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Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Surveillance Outcome Program (GnSOP) Bloodstream Infection Annual Report 2023

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Annual report

Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Surveillance Outcome Program (GnSOP) Bloodstream Infection Annual Report 2023

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. From 1 January 2023 to 31 December 2023, a total of 57 hospitals across Australia participated in the Australian Gram-negative Surveillance Outcome Program (GnSOP).

The 2023 survey tested 10,453 isolates, comprising *Enterobacterales* (9,503; 90.9%), *P. aeruginosa* (806; 7.7%) and *Acinetobacter* species (144; 1.4%), using commercial automated methods. The results were analysed using European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (January 2024). Key resistances reported are to the third-generation cephalosporin ceftriaxone in 12.9% of *Escherichia coli* and in 6.9% of *Klebsiella pneumoniae* complex isolates. Resistance rates to ciprofloxacin were 14.5% for *E. coli*; 7.8% for the *K. pneumoniae* complex; 3.2% for the *Enterobacter cloacae* complex; and 7.6% for *P. aeruginosa*. Resistance rates to piperacillin-tazobactam were 6.0%; 9.4%; 23.3%; and 13.7% for the same four species/complexes, respectively. Thirty *Enterobacterales* isolates from 30 patients were shown to harbour a carbapenemase gene: ten with a bla_{NDM} gene (bla_{NDM-1} [4], bla_{NDM-5} [4], bla_{NDM-7} [2]); nine with a bla_{OXA-48}-like gene ($bla_{OXA-244}$ [4], bla_{OXA-48} [2], $bla_{OXA-181}$ [1], $bla_{OXA-232}$ [1], $bla_{OXA-484}$ [1]); eight with bla_{IMP-4}; two with bla_{NDM-5} + a $bla_{OXA-181}$-like gene; and one with bla_{KPC-2} + bla_{NDM-5} + $bla_{OXA-181}$. Transmissible carbapenemase genes were also detected in two *Acinetobacter baumannii* complex isolates (bla_{OXA-23}; bla_{OXA-23} + bla_{OXA-58} + bla_{IMP-4}) and one *P. aeruginosa* (bla_{IMP-4}).

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-reports.

importance, was added. *E. coli* is the most common cause of community-onset urinary tract infection, while *Klebsiella* species are less common but are known to harbour important resistance genes. *Enterobacter* species are less common in the community but are 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 multiresistance 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 2023 surveillance program were:

- to monitor resistance in *Enterobacterales*, *P. aeruginosa* and *Acinetobacter* species isolated from blood cultures taken from patients presenting to hospital or already inpatients 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 2023, thirty-three laboratories servicing 57 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. An episode was defined as community-onset (CO) if the first positive blood culture was collected 48 hours or less after admission, and as hospital-onset (HO) if collected greater than 48 hours after admission.

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-N435, AST-N410) or Phoenix NMIC-422 cards were utilised by all participants throughout the survey period. The EUCAST v14 breakpoints from January 2024 have been employed in the analysis.[1]

Multidrug resistance

The definitions used by Magiorakos et al. were applied in this survey,[2] where multidrug resistance (MDR) is defined as resistance to one or more agent in three or more antimicrobial categories. The antimicrobial categories (agents) included were 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 or cefuroxime); and aminopenicillins (ampicillin).

Antimicrobials were excluded from these counts for any species with a natural resistance mechanism. For *K. pneumoniae* complex, aminopenicillins were excluded, and for *E. cloacae* complex, cephamycins, non-extended spectrum cephalosporins and aminopenicillins were excluded.

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* and *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.

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 or the Australian Genome Research Facility (AGRF) using Illumina platforms. Data were analysed using a modification of the Nullarbor bioinformatic pipeline,[3] incorporating searching contigs against the NCBI AMRFinder database[ii] using ABRicate[4] and AMRFinder,[5] followed by a custom AMR-specific pipeline which includes a read-based search using ARIBA[6] against the CARD[7] and NCBI databases. Ambiguities and potential multiple gene copies/variants were checked manually by mapping reads to reference genes[iii] using Geneious. Kleborate[8] was used to screen *K. pneumoniae* complex species for virulence loci and K (capsule) serotype.

