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Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Surveillance Outcome Program (GnSOP)

Bloodstream Infection Annual Report 2022

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Annual report

Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Surveillance Outcome Program (GnSOP)

Bloodstream Infection Annual Report 2022

Jan M Bell, Alicia Fajardo Lubian, Sally R Partridge, Thomas Gottlieb, Jennifer Robson, Jonathan R Iredell, Denise A Daley, Geoffrey W Coombs

Abstract

The Australian Group on Antimicrobial Resistance (AGAR) performs regular period-prevalence studies to monitor changes in antimicrobial resistance in selected enteric gram-negative pathogens. The 2022 survey was the tenth year to focus on blood stream infections caused by *Enterobacterales*, and the eighth year where *Pseudomonas aeruginosa* and *Acinetobacter* species were included. Fifty-five hospitals Australia-wide participated in 2022.

The 2022 survey tested 9,739 isolates, comprising *Enterobacterales* (8,773; 90.1%), *P. aeruginosa* (840; 8.6%) and *Acinetobacter* species (126; 1.3%), using commercial automated methods. The results were analysed using Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (January 2023). Key resistances included resistance to the third-generation cephalosporin ceftriaxone in 12.7%/12.7% (CLSI/EUCAST criteria) of *Escherichia coli* and in 6.6%/6.6% of *Klebsiella pneumoniae* complex. Resistance rates to ciprofloxacin were 13.7%/13.7% for *E. coli;* 7.8%/7.8% for *K. pneumoniae* complex; 5.3%/5.3% for *Enterobacter cloacae c*omplex; and 4.3%/10.0% for *P. aeruginosa*. Resistance rates to piperacillin-tazobactam were 2.8%/5.9%; 2.9%/8.7%; 18.3%/27.2%; and 6.1%/14.7% for the same four species, respectively. Twenty-nine *Enterobacterales* isolates from 28 patients were shown to harbour a carbapenemase gene: 18 $bla_{\text{IMP-4}}$; four $bla_{\text{NDM-5}}$; three $bla_{\text{NDM-1}}$; one $bla_{\text{OXA-181}}$; one $bla_{\text{OXA-244}}$; one $bla_{\text{NDM-1}}$ + $bla_{\text{OXA-181}}$; and one $bla_{\text{NDM-5}}$ + $bla_{\text{OXA-181}}$. Transmissible carbapenemase genes were also detected among two *Acinetobacter baumannii* complex isolates ($bla_{\text{OXA-23}}$) and one *P. aeruginosa* ($bla_{\text{NDM-1}}$) in the 2022 survey.

Keywords: Australian Group on Antimicrobial Resistance (AGAR); antimicrobial resistance; bacteraemia; gram-negative; *Escherichia coli*; *Enterobacter; Klebsiella*

Introduction

Emerging resistance in common pathogenic members of the *Enterobacterales* is a world-wide phenomenon and presents therapeutic problems, both in the community and in hospital practice. The Australian Group on Antimicrobial Resistance (AGAR) commenced surveillance of the key gram-negative pathogens, *Escherichia coli* and *Klebsiella* species, in 1992. Surveys were conducted biennially until 2008 when annual surveys commenced, alternating between community- and hospital-onset infections.[i] In 2004 *Enterobacter*, another genus of gram-negative pathogens in which resistance can be of clinical

i http://www.agargroup.org.au/agar-surveys.

importance, was added. *Escherichia coli* is the most common cause of community-onset urinary tract infection; *Klebsiella* species are less common but are known to harbour important resistances. *Enterobacter* species are less common in the community, but of high importance due to intrinsic resistance to first-line antimicrobials used in that setting. Taken together, these three groups of species surveyed are valuable sentinels for multi-resistance and emerging resistance in enteric gram-negative bacilli. In 2013 AGAR commenced the *Enterobacterales* Sepsis Outcome Program (EnSOP), which focused on the collection of resistance data and some demographic data on all isolates collected prospectively from patients with bacteraemia. In 2015, *Pseudomonas aeruginosa* and *Acinetobacter* species were added, with the program then referred to as the Gram-negative Sepsis Outcome Program (GnSOP), since renamed the Gram-negative Surveillance Outcome Program.

