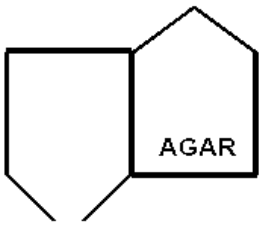

The Australian Group on Antimicrobial Resistance

Gram-negative Survey

2009 Antimicrobial Susceptibility Report

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On behalf of the Australian Group for Antimicrobial Resistance (AGAR)

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2 EXECUTIVE SUMMARY

The Australian Group on Antimicrobial Resistance (AGAR) performs regular period-prevalence studies to monitor changes in antimicrobial resistance. In 2008, AGAR moved to performing annual surveys of resistance in sentinel Gram-negative pathogens, alternating between pathogens causing community-onset infections and those causing hospital-onset infections, having previously conducted biennial surveys of all isolates regardless of infection onset. The 2009 survey focussed on hospital-onset infections, examining isolates from all specimens presumed to be causing disease. In all, 30 laboratories covering each state and mainland territory of Australia participated in the 2009 surveillance program. One thousand seven hundred and forty six *E. coli*, 547 *Klebsiella* species and 281 *Enterobacter* species were tested using a commercial automated method (Vitek 2, BioMérieux). Results were analysed using CLSI breakpoints from January 2011.

Moderately high levels of resistance to ampicillin (and therefore amoxycillin) were observed in *E. coli* (48%), only silghtly higher than that seen with community-associated strains. Rates for amoxycillin-clavulanate were 16% intermediate, and 10% resistant, significantly greater than for community-onset strains. A little over 20% of strains were resistant to cefazolin, while non-susceptibility to third-generation cephalosporins was lower but notable (ceftriaxone 7%, ceftazidime 4%). Of the strains examined for extended-spectrum β-lactamase (ESBL) production genes of the CTX-M type predominated (93/131 = 71%) while plasmid-borne AmpC genes were detected in 24/131 (18%). Moderate levels of resistance were detected to trimethoprim (22%). Ciprofloxacin resistance was found in 8% of *E. coli* isolates, higher than that of the other Gram-negative species examined, and gentamicin resistance was detected in 7%. Less than 1% of strains were resistant to piperacillin-tazobactam, and resistance to meropenem was not detected. Multi-resistant strains accounted for 14% of the test population.

Compared to *E. coli*, *Klebsiella* species showed higher levels of resistance to cefazolin, ceftriaxone, ceftazidime, cefepime and piperacillin-tazobactam, but lower levels to amoxycillin-clavulanate, ticarcicllin-clavulanate, ciprofloxacin, and trimethoprim. ESBLs were present in 41 of 45 presumptively ESBL-positive isolates of *K. pneumoniae*, 26 of which contained the CTX-M type, and 26 the TEM type. Three strains of *K. pneumoniae* and two of *K. oxytoca* haboured the bla_{IMP-4} carbapenemas, the predominant although still uncommon carbapenemase in Australia. Multi-resistance was seen in 10% of isolates of *Klebsiella* spp.

Acquired resistance in *Enterobacter* species was common to ticarcillin-clavulanate (33%), ceftriaxone (38%), ceftazidime (36%) and trimethoprim (13%). Rates of resistance to piperacillin-tazobactam, cefepime, ciprofloxacin, and gentamicin were all less than 10%. No strains had elevated meropenem MICs.

There are worrying trends in the expansion of third-generation cephalosporin resistance in hospital-onset *E. coli* and *Klebsiella* species especially those producing of CTX-M type enzymes. Other resistance patterns appear stable. There were no striking differences in resistance rates between the states/territories, apart from carbapenemase production which was solely detected in isolates from NSW/ACT.

3 BACKGROUND

3.1 OBJECTIVES OF THE PROGRAM

AGAR commenced surveillance of key Gram-negative pathogens, *Escherichia coli* and *Klebsiella* species in 1992. Surveys have been conducted biennially since then. In 2004, another genus of Gram-negative pathogens in which resistance can be of clinical importance, *Enterobacter* species, was added. In 2008, AGAR moved to performing annual surveys of resistance in sentinel Gram-negative pathogens, having previously conducted biennial surveys. Annual surveys alternate each year between pathogens causing community-onset infections and those causing hospital-onset infections. The objectives of the 2009 surveillance program were:

1. Determine proportions of resistance to the main therapeutic agents in *E. coli*, *Klebsiella* species, and *Enterobacter* species isolated from hospitalised inpatients
2. Examine the extent of co-resistance and multi-resistance in these species
3. Detect emerging resistance to extended-spectrum cephalosporins and newer last-line agents such as carbapenems

3.2 IMPORTANCE OF SPECIES SURVEYED

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 three groups surveyed are considered to be valuable sentinels for multi-resistance and emerging resistance.

E. coli is the commonest cause of upper and lower urinary tract infection, and is prominent in a number of other conditions including intra-abdominal sepsis, post-operative wound infections and neonatal sepsis, cholangitis and septicaemia in the profoundly neutropenic patient. It is one of the commonest isolates in the routine microbiology laboratory.

Klebsiella species are associated with similar conditions to those of *E. coli* but occur less frequently. They are more likely than *E. coli* to acquire and transmit resistance determinants. They are in addition an important cause of pneumonia. This genus is usually intrinsically resistant to aminopenicillins through the possession of one of a small number of natural ß-lactamases, most commonly SHV-1.

Enterobacter species are predominantly hospital-acquired pathogens. They are intrinsically resistant to aminopenicillins, first and second generation cephalosporins including cefamycins. Hence, they are naturally multiresistant. They acquire resistance to important Gram-negative agents relatively easily, and can act as a reservoir for important resistance genes.

3.3 RELEVANCE OF ANTIMICROBIALS TESTED

3.3.1 B-LACTAMS

This group of agents are the **mainstay of treatment** for Gram-negative infections in all settings, being the drugs of choice for both minor outpatient infections (e.g. lower UTI), and serious community-acquired infections (e.g. septicaemia)

Ampicillin: an aminopenicillin, used to predict resistance to ampicillin and amoxycillin. Considered the drugs of choice for susceptible *E. coli.* [Parenteral, oral; widespread community, mainly as amoxycillin, and hospital use]

Amoxycillin-clavulanate: a ß-lactamase inhibitor combination. Multiple uses including infections caused by ampicillin-resistant strains of *E. coli* and *Klebsiella* species. [Oral, widespread hospital and community use]

Piperacillin-tazobactam: a ß-lactamase inhibitor combination. Broad spectrum agent with multiple uses including against Gram-negative bacteria resistant to other agents. Similar activity to ticarcillin-clavulanate, another widely used ß-lactamase inhibitor combination. [Parenteral, limited hospital use]

Cefazolin: first-generation cephalosporin used for treating common Gram-negative and Gram-positive pathogens. Cefazolin is an important agent for surgical prophylaxis and penicillin-allergic patients. [Parenteral, cephalexin is the nearest oral equivalent, widespread community and hospital use]

Cefoxitin: second-generation cephalosporin, although better described as a cephamycin due to its unique spectrum. Very limited clinical use in surgical prophylaxis. Used in this study to screen for potential AmpC ß-lactamases. [Parenteral, very limited hospital use]

Ceftriaxone: a third-generation cephalosporin. For Enterobacteriaceae, testing results predict cefotaxime. Multiple specialised clinical uses. [Parenteral, extensive hospital use, strictly avoided in some hospitals]

Ceftazidime: a third-generation cephalosporin but with additional antipseudomonal activity. Most susceptible to extended-spectrum ß-lactamases and included in this study for that reason. Main role in Australia as an antipseudomonal agent. [Parenteral, modest hospital use in specialized units]

Cefepime: a fourth generation cephalosporin, but with activity against organisms producing AmpC ß-lactamases, both natural (chromosomal cephalosporinases) and acquired. [Parenteral, modest hospital use in specialized units]

Meropenem: a carbapenem. Predicts activity of most of the other carbapenems, imipenem and doripenem, against Enterobacteriaceae. Last-line agent used for multi-resistant Gram-negative infections, presumptive and proven. [Parenteral, modest restricted hospital use]

3.3.2 OTHER ANTIMICROBIAL CLASSES

Ciprofloxacin: a fluoroquinolone. Predicts resistance in Gram-negatives to other fluoroquinolones, ofloxacin, moxifloxacin. Resistance to ciprofloxacin confirms resistance to norfloxacin. Valuable oral agent reserved for infections caused by Gram-negatives resistant to other antibacterials, and as an antipseudomonal. [Oral, IV, restricted community and hospital use]

Gentamicin: an aminoglycoside. Generally predicts resistance in Gram-negatives to tobramycin (but not Amikacin). Valuable first line agent for presumptive Gram-negative sepsis. [IV, high first line hospital use].

Amikacin: an aminoglycoside. It is unaffected by the common aminoglycoside-modifying enzymes that cause Gram-negative bacteria to become resistant to gentamicin and tobramycin.

Trimethoprim: a folate synthesis (dihydrofolate reductase) inhibitor. Standard treatment for uncomplicated urinary tract infection. [Oral, moderate community use, limited hospital use, both mainly as cotrimoxazole]

Nitrofurantoin: a nitrofuran. A unique mechanism of action but its role, based on its pharmacology, is restricted to the treatment and prevention of urinary tract infection.

Tigecycline: a glycylcycline. A new class of antibiotics derived from tetracycline. These tetracycline analogues are specifically designed to overcome two common mechanisms of tetracycline resistance, namely resistance mediated by acquired efflux pumps and/or ribosomal protection. Used as a reserve agent for multiresistant organisms.

3.4 RESISTANCES OF CONCERN

3.4.1 B-LACTAMASES

ß-lactamases are the principal resistance mechanism to ß-lactams in Gram-negative bacteria. There is an enormous range of these enzymes now described. Like antibiotics themselves, each ß-lactamase has a “spectrum” of ß-lactams that it can hydrolyze and inactivate. The ß-lactamases of worldwide importance are listed in Table 1.

Table 1 Important ß-lactamases in Enterobacteriaceae

ß-lactamase	Mainly found in	ß-lactams affected or usual co-resistances	Comments
TEM-1,2	*E. coli*	Ampicillin, amoxycillin, piperacillin, (cephalothin)	Very common
TEM-1 hyperproduction	*E. coli*	Amoxycillin-clavulanate (piperacillin-tazobactam)	Increased prevalence in recent years
TEM, SHV and CTX-M extended spectrum ß-lactamases (ESBLs)	*E. coli*, *K. pneumoniae, Enterobacter* spp.	Ampicillin, amoxycillin, piperacillin, first-, second- (excluding cephamycins (cefoxitin) and third generation cephalosporins, monobactam	Mainly hospital-associated until recent emergence in community practice overseas
K1 hyperproduction	*K. oxytoca*	Ampicillin, amoxicillin, piperacillin, first- and second-generation cephalosporins, aztreonam, ceftriaxone > cefotaxime	Natural enzyme selected to hyperproduction
Chromosomal cephalosporinases	ESCaPPM*	Ampicillin, amoxicillin, first-, second-generation cephalosporins, third generation cephalosporins in de-repressed mutants.	Natural enzymes. Selection for stably de-repressed mutants can occur during treatment and strains with this are common
Plasmid-borne AmpC ß-lactamases	*E. coli, K. pneumoniae*	Ampicillin, amoxycillin, first, second and third-generation cephalosporins, including cephamycin	Emerging overseas as a significant problem
Carbapenemases	Rare, but increasing	Ampicillin, amoxycillin, first-, second and third-generation cephalosporins +/-aztreonam	Have been rare in Enterobacteriaceae but now being seen for the first time in Australia and overseas

* ***E****nterobacter* species, ***S****erratia* species, ***C****itrob****a****cter freundii*, ***P****roteus vulgaris* and *penneri*, ***P****rovidencia* species and ***M****organella morganii*.

