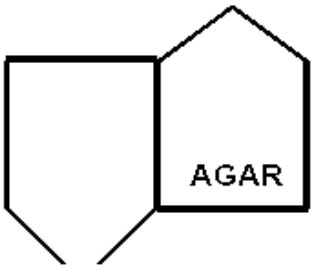

The Australian Group on Antimicrobial Resistance

Enterobacteriaceae Sepsis Outcome Programme (EnSOP)

2013 Antimicrobial Susceptibility Report

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

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2 BACKGROUND

2.1 OBJECTIVES OF THE PROGRAM

The Australian Group on Antimicrobial Resistance (AGAR) commenced surveillance of the key Gram-negative pathogens, *Escherichia coli* and *Klebsiella* species in 1992. Surveys have been conducted biennially until 2008 when annual surveys commenced alternating between community– and hospital-onset infections (http://www.agargroup.org/surveys). In 2004, another genus of Gram-negative pathogens in which resistance can be of clinical importance, Enterobacter species, was added. *E. coli* is the most common cause of community-onset urinary tract infection, while *Klebsiella* species are less common but are known to harbour important resistances. Enterobacter species are less common in the community, but of high importance due to intrinsic resistance to first-line antimicrobials in the community. Taken together, the three groups of species surveyed are considered to be valuable sentinels for multi-resistance and emerging resistance in enteric Gram-negative bacilli. In 2013 AGAR commenced the ongoing Enterobacteriaceae Sepsis Outcome Programme (EnSOP) which focuses on the prospective collection of resistance and demographic data on all isolates from patients with documented bacteraemia.

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

The objectives of the 2013 surveillance program were to:

1. Monitor resistance in Enterobacteriaceae isolated from blood cultures taken from patients presenting to the hospital or already in hospital
2. Examine the extent of co-resistance and multi-resistance in the major species, and
3. Detect emerging resistance to newer last-line agents such as carbapenems.

2.2 IMPORTANCE OF SPECIES SURVEYED

The family Enterobacteriaceae is a large collection of distantly related genuses and species sometimes referred to as the 'enteric Gram-negative bacilli'. The family contains the most common and important Gram-negative pathogens, including the *Escherichia coli*, *Klebsiella pneumoniae* and *oxytoca, Enterobacter cloacae* and *aerogenes* and *Salmonella* species. All of these named species are causes community-onset and hospital-onset Gram-negative septicaemia, where they may cause life-threatening illness. The first three genuses are key reservoirs and therefore sentinel organisms for resistances and for multi-resistance, and for the mobile genetic elements that spread resistance genes amongst members of the Enterobacteriaceae family. Broad-spectrum and even 'last-line antibiotics are now much more widely used for the treatment of Gram-negative septicaemia as a result on increasing resistance.

2.3 RELEVANCE OF ANTIMICROBIALS TESTED

2.3.1 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. Susceptible to extended-spectrum β-lactamases and to derepressed AmpC β-lactamases. Multiple specialised clinical uses. [Parenteral, extensive hospital use, strictly avoided in some hospitals]

Ceftazidime: a third-generation cephalosporin but with additional antipseudomonal activity. Susceptible to extended-spectrum ß-lactamases and to derepressed AmpC β-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]

2.3.2 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 trimethoprim or in combination with suplhamethoxazole as cotrimoxazole]

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

2.4 RESISTANCES OF CONCERN

2.4.1 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 of CTX-M types 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 cephamycins	Emerging overseas as a significant problem
Carbapenemases	Rare, but increasing	Ampicillin, amoxycillin, extended-spectrum penicillins; first-, second and third-generation cephalosporins +/-aztreonam	Have been rare in Enterobacteriaceae but now being seen for the first time locally acquired in Australia and imported from overseas

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

2.4.2 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. Plasmid-mediated quinolone resistance is emerging, but is not addressed in this report.

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.

