Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Sepsis Outcome Programme (GNSOP) Annual Report 2019

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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 2019 survey was the seventh year to focus on bloodstream infections, and included Enterobacterales, Pseudomonas aeruginosa and Acinetobacter species.

Eight thousand eight hundred and fifty-seven isolates, comprising Enterobacterales (7,983; 90.1%), P. aeruginosa (764; 8.6%) and Acinetobacter species (110; 1.2%), were tested 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 2020). Of the key resistances, resistance to the third-generation cephalosporin ceftriaxone was found in 13.3%/13.3% (CLSI/EUCAST criteria) of Escherichia coli and 8.4%/8.4% of Klebsiella pneumoniae. Resistance rates to ciprofloxacin were 16.0%/16.0% for E. coli, 10.2%/10.2% for K. pneumoniae complex, 5.9%/5.9% for Enterobacter cloacae complex, and 4.1%/9.3% for P. aeruginosa. Resistance rates to piperacillin-tazobactam were 3.2%/5.7%, 4.7%/8.5%, 14.8%/21.4%, and 6.9%/12.5% for the same four species/complex respectively. Twenty-nine isolates from 29 patients were shown to harbour a carbapenemase gene: 15 blaIMP-4*, five blaOXA-181*, four blaOXA-23 (one with blaOXA-58 also), three blaNDM-4/5*, one blaGES-5* and one blaIMP-1*. Keywords: Australian Group on Antimicrobial Resistance (AGAR); antibiotic resistance; bacteraemia; gram-negative; Escherichia coli; Enterobacter; Klebsiella

Introduction

Emerging antimicrobial resistance (AMR) in common pathogenic members of the Enterobacterales is a world-wide phenomenon and presents therapeutic problems for practitioners, 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 have been conducted biennially until 2008 when annual surveys commenced, alternating between community- and hospital-onset infections. In 2004, another genus of gram-negative pathogens in which resistance can be of clinical importance, Enterobacter species, was added. E. 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 impor-
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tance due to intrinsic resistance to first-line antimicrobials used in the community. Taken together, the three groups of species surveyed are considered to be valuable sentinels for multi-resistance and emerging resistance in enteric gram-negative bacilli. In 2013 AGAR commenced the Enterobacteriaceae Sepsis Outcome Programme (EnSOP) which focused on the collection of resistance and some demographic data on all isolates prospectively from patients with bacteraemia. In 2015, *Pseudomonas aeruginosa* and *Acinetobacter* species were added, and the program has been referred to since that date as the Gram-negative Sepsis Outcome Program (GNSOP).

Resistances of particular interest include resistance to β-lactams due to β-lactamases, especially extended-spectrum β-lactamases (ESBLs), which inactivate the third-generation cephalosporins that are normally considered reserve antimicrobials. Other resistances of interest are to agents important for treatment of these serious infections, such as gentamicin; and resistance to reserve agents such as ciprofloxacin, meropenem and colistin.

The objectives of the 2019 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;
- Examine the extent of co-resistance and multidrug resistance in the major species;
- Detect emerging resistance to newer last-line agents such as carbapenems and colistin; and
- Examine the molecular basis of resistance to third-generation cephalosporins, quinolones and carbapenems.

### Methods

#### Study design

From 1 January to 31 December 2019, 39 institutions across Australia collected either all or up to 200 isolates from different patient episodes of bacteraemia.

#### Species identification

Isolates were identified using the routine method for 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 ISO reference standard method of broth microdilution. Commercially available Vitek AST-N246, or Phoenix NMIC-404 and NMIC-422 cards were utilized by all participants throughout the survey period. The CLSI M100 and EUCAST v10.0 breakpoints from January 2020 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 was 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.

#### PCR screening and whole genome sequencing

*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;
Enterobacterales with ciprofloxacin MIC > 0.25 mg/L; Enterobacterales with meropenem MIC > 0.25 mg/L; 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 were referred to a central laboratory (Centre for Infectious Diseases and Microbiology, The Westmead Institute for Medical Research) and underwent polymerase chain reaction (PCR) to detect selected resistance genes (Centre for Infectious Diseases & Microbiology Laboratory Services, ICPMR, Westmead Hospital) and/or whole genome sequencing (WGS) (Antimicrobial Resistance Laboratory, Microbial Genomics Reference Laboratory, CIDMLS, ICPMR, Westmead Hospital).