3.4.2 NON-BETA-LACTAM ANTIBIOTICS

In Enterobacteriaceae, resistance to fluoroquinolones such as ciprofloxacin is generally the result of mutations in the *gyrA* gene, leading to amino acid changes in the target protein DNA gyrase. Two or three mutation and amino acid changes are required to develop full resistance to ciprofloxacin. Occasionally resistance can be brought about through efflux, usually in combination with DNA gyrase mutations.

Resistance to gentamicin and other aminoglycosides is most commonly the result of aminoglycoside modifying enzymes. The types prevalent in Enterobacteriaceae can vary widely by hospital, region and country.

Trimethoprim resistance is most commonly the result of mutations in the gene encoding the dihydrofolate reductase.

4 STUDY DESIGN

Thirty institutions from each State and mainland Territories of Australia participated in the Gram-negative 2009 AGAR survey. Each institution collected up to 70 *E. coli*, 20 *Klebsiella* species, 10 *Enterobacter* species from different patients hospitalised for more than 48 hours.

Table 2. Isolates Tested

Region	Number of Institutions	*E. coli*	*Enterobacter* species	*Klebsiella* species	Total
New South Wales (NSW) Australian Capital Territory (ACT)	8	443	79	137	659
Northern Territory (NT) Queensland (QLD)	7	414	65	132	611
South Australia (SA)	3	158	27	55	240
Victoria (VIC) Tasmania (TAS)	8	451	70	144	665
Western Australia (WA)	4	280	40	79	399
Total	**30**	**1,746**	**281**	**547**	**2,574**

4.1 PARTICIPITATING INSTITUTIONS

ACT/NSW (8)

Concord Hospital
Douglass Hanly Moir
Nepean Hospital
Royal North Shore Hospital
Royal Prince Alfred Hospital
Sydney South West Pathology Services
The Canberra Hospital
Westmead Hospital

QLD/NT (7)

Pathology Queensland, Cairns Base Hospital
Pathology Queensland, Gold Coast Hospital
Pathology Queensland, Prince Charles Hospital
Pathology Queensland, Princess Alexandra Hospital
Pathology Queensland, Central Laboratory
Royal Darwin Hospital
Sullivan Nicolaides Pathology

SA (3)

SA Pathology - Flinders Medical Centre
SA Pathology - Royal Adelaide Hospital
SA Pathology - Women's and Children's Hospital

VIC/TAS (8)

Alfred Hospital
Austin Health
Gribbles Pathology (now Healthscope Pathology)
Launceston General Hospital
Monash Medical Centre
Royal Children's Hospital

Royal Hobart Hospital
St Vincent's Hospital

WA (4)

PathWest Laboratory Medicine - WA, Fremantle Hospital
PathWest Laboratory Medicine - WA, QEII Medical Centre
PathWest Laboratory Medicine - WA, Royal Perth Hospital
St John of God Pathology

4.2 METHODS

4.2.1 SPECIES IDENTIFICATION

E. coli isolates were identified by one of the following methods:

Vitek®, Phoenix™ Automated Microbiology System, MicroScan®, Microbact, or ATB®
Chromogenic agar plus spot indole (DMACA) (urinary tract isolates)
Agar replication
Minimum tests for urine isolates: BGA or citrate, indole and lactose fermentation.

Klebsiella species and *Enterobacter* species were identified by one of the following methods:

API20E, MicroScan®, Vitek® (plus indole), Phoenix™ Automated Microbiology System, or ATB®
Chromogenic agar plus spot indole (DMACA) (urinary tract isolates)
Agar replication

4.2.2 SPECIES INCLUDED IN STUDY

Table 3. Species included

Group	Organism		Total
E. coli	*E. coli*		1,746
Klebsiella	*K. pneumoniae*		419
	K. oxytoca		124
	K. pneumoniae subsp *ozaenae*		2
	K. ornithinolytica		1
	Klebsiella not speciated.		1
		Total	547
Enterobacter	*E. cloacae*		202
	E. aerogenes		66
	E. asburiae		5
	E. amnigenus		3
	E. cancerogenus		2
	Enterobacter not speciated.		3
		Total	281

4.3 SUSCEPTIBILITY TESTING

4.3.1 METHOD

Testing was performed by a commercial semi-automated method, Vitek 2 (BioMérieux) which is calibrated to the ISO reference standard method of broth microdilution. Commercially available Vitek AST-N083 cards were utilized by all participants throughout the survey period. The CLSI breakpoints from Janurary 2011 have been employed in the analysis

4.3.2 ANTIBIOTICS TESTED

Table 4. Antimicrobials Tested

Antimicrobial Agent	AST N083 card Concentration range	CLSI Breakpoints (mg/L)[a]		
Ampicillin	≤2, 4, 8, 16, ≥32	≤8	16	≥32
Co-amoxyclav	≤2/1, 4/2, 8/4, 16/8, ≥32/16	≤8/4	16/8	≥32/16
Piperacillin/tazobactam	≤4/4, 8/4, 16/4, 32/4, 64/4, ≥128/4	≤16/4	32/4-64/4	≥128/4
Ticarcillin/clavulanate	≤8/2, 16/2, 32/2, 64/2, ≥128/2	≤16/2	32/2-64/2	≥128/2
Cefazolin[b]	≤4, 8, 16, 32, ≥64	≤2	4	≥8
Cefepime	≤1, 2, 4, 8, 16, 32, ≥64	≤8	16	≥32
Ceftriaxone	≤1, 2, 4, 8, 16, 32, ≥64	≤1	2	≥4
Cefoxitin	≤4, 8, 16, 32, ≥64	≤8	16	≥32
Ceftazidime	≤1, 2, 4, 8, 16, 32, ≥64	≤4	8	≥16
Meropenem	≤0.25, 0.5, 1, 2, 4, 8, ≥16	≤1	2	≥4
Gentamicin	≤1, 2, 4, 8, ≥16	≤4	8	≥16
Tobramycin	≤1, 2, 4, 8, ≥16	≤4	8	≥16
Amikacin	≤2, 4, 8, 16, 32, ≥64	≤16	32	≥64
Ciprofloxacin	≤0.25, 0.5, 1, 2, ≥4	≤1	2	≥4
Norfloxacin	≤0.5, 1, 2, 4, 8, ≥16	≤4	8	≥16
Nitrofurantoin	≤16, 32, 64, 128, 256, ≥512	≤32	64	≥128
Nalidixic Acid	≤2, 4, 8, 16, ≥32	≤16	-	≥32
Trimethoprim/sulphamethoxazole	≤1/19, 2/38, 4/76, 8/152, ≥16/304	≤2/38	-	≥4/76
Trimethoprim	≤0.5, 1, 2, 4, 8, ≥16	≤8	-	≥16
Tigecycline[c]	≤0.5, 1, 2, 4, ≥8	≤2	4	≥8

[a] The breakpoints selected to determine resistance are described in Performance Standards for Antimicrobial Susceptibility Testing: Twenty-first Information Supplement, CLSI document M100-S21, January 2011.

[b] For analysis, breakpoints of ≤4, ≥8 were appied due to the MIC range available on the Vitek card, recognising that the January 2011 breakpoint is actually susceptible ≤ 2 mg/L

[c] For tigecycline, FDA breakponts were employed as none are provided by CLSI

4.4 QUALITY CONTROL

E. coli ATCC 25922 and *E. coli* ATCC 35218 were the quality control strains for this survey

5 SOURCE OF ISOLATES

The majority of isolates were from urine. 7.6% of isolates overall were from blood cultures; comprising 6.3% of *E. coli* isolates, 9.9% of *Klebsiella* and 11.4% of *Enterobacter* species. Other sites of isolation reflect the high incidence of these species in nosocomial and pre- and post-operative surgical infections.

Table 5. Source of Isolates

Source	*E. coli*		Enterobacter		Klebsiella		Total	
Urinary tract (uncomplicated)	1201	68.8%	101	35.9%	280	51.2%	1582	61.5%
Respiratory tract	109	6.2%	58	20.6%	103	18.8%	270	10.5%
Blood	110	6.3%	32	11.4%	54	9.9%	196	7.6%
Skin and skin structure	108	6.2%	42	14.9%	30	5.5%	180	7.0%
Urinary tract (complicated)	92	5.3%	8	2.8%	36	6.6%	136	5.3%
Intra-abdominal	42	2.4%	10	3.6%	21	3.8%	73	2.8%
Other	28	1.6%	3	1.1%	4	0.7%	35	1.4%
Bone and Joint	9	0.5%	5	1.8%	2	0.4%	16	0.6%
IV line	1	0.1%	4	1.4%	4	0.7%	9	0.3%
Unknown	46	2.6%	18	6.4%	13	2.4%	77	3.0%
Total	**1746**	**100.0%**	**281**	**100.0%**	**547**	**100.0%**	**2574**	**100.0%**

6 SUSCEPTIBILITY TESTING RESULTS

Overall percentages of resistance or non-susceptibility are shown in Section 6.1 and the Appendix. Appendix 1 shows the details of percentages susceptible, intermediate and resistant for blood culture isolates and isolates from other specimen sources for each antibiotic. For some antibiotics, the concentration range tested did not distinguish between intermediate susceptibility (I) and resistant (R), and the term non-susceptible (NS) was used to describe these strains.

6.1 PERCENTAGES RESISTANT/NON-SUSCEPTIBLE

Table 6. Ampicillin

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%I	0.9%	0.5%	1.9%	0.9%	0.7%	0.9%
	%R	49.4%	48.1%	45.6%	47.7%	46.4%	47.8%

Comments: Resistance to ampicillin is intrinsic in *Klebsiella* and *Enterobacter* species, due to natural ß-lactamases, and hence resistance rates not reported here. Some strains may test as susceptible in vitro, but are generally reported as resistant

Table 7. Amoxycillin-clavulanate

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%I	16.3%	18.1%	17.1%	15.1%	13.2%	16.0%
	%R	10.2%	9.7%	9.5%	10.2%	12.1%	10.3%
***Klebsiella* spp.**	%I	7.3%	3.8%	1.8%	6.3%	5.1%	5.3%
	%R	11.7%	3.8%	14.5%	5.6%	3.8%	7.3%
K. pneumoniae	%I	7.3%	4.3%	2.6%	6.7%	4.6%	5.5%
K. pneumoniae	%R	13.5%	2.6%	13.2%	4.8%	3.1%	6.7%
K. oxytoca	%I	7.7%	0.0%	0.0%	5.0%	7.7%	4.8%
K. oxytoca	%R	7.7%	12.5%	18.8%	7.5%	7.7%	9.7%

Comments: Intermediate susceptibility or resistance to amoxycillin-clavulanate is intrinsic in *Enterobacter* species, due to natural ß-lactamases, and hence resistance rates not reported here. Some strains may test as susceptible in vitro, but are generally reported as resistant. Intermediate susceptibility is common in *E. coli* due to hyperproduction of acquired narrow-spectrum ß-lactamases, and in *Klebsiella* species due to higher levels of natural ß-lactamases.

Table 8. Ticarcillin-clavulanate

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%R	10.4%	11.4%	8.9%	10.9%	12.5%	10.9%
***Enterobacter* spp.**	%R	39.2%	36.9%	22.2%	27.1%	32.5%	33.1%
E. cloacae	%R	41.4%	45.5%	23.8%	29.8%	31.3%	36.1%
E. aerogenes	%R	33.3%	23.5%	0.0%	25.0%	37.5%	27.3%
***Klebsiella* spp.**	%R	14.6%	4.5%	9.1%	6.9%	5.1%	8.2%
K. pneumoniae	%R	15.6%	3.4%	5.3%	7.7%	3.1%	7.4%
K. oxytoca	%R	12.8%	12.5%	18.8%	5.0%	15.4%	11.3%

Comments: Resistance to ticarcillin-clavulanate in *E. coli* and *Klebsiella* species may indicate the presence of acquired plasmid-borne AmpC ß-lactamases.

