/58) than adults (72.1%, 464/644).

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	68.5 (477)	31.5 (219)	696
Enterococcus faecium	31.9 (166)	68.1 (354)	520
Vancomycin resistant	21.1 (37)	78.9 (138)	175
Vancomycin susceptible	37.2 (127)	62.8 (214)	341
Other *Enterococcus* species (*n* = 8)	63.9 (46)	36.1 (26)	72

* Insufficient numbers (<10) to calculate percentage

Note: Vancomycin susceptibility was not available for four *Enterococcus faecium* (community-onset [2], hospital-onset [2]) and six *E. faecalis* (community-onset [5], hospital-onset [1]).

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* species (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* (25.4%) and *E. faecalis* (14.5%) ($P<0.01$). There was no difference between vancomycin-resistant and vancomycin-susceptible *E. faecium* episodes (28.0% and 23.7%, $P=0.43$) respectively.

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

	Community-onset		Hospital-onset		Total	
Organism	**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	387	14.7 (57)	194	14.4 (28)	581	14.6 (85)
Enterococcus faecium	132	25.8 (34)	313	25.2 (79)	445	25.4 (113)
Vancomycin resistant	32	34.4 (11)	132	26.5 (35)	164	28.0 (46)
Vancomycin susceptible	99	23.2 (23)	179	24.0 (43)	278	23.7 (66)
Other enterococcal species (*n* = 8)	32	15.6 (5)	22	13.6 (3)	54	14.8 (8)

* Insufficient numbers (<10) to calculate percentage

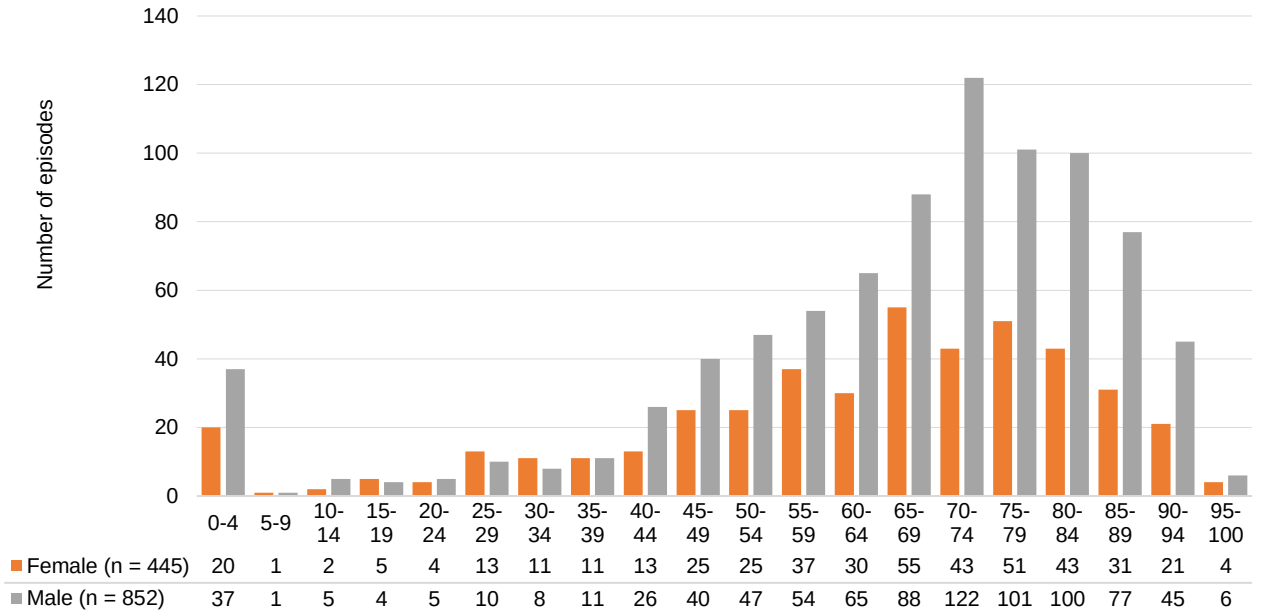
Notes: Vancomycin susceptibility was not available for three *Enterococcus faecium* (community-onset [1] hospital-onset [2]) and five *E. faecalis* (community-onset).