3 STUDY DESIGN

Twenty-five institutions from each State and mainland Territories of Australia participated in the EnSOP 2013 survey. Each institution collected either all or up to 200 isolates from different patient episodes of bacteraemia. In patients with more than one isolate, a new episode was defined as a new positive blood culture more that 2 weeks after the initial positive culture.

All laboratories obtained basic laboratory information, plus the following demographic information for each patient episode. At *Bronze* level; date of collection, date of birth, gender, postcode, admission date. Enrollment at *Silver* level participating laboratories provided discharge date, ethnicity (ASTI), device related infection, principal clinical manifestation, ICU admission, outcome at 30 days, and date of death. Additional provision of principal antimicrobial treatment was obtained with *Gold* level enrollment.

Table 2. Level of Participation

State	Number of Institutions	Level of Participation		
		Bronze	*Silver*	*Gold*
Australian Capital Territory (ACT)	1	1		
New South Wales (NSW)	4			4
Northern Territory (NT)	1			1
Queensland (QLD)	6	1	2	3
South Australia (SA)	3	1		2
Tasmania (TAS)	1			1
Victoria (VIC)	5	1		4
Western Australia (WA)	4	1		3
Total	25	5	2	18

3.1 METHODS

3.1.1 SPECIES IDENTIFICATION

Isolates sampled were all members of the Enterobacteriaceae family. Isolates were identified using the routine method for each institution; Vitek®, Phoenix™ Automated Microbiology System, or where available mass spectrometry (MALDI-TOF).

3.1.2 SUSCEPTIBILITY TESTING

Testing was performed by two commercial semi-automated methods, Vitek® 2 (BioMérieux) (n=23) or Phoenix™ (BD) (n=2), which are calibrated to the ISO reference standard method of broth microdilution. Commercially available Vitek® 2 AST-N246 (n=22), Vitek® 2 AST-N247 (n=1), Phoenix™ NMIC/ID-80 or Phoenix™ NMIC-203 cards were utilized by all participants throughout the survey period.

The CLSI M100-A24[1] and EUCAST v4.0[2] breakpoints from January 2014 have been employed in the analysis. For analysis of cefazolin, breakpoints of ≤4 for susceptible, ≥8 for resistant were applied due to the restricted minimum inhibitory concentration (MIC) range available on the commercial cards, recognising that the January 2014 breakpoint is actually susceptible ≤2 mg/L.