Table 9. Piperacillin-tazobactam

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%R	0.5%	0.7%	0.6%	0.7%	0.7%	0.6%
***Enterobacter* spp.**	%R	7.6%	7.7%	7.4%	8.6%	12.5%	8.5%
E. cloacae	%R	10.3%	11.4%	9.5%	12.8%	15.6%	11.9%
E. aerogenes	%R	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
***Klebsiella* spp.**		4.4%	3.0%	5.5%	2.8%	1.3%	3.3%
K. pneumoniae	%R	4.2%	1.7%	0.0%	1.9%	1.5%	2.1%
K. oxytoca	%R	5.1%	12.5%	18.8%	5.0%	0.0%	7.3%

Comments: Resistance to piperacillin-tazobactam in *E. coli* and *Klebsiella* species may indicate the presence of acquired plasmid-borne AmpC ß-lactamases.

Table 10. Cefazolin

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%R	21.0%	19.1%	20.3%	22.2%	20.7%	20.7%
***Enterobacter* spp.**	%R	96.2%	92.3%	88.9%	91.4%	92.5%	92.9%
E. cloacae	%R	100%	100%	85.7%	97.9%	96.9%	97.5%
E. aerogenes	%R	85.7%	76.5%	100%	75.0%	75.0%	80.3%
***Klebsiella* spp.**	%R	40.9%	19.7%	27.3%	27.1%	16.5%	27.2%
K. pneumoniae	%R	28.1%	12.9%	15.8%	11.5%	9.2%	15.8%
K. oxytoca	%R	74.4%	68.8%	56.3%	67.5%	53.8%	66.9%

Comments:
Interpretation based on MIC range available on Vitek card, which currently do not match those of the CLSI breakpoints published in 2011.
Resistance to cefazolin, representative of first generation cephalosporins, is common in *E. coli* and *Klebsiella* species. *Enterobacter* species are intrinsically resistant due to natural ß-lactamases.

Table 11. Cefoxitin

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%R	3.8%	3.1%	3.8%	5.3%	3.6%	4.0%
***Klebsiella* spp.**	%R	6.6%	5.3%	7.3%	2.1%	2.5%	4.6%
K. pneumoniae	%R	7.3%	6.0%	10.5%	2.9%	3.1%	5.5%
K. oxytoca	%R	5.1%	0.0%	0.0%	0.0%	0.0%	1.6%

Comments:
Cefoxitin is tested solely for the purpose of screening for potential plasmid-borne AmpC β-lactamases in *E. coli* and *Klebsiella* spp.. Because *Enterobacter* species have an intrinsic AmpC β-lactamase, they will test as Resistant or Intermediate

Table 12. Ceftriaxone

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%NS	7.7%	4.6%	7.6%	9.1%	6.8%	7.2%
***Enterobacter* spp.**	%NS	41.8%	43.1%	37.0%	32.9%	35.0%	38.4%
E. cloacae	%NS	46.6%	52.3%	38.1%	36.2%	31.3%	42.1%
E. aerogenes	%NS	28.6%	29.4%	25.0%	31.3%	50.0%	31.8%
***Klebsiella* spp.**	%NS	16.1%	6.8%	16.4%	9.0%	3.8%	10.2%
K. pneumoniae	%NS	19.8%	6.9%	13.2%	7.7%	4.6%	10.3%
K. oxytoca	%NS	7.7%	6.3%	25.0%	12.5%	0.0%	10.5%

Comments: In *E. coli* and *Klebsiella* species non-susceptibility to ceftriaxone is indicative of extended-spectrum ß-lactamase production. In *Enterobacter* species resistance is indicative of stable de-repression of natural chromosomal cephalosporinase.

Table 13. Ceftazidime

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%NS	4.3%	2.7%	5.7%	5.3%	3.9%	4.2%
***Enterobacter* spp.**	%NS	39.2%	41.5%	33.3%	30.0%	32.5%	35.9%
E. cloacae	%NS	43.1%	50.0%	33.3%	29.8%	31.3%	38.6%
E. aerogenes	%NS	28.6%	29.4%	25.0%	31.3%	37.5%	30.3%
***Klebsiella* spp.**	%NS	14.6%	6.1%	5.5%	4.2%	2.5%	7.1%
K. pneumoniae	%NS	18.8%	6.9%	2.6%	4.8%	3.1%	8.1%
K. oxytoca	%NS	5.1%	0.0%	12.5%	2.5%	0.0%	4.0%

Comments: In *E. coli* and *Klebsiella* species non-susceptibility to ceftazidime is indicative of extended-spectrum ß-lactamase production. In *Enterobacter* species resistance is indicative of stable de-repression of natural chromosomal cephalosporinase.

Table 14. Cefepime

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%NS	1.1%	1.2%	0.6%	0.9%	1.4%	1.1%
***Enterobacter* spp.**	%NS	2.5%	0.0%	0.0%	0.0%	0.0%	0.7%
E. cloacae	%NS	3.4%	0.0%	0.0%	0.0%	0.0%	1.0%
E. aerogenes	%NS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
***Klebsiella* spp.**	%NS	5.8%	2.3%	0.0%	2.1%	0.0%	2.6%
K. pneumoniae	%NS	8.3%	2.6%	0.0%	2.9%	0.0%	3.3%
K. oxytoca	%NS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Comments: In *E. coli* and *Klebsiella* species non-susceptibility to cefepime is suggestive of mixed or hyperproduction of extended-spectrum ß-lactamases. In *Enterobacter* species non-susceptibility is suggestive of the presence of extended-spectrum ß-lactamases.

Table 15. Meropenem

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%NS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
***Enterobacter* spp.**	%NS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
***Klebsiella* spp.**	%NS	1.5%	0.0%	0.0%	0.0%	0.0%	0.4%
K. pneumoniae	%NS	1.0%	0.0%	0.0%	0.0%	0.0%	0.2%
K. oxytoca	%NS	2.6%	0.0%	0.0%	0.0%	0.0%	0.8%

Comments: Non-susceptibility in Enterobacteriaceae suggests the presence of carbapenemases.

Table 16. Ciprofloxacin

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%NS	9.0%	6.3%	7.0%	8.9%	8.9%	8.1%
***Enterobacter* spp.**	%NS	7.6%	4.6%	7.4%	1.4%	0.0%	4.3%
E. cloacae	%NS	10.3%	6.8%	9.5%	2.1%	0.0%	5.9%
E. aerogenes	%NS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
***Klebsiella* spp.**	%NS	7.3%	3.8%	12.7%	3.5%	3.8%	5.5%
K. pneumoniae	%NS	10.4%	4.3%	15.8%	4.8%	4.6%	6.9%
K. oxytoca	%NS	0.0%	0.0%	6.3%	0.0%	0.0%	0.8%

Comments: Ciprofloxacin non-susceptibility indicates at least mutations in *gyrA*, the gene encoding the target enzyme, DNA gyrase and, and more recently, the possibility of plasmid-mediated quinolone-resistance genes

Table 17. Gentamicin

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%R	10.2%	4.6%	5.7%	6.4%	6.1%	6.8%
***Enterobacter* spp.**	%R	16.5%	6.2%	14.8%	0.0%	0.0%	7.5%
E. cloacae	%R	19.0%	9.1%	19.0%	0.0%	0.0%	9.4%
E. aerogenes	%R	9.5%	0.0%	0.0%	0.0%	0.0%	3.0%
***Klebsiella* spp.**	%R	10.9%	6.8%	12.7%	5.6%	1.3%	7.3%
K. pneumoniae	%R	13.5%	7.8%	13.2%	7.7%	1.5%	8.6%
K. oxytoca	%R	5.1%	0.0%	12.5%	0.0%	0.0%	3.2%

Comments: Gentamicin resistance indicates the presence of at least one of a range of aminoglycoside modifying enzymes.

Table 18. Trimethoprim

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%R	25.3%	24.4%	19.0%	18.8%	21.8%	22.3%
***Enterobacter* spp.**	%R	17.7%	18.5%	11.1%	8.6%	2.5%	12.8%
E. cloacae	%R	22.4%	25.0%	14.3%	12.8%	0.0%	16.3%
E. aerogenes	%R	4.8%	5.9%	0.0%	0.0%	12.5%	4.5%
***Klebsiella* spp.**	%R	13.1%	9.8%	18.2%	9.7%	6.3%	11.0%
K. pneumoniae	%R	18.8%	11.2%	21.1%	10.6%	7.7%	13.1%
K. oxytoca	%R	0.0%	0.0%	12.5%	7.5%	0.0%	4.0%

Comments: Trimethoprim resistance is the result of mutations in the gene encoding dihydrofolate reductase

Table 19. Tigecycline

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	%NS	0.0%	0.0%	0.0%	0.2%	0.0%	0.1%
***Enterobacter* spp.**	%NS	1.3%	7.7%	11.1%	4.3%	2.5%	4.6%
E. cloacae	%NS	0.0%	6.8%	9.5%	0.0%	0.0%	2.5%
E. aerogenes	%NS	5.0%	11.8%	25.0%	18.8%	12.5%	12.3%
***Klebsiella* spp.**	%NS	5.1%	4.5%	1.8%	3.5%	5.1%	4.2%
K. pneumoniae	%NS	7.3%	4.3%	2.6%	4.8%	6.2%	5.3%
K. oxytoca	%NS	0.0%	6.3%	0.0%	0.0%	0.0%	0.8%

Comments: Tigecycline resistance usually indicates the overexpression of AcrAB, a member of the RND multidrug efflux family.

6.2 SUMMARY

The following summarizes the resistance issues in the three groups of Enterobacteriaceae, except for extended-spectrum ß-lactamases (Section 6.3.1) and carbapenemases (Section 6.3.2). There are no striking differences between the states.

E. coli

Ampicillin resistance proportions have been moderately high for more than a decade, and approximately stable at around 48%. Amoxycillin-clavulanate intermediate and resistant strains have been around for some time but remain in relatively stable proportion at around 25%. Percentages of resistance to ticarcillin-clavulanate and piperacillin-tazobactam remain low. Cefazolin maintains modest levels of resistance at around 20%. Ciprofloxacin resistance appears to be increasing despite controlled usage in both the community and in hospitals. Gentamicin resistance remains fairly low despite more three decades of use in hospital practice. Trimethoprim, especially as cotrimoxazole, use has been high in the community and this is reflected in the resistance percentages in hospitals.

***Klebsiella* species**

Acquired resistances of interest include those of ß-lactamase inhibitor combinations; percentage of resistance to amoxycillin-clavulanate and piperacillin-tazobactam are still low, running at less that 8%. Percentages are substantially higher for cefazolin, a first generation cephalosporin. Resistance to gentamicin is still low. Surprisingly, resistance to ciprofloxacin and trimethoprim is less common than in *E. coli*.

***Enterobacter* species**

Ampicillin, amoxicillin-clavulanate and first-generation cephalosporins are intrinsicially inactive against *Enterobacter* species. Resistance to gentamicin is similar to that seen in *E. coli*. Levels of resistance to ciprofloxacin and trimethoprim are less than in *E. coli*.

6.3 MAJOR RESISTANCES

6.3.1 ESBLS

Extended-spectrum ß-lactamases are important problem resistances internationally. 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. ESBLs, particularly those of the CTX-M type, are starting to emerge in community isolates of *E. coli*.

Most ESBL-producing strains will be captured/recognised using the new CLSI ceftriaxone "susceptible" breakpoints of 1 mg/L. The "susceptible"breakpoint of 4 mg/L for ceftazidime is less sensitive for ESBL detection, but an MIC > 1mg/L (which is present on the Vitek 2 card) is more sensitive. Isolates with either ceftriaxone or ceftazidime MICs above 1 mg/L were selected for ESBL phenotypic confirmation and molecular testing.

Neither ceftriaxone nor ceftazidime testing will identify ESBL production in *Enterobacter* species because of their intrinsic chromosomal AmpC β-lactamase. In that species, cefepime at 1 mg/L is suggestive that an isolate of this genus harbours an ESBL. Isolates with a cefepime MIC > 1mg/L were selected for ESBL phenotypic confirmation and molecular testing.