3.4. Patient age and sex

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

Increasing age was a surrogate risk factor for bacteraemia (Figure 1); only 11.4% 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	95-100
Female (n = 445)	20	1	2	5	4	13	11	11	13	25	25	37	30	55	43	51	43	31	21	4
Male (n = 852)	37	1	5	4	5	10	8	11	26	40	47	54	65	88	122	101	100	77	45	6

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 1,133 (92.5%) patient episodes of enterococcal bacteraemia. Overall, the most frequent principal clinical manifestations were those with urinary tract infection (16.5%), intra-abdominal infection other than biliary tract (14.5%) and those with no identifiable focus (13.7%) (Table 5).

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%).

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%). 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)	*P* = 0.03
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%) enterococcal bacteraemia episodes.

Overall, 22.8% of patients remained in hospital for more than 30 days after enterococcal bacteraemia (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	21.9 (264)	28.8 (347)	26.5 (319)	22.8 (274)	1,204
E. faecalis	23.9 (156)	27.2 (178)	24.9 (163)	24.0 (157)	654
Vancomycin resistant	–* (0)	–* (0)	–* (0)	–* (0)	0
Vancomycin susceptible	23.9 (155)	27.2 (176)	24.8 (161)	24.1 (156)	648
E. faecium	18.4 (88)	30.0 (143)	29.8 (142)	21.8 (104)	477
Vancomycin resistant	18.5 (31)	24.4 (41)	31.5 (53)	25.6 (43)	168
Vancomycin susceptible	18.4 (56)	32.8 (100)	29.2 (89)	19.7 (60)	305
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	27.5 (121)	30.7 (135)	24.3 (107)	17.3 (76)	440
E. faecium	25.9 (38)	34.7 (51)	25.2 (37)	14.3 (21)	147
Vancomycin resistant	30.6 (11)	27.8 (10)	30.6 (11)	11.1 (4)	36
Vancomycin susceptible	23.9 (26)	36.7 (40)	23.9 (26)	15.6 (17)	109
Hospital-onset					
E. faecalis	15.8 (33)	20.1 (42)	25.8 (54)	38.3 (80)	209
Vancomycin resistant	–* (0)	–* (0)	–* (0)	–* (0)	0
Vancomycin susceptible	15.9 (33)	19.7 (41)	26.0 (54)	38.5 (80)	208
E. faecium	15.2 (50)	27.9 (92)	31.8 (105)	25.2 (83)	330
Vancomycin resistant*	15.2 (20)	23.5 (31)	31.8 (42)	29.5 (39)	132
Vancomycin susceptible*	15.3 (30)	30.6 (60)	32.1 (63)	21.9 (43)	196

* Insufficient numbers (<10) to calculate percentage

Note: vancomycin susceptibility not available for four *E. faecium* (community [2]; hospital-onset [2]) and six *E. faecalis* (community-onset [5]; hospital-onset [1]).

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

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 glycopeptide resistance in *E. faecium*, and high-level gentamicin resistance in *E. faecalis* is shown in Figure 2.