All referred isolates, except P. aeruginosa, Acinetobacter spp., Salmonella spp., and Enterobacterales with meropenem MIC > 0.25 mg/L which underwent WGS, were screened using real-time multiplex PCR using published primers to detect ESBLs (bla<sub>SHV-ESBL</sub> with G→A substitution at position 700 and/or 703, bla<sub>CTX-M</sub> groups 1 and 9, bla<sub>VEB</sub>), plasmid-borne AmpC (bla<sub>CMY-2-like</sub>, bla<sub>DHA</sub>) and carbapenemase (bla<sub>IMP</sub>, bla<sub>NDM</sub>, bla<sub>VIM</sub>) genes. Assays for other ESBL targets (bla<sub>ACT/MIR</sub>, bla<sub>KPC</sub>, bla<sub>OXA-48-like</sub>, bla<sub>GES</sub>, bla<sub>SM</sub>, bla<sub>AIM</sub>, bla<sub>GIM</sub>, bla<sub>SIM</sub>, bla<sub>OXA-23/24/58</sub>); aminoglycoside ribosomal methyltransferases (armA, rmtA, rmtB, rmtC, rmtD, rmtE, rmtF, rmtG, rmtH); and mobile colistin resistance genes (mcr-1, mcr-2, mcr-3, mcr-4, mcr-5) were detected using in-house, NATA-accredited primers and probes in routine use by the Centre for Infectious Diseases & Microbiology Laboratory Services, ICPMR, at Westmead Hospital.

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, CIDMLS, ICPMR, Westmead Hospital using the Illumina NextSeq 500 platform. Data were analysed using a modification of the Nullarbor bioinformatic pipeline, incorporating searching contigs against the NCBI AMRFinder database using ABRicate and AMRFinder, followed by a custom AMR-specific pipeline which includes a read-based search using ARIBA against the CARD and NCBI databases.

## Results

The species isolated, and the numbers of each by onset setting, are listed in Table 1. Enterobacterales accounted for 90.1%, followed by P. aeruginosa (8.6%) and Acinetobacter species (1.2%). Of the Enterobacterales, three genera—Escherichia (61.6%), Klebsiella (19.8%) and Enterobacter (5.5%)—contributed 86.9% of all isolates. Major resistances and non-susceptibilities for the top six ranked species are listed in Table 2. Non-susceptibility (which includes both intermediate and resistant isolates) has been included for some agents because these figures provide information about important emerging acquired resistances. Multiple acquired resistances by species are shown in Table 3. Multi-resistance was detected in 26.0% of E. coli isolates, 11.8% of K. pneumoniae complex, and 7.3% of E. cloacae complex. A more detailed breakdown of resistances and non-susceptibilities by state and territory is provided in the online AGAR report.

### Escherichia coli

Moderately high levels of resistance to ampicillin (and therefore amoxicillin) were maintained (54.4%/56.3%, CLSI/EUCAST criteria), with lower rates for amoxicillin-clavulanic acid (14.8%–intermediate, 7.8%–resistant). Non-susceptibility to third generation cephalosporins was maintained at similar levels to the 2018 survey (ceftriaxone 13.4%/13.4%, ceftazidime 7.1%/13.0%). Moderate levels of resistance were detected to cefazolin (17.0%/24.0%) and trimethoprim–sulfamethoxazole (30.9%/30.9%). Ciprofloxacin non-susceptibility was found in 19.5%/19.5% of E. coli isolates. Resistance to