Molecular testing involved multiplex screening for TEM, SHV, CTX-M and plasmid-borne AmpC genes. TEM screening does not accurately discriminiate between TEM-1/2 genes, which encode narrow-spectrum β-lactamases, and TEM genes with higher numbers that encode ESBLs. Similarly, SHV screening does not discriminate between SHV-1/11, which are narrow-spectrum β-lactamases, and SHV genes the encode ESBLs. SHV-1 is the dominant natural chromosomal enzyme of *K. pneumoniae* leading to natural ampicillin/amoxycillin resistance. Therefore, *E. coli* isolates containing only TEM genes and *Klebsiella* species containing only SHV genes have been excluded from this analysis. All CTX-M genes encode ESBLs, as do plasmid-borne AmpC genes effectively.

*Table 20. Presumptive and Confirmed Extended-spectrum β-lactamase Production**

Species	NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
Escherichia coli	35	20	14	45	21	135
Ceftriaxone > 1 mg/L	7.7%	4.6%	7.6%	9.1%	6.8%	7.2%
Ceftazidime > 1 mg/L	7.0%	3.9%	7.6%	7.8%	6.1%	6.4%
Either of above	7.9%	4.8%	8.9%	10.0%	7.5%	7.7%
Confirmed						
any ESBL (No. received)	31/35	19/20	11/14	40/42	17/20	118/131
SHV			1		1	2
CTX-M types	27	13	8	33	12	93
plasmid-borne AmpC	4	6	2	7	5	24
Klebsiella pneumoniae	20	9	5	8	3	45
Ceftriaxone > 1 mg/L	19.8%	6.1%	13.2%	7.7%	4.6%	10.1%
Ceftazidime > 1 mg/L	20.8%	7.0%	13.2%	5.8%	4.6%	10.1%
Either of above	20.8%	7.0%	13.2%	7.7%	4.6%	10.6%
Confirmed						
any ESBL (No. received)	19/20	7/9	5/5	7/8	3/3	41/45
TEM	9	5	4	5	3	26
CTX-M types	12	4	1	7	2	26
plasmid-borne AmpC	3	2	4	0	0	9
Klebsiella oxytoca	3	1	4	5	0	13
Ceftriaxone > 1 mg/L	7.7%	6.3%	25.0%	12.5%	0.0%	10.5%
Ceftazidime > 1 mg/L	5.1%	0.0%	12.5%	2.5%	0.0%	4.0%
Either of above	7.7%	6.3%	25.0%	12.5%	0.0%	10.5%
Confirmed						
any ESBL (No. received)	2/3	0/1	2/4	2/3	0	6/11
TEM	2	0	2	0	0	4
SHV	1	0	2	1	0	4

CTX-M types	0	0	0	2	0	2
plasmid-borne AmpC	0	0	0	0	0	0
***Enterobacter* species**	9	9	5	7	5	35
Cefepime > 1 mg/L	11.4%	13.8%	18.5%	10.0%	12.5%	12.5%
Confirmed						
any ESBL (No. received)	3/9	3/8	1/5	2/7	0/5	9/34
CTX-M types	1	0	0	0	0	1

* Strains may possess more than one type of ESBL gene

Based on the tests performed in this study, ESBLs were more common in *Klebsiella* species (9.0% confirmed) than in *E. coli* (6.9% confirmed). For the *Enterobacter* species 3.2% of isolates contained an ESBL. There was a notable presence of CTX-M enzymes in *E. coli* (93/131 tested), indicating their spread in hospitalised patients.

Many of the *K. oxytoca* isolates with an ESBL phenotype were hyperproducers of K1 β-lactamase, the natural chromosomal enzyme in this species, rather than ESBL producers. Hyperproducers of K1 β-lactamase are consistantly resistant to piperacillin-tazobactam, having borderline resistance to cefepime, but remain susceptible to ceftazidime. This pattern is not typical of a true ESBL producer.

6.3.2 PLASMID-BORNE AmpC β-LACTAMASES

Plasmid-borne AmpC ß-lactamases have recently emerged internationally as a growing Gram-negative resistance problem. They are the result of mobilization of natural chromosomally located genes from common and uncommon species of Enterobacteriaceae onto transmissible plasmids and into the common pathogens. There are currently 6 separate classes. Like ESBLs these enzymes confer resistance to the important third-generation cephalosporins such as ceftriaxone and ceftazidime. Routine phenotypic 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 chromosomally-encoded AmpC enzymes.

Table 21. Presumptive plasmid-borne AmpC ß-lactamase Production

Species	NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
Escherichia coli	17	13	6	24	10	70
Cefoxitin ≥ 32 mg/L	3.8%	3.1%	3.8%	5.3%	3.6%	4.0%
***Klebsiella* species**	9	7	4	3	2	25
Cefoxitin ≥ 32 mg/L	6.6%	5.3%	7.3%	2.1%	2.5%	4.6%

The proportions of *E. coli* and *Klebsiella* species with elevated cefoxitin MICs were low. Only 35% of cefoxitin-resistant *E. coli* and 28% of *Klebsiella* spp. that were available for molecular confirmation were confirmed to contain plasmid-borne AmpC; with CIT (n=22) and DHA (n=2) in *E. coli,* and CIT (n=4), and DHA (n=3) detected in *K. pneumoniae*.

6.3.3 CARBAPENEMASES

Acquired carbapenemases, in particular metallo-ß-lactamases, were first described in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. They are now being seen more commonly among members of the Enterobacteriaceae. Three *K. pneumoniae,* two *K. oxytoca* and one *E. cloacae* in the survey contained $bla_{\text{IMP-4}}$. Only two isolates were non-susceptible to meropenem (MIC range 0.5 to 2 mg.L).

6.4 IMPORTANT CO-RESISTANCES

Strains harbouring extended-spectrum ß-lactamases are much more likely to harbour resistances to unrelated drug classes. The proportion of strains with elevated MICs to ceftriaxone or ceftazidime (>1 mg/L), and confirmed to contain an extended-spectrum ß-lactamase, which were resistant to other drug classes is shown in Table 22:

Table 22. Co-resistance percentages in strains with confirmed ESBLs

Species	Category	Ciprofloxacin	Gentamicin	Trimethoprim*
E. coli (n=120)	%I	1.7%	1.7%	-
	%R	52.5%	40.8%	73.3%
Klebsiella pneumoniae (n=43)	%I	16.3%	0.0%	-
	%R	34.9%	76.7%	60.5%

* There is no intermediate category for trimethoprim

Further detail on co-resistances is contained in Appendix 2.

6.5 MULTI-RESISTANCE

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 agents 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.

Table 23. Multi-resistance in Escherichia coli

		Non-multi-resistant					Multi-resistant											
Region	Total	0	1	2	3	%	4	5	6	7	8	9	10	11	12	13	14	%
NSW/ACT	443	198	87	66	37	87.6%	20	12	9	9	2	3						12.4%
QLD/NT	414	198	79	59	37	90.1%	21	7	7	4	1	1						9.9%
SA	158	80	34	13	14	89.2%	6	2	3	3	3							10.8%
VIC/TAS	451	230	82	43	31	85.6%	26	13	9	8	7	2						14.4%
WA	280	144	42	42	18	87.9%	12	3	9	8	2							12.1%
Total	*1746*	*850*	*324*	*223*	*137*	*87.9%*	*85*	*37*	*37*	*32*	*15*	*6*						*12.1%*

Antibiotics included: ampicillin, amoxycillin-clavulanate, piperacillin-tazobactam, cefazolin, cefoxitin, ceftriaxone, ceftazidime, cefepime, gentamicin, amikacin, ciprofloxacin, nitrofurantoin, trimethoprim, meropenem

Antibiotics excluded: ticarcillin-clavulanate, tobramycin, norfloxacin, nalidixic acid, sulfamethoxazole-trimethoprim

Table 24. Multi-resistance in Klebsiella species

		Non-multi-resistant					Multi-resistant									
Region	*Total*	0	1	2	3	%	4	5	6	7	8	9	10	11	12	13	%
NSW/ACT	137	63	40	9	3	83.9%	4	4	6	5	2			1			16.1%
QLD/NT	132	77	35	6	5	93.2%	2	3	2	1	1						6.8%
SA	55	33	11		2	83.6%	2	2		2	2	1					16.4%
VIC/TAS	144	83	42	5	3	91.7%	3	2	3	3		1					8.3%
WA	79	52	18	6		96.2%		2		1							3.8%
Total	*547*	*307*	*146*	*26*	*13*	*89.9%*	*11*	*13*	*11*	*12*	*5*	*2*		*1*			*10.1%*

Antibiotics included: amoxycillin-clavulanate, piperacillin-tazobactam, cefazolin, cefoxitin, ceftriaxone, ceftazidime, cefepime, gentamicin, amikacin, ciprofloxacin, nitrofurantoin, trimethoprim, meropenem

Antibiotics excluded: ampicillin, cephalothin, ticarcillin-clavulanate, tobramycin, norfloxacin, nalidixic acid, sulfamethoxazole-trimethoprim

Table 25. Multi-resistance in Enterobacter species

		Non-multi-resistant					Multi-resistant							
Region	Total	0	1	2	3	%	4	5	6	7	8	9	10	%
NSW/ACT	79	30	14	17	5	83.5%	7	5		1				16.5%
QLD/NT	65	22	13	15	10	92.3%	3	1	1					7.7%
SA	27	14	3	4	3	88.9%	2		1					11.1%
VIC/TAS	70	38	11	12	8	98.6%	1							1.4%
WA	40	20	5	10	4	97.5%	1							2.5%
Total	*281*	*124*	*46*	*58*	*30*	*91.8%*	*14*	*6*	*2*	*1*				*8.2%*

Antibiotics included: piperacillin-tazobactam, ceftriaxone, ceftazidime, cefepime, gentamicin, amikacin, ciprofloxacin, nitrofurantoin, trimethoprim, meropenem

Antibiotics excluded: ampicillin, amoxycillin-clavulanate, cefazolin, cefoxitin, ticarcillin-clavulanate, tobramycin, norfloxacin, nalidixic acid, sulfamethoxazole-trimethoprim

6.6 LIMITATIONS OF THE STUDY

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.

2. 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.

7 STANDARDS AND INFORMATION RESOURCES

1. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. Twenty-first informational supplement. M100-S21. CLSI, Wayne, Pa, 2011.

2. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard - Eighth Edition. M07-A8. CLSI, Wayne, Pa, 2009

3. Bell JM, Turnidge JD, Jones RN; SENTRY Asia-Pacific Participants. Prevalence of extended-spectrum beta-lactamase- producing *Enterobacter cloacae* in the Asia-Pacific region: results from the SENTRY Antimicrobial Surveillance Program, 1998 to 2001. *Antimicrob Agents Chemother*. 2003 Dec;47(12):3989-93.

