# Prevalence of antimicrobial resistances in common pathogenic Enterobacteriaceae in Australia, 2004: report from the Australian Group on Antimicrobial Resistance

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## Abstract

Antibiotic resistance in 3 common pathogenic types of Enterobacteriaceae was examined in a point-prevalence study in 2004. Strains of *Escherichia coli*, *Klebsiella* and *Enterobacter* species were collected prospectively in 25 institutions in Australian capital cities and tested by broth microdilution to 12 β-lactams and 3 other antibiotics. Almost 22% of isolates tested were from blood cultures. In *E. coli*, acquired resistance to ampicillin and piperacillin was common (>40%), and clinically significant percentages of intermediate susceptibility and resistance (>8%) were observed to amoxycillin-clavulanate, cefazolin and trimethoprim. In *Klebsiella* species, clinically important acquired resistance (>8%) was seen to piperacillin, cephalothin and trimethoprim, while in *Enterobacter* species, this was found with piperacillin, ceftriaxone, ceftazidime and trimethoprim. Blood culture isolates had similar rates of resistance to isolates from other specimen sources. New South Wales/Australian Capital Territory (combined) tended to have higher percentages of resistance than the other states, which were otherwise comparable across the agents and species tested. Multi-resistance, defined as more than 3 acquired resistances to antibiotic classes, was found in 6.5% of *E. coli*, 8.3% in *Klebsiella* species and 16.9% of *Enterobacter* species. Co-resistance to ciprofloxacin, gentamicin and/or trimethoprim was common in isolates presumptively harbouring extended-spectrum ß-lactamases. Strains with extended-spectrum ß-lactamases, although common in other countries, appear to be at fairly low levels in Australia; less than 4% in *E. coli* and less than 9% in *Klebsiella* species. Rates in *Enterobacter* species were not able to be determined. Presumptive plasmid-borne AmpC ß-lactamases were seen at low levels across the country and carbapenemases have now been found for the first time in Australia in Enterobacteriaceae. Both of these types of resistance represent a significant threat to major last-line antibiotics. *Commun Dis Intell* 2007;31:106–112.

Keywords: antimicrobial resistance, *Escherichia coli,* Enterobacteriaceae*, Klebsiella*

## Introduction

Emerging resistance in common pathogenic members of the Enterobacteriaceae is a world-wide phenomenon, and presents therapeutic problems for practitioners 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 con-

ducted biennially since then. In 2004, another genus of Gram-negative pathogens in which resistance can be of clinical importance, *Enterobacter* species, was added. The objectives of the 2004 surveillance program were to:

- determine proportions of resistance to the main therapeutic agents in *Escherichia coli*, *Klebsiella* species and *Enterobacter* species in Australian institutions;
- examine the extent of co-resistance and multi-resistance in these species; and
- detect emerging resistance to newer last-line agents such as carbapenems.

All species surveyed are members of the family Enterobacteriaceae. This family contains the most important Gram-negative pathogens in a wide range of common conditions in both the community and in hospitals. The 3 groups surveyed are considered to be valuable sentinels for multi-resistance and emerging resistance.[1,2]

Resistances of particular interest include resistance to ß-lactams due to ß-lactamases, especially extended-spectrum ß-lactamases, which inactivate the reserve agents, the third-generation cephalosporins. Other resistances of interest include resistance to antibiotics commonly used in the community such as trimethoprim; resistance to agents important for serious infections, such as gentamicin; and resistance to reserve agents such as ciprofloxacin and meropenem.

## Methods

### Institutions

Twenty-five institutions from each state and territory of Australia participated in the Gram-negative 2004 AGAR survey. There were 9 institutions from New South Wales/Australian Capital Territory, 5 from Victoria/Tasmania, 4 from Queensland, 4 from Western Australia and 3 from South Australia. Each institution collected up to 25 *E. coli*, 25 *Klebsiella* species and 50 *Enterobacter* species from different patients. Limits were placed on specimen types for *E. coli* and *Klebsiella* species in order to maximise the number of isolates from more serious infections, such as bacteraemia.