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<sup>ii</sup> https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047.
Table 1. Number and proportion of species isolated, by onset setting, blood cultures, 2019

| Species                          | Percentage (n) | Onset setting percentage (n) |
|----------------------------------|----------------|------------------------------|
|                                 |                | Community onset | Hospital onset |
| *Escherichia coli*               | 55.5 (4,914)   | 83.3 (4,093)     | 16.7 (821)     |
| *Klebsiella pneumoniae* complex  | 13.5 (1,193)   | 73.0 (871)       | 27.0 (322)     |
| *Pseudomonas aeruginosa*         | 8.6 (764)      | 56.2 (429)       | 43.8 (335)     |
| *Enterobacter cloacae* complex   | 4.8 (427)      | 57.4 (245)       | 42.6 (182)     |
| *Proteus mirabilis*              | 3.0 (267)      | 84.3 (225)       | 15.7 (42)      |
| *Klebsiella oxytoca*             | 2.7 (239)      | 72.4 (173)       | 27.6 (66)      |
| *Serratia marcescens*            | 2.4 (214)      | 48.1 (103)       | 51.9 (111)     |
| *Klebsiella aerogenes*           | 1.5 (129)      | 62.0 (80)        | 38.0 (49)      |
| *Salmonella species* (non-typhoidal) | 1.4 (127) | 96.1 (122)       | 3.9 (5)        |
| *Morganella morganii*            | 1.1 (96)       | 68.8 (66)        | 31.3 (30)      |
| *Salmonella species* (typhoidal) | 0.9 (82)       | 100.0 (82)       | 0.0 (0)        |
| *Citrobacter freundii* complex   | 0.9 (77)       | 68.8 (53)        | 31.2 (24)      |
| *Acinetobacter baumannii* complex| 0.7 (62)      | 56.5 (35)        | 43.5 (27)      |
| *Citrobacter koseri*             | 0.7 (62)       | 72.6 (45)        | 27.4 (17)      |
| *Raoultella ornithinolytica*     | 0.2 (20)       | 90.0 (18)        | 10.0 (2)       |
| *Klebsiella*                     | 0.2 (19)       | 73.7 (14)        | 26.3 (5)       |
| *Acinetobacter*                  | 0.2 (14)       | 64.3 (9)         | 35.7 (5)       |
| *Acinetobacter ursingii*         | 0.1 (13)       | 69.2 (9)         | 30.8 (4)       |
| *Providencia rettgeri*           | 0.1 (13)       | 76.9 (10)        | 23.1 (3)       |
| *Acinetobacter lwoffii*          | 0.1 (12)       | 75.0 (9)         | 25.0 (3)       |
| *Pantoea agglomerans*            | 0.1 (12)       | 83.3 (10)        | 16.7 (2)       |
| *Enterobacter*                   | 0.1 (11)       | 90.9 (10)        | 9.1 (1)        |
| Other species (total n = 33)     | 1.0 (90)       | 72.2 (65)        | 27.8 (25)      |
| **Total**                        | **8,857**      | **76.5 (6,776)** | **23.5 (2,081)** |

**gentamicin (9.0%/9.5%), piperacillin-tazobactam (3.2%/5.7%) and cefepime (3.2%/4.1%) was low.** Fifteen isolates (0.3%) had elevated meropenem MICs (≥ 0.5 mg/L). For the strains with ESBL phenotype, ciprofloxacin and gentamicin resistance was found in 64.8%/64.8% and 34.2%/34.9% respectively.

Most of the referred *E. coli* with an ESBL phenotype (580/674, 86.1%) harboured Ambler class A ESBL (489/580, 84.3%), plasmid borne class C (pAmpC) (76, 13.1%) or both ESBL and pAmpC (15, 2.6%) genes. Almost all with an ESBL gene (497/504, 98.6%) had *bla*<sub>CTX-M</sub> types: *bla*<sub>CTX-M</sub> group 9 (*n* = 249), *bla*<sub>CTX-M</sub> group 1 (*n* = 246) or both (*n* = 2). *E. coli* with pAmpC harboured mostly *bla*<sub>DHA</sub> (51/91, 56%) or *bla*<sub>CMY-2</sub>-like (37/91, 41%) genes or both (*n* = 3).