4. Tigecycline USA package insert; www.wyeth.com/hcp/tygacil/moa

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APPENDIX 1. SUSCEPTIBILITY RESULTS BY REGION

Ampicillin

Genus	Region	Total	%S	%I	%R
Enterobacter species	NSW/ACT	79	12.7%	32.9%	54.4%
	QLD/NT	65	9.2%	23.1%	67.7%
	SA	27	14.8%	25.9%	59.3%
	VIC/TAS	70	17.1%	31.4%	51.4%
	WA	40	15.0%	25.0%	60.0%
	National	281	38	80	163
			13.5%	28.5%	58.0%
Escherichia coli	NSW/ACT	443	49.7%	0.9%	49.4%
	QLD/NT	414	51.4%	0.5%	48.1%
	SA	158	52.5%	1.9%	45.6%
	VIC/TAS	451	51.4%	0.9%	47.7%
	WA	280	52.9%	0.7%	46.4%
	National	1746	896	15	835
			51.3%	0.9%	47.8%
Klebsiella species	NSW/ACT	137	5.1%	24.1%	70.8%
	QLD/NT	132	1.5%	27.3%	71.2%
	SA	55	5.5%	32.7%	61.8%
	VIC/TAS	144	4.9%	38.2%	56.9%
	WA	79	1.3%	25.3%	73.4%
	National	547	20	162	365
			3.7%	29.6%	66.7%

Amoxycillin-clavulanate

Genus	Region	Total	%S	%I	%R
Enterobacter species	NSW/ACT	79	2.5%	6.3%	91.1%
	QLD/NT	65	4.6%	6.2%	89.2%
	SA	27	11.1%	3.7%	85.2%
	VIC/TAS	70	14.3%	8.6%	77.1%
	WA	40	7.5%	12.5%	80.0%
	National	281	21	21	239
			7.5%	7.5%	85.1%
Escherichia coli	NSW/ACT	443	73.6%	16.3%	10.2%
	QLD/NT	414	72.2%	18.1%	9.7%
	SA	158	73.4%	17.1%	9.5%
	VIC/TAS	451	74.7%	15.1%	10.2%
	WA	280	74.6%	13.2%	12.1%
	National	1746	1287	279	180
			73.7%	16.0%	10.3%
Klebsiella species	NSW/ACT	137	81.0%	7.3%	11.7%
	QLD/NT	132	92.4%	3.8%	3.8%
	SA	55	83.6%	1.8%	14.5%
	VIC/TAS	144	88.2%	6.3%	5.6%
	WA	79	91.1%	5.1%	3.8%
	National	547	478	29	40
			87.4%	5.3%	7.3%

Ticarcillin-clavulanate

Genus	Region	Total	%S	%I	%R
Enterobacter species	NSW/ACT	79	54.4%	6.3%	39.2%
	QLD/NT	65	55.4%	7.7%	36.9%
	SA	27	63.0%	14.8%	22.2%
	VIC/TAS	70	68.6%	4.3%	27.1%
	WA	40	62.5%	5.0%	32.5%
	National	281	169	19	93
			60.1%	6.8%	33.1%
Escherichia coli	NSW/ACT	443	75.6%	14.0%	10.4%
	QLD/NT	414	75.1%	13.5%	11.4%
	SA	158	79.1%	12.0%	8.9%
	VIC/TAS	451	77.4%	11.8%	10.9%
	WA	280	80.4%	7.1%	12.5%
	National	1746	1345	210	191
			77.0%	12.0%	10.9%
Klebsiella species	NSW/ACT	137	81.0%	4.4%	14.6%
	QLD/NT	132	88.6%	6.8%	4.5%
	SA	55	83.6%	7.3%	9.1%
	VIC/TAS	144	89.6%	3.5%	6.9%
	WA	79	92.4%	2.5%	5.1%
	National	547	476	26	45
			87.0%	4.8%	8.2%

Piperacillin-tazobactam

Genus	Region	Total	%S	%I	%R
Enterobacter species	NSW/ACT	79	72.2%	20.3%	7.6%
	QLD/NT	65	67.7%	24.6%	7.7%
	SA	27	81.5%	11.1%	7.4%
	VIC/TAS	70	77.1%	14.3%	8.6%
	WA	40	70.0%	17.5%	12.5%
	National	281	205	52	24
			73.0%	18.5%	8.5%
Escherichia coli	NSW/ACT	441	97.5%	2.0%	0.5%
	QLD/NT	414	98.1%	1.2%	0.7%
	SA	158	98.1%	1.3%	0.6%
	VIC/TAS	450	98.7%	0.7%	0.7%
	WA	280	97.5%	1.8%	0.7%
	National	1743	1708	24	11
			98.0%	1.4%	0.6%
Klebsiella species	NSW/ACT	137	92.7%	2.9%	4.4%
	QLD/NT	132	96.2%	0.8%	3.0%
	SA	55	94.5%	0.0%	5.5%
	VIC/TAS	144	94.4%	2.8%	2.8%
	WA	79	96.2%	2.5%	1.3%
	National	547	518	11	18
			94.7%	2.0%	3.3%

Cefazolin

Genus	Region	Total	%S+I	%R
Enterobacter species	NSW/ACT	79	3.8%	96.2%
	QLD/NT	65	7.7%	92.3%
	SA	27	11.1%	88.9%
	VIC/TAS	70	8.6%	91.4%
	WA	40	7.5%	92.5%
	National	281	20	261
			7.1%	92.9%
Escherichia coli	NSW/ACT	443	79.0%	21.0%
	QLD/NT	414	80.9%	19.1%
	SA	158	79.7%	20.3%
	VIC/TAS	451	77.8%	22.2%
	WA	280	79.3%	20.7%
	National	1746	1384	362
			79.3%	20.7%
Klebsiella species	NSW/ACT	137	59.1%	40.9%
	QLD/NT	132	80.3%	19.7%
	SA	55	72.7%	27.3%
	VIC/TAS	144	72.9%	27.1%
	WA	79	83.5%	16.5%
	National	547	398	149
			72.8%	27.2%

Cefoxitin

Genus	Region	Total	%S	%I	%R
Enterobacter species	NSW/ACT	79	2.5%	0.0%	97.5%
	QLD/NT	65	1.5%	0.0%	98.5%
	SA	27	11.1%	3.7%	85.2%
	VIC/TAS	70	7.1%	0.0%	92.9%
	WA	40	2.5%	2.5%	95.0%
	National	281	12	2	267
			4.3%	0.7%	95.0%
Escherichia coli	NSW/ACT	443	93.2%	2.9%	3.8%
	QLD/NT	414	94.2%	2.7%	3.1%
	SA	158	93.7%	2.5%	3.8%
	VIC/TAS	451	92.5%	2.2%	5.3%
	WA	280	93.9%	2.5%	3.6%
	National	1746	1631	45	70
			93.4%	2.6%	4.0%
Klebsiella species	NSW/ACT	137	93.4%	0.0%	6.6%
	QLD/NT	132	93.2%	1.5%	5.3%
	SA	55	90.9%	1.8%	7.3%
	VIC/TAS	144	96.5%	1.4%	2.1%
	WA	79	94.9%	2.5%	2.5%
	National	547	515	7	25
			94.1%	1.3%	4.6%

Ceftriaxone

Genus	Region	Total	%S	%I	%R
Enterobacter species	NSW/ACT	79	58.2%	0.0%	41.8%
	QLD/NT	65	56.9%	0.0%	43.1%
	SA	27	63.0%	0.0%	37.0%
	VIC/TAS	70	67.1%	1.4%	31.4%
	WA	40	65.0%	0.0%	35.0%
	National	281	173	1	107
			61.6%	0.4%	38.1%
Escherichia coli	NSW/ACT	443	92.3%	0.2%	7.4%
	QLD/NT	414	95.4%	0.0%	4.6%
	SA	158	92.4%	0.6%	7.0%
	VIC/TAS	451	90.9%	0.0%	9.1%
	WA	280	93.2%	0.4%	6.4%
	National	1746	1621	3	122
			92.8%	0.2%	7.0%
Klebsiella species	NSW/ACT	137	83.9%	0.7%	15.3%
	QLD/NT	132	93.2%	0.8%	6.1%
	SA	55	83.6%	1.8%	14.5%
	VIC/TAS	144	91.0%	0.0%	9.0%
	WA	79	96.2%	0.0%	3.8%
	National	547	491	3	53
			89.8%	0.5%	9.7%

Ceftazidime

Genus	Region	Total	%S	%I	%R
Enterobacter species	NSW/ACT	79	60.8%	1.3%	38.0%
	QLD/NT	65	58.5%	1.5%	40.0%
	SA	27	66.7%	0.0%	33.3%
	VIC/TAS	70	70.0%	1.4%	28.6%
	WA	40	67.5%	0.0%	32.5%
	National	281	180	3	98
			64.1%	1.1%	34.9%
Escherichia coli	NSW/ACT	443	95.7%	0.2%	4.1%
	QLD/NT	414	97.3%	0.0%	2.7%
	SA	158	94.3%	0.0%	5.7%
	VIC/TAS	451	94.7%	0.0%	5.3%
	WA	280	96.1%	0.0%	3.9%
	National	1746	1672	1	73
			95.8%	0.1%	4.2%
Klebsiella species	NSW/ACT	137	85.4%	0.0%	14.6%
	QLD/NT	132	93.9%	0.8%	5.3%
	SA	55	94.5%	0.0%	5.5%
	VIC/TAS	144	95.8%	0.0%	4.2%
	WA	79	97.5%	0.0%	2.5%
	National	547	508	1	38
			92.9%	0.2%	6.9%

Cefepime

Genus	Region	Total	%S	%I	%R
Enterobacter species	NSW/ACT	79	97.5%		2.5%
	QLD/NT	65	100%		
	SA	27	100%		
	VIC/TAS	70	100%		
	WA	40	100%		
	National	281	279		2
			99.3%		0.7%
Escherichia coli	NSW/ACT	443	98.9%	0.5%	0.7%
	QLD/NT	414	98.8%	0.2%	1.0%
	SA	158	99.4%	0.0%	0.6%
	VIC/TAS	451	99.1%	0.0%	0.9%
	WA	280	98.6%	0.7%	0.7%
	National	1746	1727	5	14
			98.9%	0.3%	0.8%
Klebsiella species	NSW/ACT	137	94.2%	0.0%	5.8%
	QLD/NT	132	97.7%	0.0%	2.3%
	SA	55	100%		
	VIC/TAS	144	97.9%	1.4%	0.7%
	WA	79	100%		
	National	547	533	2	12
			97.4%	0.4%	2.2%

Meropenem

Genus	Region	Total	%S	%I	%R
Enterobacter species	NSW/ACT	79	100%		
	QLD/NT	65	100%		
	SA	27	100%		
	VIC/TAS	70	100%		
	WA	40	100%		
	National	281	281		
			100%		
Escherichia coli	NSW/ACT	443	100%		
	QLD/NT	414	100%		
	SA	158	100%		
	VIC/TAS	451	100%		
	WA	280	100%		
	National	1746	1746		
			100%		
Klebsiella species	NSW/ACT	137	98.5%	1.5%	
	QLD/NT	132	100%		
	SA	55	100%		
	VIC/TAS	144	100%		
	WA	79	100%		
	National	547	545	2	
			99.6%	0.4%	

Ciprofloxacin

Genus	Region	Total	%S	%I	%R
Enterobacter species	NSW/ACT	79	92.4%	0.0%	7.6%
	QLD/NT	65	95.4%	3.1%	1.5%
	SA	27	92.6%	0.0%	7.4%
	VIC/TAS	70	98.6%	1.4%	0.0%
	WA	40	100%		
	National	281	269	3	9
			95.7%	1.1%	3.2%
Escherichia coli	NSW/ACT	443	91.0%	0.0%	9.0%
	QLD/NT	414	93.7%	0.5%	5.8%
	SA	158	93.0%	0.0%	7.0%
	VIC/TAS	451	91.1%	0.2%	8.6%
	WA	280	91.1%	0.0%	8.9%
	National	1746	1604	3	139
			91.9%	0.2%	8.0%
Klebsiella species	NSW/ACT	137	92.7%	4.4%	2.9%
	QLD/NT	132	96.2%	1.5%	2.3%
	SA	55	87.3%	1.8%	10.9%
	VIC/TAS	144	96.5%	0.7%	2.8%
	WA	79	96.2%	1.3%	2.5%
	National	547	517	11	19
			94.5%	2.0%	3.5%

Gentamicin

Genus	Region	Total	%S	%I	%R
Enterobacter species	NSW/ACT	79	83.5%	0.0%	16.5%
	QLD/NT	65	93.8%	0.0%	6.2%
	SA	27	85.2%	0.0%	14.8%
	VIC/TAS	70	100%		
	WA	40	100%		
	National	281	260	0	21
			92.5%	0.0%	7.5%
Escherichia coli	NSW/ACT	443	89.4%	0.5%	10.2%
	QLD/NT	414	95.2%	0.2%	4.6%
	SA	158	93.0%	1.3%	5.7%
	VIC/TAS	451	93.6%	0.0%	6.4%
	WA	280	93.9%	0.0%	6.1%
	National	1746	1622	5	119
			92.9%	0.3%	6.8%
Klebsiella species	NSW/ACT	137	89.1%	0.0%	10.9%
	QLD/NT	132	93.2%	0.0%	6.8%
	SA	55	87.3%	0.0%	12.7%
	VIC/TAS	144	93.8%	0.7%	5.6%
	WA	79	98.7%	0.0%	1.3%
	National	547	506	1	40
			92.5%	0.2%	7.3%