Resistance to β-lactams due to β-lactamases, especially extended-spectrum β-lactamases that inactivate the third-generation cephalosporins normally considered reserve antimicrobials, is of particular interest. Also of interest is resistance to agents important for treatment of serious infections, such as gentamicin and piperacillin-tazobactam; to highly bioavailable oral agents such as ciprofloxacin; and to reserve agents such as meropenem.

The objectives of the 2022 surveillance program were:

- to monitor resistance in *Enterobacterales*, *P. aeruginosa* and *Acinetobacter* species isolated from blood cultures taken from patients presenting to the hospital or already in hospital;
- to examine the extent of co-resistance and multidrug resistance in the major species;
- to detect emerging resistance to reserve agents such as carbapenems and colistin; and
- to examine the molecular basis of resistance to third-generation cephalosporins, quinolones and carbapenems.

Methods

Study design

From 1 January to 31 December 2022, thirty-three laboratories servicing 55 hospitals across Australia, including seven children's hospitals and 13 regional or district hospitals from north-west Western Australia, collected either all or up to 200 isolates from different patient episodes of bacteraemia.

Species identification

Species were identified using the routine method at each institution; Vitek®, Phoenix™ automated microbiology systems or, where available, matrix assisted laser desorption/ionisation – time of flight (MALDI-ToF) mass spectrometry.

Susceptibility testing

Testing was performed by two commercial semi-automated methods, Vitek® 2 (BioMérieux, France) or Phoenix™ (Becton Dickinson, USA), which are calibrated to the International Organization for Standardization (ISO) reference standard method of broth microdilution. Commercially available Vitek (AST-N246, AST N-435, AST N-410) or Phoenix NMIC-422 cards were utilised by all participants throughout the survey period. The CLSI M100 and EUCAST v13.1 breakpoints from January 2023 have been employed in the analysis.[1,2]

Multidrug resistance

The definitions used by Magiorakos et al. were applied in this survey,[3] where multidrug resistance (MDR) is defined as resistance to one or more agent in three or more antimicrobial categories. For each species, antimicrobials were excluded from the count if they are affected by natural resistance mechanisms.

Whole genome sequencing

The following isolates were referred to a central laboratory (Centre for Infectious Diseases and Microbiology, The Westmead Institute for Medical Research):

- *E. coli*, *Klebsiella* spp., *Proteus* spp. and *Salmonella* spp. with ceftazidime or ceftriaxone minimum inhibitory concentration (MIC) > 1 mg/L, or cefoxitin MIC > 8 mg/L;
- any other *Enterobacterales* with cefepime MIC > 1 mg/L;
- *Salmonella* spp. with ciprofloxacin MIC > 0.25 mg/L;
- all *Enterobacterales* with meropenem MIC > 0.125 mg/L (> 0.25 mg/L if tested using Vitek);
- all *P. aeruginosa* or *Acinetobacter* spp. with meropenem MIC > 4 mg/L;
- all isolates with amikacin MIC > 32 mg/L;
- and all isolates with colistin MIC > 4 mg/L (except those with intrinsic resistance to colistin).

All referred isolates underwent whole genome sequencing (WGS).

Genomic DNA for WGS was extracted using the DNeasy® Blood & Tissue Kit (Qiagen) according to the manufacturer's instructions for gram-negative bacteria. WGS was performed by the Antimicrobial Resistance Laboratory, Microbial Genomics Reference Laboratory, Centre for Infectious Diseases and Microbiology Laboratory Services (CIDMLS), Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital using the Illumina NextSeq™ 500 platform. Data were analysed using a modification of the Nullarbor bioinformatic pipeline,[4] incorporating searching contigs against the NCBI AMRFinder database[ii] using ABRicate[5] and AMRFinder,[6] followed by a custom AMR-specific pipeline which included a read-based search using ARIBA[7] against the CARD[8] and NCBI databases. Ambiguities and potential multiple gene copies/variants were checked manually by mapping reads to reference genes[iii] using Geneious.