### Laboratory methods

Participating laboratories were required to meet standards for species identification. Susceptibility testing was performed using custom made panels prepared commercially by Dade-Behring Microscan® (West Sacramento, CA). The following agents were tested: ampicillin, amoxycillin-clavulanate, piperacillin, piperacillin-tazobactam, cephalothin, cefazolin, cefoxitin, ceftriaxone, ceftazidime, cefepime, aztreonam, meropenem, ciprofloxacin, gentamicin and trimethoprim. Interpretive criteria for susceptibility were those recommended by the Clinical and Laboratory Standards Institute (CLSI).[1] *E. coli* ATCC® 25922 and *E. coli* ATCC® 35218 were used for quality control strains. The presence of extended-spectrum ß-lactamases was tested for using published CLSI and other methods.[3,4]

## Results

### Source of isolates

The majority of isolates were from urine. There were 596 isolates of *E. coli*, 590 *Klebsiella* species and 1,204 *Enterobacter* species. Twenty-two per cent of isolates overall were from blood cultures. More than one third (35.2%) of the *E. coli* isolates were from blood cultures, with lower percentages for *Klebsiella* (24.7%) and *Enterobacter* species (13.2%). Urinary isolates accounted for almost half of the isolates (42.7%). Other sites of isolation reflected the high incidence of these species in nosocomial and pre- and post-operative surgical infections.

### Susceptibility testing results

A summary of resistance rates for all antibiotics against the 3 groups of bacteria are shown in Tables 1 to 3. There were no significant differences between the states for any of the agents tested, with the exception of New South Wales/Australian Capital Territory which has higher percentages of acquired resistance to many drug classes in *Enterobacter* species compared to the other states. Furthermore, isolates causing bacteraemia had similar percentages of resistance to isolates from other specimen sources (data not shown).

#### *Escherichia coli*

Ampicillin resistance proportions have been high for many years at around 45%; we found 46.5% were resistant in 2004. Amoxycillin-clavulanate intermediate and resistant strains were a relatively low proportion at 8.4% (range 4.8–12.0%). Percentages of resistance to piperacillin and piperacillin-tazobactam reflected those of ampicillin and amoxycillin-clavulanate respectively. Cephalothin is known to have marginal activity against *E. coli*, while intermediate + resistant percentages to cefazolin resembled those of amoxycillin-clavulanate. The ciprofloxacin resistance proportion was less than 4%. Gentamicin resistance was fairly low but there was a moderate percentage of resistance to trimethoprim (Table 1).

#### *Klebsiella* species

Ampicillin resistance is normal in these species due to the presence of specific chromosomal ß-lactamases.

The percentage of resistance to amoxycillin-clavulanate and piperacillin-tazobactam was low (< 5%). Percentages were substantially higher for first-generation cephalosporins cephalothin and cefazolin (~ 25%). Resistance to gentamicin was low, although higher than for *E. coli*. Resistance to ciprofloxacin and trimethoprim was less common than in *E. coli* (< 2% and < 10% respectively) (Table 2).

### *Enterobacter* species

Ampicillin, amoxicillin-clavulanate and first-generation cephalosporins are generally considered inactive against *Enterobacter* species due to intrinsic chromosomal β-lactamases. Resistance to gentamicin was more common than that seen in *E. coli* and *Klebsiella* species. About 25% of strains were resistant to third-