Trimethoprim

Genus	Region	Total	%S		%R
Enterobacter species	NSW/ACT	79	82.3%		17.7%
	QLD/NT	65	81.5%		18.5%
	SA	27	88.9%		11.1%
	VIC/TAS	70	91.4%		8.6%
	WA	40	97.5%		2.5%
	National	281	245		36
			87.2%		12.8%
Escherichia coli	NSW/ACT	443	74.7%		25.3%
	QLD/NT	414	75.6%		24.4%
	SA	158	81.0%		19.0%
	VIC/TAS	451	81.2%		18.8%
	WA	280	78.2%		21.8%
	National	1746	1357		389
			77.7%		22.3%
Klebsiella species	NSW/ACT	137	86.9%		13.1%
	QLD/NT	132	90.2%		9.8%
	SA	55	81.8%		18.2%
	VIC/TAS	144	90.3%		9.7%
	WA	79	93.7%		6.3%
	National	547	487		60
			89.0%		11.0%

Tigecycline

Genus	Region	Total	%S		%R
Enterobacter species	NSW/ACT	78	98.7%	0.0%	1.3%
	QLD/NT	65	92.3%	0.0%	7.7%
	SA	27	88.9%	0.0%	11.1%
	VIC/TAS	70	95.7%	0.0%	4.3%
	WA	40	97.5%	2.5%	0.0%
	National	280	267	1	12
			95.4%	0.4%	4.3%
Escherichia coli	NSW/ACT	441	100%		
	QLD/NT	414	100%		
	SA	158	100%		
	VIC/TAS	451	99.8%	0.0%	0.2%
	WA	280	100%		
	National	1744	1743	0	1
			99.9%	0.0%	0.1%
Klebsiella species	NSW/ACT	137	94.9%	4.4%	0.7%
	QLD/NT	132	95.5%	1.5%	3.0%
	SA	55	98.2%		1.8%
	VIC/TAS	144	96.5%		3.5%
	WA	79	94.9%	1.3%	3.8%
	National	547	524	9	14
			95.8%	1.6%	2.6%

APPENDIX 2. ANTIBIOTIC PROFILES BY FREQUENCY

Enterobacter species (n = 281)

Antibiotic Profile				Region					
PtzCtrCazCpmGenAmkTmpNitCipMer				AUS	QLD/NT	NSW/AC	VIC/TAS	SA	WA
			Nit	126	27	38	28	11	22
PtzCtrCaz			Nit	52	13	14	12	4	9
				30	4	4	14	5	3
PtzCtrCaz				13	3	3	3	1	3
		TmpNit		10	4	1	4		1
CtrCaz			Nit	8	3	1	3		1
CtrCaz	Gen	TmpNit		6	1	4		1	
Ctr			Nit	4			2	1	1
CtrCaz				4	1	1	1	1	
PtzCtrCaz		TmpNit		3	2		1		
	Gen	TmpNit		2		1		1	
CtrCaz	Gen	Tmp		2		2			
CtrCaz	Gen	TmpNitCip		2		1		1	
PtzCtrCaz	Gen	Tmp	Cip	2		2			
		Tmp		1		1			
		TmpNitCip		1	1				
	Gen	Nit		1	1				
Caz				1			1		
Ctr			NitCip	1		1			
Ctr		TmpNit		1	1				
Ctr		TmpNitCip		1			1		
CtrCaz		TmpNit		1	1				
CtrCaz	Gen			1		1			
CtrCaz	Gen		Cip	1				1	
CtrCazCpmGen		TmpNitCip		1		1			
Ptz			Nit	1		1			
PtzCtr	Gen	TmpNitCip		1		1			
PtzCtrCaz			NitCip	1	1				
PtzCtrCaz	Gen	TmpNit		1	1				
PtzCtrCaz	Gen	TmpNitCip		1	1				
PtzCtrCazCpm			Nit	1		1			

Ptz = piperacillin-tazobactam, Ctr = ceftriaxone, Caz = ceftazidime, Cpm = cefepime, Gen = gentamicin, Amk = amikacin, Tmp = trimethoprim, Nit = nitrofurantoin, Cip = ciprofloxacin, Mer = meropenem

Escherichia coli (n = 1,746)

Antibiotic Profile												Region					
Amp	Amc	Ptz	Czl	Cft	Ctr	Caz	Cpm	Gen	Amk	Tmp	Nit	Cip	Mer	AUS	QLD/NT	NSW/AC	VIC/TAS	SA	WA
														819	192	191	221	75	140
Amp														183	34	45	55	20	29
Amp	Amc													96	28	25	23	12	8
Amp										Tmp				88	24	27	19	4	14
Amp	Amc		Czl											87	20	21	24	9	13
Amp	Amc		Czl							Tmp				48	16	13	7	4	8
										Tmp				38	13	15	4	5	1
Amp	Amc									Tmp				25	11	5	2	1	6
Amp	Amc		Czl	Cfx										22	6	4	4	2	6
											Nit			15	4	2	4	2	3
Amp			Czl											14	3	4	4		3
Amp	Amc		Czl	Cfx	Ctr	Caz								13	3	1	6		3
Amp								Gen		Tmp				12	3	5	2		2
Amp	Amc	Ptz	Czl											11	2	3	2	1	3
Amp										Tmp		Cip		10	2	1	1	3	3
Amp											Nit			9	2	3	1		3
Amp	Amc		Czl		Ctr	Caz		Gen		Tmp	Nit	Cip		9		2	5	1	1
Amp								Gen						8	3	2	2		1
Amp								Gen		Tmp		Cip		8	1	2	3	1	1
Amp								Gen				Cip		7	1	4	1		1
Amp			Czl		Ctr					Tmp		Cip		7		3	4		
Amp	Amc		Czl							Tmp	Nit			7	1	2	3	1	
Amp												Cip		6	1	2	2		1
Amp	Amc		Czl	Cfx						Tmp				6		2	3		1
Amp			Czl		Ctr					Tmp				5	1		2	2	
Amp	Amc									Tmp		Cip		5			3		2
Amp	Amc		Czl								Nit			5	3	2			
Amp	Amc		Czl		Ctr					Tmp				5	1		4		
Amp	Amc		Czl		Ctr	Caz		Gen		Tmp		Cip		5	1	1		1	2
Amp										Tmp	Nit			4	1		1		2
Amp				Cfx						Tmp		Cip		4	2	1	1		
Amp	Amc		Czl					Gen		Tmp				4	1	1	1		1
Amp	Amc		Czl					Gen		Tmp		Cip		4		1		1	2
Amp	Amc		Czl	Cfx	Ctr	Caz				Tmp				4	1		1		2
Amp	Amc	Ptz	Czl	Cfx	Ctr	Caz								4	1	2		1	
										Tmp	Nit			3	1		1		1
								Gen						3		2		1	
				Cfx										3		1	2		
Amp				Cfx										3	1	1		1	
Amp	Amc							Gen						3		3			
Amp	Amc			Cfx						Tmp		Cip		3	2	1			
Amp	Amc		Czl		Ctr					Tmp		Cip		3		1			2
Amp	Amc		Czl		Ctr			Gen						3		2	1		
Amp	Amc		Czl		Ctr			Gen		Tmp				3	1	1		1	
Amp	Amc		Czl		Ctr	Caz		Gen		Tmp				3		1	1	1	
Amp	Amc		Czl	Cfx	Ctr	Caz				Tmp		Cip		3		2	1		
Amp	Amc		Czl	Cfx	Ctr	Caz		Gen		Tmp	Nit	Cip		3			3		

Antibiotic Profile																			Region					
Amp	Amc	Ptz	Czl	Cft	Ctr	Caz	Cpm	Gen	Amk	Tmp	Nit	Cip	Mer						AUS	QLD/NT	NSW/AC	VIC/TAS	SA	WA
Amp	Amc	Ptz	Czl								Nit								3	2		1		
Amp	Amc	Ptz	Czl							Tmp									3	2				1
	-																		2		2			
												Cip							2	1				1
										Tmp		Cip							2	1				1
								Gen		Tmp									2		2			
Amp		Czl		Ctr				Gen											2			2		
Amp		Czl		Ctr				Gen		Tmp									2	1	1			
Amp		Czl		CtrCaz															2		2			
Amp		Czl		CtrCaz				Gen		TmpNit		Cip							2	1			1	
Amp		Czl	Cfx	Ctr	Caz					Tmp		Cip							2			1	1	
Amp	Amc							Gen			Nit	Cip							2			2		
Amp	Amc							Gen		Tmp									2		1		1	
Amp	Amc			Cfx				Gen		Tmp									2		2			
Amp	Amc	Czl						Gen				Cip							2			1		1
Amp	Amc	Czl		Ctr				Gen		Tmp		Cip							2		1	1		
Amp	Amc	Czl		Ctr			Cpm			Tmp		Cip							2	1	1			
Amp	Amc	Czl		CtrCaz						Tmp									2	1	1			
Amp	Amc	Czl		CtrCaz	Cpm							Cip							2	1		1		
Amp	Amc	Czl	Cfx									Cip							2		1	1		
Amp	Amc	Czl	Cfx					Gen		Tmp		Cip							2	1	1			
Amp	Amc	Czl	Cfx	Ctr															2	1		1		
Amp	Amc	Czl	Cfx	Ctr				Gen		Tmp		Cip							2			1		1
Amp	Amc	Czl	Cfx	Ctr	Caz	Cpm	Gen			Tmp		Cip							2					2
Amp	Amc	Ptz	Czl		Ctr					Tmp		Cip							2		1			1
Amp	Amc	Ptz	Czl	Cfx															2	1		1		
								Gen		Tmp		Cip							1		1			
					Ctr														1					1
				Cfx								Cip							1		1			
				Cfx							Nit	Cip							1		1			
				Cfx						Tmp		Cip							1	1				
			Czl							TmpNit									1		1			
		Ptz																	1		1			
Amp								Gen		TmpNit		Cip							1	1				
Amp				Cfx						Tmp									1	1				
Amp				Cfx				Gen		Tmp		Cip							1	1				
Amp		Czl								Tmp		Cip							1	1				
Amp		Czl								TmpNit									1			1		
Amp		Czl						Gen		Tmp		Cip							1	1				
Amp		Czl		Ctr															1					1
Amp		Czl		Ctr				Gen		Tmp		Cip							1		1			
Amp		Czl		CtrCaz						Tmp									1			1		
Amp		Czl		CtrCaz	Cpm	Gen						Cip							1		1			
Amp		Czl	Cfx							Tmp									1			1		
Amp		Czl	Cfx	Ctr	Caz			Gen		Tmp		Cip							1			1		
Amp		Czl	Cfx	Ctr	Caz	Cpm	Gen			Tmp		Cip							1		1			
Amp	Amc											Cip							1	1				