Results

The species isolated, and the numbers of each, are listed in Table 1. *Enterobacterales* accounted for 90.1%, followed by *P. aeruginosa* (8.6%) and *Acinetobacter* species (1.3%). In the *Enterobacterales*, 86.7% of all isolates belonged to three genera—*Escherichia* (60.1%), *Klebsiella* (20.9%) and *Enterobacter* (5.7%). Major resistances and non-susceptibilities for the top six ranked species are listed in Table 2. We utilised non-susceptibility as an epidemiological tool to provide important information about emerging acquired resistance, recognising that even though some of these isolates remain within therapeutic range for specific antibiotics, these isolates tend to be divergent from the wild-type distribution. In addition to resistant isolates, isolates categorised as 'intermediate' according to CLSI were included as non-susceptible. Multiple acquired resistances by species are shown in Table 3. Almost one-quarter of *E. coli* isolates (23.4%), 8.0% of *K. pneumoniae* complex isolates, and 8.4% of *E. cloacae* complex isolates would be considered multi-drug resistant. A more detailed breakdown of resistance and non-susceptibility by state and territory is provided in the online GnSOP 2022 report.[iv]

Escherichia coli

The moderately high levels of resistance to ampicillin (and therefore amoxicillin) observed were at similar to levels in the 2021 survey (2022: 50.0%/51.5%; versus 2021: 51.4%/53.2%, CLSI/EUCAST criteria), with

ii https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047.

iii https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/.

iv https://agargroup.org.au/agar-surveys/.

Table 1: Number and proportion of species isolated, blood cultures, AGAR, 2022

		Onset setting, percentage (*n*)	
Species	**Percentage (n)**	**Community onset**	**Hospital onset**
Escherichia coli	54.1 (5,273)	82.5 (4,349)	17.5 (924)
Klebsiella pneumoniae complex	14.3 (1,395)	69.4 (968)	30.6 (427)
Pseudomonas aeruginosa	8.6 (840)	56.4 (474)	43.6 (366)
Enterobacter cloacae complex	4.9 (477)	52.4 (250)	47.6 (227)
Proteus mirabilis	3.3 (324)	82.4 (267)	17.6 (57)
Klebsiella oxytoca	3.0 (297)	66.0 (196)	34.0 (101)
Serratia marcescens	2.6 (257)	44.4 (114)	55.6 (143)
Klebsiella aerogenes	1.3 (130)	60.8 (79)	39.2 (51)
Morganella morganii	1.1 (110)	70.9 (78)	29.1 (32)
Citrobacter freundii complex	1.0 (97)	74.2 (72)	25.8 (25)
Salmonella species (non-typhoidal)	1.0 (97)	91.8 (89)	8.2 (8)
Citrobacter koseri	0.8 (80)	82.5 (66)	17.5 (14)
Acinetobacter baumannii complex	0.7 (70)	58.6 (41)	41.4 (29)
Salmonella species (typhoidal)	0.4 (38)	94.7 (36)	5.3 (2)
Raoultella ornithinolytica	0.3 (28)	78.6 (22)	21.4 (6)
Enterobacter species[a]	0.2 (23)	82.6 (19)	17.4 (4)
Providencia rettgeri	0.2 (19)	84.2 (16)	15.8 (3)
Acinetobacter lwoffii	0.2 (16)	81.3 (13)	18.8 (3)
Acinetobacter species[a]	0.2 (16)	75.0 (12)	25.0 (4)
Providencia stuartii	0.1 (13)	92.3 (12)	7.7 (1)
Acinetobacter ursingii	0.1 (12)	66.7 (8)	33.3 (4)
Pantoea agglomerans	0.1 (12)	66.7 (8)	33.3 (4)
Proteus hauseri	0.1 (11)	90.9 (10)	9.1 (1)
Hafnia alvei	0.1 (10)	70.0 (7)	30.0 (3)
Other species (total $n = 36$)	1.0 (94)	63.8 (60)	36.2 (34)
Total	**9,739**	**74.6 (7,266)**	**25.4 (2,473)**