## Table 1. *Escherichia coli* (n = 596)

| Antibiotic | Cat* % | NSW/ACT % | Qld/NT % | SA % | Vic/Tas % | WA % | Australia % |
|---|---|---|---|---|---|---|---|
| Ampicillin | R | 50.2 | 52.7 | 49.3 | 33.6 | 47.0 | 46.5 |
| Amoxycillin-clavulanate | I | 6.8 | 8.8 | 5.3 | 3.2 | 10.0 | 6.7 |
| | R | 2.4 | 1.1 | 0.0 | 1.6 | 2.0 | 1.7 |
| Piperacillin | R | 42.0 | 44.0 | 45.3 | 28.8 | 44.0 | 40.3 |
| Piperacillin-tazobactam | R | 2.0 | 1.1 | 0.0 | 0.0 | 2.0 | 1.2 |
| Cephalothin | I | 27.8 | 20.9 | 36.0 | 36.8 | 21.0 | 28.5 |
| | R | 23.9 | 25.3 | 38.7 | 16.0 | 33.0 | 25.8 |
| Cefazolin | I | 2.9 | 1.1 | 6.7 | 0.0 | 10.0 | 3.7 |
| | R | 6.3 | 11.0 | 14.7 | 4.0 | 9.0 | 8.1 |
| Ceftriaxone | NS | 1.5 | 1.1 | 1.3 | 1.6 | 2.0 | 1.5 |
| Ceftazidime | NS | 1.5 | 0.0 | 1.3 | 1.6 | 1.0 | 1.2 |
| Cefepime | NS | 1.5 | 0.0 | 0.0 | 0.8 | 1.0 | 0.8 |
| Meropenem | NS | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Ciprofloxacin | NS | 2.9 | 4.4 | 2.7 | 1.6 | 6.0 | 3.4 |
| Gentamicin | R | 2.4 | 3.3 | 2.7 | 0.0 | 4.0 | 2.3 |
| Trimethoprim | R | 18.0 | 23.1 | 10.7 | 9.6 | 21.0 | 16.6 |

* Category: R = resistant, I = intermediate, NS = not susceptible (intermediate + resistant).

## Table 2. *Klebsiella* species (n = 590)

| Antibiotic | Cat* % | NSW/ACT % | Qld/NT % | SA % | Vic/Tas % | WA % | Australia % |
|---|---|---|---|---|---|---|---|
| Ampicillin | R | 82.2 | 97.9 | 86.5 | 74.8 | 81.4 | 83.6 |
| Amoxycillin-clavulanate | I | 4.0 | 2.1 | 6.8 | 2.4 | 4.1 | 3.7 |
| | R | 0.5 | 0.0 | 2.7 | 2.4 | 0.0 | 1.0 |
| Piperacillin | R | 23.8 | 35.1 | 43.2 | 13.8 | 14.4 | 24.4 |
| Piperacillin-tazobactam | R | 5.0 | 1.1 | 8.1 | 4.1 | 3.1 | 4.2 |
| Cephalothin | I | 7.9 | 3.2 | 10.8 | 9.8 | 8.2 | 8.0 |
| | R | 15.8 | 18.1 | 27.0 | 19.5 | 15.5 | 18.3 |
| Cefazolin | I | 4.5 | 2.1 | 5.4 | 13.8 | 4.1 | 6.1 |
| | R | 15.3 | 10.6 | 32.4 | 19.5 | 18.6 | 18.1 |
| Ceftriaxone | NS | 7.4 | 5.3 | 12.2 | 4.9 | 6.2 | 6.9 |
| Ceftazidime | NS | 3.5 | 3.2 | 5.4 | 4.1 | 2.1 | 3.6 |
| Cefepime | NS | 3.0 | 0.0 | 5.4 | 1.6 | 1.0 | 2.2 |
| Meropenem | NS | 0.0 | 0.0 | 0.0 | 0.8 | 0.0 | 0.2 |
| Ciprofloxacin | NS | 4.0 | 0.0 | 0.0 | 1.6 | 1.0 | 1.9 |
| Gentamicin | R | 1.5 | 6.4 | 8.1 | 5.7 | 2.1 | 4.1 |
| Trimethoprim | R | 9.9 | 10.6 | 10.8 | 8.1 | 9.3 | 9.7 |

* Category: R = resistant, I = intermediate, NS = not susceptible (intermediate + resistant).

generation cephalosporins, similar to proportions seen in the past. Levels of resistance to ciprofloxacin and trimethoprim were similar to those observed with the other two species (Table 3).