Table 8: Antimicrobial resistances (CLSI and EUCAST), AGAR, 2021

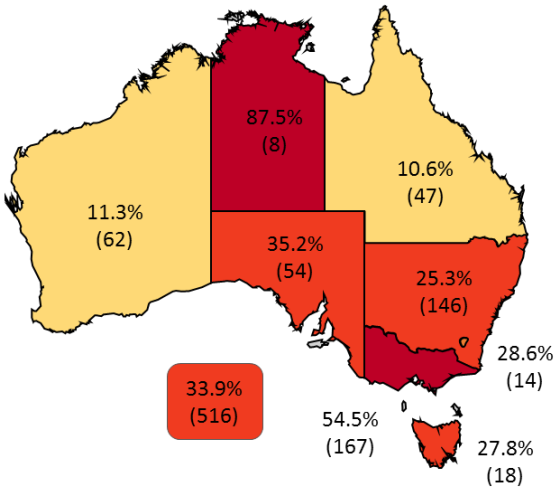
Species and antimicrobial	Isolates (n)	CLSI		EUCAST	
		Intermediate % (*n*)	Resistant % (*n*)	Susceptible, increased exposure % (*n*)	Resistant % (*n*)
Enterococcus faecalis					
Ampicillin	696	–*	0.1 (1)	0.0 (0)	0.1 (1)
Benzylpenicillin	588	–*	0.9 (5)	–†	–†
Ciprofloxacin	419	0.0 (0)	4.5 (19)	–*	4.5 (19)§
Daptomycin	649	42.4 (275)	0.3 (2)	–†	–†
Linezolid	685	4.8 (33)	0.3 (2)	–*	0.3 (2)
Teicoplanin	693	0.0 (0)	0.0 (0)	–*	0.3 (2)
Vancomycin	696	0.0 (0)	0.0 (0)	–*	0.0 (0)
Enterococcus faecium					
Ampicillin	514	–*	90.3 (464)	0.0 (0)	90.3 (464)
Benzylpenicillin	436	–*	89.9 (392)	–†	–†
Ciprofloxacin	322	2.8 (9)	88.2 (284)	–*	–#
Linezolid	62	98.4 (61)	1.6 (1)	–†	–†
Teicoplanin	514	1.2 (6)	0.2 (1)	–*	0.2 (1)
Vancomycin	501	0.6 (3)	12.0 (60)	–*	13.4 (67)

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing

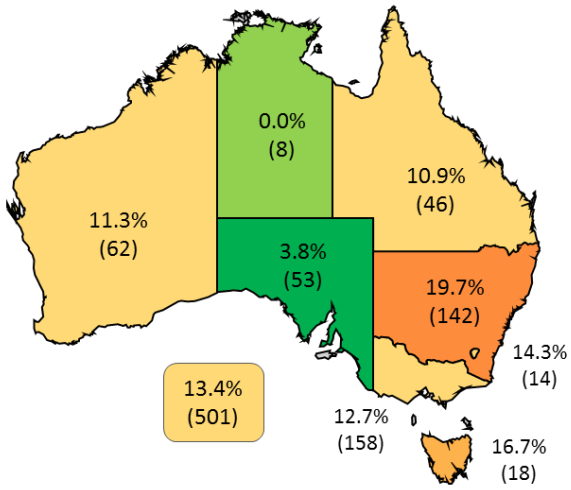
* No category defined
† No guidelines for indicated species
§ The ciprofloxacin ECOFF (4 mg/L, *E. faecalis*) was used to distinguish between isolates with and without acquired resistance mechanisms, as breakpoints apply to uncomplicated urinary tract infections only
\# The ciprofloxacin concentration range available on Vitek and Phoenix cards restricts the ability to determine non-wild type (ECOFF 8 mg/L) *E. faecium*

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

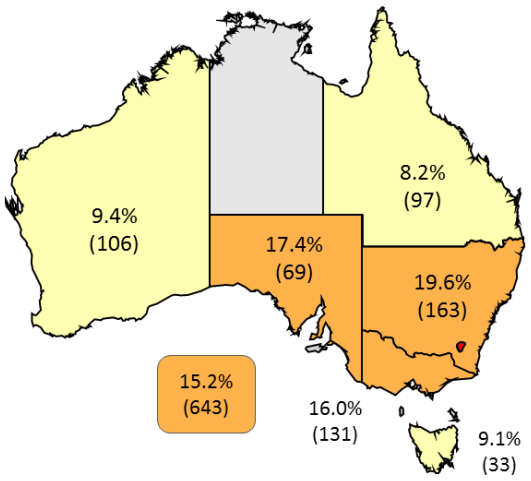
A. Vancomycin

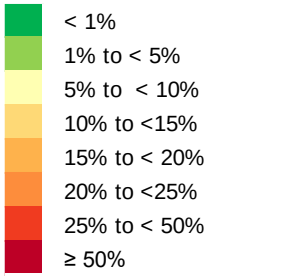


B. Teicoplanin



C. High-level gentamicin





Numbers for Australia in box

Note: <10 isolates in the Northern Territory (25%, 8)