a Species not determined

similar lower rates for amoxicillin-clavulanic acid (9.9%/– intermediate, 7.4%/– resistant). Non-susceptibility to third generation cephalosporins was also maintained versus 2021 (ceftriaxone, 2022: 12.8%/12.7% versus 2021: 12.6%/12.5%; ceftazidime, 2022: 5.9%/5.9% versus 2021: 6.3%/6.3%). An extended spectrum β-lactamase (ESBL) phenotype was significantly more prevalent among hospital-onset (HO) than community-onset (CO) episodes of *E. coli* (17.2% versus 13.8%, $p < 0.01$). Moderate levels of resistance to cefazolin (22.2%/22.2%) and trimethoprim–sulfamethoxazole (28.0%/27.9%) were detected. Ciprofloxacin non-susceptibility was found in 17.4%/17.4% of *E. coli* isolates, 0.8 percentage points higher than the 2021 survey. Resistance to gentamicin (7.9%/8.3%), piperacillin-tazobactam (2.8%/5.9%), and cefepime (2.1%/3.1%) was low. Ten isolates (0.2%) had elevated meropenem MICs (≥ 0.5 mg/L). For the isolates with an ESBL phenotype, ciprofloxacin and gentamicin resistance was found in 50.4%/50.4% and 29.9%/30.7% respectively.

Table 2: Non-susceptibility and resistance rates for the top six ranked species tested, AGAR, 2022

		E. coli (%)		*K. pneumoniae* **complex** (%)		*P. aeruginosa* (%)		*E. cloacae* **complex** (%)		*P. mirabilis* (%)		*K. oxytoca* (%)	
Antimicrobial	**Category**[a]	**CLSI**[b]	**EUCAST**[b]	**CLSI**[b]	**EUCAST**[b]	**CLSI**[b]	**EUCAST**[b]	**CLSI**[b]	**EUCAST**[b]	**CLSI**[b]	**EUCAST**[b]	**CLSI**[b]	**EUCAST**[b]
Ampicillin	R	50.0	51.5	*c*	*c*	na	na	*c*	*c*	15.8	16.4	*c*	*c*
Amoxicillin-clavulanic acid (2:1)[d]	R	7.4	*d*	3.2	*d*	na	na	*c*	*c*	3.2	*d*	7.4	*d*
Piperacillin-tazobactam	R	2.8	5.9	2.9	8.7	6.1	14.7	18.3	27.2	0.0	0.0	8.1	11.5
Cefazolin	R	22.2	22.2	10.1	10.1	na	na	*c*	*c*	17.7	17.7	58.1	58.1
Cefoxitin	R	3.3	/	3.3	/	na	na	*c*	*c*	0.3	/	0.7	/
Ceftriaxone	NS	12.8	12.7	6.7	6.6	na	na	28.8	28.4	1.9	1.2	6.1	5.7
Ceftazidime	NS	5.9	5.0	5.3	5.3	10.6	10.6[e]	24.6	24.6	0.9	0.9	0.7	0.7
Cefepime	NS	4.2	3.1	2.7	2.2	6.2	6.2[e]	5.5	3.4	1.2	0.6	0.3	0.3
Meropenem	NS	< 0.1	< 0.1	0.8	0.5	5.9[e]	4.3[e]	2.7	2.1	0.0	0.0	0.7	0.0
Ciprofloxacin	NS	17.4	13.7	9.9	7.8	10.0	10.0[e]	6.3	5.3	4.6	4.0	1.0	0.7
Gentamicin	R	7.9	8.3	3.0	3.4	na	na	5.5	6.1	1.9	5.0	1.0	1.0
Tobramycin	R	2.4	8.6	1.4	4.1	0.4	0.7	3.7	6.7	1.9	3.7	0.0	1.0
Trimethoprim–sulfamethoxazole	R	28.0	27.9	13.0	12.9	na	na	17.6	17.6	13.6	13.6	6.4	6.4
Nitrofurantoin	R	0.5	0.5	27.6	/	na	na	11.4	/	*c*	*c*	1.6	/