### Extended-spectrum and plasmid-borne AmpC β-lactamases

The prevalence of presumptive extended-spectrum and plasmid-borne β-lactamases is shown in Table 4. Strains with minimum inhibitory concentrations (MIC) of ceftriaxone and/or ceftazidime above 1 mg/L were considered presumptive evidence of the presence of an extended-spectrum or related β–lactamase in *E. coli* and *Klebsiella* species. A cefepime MIC above 0.5 mg/L was considered presumptive of an extended-spectrum β-lactamase in *Enterobacter* species. About half of these were confirmed to be extended-spectrum ß-lactamases by the clavulanate enhancement test.

Plasmid-borne AmpC ß-lactamases are suspected when *E. coli* or *Klebsiella* species are not susceptible to cefoxitin. Three per cent of *E. coli* and 6.6% of *Klebsiella* species were not susceptible to cefoxitin (MIC >8 mg/L).

### Carbapenemases

One strain of *Klebsiella pneumoniae* and 5 strains of *Enterbacter cloacae* were not susceptible to meropenem. The strains came from 4 institutions in 2 states. In 3 of these 6 strains, the presence of a carbapenemase (metallo-β-lactamase) was confirmed by molecular methods. These are among the first known recordings of metallo-β-lactamases in Australia.[5]

### Multi-resistance

The rates of multiple resistances are shown in Table 5. Multi-resistance was defined as resistance to three or more classes of antibiotics to which the genus/species has no natural resistance. Multi-resistance was reasonably common, above 5% in all 3 species groups. It was above 15% for *Enterobacter* species.

## Discussion

Amongst the most troublesome international trends in resistance in Enterobacteriaceae has been the emergence of extended-spectrum ß-lactamases (ESBLs), all of which are plasmid-borne. They have been predominantly a problem in hospital practice, and initially were more common in *Klebsiella* species than in *E. coli*. Recently, two new trends have emerged: the presence of ESBLs in *Enterobacter* species, and the emergence of specific types of ESBLs (so-called CTX-M enzymes). ESBLs are important as they compromise the efficacy of third-generation cephalosporins, which have been such a useful therapeutic alternative in hospital practice. Outbreaks of ESBL-producing *Klebsiella* species and *E. coli* have led some hospitals in Australia to severely restrict or abandon third-generation cephalosporin use. Overall ESBL rates in Australia remain low when compared to many other countries.[6] At least

Table 3. *Enterobacter* species (N = 1204)

| Antibiotic | Cat* % | NSW/ACT % | Qld/NT % | SA % | Vic/Tas % | WA % | Australia % |
|---|---|---|---|---|---|---|---|
| Ampicillin | R | 87.2 | 86.1 | 92.7 | 83.6 | 83.8 | 86.5 |
| Amoxycillin-clavulanate | I | 23.1 | 24.1 | 20.0 | 23.4 | 25.8 | 23.3 |
| | R | 70.9 | 67.5 | 76.0 | 70.5 | 68.2 | 70.5 |
| Piperacillin | R | 27.6 | 17.5 | 25.3 | 14.3 | 16.2 | 21.3 |
| Piperacillin-tazobactam | R | 7.0 | 4.2 | 8.0 | 4.5 | 6.1 | 6.1 |
| Cephalothin | I | 0.4 | 0.6 | 0.0 | 0.8 | 1.5 | 0.7 |
| | R | 98.2 | 98.8 | 100.0 | 98.0 | 96.0 | 98.1 |
| Cefazolin | I | 0.9 | 24.7 | 4.7 | 1.2 | 3.0 | 5.1 |
| | R | 94.4 | 72.9 | 93.3 | 95.1 | 93.9 | 91.4 |
| Ceftriaxone | NS | 28.9 | 20.5 | 28.0 | 20.5 | 24.2 | 25.2 |
| Ceftazidime | NS | 30.0 | 19.3 | 26.0 | 21.7 | 23.7 | 25.3 |
| Cefepime | NS | 6.1 | 3.0 | 10.0 | 4.9 | 2.5 | 5.3 |
| Meropenem | NS | 0.9 | 0.0 | 0.0 | 0.4 | 0.0 | 0.4 |
| Ciprofloxacin | NS | 4.5 | 0.6 | 0.7 | 0.8 | 1.0 | 2.2 |
| Gentamicin | R | 13.7 | 7.8 | 6.7 | 2.0 | 0.5 | 7.5 |
| Trimethoprim | R | 20.0 | 12.0 | 9.3 | 6.1 | 8.6 | 12.9 |

* Category: R = resistant, I = intermediate, NS = not susceptible (intermediate + resistant).