*Klebsiella pneumoniae complex*  
*K. pneumoniae* complex showed slightly higher levels of resistance to piperacillin-tazobactam than did *E. coli*, but lower rates of resistance to
Table 2. Non-susceptibility and resistance rates for the top six ranked species tested, 2019

| Antimicrobial                          | Category | E. coli (%)(a) | K. pneumoniae complex (%) | P. aeruginosa (%)(a) | E. cloacae complex (%)(a) | P. mirabilis (%)(a) | K. oxytoca (%)(a) |
|----------------------------------------|----------|---------------|--------------------------|----------------------|--------------------------|-------------------|------------------|
|                                        |          | CLSI          | EUCAST                   | CLSI                 | EUCAST                   | CLSI              | EUCAST           |
| Ampicillin                              | I        | 1.9           | —                        | b                    | b                        | na                | na               |
|                                        | R        | 54.4          | 56.3                     | b                    | b                        | b                 | 0.0              |
|                                        |          |               |                          |                      |                          |                   |                  |
| Amoxicillin-clavulanic acid (2:1)(c)    | I        | 14.8          | c                        | 5.2                  | c                        | na                | na               |
|                                        | R        | 7.8           | c                        | 6.7                  | c                        | na                | b                |
|                                        |          |               |                          |                      |                          |                   |                  |
| Piperacillin-tazobactam                 | R        | 3.2           | 5.7                      | 4.7                  | 8.5                      | 6.9              | 12.5             |
|                                        |          |               |                          |                      |                          | 14.8             | 21.4             |
|                                        |          |               |                          |                      |                          | 0.0              | 0.0              |
|                                        |          |               |                          |                      |                          | 79               | 9.2              |
| Cefazolin                               | R        | 17.0          | 24.0                     | 11.4                 | 13.0                     | 2.1              | 16.8             |
|                                        |          |               |                          |                      |                          |                   | 24.7             |
|                                        |          |               |                          |                      |                          |                   | 56.3             |
| Cefoxitin                               | R        | 3.4           | /                        | 5.9                  | /                        | na                | na               |
|                                        |          |               |                          |                      |                          |                   | b                |
|                                        |          |               |                          |                      |                          |                   | 0.4              |
|                                        |          |               |                          |                      |                          |                   | 0.4              |
| Ceftriaxone                             | NS       | 13.4          | 13.4                     | 8.7                  | 8.7                      | 24.1             | 24.1             |
|                                        |          |               |                          |                      |                          | 1.5              | 1.5              |
|                                        |          |               |                          |                      |                          |                   | 7.6              |
|                                        |          |               |                          |                      |                          |                   | 7.6              |
| Ceftazidime                             | NS       | 7.1           | 13.0                     | 7.2                  | 9.7                      | 9.0              | 9.0             |
|                                        |          |               |                          |                      |                          | 21.5             | 24.1             |
|                                        |          |               |                          |                      |                          | 0.4              | 0.8              |
|                                        |          |               |                          |                      |                          |                   | 1.3              |
|                                        |          |               |                          |                      |                          |                   | 3.0              |
| Cefepime                                | NS       | 5.3           | 10.7                     | 3.7                  | 7.0                      | 5.8              | 5.8             |
|                                        |          |               |                          |                      |                          | 4.5              | 10.0             |
|                                        |          |               |                          |                      |                          | 1.1              | 1.1              |
|                                        |          |               |                          |                      |                          |                   | 0.4              |
|                                        |          |               |                          |                      |                          |                   | 1.3              |
| Meropenem                               | NS       | 0.2           | 0.1                      | 1.1                  | 0.9                      | 7.2              | 7.2              |
|                                        |          |               |                          |                      |                          | 2.6              | 2.1              |
|                                        |          |               |                          |                      |                          | 0.8              | 0.4              |
|                                        |          |               |                          |                      |                          |                   | 0.0              |
|                                        |          |               |                          |                      |                          |                   | 0.0              |
| Ciprofloxacin                           | NS       | 19.5          | 19.5                     | 11.5                 | 11.5                     | 9.3              | 9.3             |
|                                        |          |               |                          |                      |                          | 7.1              | 7.1              |
|                                        |          |               |                          |                      |                          | 2.3              | 2.3              |
|                                        |          |               |                          |                      |                          |                   | 1.7              |
|                                        |          |               |                          |                      |                          |                   | 1.7              |
| Gentamicin                              | R        | 9.0           | 9.5                      | 5.1                  | 5.4                      | 0.9              | na               |
|                                        |          |               |                          |                      |                          | 4.9              | 6.1              |
|                                        |          |               |                          |                      |                          | 1.1              | 11.7             |
|                                        |          |               |                          |                      |                          |                   | 0.4              |
|                                        |          |               |                          |                      |                          |                   | 0.4              |
| Trimethoprim–sulfamethoxazole           | R        | 30.9          | 30.9                     | 16.3                 | 16.1                     | 16.9             | 16.9             |
|                                        |          |               |                          |                      |                          | 15.8             | 15.8             |
|                                        |          |               |                          |                      |                          | 5.0              | 5.0              |
| Nitrofurantoin                          | R        | 0.9           | 0.9                      | 30.5                 | /                        | na               | na               |
|                                        |          |               |                          |                      |                          |                   | 11.9             |
|                                        |          |               |                          |                      |                          |                   | b                |
|                                        |          |               |                          |                      |                          |                   | b                |
|                                        |          |               |                          |                      |                          |                   | 0.9              |
|                                        |          |               |                          |                      |                          |                   | /                |