Antibiotic Profile	Region					
AmpAmcPtzCzlCftCtrCazCpmGenAmkTmpNitCipMer	AUS	QLD/NT	NSW/AC	VIC/TAS	SA	WA
AmpAmc Nit	1	1				
AmpAmc Gen TmpNitCip	1	1				
AmpAmc Cfx Gen Cip	1			1		
AmpAmc Cfx Gen TmpNitCip	1		1			
AmpAmc Czl Cip	1			1		
AmpAmc Czl Gen	1		1			
AmpAmc Czl Caz Tmp	1			1		
AmpAmc Czl Ctr	1			1		
AmpAmc Czl Ctr Cpm Tmp	1	1				
AmpAmc Czl Ctr CpmGen Tmp Cip	1					1
AmpAmc Czl CtrCaz Tmp Cip	1		1			
AmpAmc Czl CtrCaz Gen	1		1			
AmpAmc Czl CtrCazCpm Tmp Cip	1					1
AmpAmc Czl CtrCazCpmGen Tmp Cip	1	1				
AmpAmc Czl CtrCazCpmGen TmpNitCip	1		1			
AmpAmc CzlCfx Nit	1				1	
AmpAmc CzlCfx Tmp Cip	1			1		
AmpAmc CzlCfx Caz GenAmk	1				1	
AmpAmc CzlCfxCtr Cip	1	1				
AmpAmc CzlCfxCtr NitCip	1				1	
AmpAmc CzlCfxCtr Gen Tmp	1					1
AmpAmc CzlCfxCtr CpmGen Tmp Cip	1		1			
AmpAmc CzlCfxCtr CpmGen TmpNitCip	1			1		
AmpAmc CzlCfxCtrCaz Cip	1			1		
AmpAmc CzlCfxCtrCaz TmpNitCip	1		1			
AmpAmc CzlCfxCtrCaz Gen Tmp Cip	1		1			
AmpAmc CzlCfxCtrCazCpm Tmp Cip	1				1	
AmpAmc CzlCfxCtrCazCpmGen TmpNitCip	1	1				
AmpAmc - CzlCfxCtrCazCpm TmpNitCip	1			1		
AmpAmcPtz	1					1
AmpAmcPtzCzl TmpNit	1			1		
AmpAmcPtzCzlCfx Tmp	1		1			
AmpAmcPtzCzlCfx Tmp Cip	1					1
AmpAmcPtzCzlCfx Gen Tmp	1		1			
AmpAmcPtzCzlCfx Cpm AmkTmpNitCip	1			1		
AmpAmcPtzCzlCfxCtr Tmp Cip	1		1			
AmpAmcPtzCzlCfxCtr Gen Tmp Cip	1		1			
AmpAmcPtzCzlCfxCtrCaz GenAmk	1				1	

Amp = ampicillin, Amc = amoxycillin-calvulanate, Ptz = piperacillin-tazobactam, Czl = cefazolin, Cft = cefoxitin, Ctr = ceftriaxone, Caz = ceftazidime, Cpm = cefepime, Gen = gentamicin, Amk = amikacin, Tmp = trimethoprim, Nit = nitrofurantoin, Cip = ciprofloxacin, Mer = meropenem

Klebsiella species (n = 547)

Antibiotic Profile	Region					
AmcPtzCzlCftCtrCazCpmGenAmkTmpNitCipMer	AUS	QLD/NT	NSW/AC	VIC/TAS	SA	WA
Nit	262	71	50	71	30	40
	99	23	22	27	8	19
Czl	37	2	14	12	5	4
Czl Nit	34	8	13	10		3
TmpNit	14	6	3	1	1	3
Cfx Nit	10	3	1	3		3
AmcPtzCzl Nit	5	1	4			
TmpNitCip	4	2	2			
Amc CzlCfxCtr Gen TmpNitCip	4			1	3	
Amc Czl	3		1	1		1
Amc Czl Nit	3	2		1		
Amc Czl CtrCazCpmGen TmpNitCip	3		1	2		
AmcPtzCzl Ctr	3	1	1		1	
AmcPtzCzl Ctr Nit	3			3		
Tmp	2		1	1		
Czl CtrCaz Gen Tmp	2	1			1	
Czl CtrCaz Gen TmpNit	2		1	1		
Amc Nit	2			1		1
Amc TmpNit	2		1	1		
Amc Czl TmpNit	2		1		1	
Amc Czl CtrCaz Gen TmpNit	2		1	1		
Amc Czl CtrCazCpmGen NitCip	2		2			
Amc Czl CtrCazCpmGen Tmp	2		2			
Amc CzlCfxCtrCaz Gen Nit	2		2			
Amc CzlCfxCtrCaz Gen Nit Mer	2		2			
Amc CzlCfxCtrCaz Gen TmpNitCip	2	1			1	
AmcPtzCzl TmpNit	2			2		
NitCip	1		1			
Gen	1	1				
Cfx TmpNitCip	1				1	
Czl Tmp	1	1				
Czl TmpNit	1		1			
Czl Gen	1	1				
Czl Ctr Gen Nit	1	1				
Czl Ctr Gen TmpNitCip	1			1		
Czl CtrCaz Nit	1		1			
Czl CtrCaz Gen Cip	1		1			
Czl CtrCazCpmGen Nit	1	1				
CzlCfxCtrCazCpmGen Nit	1	1				
Amc Czl Ctr Nit	1					1
Amc Czl Ctr Gen TmpNit	1			1		
Amc Czl Ctr Gen TmpNitCip	1				1	
Amc Czl CtrCaz Nit	1		1			
Amc Czl CtrCaz Tmp Cip	1					1
Amc Czl CtrCaz TmpNit	1		1			
Amc Czl CtrCazCpmGen Tmp Cip	1	1				
Amc CzlCfxCtrCaz Nit	1	1				

Antibiotic Profile	Region					
AmcPtzCzlCftCtrCazCpmGenAmkTmpNitCipMer	AUS	QLD/NT	NSW/AC	VIC/TAS	SA	WA
Amc CzlCfxCtrCaz Gen	1		1			
AmcPtzCzl	1					1
AmcPtzCzl Ctr NitCip	1				1	
AmcPtzCzl Ctr TmpNit	1			1		
AmcPtzCzl Ctr TmpNitCip	1		1			
AmcPtzCzl CtrCaz Gen NitCip	1					1
AmcPtzCzl CtrCaz Gen Tmp	1				1	
AmcPtzCzl CtrCazCpmGen TmpNit	1		1			
AmcPtzCzl CtrCazCpmGen TmpNitCip	1			1		
AmcPtzCzlCfx Nit	1	1				
AmcPtzCzlCfx TmpNitCip	1					1
AmcPtzCzlCfx Caz Gen TmpNitCip	1	1				
AmcPtzCzlCfxCtrCaz Nit	1	1				
AmcPtzCzlCfxCtrCaz NitCip	1		1			
AmcPtzCzlCfxCtrCaz GenAmk	1			1		
AmcPtzCzlCfxCtrCazCpm Nit	1		1			
AmcPtzCzlCfxCtrCazCpmGen TmpNitCip	1		1			

Amp = ampicillin, Ptz = piperacillin-tazobactam, Czl = cefazolin, Cft = cefoxitin, Ctr = ceftriaxone, Caz = ceftazidime, Cpm = cefepime, Gen = gentamicin, Amk = amikacin, Tmp = trimethoprim, Nit = nitrofurantoin, Cip = ciprofloxacin, Mer = meropenem

APPENDIX 3. ESBL PROFILES BY FREQUENCY

TEM molecular screening does not discriminate between TEM-1/2 genes, which encode narrow-spectrum β-lactamases, and TEM genes with higher numbers that encode ESBLs. Similarly, SHV screening does not discriminate between SHV-1/11, which are narrow-spectrum β-lactamases, and SHV genes the encode ESBLs. SHV-1 is the dominant natural chromosomal enzyme of *K. pneumoniae* leading to natural ampicillin/amoxycillin resistance. Therefore, *E. coli* isolates containing **only** TEM genes and *Klebsiella* species containing **only** SHV genes have not been included in this table. When detected in the presence of a known ESBL gene (SHV, CTX-M and/or ampC in *E. coli*; TEM, CTX-M and/or ampC in *Klebsiella* spp.), they are included in this table.

ESBL Profile[a]	Region					
TemShvCTXampC	AUS	NSW/ACT	QLD/NT	SA	VIC/TAS	WA
Escherichia coli (n=135)						
- - CTX -	48	14	8	4	16	6
Tem - CTX -	44	13	5	4	17	5
- - - ampC	17	4	5		6	2
- - - -	9	3	1	2	1	2
Tem - - ampC	6		1	2	1	2
Tem - - -	4	1		1	1	1
TemShv - -	2			1		1
- - CTXampC	1					1
(not received)	4				3	1
Klebsiella oxytoca (n=13)						
- - CTX -	1				1	
- - - -	5	1	1	2	1	
Tem - - -	1	1				
TemShv - -	3	1		2		
- ShvCTX -	1				1	
(not received)	2				2	
Klebsiella pneumoniae (n=45)						
TemShv - -	6	4	1			1
- Shv - -	4	1	2		1	
- Shv - ampC	3	2	1			
- ShvCTX -	12	8	1	1	2	
TemShv - ampC	6	1	1	4		
TemShvCTX -	14	4	3		5	2

[a] Tem = TEM, Shv = SHV, Ctx = CTX-M types, ampC = plasmid-borne AmpC, - = no gene detected

APPENDIX 4. MIC DISTRIBUTIONS

Enterobacter aerogenes

Drug	Number (percentage) of Minimum Inhibitory Concentrations (mg/L) at: [a]															Total	%S	%IR
	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256			
ampicillin								4 (6.1)	3 (4.5)	6 (9.1)	20 (30.3)	33 (50.0)				66	19.7%	80.3%
co-amoxyclav								2 (3.0)	4 (6.1)	2 (3.0)	6 (9.1)	52 (78.8)				66	12.1%	87.9%
Ticarcillin/clavulanate										35 (53.0)	4 (6.1)	4 (6.1)	5 (7.6)	18 (27.3)		66	59.1%	40.9%
piperacillin/tazobactam									42 (63.6)	8 (12.1)	1 (1.5)	3 (4.5)	12 (18.2)			66	77.3%	22.7%
cefazolin									13 (19.7)				53 (80.3)			66	19.7%	80.3%
cefoxitin									3 (4.5)	1 (1.5)	1 (1.5)	2 (3.0)	59 (89.4)			66	6.1%	93.9%
ceftriaxone							45 (68.2)		1 (1.5)	3 (4.5)	12 (18.2)		5 (7.6)			66	68.2%	31.8%
ceftazidime							42 (63.6)	1 (1.5)	3 (4.5)	2 (3.0)	6 (9.1)	2 (3.0)	10 (15.2)			66	69.7%	30.3%
cefepime							65 (98.5)	1 (1.5)								66	100%	
gentamicin							64 (97.0)				2 (3.0)					66	97.0%	3.0%
tobramycin							63 (95.5)		1 (1.5)	2 (3.0)						66	97.0%	3.0%
amikacin								95 (98.5)	1 (1.5)							66	100%	
nalidixic acid								28 (42.4)	26 (39.4)	2 (3.0)	4 (6.1)	6 (9.1)				66	90.9%	9.1%
ciprofloxacin					63 (95.5)	2 (3.0)	1 (1.5)									66	100%	

Drug	Number (percentage) of Minimum Inhibitory Concentrations (mg/L) at: [a]															Total	%S	%IR
	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256			
norfloxacin						59	3	4								66		
						(89.4)	(4.5)	(6.1)									100	
trimethoprim						51	5	7			3					66		
						(77.3)	(7.6)	(10.6)			(4.5)						95.5%	4.5%
Trimethoprim/sulfa							64				2					66		
							(97.0)				(3.0)						97.0%	3.0%
meropenem					65		1									66		
					(98.5)		(1.5)										100%	
tigecycline						40	16	1	1	7						66		
						(61.5)	(24.6)	(1.5)	(1.5)	(10.8)							87.7%	12.3%

[a] Shaded areas indicate ≤ and ≥ MIC values available on the Vitek ASTN083 card; vertical lines indicate CLSI M100-S21 susceptible (blue) and resistant (red) breakpoints.