Results

The species isolated, and the numbers of each, are listed in Table 1. *Enterobacterales* accounted for 90.9%, followed by *P. aeruginosa* (7.7%) and *Acinetobacter* species (1.4%). In the *Enterobacterales*, 86.3% of all isolates belonged to three genera—*Escherichia* (60.1%), *Klebsiella* (20.3%) and *Enterobacter* (5.9%). Major resistances for the top six ranked species are listed in Table 2. For gram-negative species, 77.0% of all episodes were CO, with differences seen between *Enterobacterales* (78.7%), *Acinetobacter* species (63.9%) and *P. aeruginosa* (59.4%).

The activity of antimicrobial agents tested against *E. coli* and *K. pneumoniae* complex by place of onset are shown in Table 3.

A more detailed breakdown of resistance by state and territory is provided in the online GnSOP 2023 report.[iv]

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

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

iv www.agargroup.org.au/agar-reports.

Table 1: Number and proportion of species isolated, blood cultures, AGAR, 2023

Species	Percentage (*n*)	Onset setting, percentage (*n*)	
		Community onset	Hospital onset
Escherichia coli	54.6 (5,705)	84.3 (4,808)	15.7 (897)
Klebsiella pneumoniae complex	13.8 (1,442)	73.6 (1,061)	26.4 (381)
Pseudomonas aeruginosa	7.7 (806)	59.4 (479)	40.6 (327)
Enterobacter cloacae complex	5.3 (557)	54.0 (301)	46.0 (256)
Proteus mirabilis	3.4 (354)	81.9 (290)	18.1 (64)
Klebsiella oxytoca	3.0 (315)	70.5 (222)	29.5 (93)
Serratia marcescens	2.3 (242)	59.5 (144)	40.5 (98)
Klebsiella aerogenes	1.6 (166)	57.8 (96)	42.2 (70)
Salmonella species (non-typhoidal)	1.3 (140)	91.4 (128)	8.6 (12)
Citrobacter freundii complex	1.1 (112)	67.9 (76)	32.1 (36)
Morganella morganii	1.0 (106)	67.9 (72)	32.1 (34)
Salmonella species (typhoidal)	0.9 (90)	97.8 (88)	2.2 (2)
Acinetobacter baumannii complex	0.8 (87)	58.6 (51)	41.4 (36)
Citrobacter koseri	0.7 (74)	71.6 (53)	28.4 (21)
Raoultella ornithinolytica	0.3 (31)	61.3 (19)	38.7 (12)
Pantoea agglomerans	0.2 (22)	68.2 (15)	31.8 (7)
Acinetobacter species[a]	0.2 (21)	57.1 (12)	42.9 (9)
Proteus vulgaris	0.2 (20)	75.0 (15)	25.0 (5)
Providencia rettgeri	0.2 (18)	83.3 (15)	16.7 (3)
Hafnia alvei	0.2 (16)	50.0 (8)	50.0 (8)
Pantoea species[a]	0.1 (13)	69.2 (9)	30.8 (4)
Acinetobacter ursingii	0.1 (12)	83.3 (10)	16.7 (2)
Other species (total *n* = 38)	1.0 (94)	74.0 (77)	26.0 (27)
Total	**10,453**	**77.0 (8,049)**	**23.0 (2,404)**

a Species not determined.

Table 2: Resistance rates for the top six ranked gram-negative species isolated from blood, AGAR, 2023