Antimicrobial resistance by place of onset

Antimicrobial resistances (CLSI and EUCAST) 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	Number	Community-onset		Hospital-onset	
		% intermediate	% resistant	% susceptible, increased exposure	% resistant
Enterococcus faecalis					
Ampicillin	696	–*, 0.0	0.2, 0.2	–*, 0.0	0.0, 0.0
Benzylpenicillin	588	–*, –†	0.2, –†	–*, –†	2.2, –†
Ciprofloxacin	419	0.0, –*	4.8, –*	0.0, –*	3.9, –*
Daptomycin	649	41.7, –†	0.2, –†	43.8, –†	0.5, –†
Linezolid	678	4.9, –*	0.4, 0.4	4.8, –*	0.0, 0.0
Teicoplanin	693	0.0, –*	0.0, 0.2	0.0, –*	0.0, 0.5
Vancomycin	696	0.0, –*	0.0, 0.0	0.0, –*	0.0, 0.0
Enterococcus faecium					
Ampicillin	514	–*, 0.0	81.6, 81.6	–*, 0.0	94.3, 94.3
Benzylpenicillin	436	–*, –†	80.5, –†	–*, –†	94.8, –†
Ciprofloxacin	322	0.0, –†	72.0, –#	0.0, –†	91.9, –§
Linezolid	504	2.5, –*	0.6, 0.6	0.6, –*	0.0, 0.0
Teicoplanin	501	0.6, –*	5.0, 5.7	0.6, –*	15.2, 17.0
Vancomycin	516	0.6, –*	22.0, 22.6	2.0, –*	37.2, 39.2

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing

* No category defined
† No guidelines 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*

3.8. Multidrug resistance

Enterococci have expected resistance phenotypes to several antimicrobial classes and any additional acquired resistance severely limits the number of treatment options. The range of antimicrobials available on the test panels limits the ability to determine multiple acquired resistances in *E. faecalis* and *E. faecium*. Vancomycin-resistant enterococci 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*. 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*

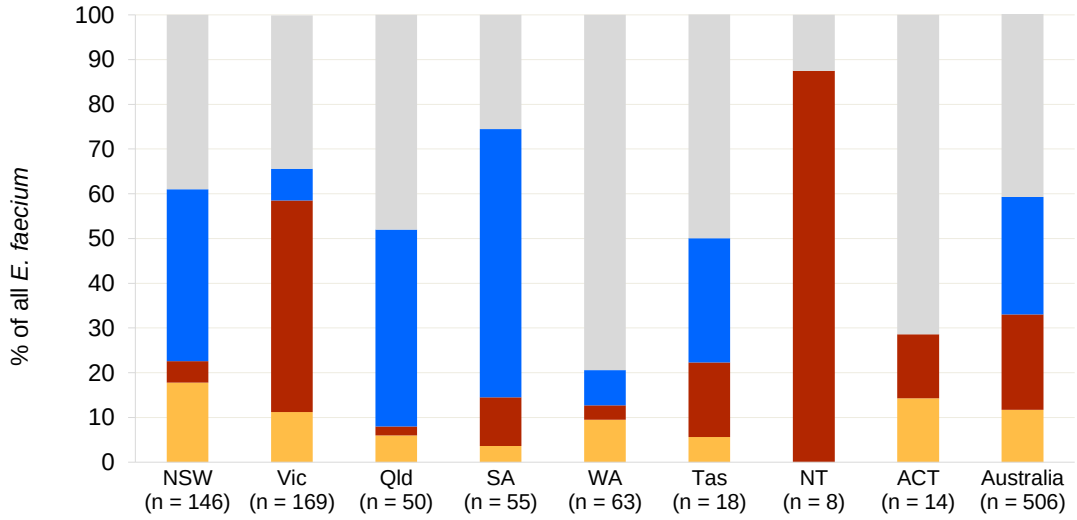
van genes

Results of PCR testing for *vanA* and *vanB* genes were available for 390 (74.6%) of the 523 *E. faecium* isolates. *van* genes were detected in 167/390 (42.8%) of *E. faecium*; *vanA* in 59 (15.1%) and *vanB* in 108 (27.7%) (Figure 3).