Enterobacter cloacae

Drug	Number (percentage) of Minimum Inhibitory Concentrations (mg/L) at: [a]															Total	%S	%IR
	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256			
ampicillin								2 (1.0)	5 (2.5)	18 (8.9)	54 (26.7)	123 (60.9)				202	12.4%	87.6%
co-amoxyclav								4 (2.0)	4 (2.0)	2 (1.0)	14 (6.9	178 (88.1)				202	5.0%	95.0%
Ticarcillin/clavulanate										104 (51.5)	17 (8.4)	6 (3.0)	2 (1.0)	73 (36.1)		202	59.9%	40.1%
piperacillin/tazobactam									126 (62.4)	13 (6.4)	4 (2.0)	5 (2.5)	30 (14.9)	24 (11.9)		202	70.8%	29.2%
cefazolin									5 (2.5)			2 (1.0)	195 (96.5)			202	2.5%	97.5%
cefoxitin									3 (1.5)	2 (1.0)	1 (0.5)	7 (3.5)	189 (93.6)			202	2.5%	97.5%
ceftriaxone							117 (57.9)	1 (0.5)	2 (1.0)	5 (2.5)	8 (4.0)	9 (4.5)	60 (29.7)			202	57.9%	42.1%
ceftazidime							121 (60.2)	1 (0.5)	2 (1.0)		8 (4.0)	1 (0.5)	68 (33.8)			202	61.7%	38.3%
cefepime							168 (83.2)	24 (11.9)	8 (4.0)			1 (0.5)	1 (0.5)			202	99.0%	1.0%
gentamicin							176 (87.1)		7 (3.5)		19 (9.4)					202	90.6%	9.4%
tobramycin							178 (88.1)	4 (2.0)	3 (1.5)	11 (5.4)	6 (3.0)					202	91.6%	8.4%
amikacin								192 (95.0)	4 (2.0)	2 (1.0)	4 (2.0)					202	100%	
nalidixic acid								104 (51.5)	63 (31.2)	8 (4.0)	5 (2.5)	22 (10.9)				202	89.1%	10.9%
ciprofloxacin					182 (90.1)	3 (1.5)	5 (2.5)	3 (1.5)	9 (4.5)							202	94.1%	5.9%
norfloxacin						178 (88.1)	2 (1.0)	13 (6.4)	1 (0.5)	4 (2.0)	4 (2.0)					202	96.0%	4.0%

Drug	Number (percentage) of Minimum Inhibitory Concentrations (mg/L) at: [a]															Total	%S	%IR
	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256			
trimethoprim						115 (56.9)	51 (25.2)		2 (1.0)	1 (0.5)	33 (16.3)					202	83.7%	16.3%
Trimethoprim/sulfa							170 (84.2)				32 (15.8)					202	84.2%	15.8%
meropenem					200 (99.0)	1 (0.5)	1 (0.5)									202	100%	
tigecycline						86 (42.6)	96 (47.5)	15 (7.4)		5 (2.5)						202	97.5%	2.5%

[a] Shaded areas indicate ≤ and ≥ MIC values available on the Vitek ASTN083 card; vertical lines indicate CLSI M100-S21 susceptible (blue) and resistant (red) breakpoints.

Escherichia coli

Drug	Number (percentage) of Minimum Inhibitory Concentrations (mg/L) at: [a]															Total	%S	%IR
	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256			
ampicillin								677 (38.3)	153 (8.8)	65 (3.8)	15 (0.9)	835 (47.8)				1746	51.3%	48.7%
co-amoxyclav								547 (31.3)	492 (28.2)	248 (14.2)	279 (16.0)	180 (10.3)				1746	73.7%	26.3%
Ticarcillin/clavulanate										1007 (57.7)	338 (19.4)	146 (8.4)	64 (3.7)	191 (10.9)		1746	77.0%	23.0%
piperacillin/tazobactam									1643 (94.3)	60 (3.4)	5 (0.3)	9 (0.5)	15 (0.9)	11 (0.6)		1743	98.0%	2.0%
cefazolin									1384 (79.3)	44 (2.5)	88 (5.0)	14 (0.8)	216 (12.4)			1746	79.3%	20.7%
cefoxitin									1553 (88.9)	78 (4.5)	45 (2.6)	30 (1.7)	40 (2.3)			1746	93.4%	6.6%
ceftriaxone							1621 (92.8)	3 (0.2)	1 (0.1)	9 (0.5)	12 (0.7)	13 (0.7)	87 (5.0)			1746	92.8%	7.2%
ceftazidime							1635 (98.6)	2 (0.1)	35 (2.0)	1 (0.1)	58 (3.3)	1 (0.1)	14 (0.8)			1746	95.8%	4.2%
cefepime							1663 (95.2)	30 (1.7)	14 (0.8)	20 (1.1)	5 (0.3)	4 (0.2)	10 (0.6)			1746	98.9%	1.1%
gentamicin							1526 (87.4)	71 (4.1)	25 (1.4)	5 (0.3)	119 (6.8)					1746	92.9%	7.1%
tobramycin							1570 (89.9)	32 (1.8)	28 (1.6)	66 (3.8)	50 (2.9)					1746	93.4%	6.6%
amikacin								1290 (73.9)	367 (21.0)	50 (2.9)	36 (2.1)	1 (0.1)	2 (0.1)			1746	99.8%	0.2%
nalidixic acid								1330 (76.2)	127 (7.3)	34 (1.9)	8 (0.5)	247 (14.1)				1746	85.9%	14.1%
ciprofloxacin					1554 (89.0)	27 (1.5)	23 (1.3)	3 (0.2)	139 (8.0)							1746	91.9%	8.1%
norfloxacin						1501 (86.0)	13 (0.7)	91 (5.2)		7 (0.4)	134 (7.7)					1746	91.9%	8.1%

Drug	Number (percentage) of Minimum Inhibitory Concentrations (mg/L) at: [a]															Total	%S	%IR
	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256			
trimethoprim						1308 (74.9)	24 (1.4)	11 (0.6)	6 (0.3)	8 (0.5)	389 (22.3)					1746	77.7%	22.3%
Trimethoprim/sulfa							1383 (79.2)	13 (0.7)	6 (0.3)	1 (0.1)	343 (19.6)					1746	80.0%	20.0%
meropenem					1745 (99.9)		1 (0.1)									1746	100%	
tigecycline						1732 (99.3)	7 (0.4)	4 (0.2)		1 (0.1)						1744	99.9%	0.1%

[a] Shaded areas indicate ≤ and ≥ MIC values available on the Vitek ASTN083 card; vertical lines indicate CLSI M100-S21 susceptible (blue) and resistant (red) breakpoints.

Klebsiella oxytoca

Drug	Number (percentage) of Minimum Inhibitory Concentrations (mg/L) at: [a]															Total	%S	%IR
	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256			
ampicillin								1 (0.8)		3 (2.4)	26 (21.0)	94 (75.8)				124	3.2%	96.8%
co-amoxyclav								68 (54.8)	30 (24.2)	8 (6.5)	6 (4.8)	12 (9.7)				124	85.5%	14.5%
Ticarcillin/clavulanate										106 (85.5)	1 (0.8)	1 (0.8)	2 (1.6)	14 (11.3)		124	86.3%	13.7%
piperacillin/tazobactam									107 (86.3)	3 (2.4)		1 (0.8)	4 (3.2)	9 (7.3)		124	88.7%	11.3%
cefazolin									41 (33.1)	27 (21.8)	12 (9.7)	1 (0.8)	43 (34.7)			124	33.1%	66.9%
cefoxitin									118 (95.2)	3 (2.4)	1 (0.8)		2 (1.6)			124	97.6%	2.4%
ceftriaxone							111 (89.5)	1 (0.8)		8 (6.5)	3 (2.4)		1 (0.8)			124	89.5%	10.5%
ceftazidime							119 (96.0)				3 (2.4)		2 (1.6)			124	96.0%	4.0%
cefepime							123 (99.2)	1 (0.8)								124	100%	
gentamicin							119 (96.0)			1 (0.8)	4 (3.2)					124	96.0%	4.0%
tobramycin							118 (95.2)			4 (3.2)	2 (1.6)					124	95.2%	4.8%
amikacin								122 (98.4)			2 (1.6)					124	100%	
nalidixic acid								103 (83.1)	11 (8.9)	3 (2.4)	5 (4.0)	2 (1.6)				124	98.4%	1.6%
ciprofloxacin					121 (97.6)	1 (0.8)	1 (0.8)	1 (0.8)								124	99.2%	0.8%
norfloxacin						121 (97.6)		3 (2.4)								124	100%	

Drug	Number (percentage) of Minimum Inhibitory Concentrations (mg/L) at: [a]															Total	%S	%IR
	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256			
trimethoprim						113	5	1			5					124		
						(91.1)	(4.0)	(0.8)			(4.0)						96.0%	4.0%
Trimethoprim/sulfa							119				5					124		
							(96.0)				(4.0)						96.0%	4.0%
meropenem					122		1	1								124		
					(98.4)		(0.8)	(0.8)									99.2%	0.8%
tigecycline						119	2	2	1							124		
						(96.0)	(1.6)	(1.6)	(0.8)								99.2%	0.8%

[a] Shaded areas indicate ≤ and ≥ MIC values available on the Vitek ASTN083 card; vertical lines indicate CLSI M100-S21 susceptible (blue) and resistant (red) breakpoints.

Klebsiella pneumoniae

Drug	Number (percentage) of Minimum Inhibitory Concentrations (mg/L) at: [a]															Total	%S	%IR
	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256			
ampicillin								6 (1.4)	1 (0.2)	9 (2.1)	133 (31.7)	270 (64.4)				419	3.8%	96.2%
co-amoxyclav								258 (61.6)	87 (20.8)	23 (5.5)	23 (5.5)	28 (6.7)				419	87.8%	12.2%
Ticarcillin/clavulanate										331 (79.0)	34 (8.1)	16 (3.8)	7 (1.7)	31 (7.4)		419	87.1%	12.9%
piperacillin/tazobactam									360 (85.9)	40 (9.5)	4 (1.0)	3 (0.7)	3 (0.7)	9 (2.1)		419	96.4%	3.6%
cefazolin									353 (84.2)	5 (1.2)	5 (1.2)	2 (0.5)	54 (12.9)			419	84.2%	15.8%
cefoxitin									374 (89.3)	16 (3.8)	6 (1.4)	10 (2.4)	13 (3.1)			419	93.1%	6.9%
ceftriaxone							376 (89.7)	2 (0.5)	2 (0.5)	5 (1.2)	8 (1.9)	4 (1.0)	22 (5.3)			419	89.7%	10.3%
ceftazidime							376 (89.7)		9 (2.1)	1 (0.2)	10 (2.4)	3 (0.7)	20 (4.8)			419	91.9%	8.1%
cefepime							392 (93.6)	11 (2.6)	1 (0.2)	1 (0.2)	2 (0.5)	4 (1.0)	8 (1.9)			419	96.7%	3.3%
gentamicin							377 (90.0)	1 (0.2)	5 (1.2)		36 (8.6)					419	91.4%	8.6%
tobramycin							380 (90.7)	5 (1.2)	2 (0.5)	17 (4.1)	15 (3.6)					419	92.4%	7.6%
amikacin								400 (95.5)	11 (2.6)	3 (0.7)	4 (1.0)		1 (0.2)			419	99.8%	0.2%
nalidixic acid								249 (59.4)	85 (20.3)	22 (5.3)	14 (3.3)	49 (11.7)				419	88.3%	11.7%
ciprofloxacin					367 (87.6)	9 (2.1)	14 (3.3)	10 (2.4)	19 (4.5)							419	93.1%	6.9%
norfloxacin						353 (84.2)	6 (1.4)	37 (8.8)	3 (0.7)	9 (2.1)	11 (2.6)					419	95.2%	4.8%

Drug	Number (percentage) of Minimum Inhibitory Concentrations (mg/L) at: [a]															Total	%S	%IR
	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256			
trimethoprim						328	17	8	6	5	55					419		
						(78.3)	(4.1)	(1.9)	(1.4)	(1.2)	(13.1)						86.9%	13.1%
Trimethoprim/sulfa							366	10	2		41					419		
							(87.4)	(2.4)	(0.5)		(9.8)						89.7%	10.3%
meropenem					413	4	1	1								419		
					(98.6)	(1.0)	(0.2)	(0.2)									99.8%	0.2%
tigecycline						292	83	22	8	14						419		
						(69.7)	(19.8)	(5.3)	(1.9)	(3.3)							94.7%	5.3%

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