a R: resistant; I: intermediate (CLSI) or susceptible, increased exposure (EUCAST); NS: non-susceptible (intermediate + resistant), using criteria as published by the CLSI [2022] and EUCAST [2022].
b –: no category defined; /: no breakpoints defined; na: not applicable (testing not recommended).
c Considered largely intrinsically resistant.
d For EUCAST interpretation, clavulanic acid is fixed at 2 mg/L, rather than the 2:1 ratio of amoxicillin to clavulanic acid used in CLSI guidelines. As 90% of pathology services (27/30) used susceptibility test cards with a 2:1 ratio of clavulanate, no EUCAST category has been applied.
e Percent resistant.

Table 3: Multiple acquired resistances by species, AGAR, 2022

		Number of acquired resistances (EUCAST breakpoints)[a,b]											
		Non multi-drug resistant				Multi-drug resistant							
Species	Total	0	1	2	Cumulative %	3	4	5	6	7	8	9	Cumulative %
E. coli	5,181	2,262	923	782		400	352	304	100	44	13	1	
	%	43.7	17.8	15.1	76.6	7.7	6.8	5.9	1.9	0.8	0.3	< 0.1	23.4
K. pneumoniae complex[c]	1,366	1,066	105	86		33	29	14	24	5	4	na	
	%	78.0	7.7	6.3	92.0	2.4	2.1	1.0	1.8	0.4	0.3		8.0
E. cloacae complex[d]	467	279	50	99		12	15	7	5	na	na	na	
	%	59.7	10.7	21.2	91.6	2.6	3.2	1.5	1.1				8.4
P. mirabilis[e]	322	247	35	28		5	5	2	0	0	0	na	
	%	76.7	10.9	8.7	96.3	1.6	1.6	0.6	0.0	0.0	0.0		3.7
K. oxytoca[f]	295	242	30	21		1	1	0	0	0	na	na	
	%	82.0	10.2	7.1	99.3	0.3	0.3	0.0	0.0	0.0			0.7
Salmonella species (non-typhoidal)[f]	96	82	9	2		1	2	0	0	na	na	na	
	%	85.4	9.4	2.1	96.9	1.0	2.1	0.0	0.0				3.1
S. marcescens[g]	212	64	113	25		5	5	0	0	0	na	na	
	%	30.2	53.3	11.8	95.3	2.4	2.4	0.0	0.0	0.0			4.7
K. aerogenes[d]	129	76	9	39		3	2	0	0	na	na	na	
	%	58.9	7.0	30.2	96.1	2.3	1.6	0.0	0.0				3.9

a Antimicrobial categories (agents) included: aminoglycosides (gentamicin and/or tobramycin); antipseudomonal penicillins + β-lactamase inhibitor (piperacillin–tazobactam); carbapenems (meropenem); extended-spectrum cephalosporins (ceftriaxone and/or ceftazidime); cephamycins (cefoxitin); fluoroquinolones (ciprofloxacin); folate pathway inhibitors (trimethoprim–sulfamethoxazole); non-extended-spectrum cephalosporins (cefazolin and/or cefuroxime); and penicillins (ampicillin).
b na: not applicable.
c Antimicrobial categories excluded: penicillins.
d Antimicrobial categories excluded: cephamycins, non-extended-spectrum cephalosporins, penicillins.
e Antimicrobial categories excluded: non-extended-spectrum cephalosporins.
f Antimicrobial categories excluded: non-extended-spectrum cephalosporins, penicillins.
g Antimicrobial categories excluded: aminoglycosides, cephamycins, non-extended-spectrum cephalosporins.