For vancomycin-resistant *E. faecium* (MIC > 4 mg/L), *vanA* was detected in 49/141 (34.8%) and *vanB* in 91/108 (64.5%).

In 25/245 (10.2%) of vancomycin-susceptible *E. faecium*, *van* genes were detected: eight with *vanA* and 17 with *vanB*. All 25 isolates had vancomycin MIC ≤ 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 = 506)
not vanA or vanB (n =1753)	39.0	34.3	48.0	25.5	79.4	50.0	12.5	71.4	44.1
To follow (n = 133)	38.4	7.1	44.0	60.0	7.9	27.8	0.0	0.0	26.3
vanA and vanB (n = 0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
vanB (n = 108)	4.8	47.3	2.0	10.9	3.2	16.7	87.5	14.3	21.3
vanA (n = 59)	17.8	11.2	6.0	3.6	9.5	5.6	0.0	14.3	11.7

Multi-locus sequence type

Of the 523 *E. faecium* isolates reported, 390 (74.6%) were available for typing by whole genome sequencing to date. (Table 10). Based on the MLST, 54 sequence types (STs) were identified. Overall, 74.4% of *E. faecium* could be characterised into six STs: ST17 (*n* = 87); ST1424, formerly known as M-type 3 (*n* = 65); ST796 (*n* = 46); ST78 (*n* = 39); ST80 (*n* = 33) and ST1421, formerly known as M-type 1 (*n* = 20). The *pstS* housekeeping gene is absent in the M-type isolates. M-type 1 was initially identified in the 2015 AESOP survey.[14] There were 31 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.

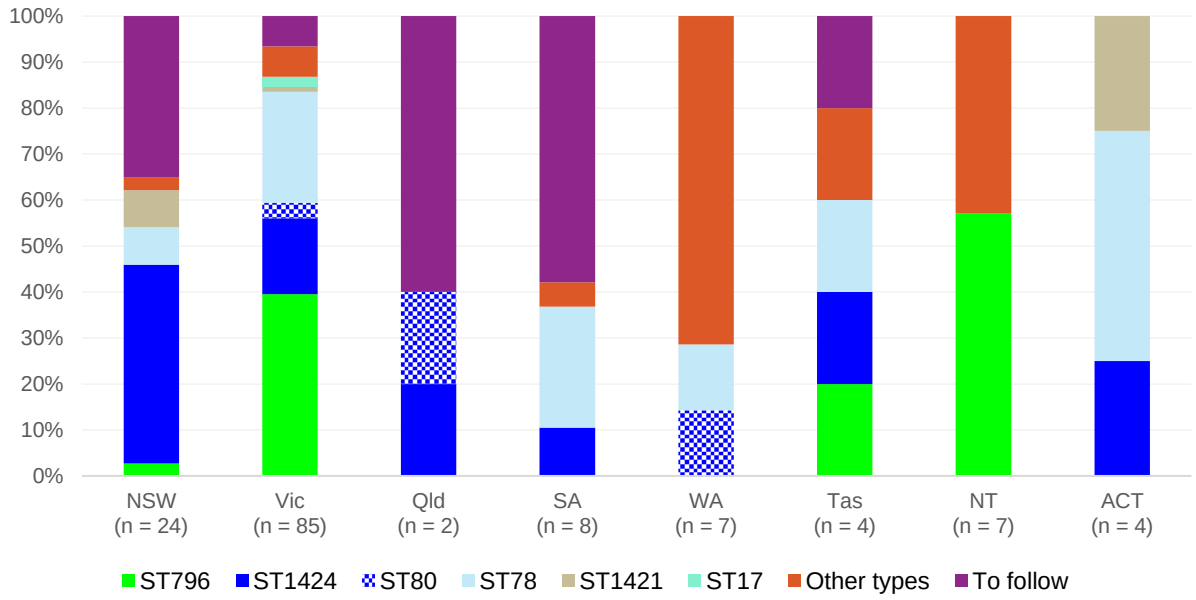
Table 10: *Enterococcus faecium* MLST, by state and territory, AGAR, 2021