## Table 4. Presumptive/confirmed extended-spectrum ß-lactamase production

| Species and antibiotic | NSW/ACT % | Qld/NT % | SA % | Vic/Tas % | WA % | Australia % |
|---|---|---|---|---|---|---|
| ***E. coli*** | | | | | | |
| Ceftriaxone >1 | 2.4 | 3.3 | 1.3 | 1.6 | 2.0 | 2.2 |
| Ceftazidime >1 | 2.9 | 4.4 | 2.7 | 1.6 | 2.0 | 2.7 |
| Aztreonam >8 | 2.9 | 2.2 | 1.3 | 1.6 | 1.0 | 2.0 |
| Any of above | 4.9 | 6.6 | 2.7 | 1.6 | 2.0 | 3.7 |
| Confirmed | 1.5 | 1.1 | 1.3 | 0.8 | 1.0 | 1.2 |
| ***Klebsiella* spp.** | | | | | | |
| Ceftriaxone >1 | 8.4 | 6.4 | 13.5 | 6.5 | 6.2 | 8.0 |
| Ceftazidime >1 | 5.0 | 5.3 | 6.8 | 5.7 | 4.1 | 5.3 |
| Aztreonam >8 | 8.4 | 6.4 | 10.8 | 4.1 | 5.2 | 6.9 |
| Any of above | 9.4 | 6.4 | 13.5 | 7.3 | 8.2 | 8.8 |
| Confirmed | 6.9 | 4.3 | 8.1 | 4.9 | 2.1 | 5.4 |
| ***Enterobacter* spp.** | | | | | | |
| Cefepime >0.5 | 23.5 | 15.7 | 21.3 | 13.1 | 11.6 | 18.1 |

## Table 5. Multi-resistance: counts of numbers of strains versus the number of antibiotic classes to which genus/species was resistant

| Species | Non-multi-resistant (Number of antibiotic classes) | | | | | Multi-resistant (Number of antibiotic classes) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | % | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | % |
| *E. coli** | 290 | 42 | 157 | 68 | 93.5 | 21 | 7 | 4 | | 4 | 2 | | | | 1 | | 6.5 |
| *Klebsiella*† | 415 | 65 | 46 | 15 | 91.7 | 10 | 9 | 17 | 6 | 3 | 1 | 3 | | | | | 8.3 |
| *Enterobacter*‡ | 787 | 72 | 80 | 61 | 83.1 | 65 | 43 | 53 | 28 | 12 | 2 | 1 | | | | | 16.9 |

* *Antibiotics included*: ampicillin, piperacillin, amoxycillin-clavulanate, piperacillin-tazobactam, cefazolin, cefoxitin, ceftriaxone, ceftazidime, cefepime, aztreonam, meropenem, ciprofloxacin, gentamicin, trimethoprim
*Antibiotics excluded*: cephalothin.

† *Antibiotics included*: piperacillin, amoxycillin-clavulanate, piperacillin-tazobactam, cephalothin, cefazolin, cefoxitin, ceftriaxone, ceftazidime, cefepime, aztreonam, meropenem, ciprofloxacin, gentamicin, trimethoprim
Antibiotics excluded: ampicillin.

‡ *Antibiotics included*: piperacillin, piperacillin-tazobactam, ceftriaxone, ceftazidime, cefepime, ciprofloxacin, gentamicin, trimethoprim *Antibiotics excluded*: ampicillin, amoxycillin-clavulanate, cephalothin, cefazolin, cefoxitin

some of this may be attributed to fairly tight controls on third-generation cephalosporin use, both in Australian hospitals and in the community. Where hospital prolonged outbreaks have occurred, control has usually been achieved by switching to a ß-lactamase inhibitor combination for the most common indications. The methods used in our study for detecting ESBLs are considered indicative only. The diversity of enzymes means that molecular methods are required to supplement our knowledge of which enzymes are circulating.

