Communicable Diseases Intelligence
Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Surveillance Outcome Program (GnSOP)
Bloodstream Infection Annual Report 2022

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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 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%/7.8% for E. coli; 7.8%/7.8% for K. pneumoniae complex; 5.3%/5.3% for Enterobacter cloacae complex; 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. In 2004 Enterobacter, another genus of gram-negative pathogens in which resistance can be of clinical
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 northwest 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, incorporating searching contigs against the NCBI AMRFinder database

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.

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

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

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

<sup>a</sup>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

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Category*</th>
<th>CLSIb</th>
<th>EUCASTb</th>
<th>CLSIb</th>
<th>EUCASTb</th>
<th>CLSIb</th>
<th>EUCASTb</th>
<th>CLSIb</th>
<th>EUCASTb</th>
<th>CLSIb</th>
<th>EUCASTb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin-clavulanic acid (2:1)</td>
<td>R</td>
<td>50.0</td>
<td>51.5</td>
<td>c</td>
<td>c</td>
<td>na</td>
<td>na</td>
<td>c</td>
<td>c</td>
<td>15.8</td>
<td>16.4</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>R</td>
<td>7.4</td>
<td>d</td>
<td>3.2</td>
<td>d</td>
<td>na</td>
<td>na</td>
<td>c</td>
<td>c</td>
<td>3.2</td>
<td>7.4</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>R</td>
<td>2.8</td>
<td>5.9</td>
<td>2.9</td>
<td>8.7</td>
<td>6.1</td>
<td>14.7</td>
<td>18.3</td>
<td>27.2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>R</td>
<td>22.2</td>
<td>22.2</td>
<td>10.1</td>
<td>10.1</td>
<td>na</td>
<td>na</td>
<td>c</td>
<td>c</td>
<td>17.7</td>
<td>17.7</td>
</tr>
<tr>
<td>Cephalosporin (2)</td>
<td>NS</td>
<td>6.7</td>
<td>6.6</td>
<td>na</td>
<td>na</td>
<td>28.8</td>
<td>28.4</td>
<td>1.9</td>
<td>1.2</td>
<td>6.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>NS</td>
<td>3.9</td>
<td>3.1</td>
<td>2.7</td>
<td>2.2</td>
<td>6.2</td>
<td>6.2</td>
<td>5.5</td>
<td>3.4</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Meropenem</td>
<td>NS</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
<td>0.8</td>
<td>0.5</td>
<td>5.9</td>
<td>4.3</td>
<td>2.7</td>
<td>2.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>NS</td>
<td>17.4</td>
<td>13.7</td>
<td>9.9</td>
<td>7.8</td>
<td>10.0</td>
<td>10.0</td>
<td>6.3</td>
<td>5.3</td>
<td>4.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>R</td>
<td>7.9</td>
<td>8.3</td>
<td>3.0</td>
<td>3.4</td>
<td>na</td>
<td>na</td>
<td>5.5</td>
<td>6.1</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>R</td>
<td>2.4</td>
<td>8.6</td>
<td>1.4</td>
<td>4.1</td>
<td>0.4</td>
<td>0.7</td>
<td>3.7</td>
<td>6.7</td>
<td>1.9</td>
<td>3.7</td>
</tr>
<tr>
<td>Trimethoprim–sulfamethoxazole</td>
<td>R</td>
<td>28.0</td>
<td>27.9</td>
<td>13.0</td>
<td>12.9</td>
<td>na</td>
<td>na</td>
<td>17.6</td>
<td>17.6</td>
<td>13.6</td>
<td>13.6</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>R</td>
<td>0.5</td>
<td>0.5</td>
<td>27.6</td>
<td>/</td>
<td>na</td>
<td>na</td>
<td>11.4</td>
<td>/</td>
<td>c</td>
<td>c</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Species</th>
<th>Total</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>Cumulative %</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli</strong></td>
<td>5,181</td>
<td>2,262</td>
<td>923</td>
<td>782</td>
<td>43.7</td>
<td>7.7</td>
<td>6.8</td>
<td>5.9</td>
<td>1.9</td>
<td>0.8</td>
<td>0.3</td>
<td>&lt;0.1</td>
<td>23.4</td>
</tr>
<tr>
<td><strong>K. pneumoniae complex</strong></td>
<td>1,366</td>
<td>1,066</td>
<td>105</td>
<td>86</td>
<td>78.0</td>
<td>2.4</td>
<td>2.1</td>
<td>1.0</td>
<td>1.8</td>
<td>0.4</td>
<td>0.3</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td><strong>E. cloacae complex</strong></td>
<td>467</td>
<td>279</td>
<td>50</td>
<td>99</td>
<td>59.7</td>
<td>2.6</td>
<td>3.2</td>
<td>1.5</td>
<td>1.1</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td><strong>P. mirabilis</strong></td>
<td>322</td>
<td>247</td>
<td>35</td>
<td>28</td>
<td>76.7</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>na</td>
<td>na</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>K. oxytoca</strong></td>
<td>295</td>
<td>242</td>
<td>30</td>
<td>21</td>
<td>82.0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>na</td>
<td>na</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Salmonella species (non-typhoidal)</strong></td>
<td>96</td>
<td>82</td>
<td>9</td>
<td>2</td>
<td>85.4</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>S. marcescens</strong></td>
<td>212</td>
<td>64</td>
<td>113</td>
<td>25</td>
<td>30.2</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>K. aerogenes</strong></td>
<td>129</td>
<td>76</td>
<td>9</td>
<td>39</td>
<td>58.9</td>
<td>2</td>
<td>1.6</td>
<td>0.0</td>
<td>0.0</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>3.9</td>
</tr>
</tbody>
</table>

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**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 β-lactamase 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. cloa- cae* 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. cloa- cae* 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. cloa- cae* 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* \(_{\text{KPC}}\)-like genes. *E. cloa- cae* complex isolates harboured *bla* \(_{\text{KPC}}\) genes in *K. pneumoniae* (9, *n* = 5), *Serratia marcescens* (3) and *E. coli* (1). Other types detected in *Enterobacteriales* were *bla* \(_{\text{NDM}}\) (*n* = 7), *bla* \(_{\text{OXA-181}}\) (*n* = 1). The *bla* \(_{\text{OXA-244}}\) gene was detected in two *Acinetobacter baumannii* complex isolates, and *bla* \(_{\text{NDM-1}}\) was detected in one *P. aeruginosa* isolate. No *bla* \(_{\text{KPC}}\) 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. cloa- cae* 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. In 2013, the first survey of antimicrobial resistance among *Enterobacteriales* isolates from bacteraemic patients throughout Australia was conducted using an approach similar to the European EARS-Net program. 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\textsubscript{IMP-4} accounted for 62.1% (18/29) of all carbapenemase-producing Enterobacterales (CPE) in 2022, and half of the bla\textsubscript{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,\textsuperscript{11,12} but similar to those observed in 2021 in many Northern European countries.\textsuperscript{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.\textsuperscript{16} 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\textsubscript{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,\textsuperscript{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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