	Percentage, % (*n*)								
MLST	**NSW**	**Vic**	**QLD**	**SA**	**WA**	**Tas**	**NT**	**ACT**	**Australia**
ST17	11.1 (10)	13.4 (21)	53.6 (15)	22.7 (5)	55.2 (32)	23.1 (3)	–* (0)	7.1 (1)	22.3 (87)
ST1424†	37.8 (34)	12.7 (20)	3.6 (1)	9.1 (2)	0.0 (0)	15.4 (2)	–* (0)	42.9 (6)	16.7 (65)
ST796	1.1 (1)	25.5 (40)	0.0 (0)	0.0 (0)	0.0 (0)	7.7 (1)	–* (4)	0.0 (0)	11.8 (46)
ST78	4.4 (4)	15.9 (25)	0.0 (0)	22.7 (5)	3.4 (2)	7.7 (1)	–* (0)	14.3 (2)	10.0 (39)
ST80	3.3 (3)	9.6 (15)	17.9 (5)	9.1 (2)	6.9 (4)	7.7 (1)	–* (0)	21.4 (3)	8.5 (33)
ST1421†	18.9 (17)	0.6 (1)	3.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	–* (0)	7.1 (1)	5.1 (20)
Other types (n = 48)	23.3 (21)	22.3 (35)	21.4 (6)	36.4 (8)	34.5 (20)	38.5 (5)	–* (4)	7.1 (1)	25.6 (100)
Total	**90**	**157**	**28**	**22**	**58**	**13**	**8**	**14**	**390**

MLST = multi-locus sequence type

* Insufficient numbers (<10) to calculate percentage
† *pstS*-null

Figure 5: 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 (1/87, 1.1%), ST1424 (38/65, 58.5%), ST80 (3/33, 9.1%), ST1421 (12/20, 60.0%) and ST117 (5/7, 71.4%).

The *vanB* gene was detected in 11 STs: ST17 (4/87, 4.6%), ST796 (46/46, 100%), ST78 (39/39, 100%), ST80 (2/33, 6.1%), ST555 (8/9, 88.9%), ST203 (3/3, 100%), ST1543 (2/2, 100%), and one each of ST18, ST233, ST2082 and ST538 (Table 11).

Table 11: *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	1.1 (1)	4.6 (4)	0.0 (0)	94.3 (82)	87
ST1424	58.5 (38)	0.0 (0)	0.0 (0)	41.5 (27)	65
ST796	0.0 (0)	100.0 (46)	0.0 (0)	0.0 (0)	46
ST78	0.0 (0)	100.0 (39)	0.0 (0)	0.0 (0)	39
ST80	9.1 (3)	6.1 (2)	0.0 (0)	84.8 (28)	33
ST1421	60.0 (12)	0.0 (0)	0.0 (0)	40.0 (8)	20
Other types (n =48)	6.5 (5)	11.7 (9)	0.0 (0)	81.8 (63)	77
Total	15.1 (59)	27.7 (108)	0.0 (0)	57.2 (223)	390