Antimicrobial	Percentage resistant, EUCAST breakpoints (number)[a]					
	E. coli	*K. pneumoniae* complex	*P. aeruginosa*	*E. cloacae* complex	*P. mirabilis*	*K. oxytoca*
Ampicillin	52.3 (5,648)	*b*	na	*b*	18.7 (353)	*b*
Amoxicillin–clavulanic acid (2:1 ratio)[c]	9.4 (4,295)	3.9 (1,030)	na	*b*	4.6 (262)	2.6 (234)
Cefazolin	22.7 (4,921)	11.3 (1,246)	na	*b*	25.3 (289)	61.5 (244)
Cefepime	3.4 (5,646)	2.2 (1,428)	5.8 (787)	3.8 (555)	1.1 (353)	0.3 (312)
Ceftazidime	6.5 (5,647)	6.0 (1,428)	8.9 (790)	22.0 (555)	1.7 (351)	1.9 (312)
Ceftriaxone	12.9 (5,649)	6.9 (1,428)	na	25.0 (555)	2.0 (353)	7.4 (312)
Ciprofloxacin	14.5 (5,634)	7.8 (1,421)	7.6 (789)	3.2 (554)	3.3 (351)	0.6 (311)
Gentamicin	8.1 (5,645)	3.3 (1,427)	na	4.1 (555)	7.7 (352)	1.9 (312)
Meropenem	0.2 (5,649)	0.4 (1,427)	2.0 (789)	1.1 (554)	0.0 (362)	1.0 (312)
Nitrofurantoin	0.5 (4,902)	na	na	na	*b*	na
Piperacillin-tazobactam	6.0 (5,629)	9.4 (1,425)	13.7 (788)	23.3 (553)	0.0 (353)	12.5 (311)
Tobramycin	8.6 (5,616)	3.7 (1,414)	0.9 (786)	4.1 (543)	6.3 (352)	1.9 (308)
Trimethoprim[d]	32.6 (4,910)	16.8 (1,203)	na	14.2 (466)	21.5 (307)	5.6 (284)
Trimethoprim–sulfamethoxazole	29.5 (5,646)	13.7 (1,428)	na	13.2 (555)	17.3 (353)	5.1 (312)

a EUCAST: European Committee on Antimicrobial Susceptibility Testing; na: not applicable (testing not recommended).

b Considered largely intrinsically resistant.

c For susceptibility testing purposes, the Clinical and Laboratory Standards Institute (CLSI) uses a 2:1 ratio. EUCAST fixes the concentration of clavulanic acid at 2 mg/L; this formulation is only available on specific cards. Data for the CLSI formulation is shown.

d Breakpoints apply only to isolates from patients with uncomplicated urinary tract infection.

Table 3: Number and resistance rates for *Escherichia coli* and *Klebsiella pneumoniae* complex isolated from blood, by place of onset, AGAR, 2023

	Community-onset[a]			Hospital-onset[a]		
Species and antimicrobial	**No.**	**S-IE, %**	**R, %**	**No.**	**S-IE, %**	**R, %**
Escherichia coli						
Ampicillin	4,758	—[b]	50.8	890	—[b]	60.6
Amoxicillin-clavulanic acid (2:1 ratio)[c]	3,642	9.7[d]	7.2	653	8.1[d]	13.8
Piperacillin–tazobactam	4,743	—[b]	4.8	886	—[b]	12.0
Cefazolin	4,167	78.8	21.2	754	69.0	31.0
Cefuroxime	437	85.4	14.6	111	71.2	28.8
Ceftriaxone	4,759	0.1	12.0	890	0.1	17.8
Ceftazidime	4,757	7.4	5.7	890	9.8	10.8
Cefepime	4,757	6.2	2.8	889	7.5	6.3
Gentamicin	4,757	—[b]	7.9	888	—[b]	9.1
Tobramycin	4,735	—[b]	8.3	881	—[b]	10.1
Amikacin	4,757	—[b]	1.1	889	—[b]	2.1
Ciprofloxacin	4,746	5.0	13.9	888	5.3	17.7
Meropenem	4,759	0.0	0.1	890	0.3	0.4
***Klebsiella pneumoniae* complex**						
Amoxicillin–clavulanic acid (2:1 ratio)[c]	767	2.7[d]	2.1	263	5.3[d]	9.1
Piperacillin–tazobactam	1,046	—[b]	7.0	379	—[b]	16.1
Cefazolin	927	90.6	9.4	319	83.1	16.9
Cefuroxime	92	91.3	8.7	47	85.1	14.9
Ceftriaxone	1,049	0.2	6.3	379	0.0	8.4
Ceftazidime	1,049	1.2	5.2	379	4.0	7.9
Cefepime	1,049	3.4	1.7	379	3.4	3.7
Gentamicin	1,048	—[b]	3.0	379	—[b]	4.2
Tobramycin	1,042	—[b]	3.1	372	—[b]	5.6
Amikacin	1,049	—[b]	0.2	379	—[b]	1.3
Ciprofloxacin	1,043	3.5	6.9	378	5.0	10.3
Meropenem	1,049	0.0	0.4	378	0.3	0.5

a No.: number of isolates; S-IE: susceptible, increased exposure; R: resistant.

b No category defined.

c For susceptibility testing purposes, the Clinical and Laboratory Standards Institute (CLSI) uses a 2:1 ratio. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) fixes the concentration of clavulanic acid at 2 mg/L; this formulation is only available on specific cards. Data for the CLSI formulation is shown.

d Percentage sensitive dose dependent (CLSI breakpoints).