Based on the tests performed in this study, ESBLs appear most common in *Enterobacter* species, but the study design did not lend itself to determining the true prevalence of ESBLs in these species. Molecular studies would be required to confirm their presence in *Enterobacter* species because a considerable amount of resistance to third-generation cephalosporins in this species results from stable de-repression of the natural chromosomal cephalosporinase (of the AmpC type). ESBLs are more common in *Klebsiella* species than in *E. coli;* a situation that has prevailed in Australia since their original emergence here. The lower rate of confirmation of ESBLs suggests that current routine screening methods are inadequate because the extended range of substrates used in this study and the screening concentrations used are more likely to detect true ESBLs.

Plasmid-borne AmpC ß-lactamases have recently emerged internationally as a growing Gram-negative resistance problem. They are the result of mobilisation of natural chromosomally located genes from uncommon species onto transmissible plasmids and into the common pathogens. Already there are 6 separate classes. Like ESBLs these enzymes confer resistance to the important third-generation cephalosporins. Routine detection methods have not yet been effectively developed. Nevertheless, it is possible to exploit a special feature of these enzymes; their ability to inactivate the cephamycins, represented by cefoxitin. *Enterobacter* species already naturally possess AmpC enzymes: their chromosomal cephalosporinases. These enzymes are present in Australia, but their exact prevalence in unknown.[7]

Acquired carbapenemases, in particular metallo-ß-lactamases, were first described in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. They are now being seen for the first time among members of the Enterobacteriaceae, and some were detected in this study. These are among the first known incidences of metallo-ß-lactamases in Australia. These are particularly troublesome resistance mechanisms as they inactivate a broad range of ß-lactams including the last-line carbapenems. Recent experience in one institution has shown that this resistance mechanism can spread amongst a range of Gram-negatives.[5]

The most problematic Gram-negative pathogens are those with multiple acquired resistances. Although there is no agreed benchmark for the definition of multi-resistance in Enterobacteriaceae, we have chosen acquired resistance to more than 3 classes to define multi-resistance in our survey. For each species, antibiotics were excluded from the count if they were affected by natural resistance mechanisms, so that only true acquired resistances were included. For the purposes of this analysis, resistance included intermediate susceptibility when the tested range did not go beyond the susceptible category.

It is clear that multi-resistance is more common in *Enterobacter* species. Some clustering of resistance is also noticeable in *Klebsiella* and *Enterobacter* species, as acquired resistance to 6 agents was more common than acquired resistance to 5 agents.

Although this study is comprehensive in its coverage of Australia, and the methodology follows international standards, there are a small number of limitations to the data and its interpretation.

1. The data are not denominator controlled. There is currently no consensus on an appropriate denominator for such surveys. Institution size, throughput, patient complexity and local antibiotic use patterns very much determine the types of resistance likely to be observed. As such, simple denominators such as occupied bed days over the period of collection would not provide meaningful comparisons between institutions.

2. Apart from blood cultures and sterile site isolates, the clinical significance of the isolates cannot be ascertained with certainty. Every attempt has been made by the participating laboratories to ascertain the clinical significance of isolates; however, the laboratories are dependent on (sometimes very limited) clinical information supplied on request forms. Gathering detailed clinical information sufficient to make a judgment on significance would require much greater resources than were available for this survey.

3. Molecular analyses for resistances of importance were not undertaken. They would be of greatest interest in the emerging resistances: ESBLs, plasmid-borne AmpC β-lactamases and carbapenemases. The major role of interspecies transfer of these types of resistance genes means that molecular characterization of these 3 enzyme types should be planned for in future surveys.

A full detailed report of this study may be found on the Australian Group on Antimicrobial Resistance web site at: http://www.antimicrobial-resistance.com/, under 'AMR surveillance'.

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