Most of the referred *E. coli* with an ESBL phenotype (664/703; 94.5%) harboured an Ambler class A ESBL gene (546/664, 82.2%); a plasmid borne class C gene (pAmpC) (95/664; 14.3%); or a carbapenemase gene (2/664; 0.3%) alone, or both an ESBL and pAmpC gene (16/664; 2.4%), or both a carbapenemase gene and an ESBL (4/664; 0.6%), or both a carbapenemase gene and pAmpC gene (1/664, 0.2%). The dominant β-lactamase genes in E. coli were $bla_{\text{CTX-M}}$ types, as found previously. Of 664 *E. coli* isolates with a confirmed βlactamase gene, 563 (84.8%) had one or more $bla_{\text{CTX-M}}$ genes detected by WGS, either $bla_{\text{CTX-M}}$ group 1 (n = 290); $bla_{\text{CTX-M}}$ group 9 (n = 272); or a $bla_{\text{CTX-M}}$ group 1/9/1 hybrid (n = 1). Of 112 *E. coli* isolates with pAmpC, 62 (55.4%) harboured $bla_{\text{DHA-1}}$; 49 (43.8%) harboured a $bla_{\text{CMY-2}}$-like gene; and one (0.9%) harboured both $bla_{\text{DHA-1}}$ and a $bla_{\text{CMY-42}}$ gene.

Klebsiella pneumoniae complex

K. pneumoniae complex isolates showed slightly higher levels of resistance to piperacillin-tazobactam than did *E. coli*, but showed lower rates of resistance to amoxicillin-clavulanic acid, cefazolin, ceftriaxone, ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole. An ESBL phenotype was higher among HO than CO episodes (12.7% versus 5.3%, $p < 0.01$). Sixteen *K. pneumoniae* complex isolates (1.1%) had elevated meropenem MICs (see below). Most of the referred *K. pneumoniae* complex isolates with an ESBL phenotype (88/100; 88.0%) harboured an ESBL gene (72; 81.8%), a pAmpC gene (7; 8.0%), or a carbapenemase gene (3, 3.4%) alone; or an ESBL and pAmpC gene (1; 1.1%); or a carbapenemase gene coproduced with either an ESBL or pAmpC gene ESBL (5; 5.7%). The majority of ESBL genes (70/83; 84.3%) were $bla_{\text{CTX-M}}$ types, mostly $bla_{\text{CTX-M}}$ group 1 (64/70; 91.4%). *K. pneumoniae* complex isolates harboured either $bla_{\text{DHA-1}}$ (8/10, 80.0%) or $bla_{\text{CMY-2}}$-like genes (2/10).

Enterobacter cloacae complex

Acquired resistance was common among *E. cloacae* complex isolates, to piperacillin-tazobactam (18.3%/27.2%); ceftriaxone (28.4%/28.4%); and ceftazidime (24.6%/28.2%). There was a moderate level of resistance to trimethoprim–sulfamethoxazole (17.6%/17.6%); cefepime, ciprofloxacin and gentamicin resistance all remained at less than 10%. Although *E. cloacae* complex isolates are generally more resistant than *E. coli* to β-lactam antimicrobials, resistance rates to non-β-lactams tend to be lower. Twenty-three *E. cloacae* complex isolates (4.8%) had elevated meropenem MICs.

Carbapenemase genes

Overall, 32 isolates (31 patients) from 18 hospitals from six states/territories were found to harbour a carbapenemase gene. Eighteen isolates harboured $bla_{\text{IMP-4}}$: *E. cloacae* complex (n = 9), *K. pneumoniae* (n = 5), *Serratia marcescens* (n = 3) and *E. coli* (n = 1). Other types detected in *Enterobacterales* were bla_{NDM} (n = 7), bla_{NDM} + $bla_{\text{OXA-181}}$ (n = 2), $bla_{\text{OXA-181}}$ (n = 1), and $bla_{\text{OXA-244}}$ (n = 1) genes. The $bla_{\text{OXA-23}}$ gene was detected in two *Acinetobacter baumannii* complex isolates, and $bla_{\text{NDM-1}}$ was detected in one *P. aeruginosa* isolate. No bla_{KPC} genes were detected in the 2022 survey.

Plasmid-borne colistin determinants

The only mobile colistin resistance (*mcr*) genes detected among referred isolates were *mcr-9* and *mcr-1*, almost all in *E. cloacae* complex isolates (16/17). No other resistance genes were identified in almost one-half (8/17, 47.1%) of the isolates with an *mcr* gene.