– no intermediate category; / no breakpoints defined; na = not applicable (testing not recommended).

a R = resistant, I = intermediate, NS = non-susceptible (intermediate + resistant), using criteria as published by CLSI [2020] and EUCAST [2020].
b Considered largely intrinsically resistant.
c For EUCAST interpretation, the clavulanic acid concentration is fixed at 2 mg/L, rather than the 2:1 ratio of amoxicillin to clavulanic acid used in CLSI guidelines. As all susceptibility test cards used have a 2:1 ratio of amoxicillin to clavulanic acid no EUCAST category has been applied.
d Percent resistant.
| Species                        | Total | Non-multi-resistant | Cumulative | Multi-resistant |
|-------------------------------|-------|---------------------|------------|-----------------|
|                               |       |                     |            | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | Cumulative |
|                               |       | 0      | 1      | 2  | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  |          |
| Escherichia coli              | 4,358 | 1,720  | 762    | 744 | 312 | 274 | 290 | 159 | 64  | 26  | 6   | 1   | 26.0     |
| %                             |       | 39.5   | 17.5   | 17.1 | 74.0 | 7.2 | 6.3 | 6.7 | 3.6 | 1.5 | 0.6 | 0.1 | 0.0       |
| Klebsiella pneumoniae complex | 1,064 | 794    | 91     | 53  | 74.6 | 23  | 28  | 31  | 20  | 12  | 8   | 4   | na        |
| %                             |       | 74.6   | 8.6    | 5.0  | 88.2 | 2.2 | 2.6 | 2.9 | 1.9 | 1.1 | 0.8 | 0.4 | 11.8     |
| Enterobacter cloacae complex  | 358   | 234    | 41     | 57  | 65.4 | 5   | 12  | 6   | 3   | na  | na  | na  | na        |
| %                             |       | 65.4   | 11.5   | 15.9 | 92.7 | 1.4 | 3.4 | 1.7 | 0.8 |     |     |     | 7.3       |
| Proteus mirabilis             | 235   | 162    | 40     | 15  | 68.9 | 3.4 | 2.1 | 0.9 | 0.9 | 0.0 | 0.4 | 0.0 | 0.0       |
| %                             |       | 68.9   | 17.0   | 6.4  | 92.3 | 3.4 | 2.1 | 0.9 | 0.9 | 0.0 | 0.4 | 0.0 | 0.0       |
| Klebsiella oxytoca            | 215   | 90     | 94     | 15  | 41.9 | 5   | 7   | 3   | 0   | 0   | 1   | 0   | na        |
| %                             |       | 41.9   | 43.7   | 7.0  | 92.6 | 2.3 | 3.3 | 1.4 | 0.0 | 0.0 | 0.5 | 0.0 | 7.4       |
| Salmonella species (non-typhoidal) | 119 | 109    | 7      | 2   | 91.6 | 0   | 0   | 0   | 1   | 0   | 0   | 0   | na        |
| %                             |       | 91.6   | 5.9    | 1.7  | 99.2 | 0.0 | 0.0 | 0.0 | 0.8 | 0.0 | 0.0 | 0.0 | 0.8       |
| Serratia marcescens           | 159   | 49     | 76     | 28  | 30.8 | 1   | 4   | 1   | 0   | 0   | na  | na  | na        |
| %                             |       | 30.8   | 47.8   | 17.6 | 96.2 | 0.6 | 2.5 | 0.6 | 0.0 | 0.0 |     |     | 3.8       |
| Klebsiella aerogenes          | 115   | 71     | 3      | 39  | 61.7 | 1   | 1   | 0   | 0   | na  | na  | na  | na        |
| %                             |       | 61.7   | 2.6    | 33.9 | 98.3 | 0.9 | 0.9 | 0.0 | 0.0 |     |     |     | 1.7       |