Escherichia coli

The moderately high levels of resistance to ampicillin (and therefore amoxicillin) observed in *E. coli* were similar to those in the 2022 survey (2023: 52.3% versus 2022: 51.5%). Resistance to third generation cephalosporins was also maintained compared with 2022 (ceftriaxone 2023: 12.9% versus 2022: 12.7%; ceftazidime 2023: 6.5% versus 2022: 5.9%). An extended spectrum β-lactamase (ESBL) phenotype was significantly more prevalent among HO than CO episodes of *E. coli* (21.6% versus 14.1%; $p < 0.01$). Moderate levels of resistance to cefazolin (22.7%) and trimethoprim–sulfamethoxazole (29.5%) were detected. Ciprofloxacin resistance was found in 14.5% of *E. coli* isolates, 0.8 percentage points higher than in the 2022 survey. Resistance to gentamicin (8.1%), piperacillin-tazobactam (6.0%) and cefepime (3.4%) was low. Twenty-two isolates (0.4%) had an elevated meropenem MIC (≥ 0.5 mg/L), up from ten isolates (0.2%) in 2022. For the isolates with an ESBL phenotype, 51.7% and 30.2% were resistant to ciprofloxacin and gentamicin, respectively. Almost one-quarter of *E. coli* isolates (24.5%) would be considered multi-drug resistant.

Most of the referred *E. coli* with an ESBL phenotype (753/791; 95.2%) harboured an Ambler class A ESBL gene (579/791; 76.9%), a plasmid borne class C gene (pAmpC) (133; 17.7%), or a carbapenemase gene alone (3; 0.4%); or an ESBL plus a pAmpC gene (29; 3.9%); or a carbapenemase gene plus either an ESBL gene or a pAmpC gene (9; 1.1%). $bla_{\text{CTX-M}}$ types continue to be the dominant β-lactamase genes in *E. coli*. Of 753 isolates with a confirmed β lactamase gene, 609 (80.9%) had one or more $bla_{\text{CTX-M}}$ genes detected by WGS, predominantly $bla_{\text{CTX-M-27}}$ ($n = 271$) or $bla_{\text{CTX-M-15}}$ ($n = 268$). *E. coli* with pAmpC harboured $bla_{\text{DHA-1}}$ (116/166; 69.9%) or a $bla_{\text{CMY-2}}$-like gene (50/166; 30.1%).

Klebsiella pneumoniae complex

K. pneumoniae complex isolates showed slightly higher levels of resistance to piperacillin-tazobactam compared with *E. coli*, but lower rates of resistance to cefazolin, ceftriaxone, ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole. An ESBL phenotype was higher among HO than CO episodes (12.4% versus 7.1%, $p < 0.01$). Twelve *K. pneumoniae* complex isolates (0.8%) had an elevated meropenem MIC (see below). Most of the referred *K. pneumoniae* complex isolates with an ESBL phenotype (97/110; 88.2%) harboured an ESBL gene (74; 76.3%), a pAmpC gene (16; 16.5%), or a carbapenemase gene (1; 1.0%) alone; or an ESBL gene and a pAmpC gene (2; 2.1%); or a carbapenemase gene with either an ESBL gene or a pAmpC gene (4; 4.1%). Almost all the ESBL genes (78/79; 98.7%) were $bla_{\text{CTX-M}}$ types, mostly $bla_{\text{CTX-M-15}}$ (64/78; 82.1%). *K. pneumoniae* complex isolates harboured either $bla_{\text{DHA-1}}$ (19/20; 95.0%) or a $bla_{\text{CMY-2}}$-like gene (1/20). In 2023, the proportion of *K. pneumoniae* complex isolates which would be considered multi-drug resistant was 8.9%.