MLST = multi-locus sequence type

* Percentage of total with *van* genes

3.10. Trend analysis (2013–2021)

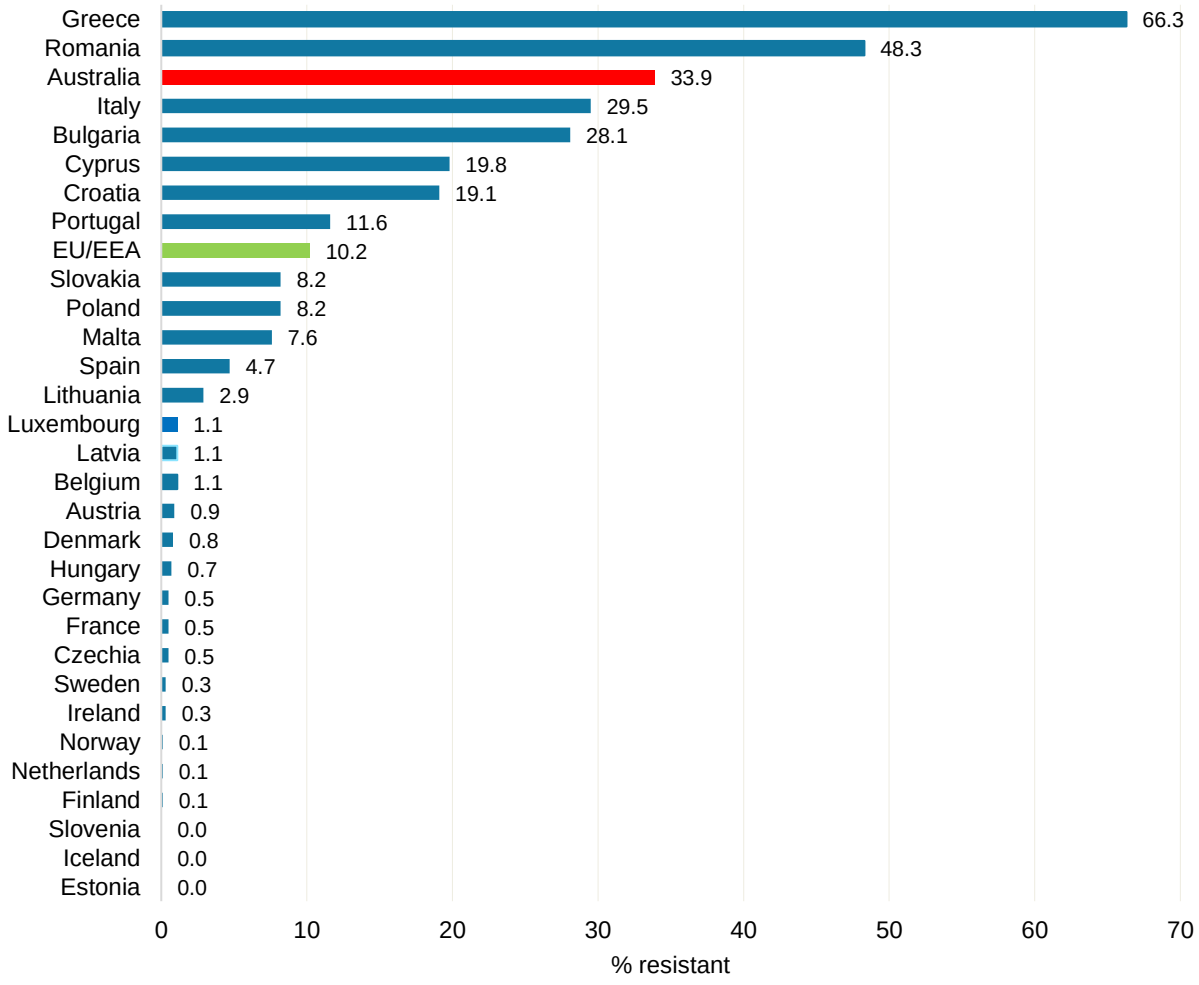
Trend data will be available in the AESOP 2021 final report.

4. International comparisons

Data from AGAR can be compared with data from the European Antimicrobial Resistance Surveillance Network (EARs-Net) program[15], as both programs examine resistance in bacterial pathogens found in blood cultures.

Australia ranks third in the rate of resistance to vancomycin in *E. faecium* compared to all European countries participating (Figure 6). In 2020, Australia ranked ninth.

Figure 6: 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]

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 is 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 bacteraemia in Australia had their onset overwhelmingly in the community. For the AESOP bacteraemia program, 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, and for each of *E. faecalis* and *E. faecium*.

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 5.4 days.[17] Thirty-day all-cause mortality due to *E. faecium* in 2021 was 25.2% (CO, 25.4%; HO, 25.2%); there were no significant differences in 30-day all-cause mortality between vancomycin-susceptible and resistant episodes.