Table 3. Multiple acquired resistances by species, 2019

a Antimicrobial categories (agents) included: aminoglycosides (gentamicin or tobramycin or amikacin), antipseudomonal penicillins + β-lactamase inhibitor (piperacillin–tazobactam), carbapenems (meropenem), non-extended cephalosporins (cefazolin), extended-spectrum cephalosporins (ceftriaxone or ceftazidime or cefepime), cephamycins (cefoxitin), fluoroquinolones (ciprofloxacin), folate pathway inhibitors (trimethoprim–sulfamethoxazole), penicillins (ampicillin), and penicillins + β-lactamase inhibitor (amoxicillin-clavulanic acid, CLSI), na = not applicable.
b Antimicrobial categories excluded: penicillins.
c Antimicrobial categories excluded: penicillins, non-extended cephalosporins, cephamycins, penicillins + β-lactamase inhibitor.
d Antimicrobial categories excluded: aminoglycosides.
e Antimicrobial categories excluded: penicillins, non-extended cephalosporins, penicillins + β-lactamase inhibitor.
amoxicillin-clavulanic acid, cefazolin, ceftriaxone, ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole. Twenty-one K. pneumoniae complex isolates (1.8%) had elevated meropenem MICs (see below). A substantial majority of the referred K. pneumoniae complex with an ESBL phenotype (92/118; 78.0%) harboured ESBL (76/72; 86.1%). A substantial majority of the K. pneumoniae complex with pAmpC harboured bla<sub>DHA</sub> (13/16; 81%).

**Enterobacter cloacae complex**

Acquired resistance was common among E. cloacae complex isolates, to piperacillin-tazobactam (14.8%/21.4%) ceftriaxone (23.4%/23.4%), ceftazidime (21.3%/21.5%) and trimethoprim-sulfamethoxazole (16.9%/16.9%). Cefepime, ciprofloxacin and gentamicin resistance remain at less than 10%. Seventeen (4.0%) E. cloacae complex isolates had elevated meropenem MICs.

**Carbapenemases**

Overall, 29 isolates (29 patients) in fourteen institutions from four states/territories were found to harbour a carbapenemase gene. bla<sub>IMP-4</sub> was detected in 15 isolates: K. pneumoniae (five), E. cloacae (five), E. hormaechei (three), one K. variicola, and one E. coli. bla<sub>NDM-4</sub> was detected in five K. pneumoniae. bla<sub>NDM-5</sub> was detected in two K. pneumoniae and in one E. coli. bla<sub>NDM-5</sub> was detected in three A. baumannii, one of which also harboured bla<sub>NDM</sub> and one Proteus mirabilis. Among Pseudomonas aeruginosa, one bla<sub>GES-5</sub> and one bla<sub>IMP-1</sub> were detected. Just over one quarter of the carbapenemase-producing organisms were from one institution.