Discussion

AGAR has been tracking resistance in sentinel enteric gram-negative bacteria since 1992. From 2008, surveillance was separated into hospital-onset versus community-onset infections. The last year of hospital-onset only surveillance was 2011.[9] In 2013, the first survey of antimicrobial resistance among *Enterobacterales* isolates from bacteraemic patients throughout Australia was conducted using an approach similar to the European EARS-Net program.[10] The 2022 survey was the tenth of

antimicrobial resistance among *Enterobacterales*, and the eighth for *P. aeruginosa* and *Acinetobacter* spp. from bacteraemic patients through Australia.

The percentages of resistant *E. coli* in 2022 were similar to those seen in 2021 for all antimicrobial agents tested, except for ciprofloxacin, where it increased from 12.3% in 2021 to 13.7% in 2022. For *K. pneumoniae* complex, the percentage of resistant isolates in 2022 was similar to that seen in 2021 for all antimicrobials.

AGAR data show a longitudinal trend of increasing *E. coli* resistance to key anti-gram-negative antimicrobial agents, such as ceftriaxone and ciprofloxacin. Resistance to both agents stabilised in 2018 to 2020 (ceftriaxone 13.3–13.4%, ciprofloxacin 15.2–16.1%); the level of resistance declined to 12.5% and 12.3% respectively in 2021. In 2022, the level of resistance remained stable (12.7% and 13.7%). The steady rise in resistance to fluoroquinolones in *E. coli* is more striking in hospital-onset bacteraemia, with a change from 13.7% to 19.8% between 2013 and 2018, to 21.3% in 2019, and to 21.8% in 2020. In 2021, the level of resistance fell to 16.7%, and it increased slightly to 17.8% in 2022. In *K. pneumoniae* complex isolates, rates of resistance to ciprofloxacin were lower than for *E. coli*. Resistance in *K. pneumoniae* complex isolates peaked in 2018–2019 at 11.0% and 10.2%, falling to 7.2% in 2021, and was 7.8% in 2022.

Carbapenem resistance attributable to acquired carbapenemase genes is still uncommon in patients with bacteraemia in Australia. $bla_{\text{IMP-4}}$ accounted for 62.1% (18/29) of all carbapenemase-producing *Enterobacterales* (CPE) in 2022, and half of the $bla_{\text{IMP-4}}$ genes were found in *E. cloacae* complex isolates. Compared with many other countries in our region, antimicrobial resistance rates in Australian gram-negative bacteria are still relatively low,[11,12] but similar to those observed in 2021 in many Northern European countries.[13,14] Resistance to third generation cephalosporins in *E. coli* from bacteraemic patients in Australia is similar to the European Union and European Economic Area average.[14] Although we see rates of ceftriaxone and ciprofloxacin resistance in *E. coli* that parallel Northern Europe, rates in *Klebsiella pneumoniae* are lower in Australia, compared to rates of resistance > 25% in parts of Europe. Some of this is explained by the relatively greater predisposition for Klebsiella species to carry carbapenemase types found in Europe (such as KPC) and to the unregulated fluoroquinolone use in Europe compared to Australia where this antimicrobial class has been under greater usage scrutiny and regulation. Nonetheless, this illustrates the potential for greater rises in resistance rates over time and the need for ongoing surveillance.

Just under one-fifth of *E. coli* would be classed as MDR, a proportion little changed from the 2021 survey. The proportion of *K. pneumoniae* complex isolates classed as MDR fell from 9.9% in 2019 and 2020 to 6.2% in 2021 and remained at 6.3% in 2022.

The impact of the SARS-CoV-2 pandemic on antimicrobial resistance remains unclear. Australian borders were closed to international travellers and Australians from March 2020 until November 2021. Imported antimicrobial resistance via travellers and returning residents has always been an important source of resistant isolates, in particular *Enterobacterales*. Such border closures are likely to have resulted in decreased introduction of resistant clones into Australia. During the pandemic antibiotic usage in the community decreased significantly (possibly due to limited access to general practitioners); this may be another contributing factor to the declining resistance rates. Compared to previous AGAR surveys, there was an increase in the number of bla_{NDM} genes reported from patients with bacteraemia in 2022. This may be due to the return of international travel.