In GnSOP 2023, twelve *K. pneumoniae* isolates (and one *K. oxytoca*) would be classified as hypervirulent (virulence score ≥ 3) by Kleborate.[8] Nine isolates had a K1 or K2 capsule serotype, the most common types in hypervirulent *K. pneumoniae* (hvKp). Five isolates were ST23-K1, already identified globally as a high-risk clone of hvKp carrying carbapenamase genes. Four of these had a virulence score of 5, with each carrying *ybt*, *clb* and *iuc*, but no ESBL or carbapenemase genes. One ST23-K1 isolate with a virulence score of 3 (*iuc* only) had $bla_{\text{CTX-M-15}}$.

Enterobacter cloacae complex

Acquired resistance was common among *E. cloacae* complex isolates, to piperacillin-tazobactam (23.3%), ceftriaxone (25.0%) or ceftazidime (22.0%). There was a moderate level of resistance to trimethoprim–sulfamethoxazole (13.2%); cefepime, ciprofloxacin and gentamicin resistance all remain at less than 5%. 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-two (4.0%) *E. cloacae* complex isolates had an elevated meropenem MIC. In 2023, the proportion of *E. cloacae* complex isolates that would be considered multi-drug resistant was 8.5%.

Carbapenemase genes

Overall, 33 isolates (33 patients) from 18 hospitals from six states/territories were found to harbour a carbapenemase gene. A bla_{NDM} gene was detected in ten isolates: five *E. coli* ($bla_{\text{NDM-5}}$ [4]; $bla_{\text{NDM-7}}$ [1]), two *K. pneumoniae* complex ($bla_{\text{NDM-1}}$), two *E. cloacae* complex ($bla_{\text{NDM-1}}$) and one *K. oxytoca* ($bla_{\text{NDM-7}}$). A $bla_{\text{OXA-48}}$-like gene was detected in nine isolates: seven *E. coli* ($bla_{\text{OXA-244}}$ [4]; $bla_{\text{OXA-48}}$ [2]; $bla_{\text{OXA-484}}$ [1]), one *K. oxytoca* ($bla_{\text{OXA-232}}$) and one *K. aerogenes* ($bla_{\text{OXA-232}}$). $bla_{\text{IMP-4}}$ was detected in nine isolates: *E. cloacae* complex (three), *E. coli* (two), *K. oxytoca* (one), *Citrobacter freundii* complex (one), *Serratia marcescens* (one), and *P. aeruginosa* (one). Other *Enterobacterales* had multiple carbapenemase genes: $bla_{\text{NDM-5}}$ + a $bla_{\text{OXA 181}}$-like gene (n = 2), or $bla_{\text{KPC-2}}$ + $bla_{\text{NDM-5}}$ + $bla_{\text{OXA-181}}$ (n = 1). $bla_{\text{OXA-23}}$ was detected in two *Acinetobacter baumannii* complex isolates, one of which also had $bla_{\text{OXA-58}}$ and $bla_{\text{IMP-4}}$.

Plasmid-borne colistin determinants

Two isolates with bla_{NDM} carbapenemase genes also harboured *mcr-9.1* (*E. cloacae* complex $bla_{\text{NDM-1}}$, *K. oxytoca* $bla_{\text{NDM-7}}$). Seven additional isolates (*E. cloacae* complex, n = 5; *E. coli*, n = 1; *K. oxytoca*, n = 1) that did not carry a carbapenemase gene had either *mcr-9* (n = 5) or *mcr-10* (n = 2). *mcr-9* has recently been found among several species of *Enterobacterales*. It is not associated with a resistant phenotype,[9] but is typically carried on HI2 plasmids.[10,11]

Discussion

AGAR has been tracking resistance in sentinel enteric gram-negative bacteria since 1992. From 2008, surveillance was separated into HO versus CO infections. The last year of HO-only surveillance was 2011.[12] 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.[13] The 2023 survey was the eleventh of antimicrobial resistance among *Enterobacterales*, and the ninth for *P. aeruginosa* and *Acinetobacter* spp. from bacteraemic patients through Australia.