In the 2021 survey, 42.8% 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 decreased to 36.3%. In the 2021 survey 34.1% of *E. faecium* bacteraemia harboured the *vanA* gene. This type of vancomycin resistance has emerged rapidly, 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 18.2%. Australia ranks third in rates of resistance to vancomycin in *E. faecium* (33.9%) compared to all European countries, In 2020 it was ranked ninth; and in 2019, fourth.[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 multidrug-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, such as certain CPEs. 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
ANCU	*AURA National Coordinating Unit*
APAS	Australian Passive AMR Surveillance
AURA	Antimicrobial Use and Resistance in Australia
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
GLASS	Global Antimicrobial Resistance Surveillance System
EUCAST	European Committee on Antimicrobial Susceptibility Testing
MDR	Multi-drug resistant
MIC	Minimum inhibitory concentration
PCR	Polymerase chain reaction
WGS	Whole genome sequencing
WHO	World Health Organization

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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
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Children's Hospital Westmead, NSW	Alison Kesson and Andrew Jarrett
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Reference laboratories

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Appendix A. Study design

Forty-eight institutions participated in the 2020 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* = 2)
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 laboratories that participated 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 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* = 34) and Phoenix (BD) (*n* = 4), 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.

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)

* 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 years
- 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	68	107	33	8	36	696
	%R	81.9, 81.9	98.8, 98.8	50.0, 50.0	75.0, 75.0	57.9, 57.9	54.5, 54.5	n/a	38.9, 38.9	73.9, 73.9
Enterococcus faecium	n	129	152	46	46	56	13	8	14	464
	%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
Benzylpenicillin										
Enterococcus faecalis	n	164	96	97	68	106	13	8	36	588
	%R	98.2, –†	100.0, –†	100.0, –†	100.0, –†	98.1, –†	100.0, –†	n/a	100.0, –†	99.1, –†
Enterococcus faecium	n	140	100	49	53	62	10	8	14	436
	%R	9.3, –†	11.0, –†	6.1, –†	17.0, –†	8.1, –†	30.0, –†	n/a	0.0, –†	10.1, –†
Ciprofloxacin										
Enterococcus faecalis	n	109	140	0	43	106	13	8	0	419
	%R/ecoff §	9.2, 9.2	2.1, 1.4	n/a	4.7, 4.7	5.7, 4.7	0.0, 0.0	n/a	n/a	5.0, 4.5
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	174	169	96	47	106	13	8	36	649
	%R	0.6, –†	0.0, –†	1.0, –†	0.0, –†	0.0, –†	0.0, –†	n/a	0.0, –†	0.3, –†
Enterococcus faecium	n	35	0	0	24	3	0	0	0	62
	%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	97	59	107	33	8	36	685
	%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	167	49	51	63	18	8	14	514
	%R	0.7, 0.7	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	0.2, 0.2
Teicoplanin										
Enterococcus faecalis	n	177	169	97	67	106	33	8	36	693
	%R	0.0, 1.1	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, 0.3

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	142	158	46	53	62	18	8	14	501
	%R	18.3, 19.7	10.8, 12.7	10.9, 10.9	3.8, 3.8	9.7, 11.3	11.1, 16.7	n/a	14.3, 14.3	12.0, 13.4
Tetracycline/doxycycline**										
Enterococcus faecalis	n	181	94	78	44	89	13	5	1	505
	%NS	70.7, –†	75.5, –†	70.5, –†	65.9, –†	66.3, –†	76.9, –†	n/a	n/a	70.7, –†
Enterococcus faecium	n	156	87	32	26	62	5	6	0	374
	%NS	60.3, –†	81.6, –†	71.9, –†	3.8, –†	69.4, –†	n/a	n/a	n/a	64.2, –†
Vancomycin										
Enterococcus faecalis	n	178	169	98	67	107	33	8	36	696
	%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	167	47	54	62	18	8	14	516
	%R	24.7, 25.3	50.3, 54.5	10.6, 10.6	35.2, 35.2	11.3, 11.3	27.8, 27.8	n/a	28.6, 28.6	32.4, 33.9

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