Increasing awareness of and utilization of antimicrobial stewardship, as part of the National Safety and Quality Health Service Standards implementation and accreditation Australia-wide,[15] may have reduced some resistance, particularly against ESBLs.

Future AGAR surveys will help determine if the observed reduction in resistance rates is sustained.

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Members of AGAR in 2022 were:

Australian Capital Territory

Peter Collignon and Susan Bradbury, Canberra Hospital

New South Wales

Alison Kesson and Andrew Jarrett, Children's Hospital Westmead

Thomas Gottlieb and John Huynh, Concord Hospital

Gabrielle O'Kane and Nola Hitchick, Gosford Hospital

Hemalatha Varadhan and Bree Harris, John Hunter Hospital

Michael Maley and Helen Ziochos, Liverpool Hospital

James Branley and Linda Douglass, Nepean Hospital

Angela Wong, Royal North Shore Hospital

Sebastiaan van Hal and Thomas Le, Royal Prince Alfred Hospital

David Lorenz, St Vincent's Hospital Sydney

Monica Lahra and Peter Huntington, Sydney Children's Hospital and Prince of Wales Hospital

Jonathan Iredell and Elena Martinez, Westmead Hospital

Peter Newton and Melissa Hoddle, Wollongong Hospital

Northern Territory

James McLeod, Alice Springs Hospital

Rob Baird and Jann Hennessy, Royal Darwin Hospital

Queensland

Claire Heney and Narelle George, Pathology Queensland Central Laboratory, Royal Brisbane and Women's Hospital, Queensland Children's Hospital

Petra Derrington and Cheryl Curtis, Pathology Queensland Gold Coast University Hospital

Robert Horvath and Laura Martin, Pathology Queensland Prince Charles Hospital

Naomi Runnegar and Joel Douglas, Pathology Queensland Princess Alexandra Hospital

Jennifer Robson and Marianne Allen, Sullivan Nicolaides Pathology, Greenslopes Private Hospital and Mater private Hospital Townsville

South Australia

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

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

Tasmania

Pankaja Kalukottege and Kathy Wilcox, Launceston General Hospital

Louise Cooley and David Jones, Royal Hobart Hospital

Victoria

Adam Jenney and Jacqueline Williams, Alfred Hospital

Marcel Leroi and Elizabeth Grabsch, Austin Health

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

Katherine Bond and Rose Cotronei, Royal Melbourne Hospital

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

Amy Crowe and Lisa Brenton, St Vincent's Hospital

Western Australia

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

Denise Daley, PathWest Laboratory Medicine WA, Fiona Stanley Hospital

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

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

Michael Leung, PathWest Laboratory Medicine WA, north-west regional WA

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

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

Author details

Ms Jan M Bell[1]

Dr Alicia Fajardo Lubian[2,3]

A/Prof Sally R Partridge[2,3,4]

A/Prof Thomas Gottlieb[3,5]

Dr Jennifer Robson[6]

Prof Jonathan R Iredell[2,3,4]

Ms Denise A Daley[7]

Prof Geoffrey W Coombs[8,9]

1. Australian Group on Antimicrobial Resistance, Adelaide, South Australia, Australia

2. Westmead Institute for Medical Research, Westmead, New South Wales, Australia

3. University of Sydney, New South Wales, Australia

4. Westmead Hospital, Westmead, New South Wales, Australia

5. Department of Microbiology and Infectious Diseases, Concord Hospital, Concord, New South Wales, Australia

6. Department of Microbiology, Sullivan Nicolaides Pathology, Bowen Hills, Queensland

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

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

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

Corresponding author

A/Prof Thomas Gottlieb

University of Sydney, New South Wales, Australia

Telephone: (02) 9767 7533

Email: thomas.gottlieb@health.nsw.gov.au

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