**Discussion**

AGAR has been tracking resistance in sentinel enteric gram-negative bacteria since 1992. From 2008, surveillance was segregated into hospital-versus community-onset infections. The last year of hospital-onset only surveillance was 2011. In 2013, the first survey of antimicrobial resistance among Enterobacterales isolates from bacteraemic patients throughout Australia was conducted using an approach similar to that conducted by the European EARS-Net program. 2019 was the seventh survey of antimicrobial resistance among Enterobacterales, and the fifth for P. aeruginosa and Acinetobacter spp. from bacteraemic patients through Australia.

Relative to 2018, the percentage resistance in E. coli declined for almost two-thirds (7/11; 60%) of the antimicrobial agents tested, and for K. pneumoniae complex by half (5/10). AGAR data show a longitudinal trend of increasing E. coli resistance to key anti-gram-negative antimicrobial agents, such as ceftriaxone and ciprofloxacin. The steady rise in resistance to fluoroquinolones is more striking in hospital-onset bacteremia, with a change from 13.7% to 21.3% between 2013 and 2019.

Carbapenem resistance attributable to acquired carbapenemase genes is still uncommon in patients with bacteremia in Australia, although five different types (IMP, NDM, OXA-48-like, OXA-23, and GES-5) were detected in isolates from fourteen of the participating institutions. Compared with many other countries in our region, resistance rates in Australian gram-negative bacteria are still relatively low, but similar to those observed in 2018 in many Northern European countries. Resistance to third generation cephalosporins in E. coli from bacteraemic patients in Australia is similar to the European Union and European Economic Area average.

One quarter of E. coli and 12% of K. pneumoniae complex were multi-resistant. This is likely to drive more broad-spectrum antibiotic use and increase the resistance selection pressure for important reserve classes, especially the carbapenems.
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Members of AGAR in 2019 were:

**Australian Capital Territory**
- Peter Collignon and Susan Bradbury, Canberra Hospital

**New South Wales**
- Thomas Gottlieb and Steven Siarakis, Concord Hospital
- Rodney Givney and Kimberly Ross, John Hunter Hospital
- Michael Maley and Helen Ziochos, Liverpool Hospital
- James Branley and Linda Douglass, Nepean Hospital
- Angela Wong, Royal North Shore Hospital

**Queensland**
- Monica Lahra and Peter Huntington, Sydney Children’s Hospital
- Jon Iredell and Andrew Ginn, Westmead Hospital
- Peter Newton and Melissa Hoddle, Wollongong Hospital
- James McLeod, Alice Springs Hospital
- Rob Baird and Jann Hennessy, Royal Darwin Hospital
- Enzo Binotto and Bronwyn Thomsett, Pathology Queensland Cairns Base Hospital
- Graeme Nimmo and Narelle George, Pathology Queensland Central Laboratory, Royal Brisbane and Women’s Hospital
- Clare Nourse, Pathology 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 Georgia Peachey, Sullivan Nicolaides Pathology

**Northern Territory**
- Jock Harkness and David Lorenz, St Vincent’s Hospital Sydney
- Monica Lahra and Peter Huntington, Sydney Children’s Hospital

**South Australia**
- Sebastiaan van Hal and Alicia Beukers, Royal Prince Alfred Hospital
- Kelly Papanoum 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

Denis Spelman and Chris Lee, Alfred Hospital

Marcel Leroi and Elizabeth Grabsch, Austin Health

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

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

Mary Jo Waters and Lisa Brenton, St Vincent’s Hospital

Western Australia

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

David McGechie and Denise Daley, PathWest Laboratory Medicine WA, Fiona Stanley Hospital

Chris 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, Northwest WA

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

Sudha Pottumarthy-Boddu and Fay Kappler, Australian Clinical Laboratories, St John of God Hospital Murdoch

Author details

Ms Jan M Bell

Dr Alicia Fajardo Lubian

A/Prof Sally Partridge

A/Prof Thomas Gottlieb

Prof Jonathan Iredell

Ms Denise A Daley

Prof Geoffrey W Coombs

1. University of Adelaide, Adelaide, South Australia, Australia

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

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

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

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