The percentages of resistant *E. coli* in 2023 were similar to those seen in 2022 for all antimicrobial agents tested, except for trimethoprim-sulfamethoxazole, which increased slightly from 27.9% in 2022 to 29.5% in 2023. For the *K. pneumoniae* complex, the percentage of resistant isolates in 2023 was similar to that seen in 2022 for all antimicrobials, with slight increases (0.7 percentage point each) in resistance to both piperacillin-tazobactam and trimethoprim-sulfamethoxazole.

AGAR data show a longitudinal trend of increasing *E. coli* resistance to key anti-gram-negative antimicrobial agents, including ceftriaxone and ciprofloxacin. Resistance to both agents stabilised in 2018–2020 (ceftriaxone 13.3–13.4%, ciprofloxacin 15.2–16.1%); the levels of resistance declined to 12.5% and 12.3% respectively in 2021. In 2023, the level of resistance increased (12.9% and 14.5%). The steady rise in resistance to fluoroquinolones in *E. coli* is more striking in HO 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%; it increased slightly to 17.8% in 2022, and was 17.7% in 2023. 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% respectively, falling to 7.3% in 2021, and was at 7.8% in both 2022 and 2023.

Carbapenem resistance attributable to acquired carbapenemase genes is still uncommon in patients with bacteraemia in Australia. Seven different gene profiles (bla_{NDM} [10]; bla_{OXA-48}-like [9]; bla_{IMP-4} [9]; bla_{NDM-5} + $bla_{OXA\ 181}$-like [2]; bla_{KPC-2} + bla_{NDM-5} + $bla_{OXA-181}$ [1]; bla_{OXA-23} [1]; and bla_{OXA-23} + bla_{OXA-58} + bla_{IMP-4} [1]) were detected in 33 isolates from 18 of the participating hospitals. Compared with many other countries in our region, antimicrobial resistance rates in Australian gram-negative bacteria are still relatively low,[14,15] but similar to those observed in 2022 in many Northern European countries.[16,17] Resistance to third generation cephalosporins in *E. coli* from bacteraemic patients in Australia is similar to the European Union and European Economic Area average.[17] Rates of resistance in *K. pneumoniae* complex are low in Australia (< 10%) , compared to rates > 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 bla_{KPC}) and to the unregulated fluoroquinolone use compared to Australia where this antimicrobial class has been under greater usage scrutiny and regulation in both the human and animal husbandry sectors. Nonetheless this illustrates the potential for greater increases in resistance rates over time and the need for ongoing surveillance.

Just under one-fifth of *E. coli* would be classed as MDR, little changed from the 2022 survey. The proportion of *K. pneumoniae* complex isolates classed as MDR fell from 9.9% in 2019 and 2020 to 8.8% in 2021 and 8.0% in 2022. In 2023, the MDR proportion increased to 8.8%.

The impact of the SARS-CoV-2 pandemic on antimicrobial resistance may be due to a number of contributing factors. A combination of coronavirus disease 2019 (COVID-19)-related travel restrictions on incoming travellers throughout much of 2020 and 2021,[18] and an increasing awareness of and utilization of antimicrobial stewardship as part of the Australia-wide implementation and accreditation of National Safety and Quality Health Service Standards,[19] may have reduced some resistance rates particularly for ESBLs.

Compared to previous AGAR surveys, there was an increase in the number of bla_{NDM} genes reported in isolates from patients with bacteraemia in 2023.[20] This may be due to the return of international travel. In 2023, one-third (10/30, 33.3%) of all CPE carried a bla_{NDM} gene, 30.0% carried a bla_{OXA-48}-like gene (n = 9), 10.0% carried both bla_{NDM} and bla_{OXA-48}-like genes (n = 3), and 26.7% carried $bla_{IMP\ 4}$ (n = 8); the latter compared with 62.1% (18/29) CPE in 2022. More than three-quarters (23/30; 76.7%) of all CPE in 2023 were from New South Wales (n = 17; 56.7%) or Victoria (n = 6; 20.0%).

The 2023 survey suggests that there was a slight increase in resistance rates versus 2022 to pre-COVID-19 levels. Future AGAR surveys will help determine if this observed increase in resistance rates is sustained.

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