3.1.3 ANTIBIOTICS TESTED

Table 3. Antimicrobials Tested

	Breakpoints (mg/L)						
	CLSI M100 [a]				EUCAST v4.0 [b]		
Antimicrobial Agent	**S**	**SDD**	**I**	**R**	**S**	**I**	**R**
Ampicillin	≤ 8		16	≥ 32	≤ 8	.	≥ 16
Amoxicillin-Clavulanic Acid	≤ 8/4		16/8	≥ 32/16	≤ 8	.	≥ 16
Amikacin	≤ 16		32	≥ 64	≤ 8	16	≥ 32
Aztreonam	≤ 4		8	≥ 16	≤ 1	2 - 4	≥ 8
Ceftazidime	≤ 4		8	≥ 16	≤ 1	2 - 4	≥ 8
Ciprofloxacin	≤ 1		2	≥ 4	≤ 1	2 - 4	≥ 8
Ciprofloxacin (*Salmonella* spp.)[c]	≤ 0.06		0.12 - 0.5	≥ 1	≤ 0.06	.	≥ 0.12
Ceftriaxone	≤ 1		2	≥ 4	≤ 1	2	≥ 4
Cephalothin	≤ 4		8	≥ 16	-	-	-
Cefazolin (Australian)[d]	≤ 2		4	≥ 8	-	-	-
Cephalexin	-		-	-	≤ 16	.	≥ 32
Cefepime	≤ 2	4 - 8	-	≥ 16	≤ 1	2 - 4	≥ 8
Cefoxitin	≤ 8		16	≥ 32	-	-	-
Chloramphenicol	≤ 8		16	≥ 32	≤ 8	.	≥ 16
Colistin	-		-	-	≤ 2	.	≥ 4
Ertapenem	≤ 0.5		1	≥ 2	≤ 0.5	1	≥ 2
Fosfomycin	≤ 64		128	≥ 256	≤ 32	.	≥ 64
Gentamicin	≤ 4		8	≥ 16	≤ 2	4	≥ 8
Imipenem	≤ 1		2	≥ 4	≤ 2	4 - 8	≥ 16
Meropenem	≤ 1		2	≥ 4	≤ 2	4 - 8	≥ 16
Moxifloxacin	-		-	-	≤ 0.5	1	≥ 2
Nitrofurantoin	≤ 32		64	≥ 128	≤ 64	.	≥ 128
Norfloxacin	≤ 4		8	≥ 16	≤ 0.5	1	≥ 2
Tetracycline	≤ 4		8	≥ 16	-	-	-
Ticarcillin-Clavulanic Acid	≤ 16/2		32/2 - 64/2	≥ 128/2	≤ 8	16	≥ 32
Tigecycline	-		-	-	≤ 1	2	≥ 4
Trimethoprim	≤ 8		-	≥ 16	≤ 2	4	≥ 8
Trimethoprim-Sulfamethoxazole	≤ 2/38		-	≥ 4/76	≤ 2/38	4/76	≥ 8/152
Tobramycin	≤ 4		8	≥ 16	≤ 2	4	≥ 8
Piperacillin-Tazobactam	≤ 16/4		32/4 - 64/4	≥ 128/4	≤ 8	16	≥ 32

[a] The breakpoints selected to determine resistance are described in Performance Standards for Antimicrobial Susceptibility Testing: Twenty-forth Information Supplement, CLSI document M100-S24, January 2014

[b] The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0, 2014. http://www.eucast.org.

[c] Concentration range available on the cards restricts ability to determine susceptible category.

[d] For analysis, breakpoints of ≤4 mg/L for susceptible and ≥8 mg/L for resistant were appied due to the MIC range available on the Vitek card, recognising that the January 2013 breakpoint is actually susceptible ≤ 2 mg/L

3.1.4 MOLECULAR CONFIRMATION OF RESISTANCE

E. coli, *Klebsiella* spp., *Proteus* spp. and *Salmonella* spp. with ceftazidime or ceftriaxone MIC >1 mg/L, or cefoxitin MIC >8 mg/L; any other Enterobacteriaceae with cefepime MIC >1 mg/L; all isolates with ciprofloxacin MIC > 0.25 mg/L; and all isolates with meropenem MIC >0.25 mg/L were referred to a central laboratory (SA Pathology) for molecular confirmation of resistance.

All referred isolates were screened for the presence of the bla_{TEM}, and bla_{SHV} genes using a real-time polymerase chain reaction (PCR) platform (LC-480) and published primers.[3,4] A multiplex real-time TaqMan PCR was used to detect CTX-M-type genes.[5] Strains were probed for plasmid-borne AmpC enzymes using the method described by Pérez-Pérez and Hanson,[6]. and subjected to molecular tests for MBL (bla_{VIM}, bla_{IMP}, and bla_{NDM}), bla_{KPC}, and $bla_{OXA-48-like}$ genes using real-time PCR.[7,8] Known plasmid mediated quinolone resistance (PMQR) mechanisms (Qnr, efflux (*qepA*, *oqxAB*), and *aac(6')-Ib-cr*) were examined by PCR on all referred isolates with ciprofloxacin MIC>0.25 mg/L using published methods.[9,10] All referred *E. coli* were examined for phylogenetic group and membership of the O25b-ST131 clone and its *H30*- and *H30*-Rx subclones.[11-13]

3.1.5 QUALITY CONTROL

Quality control strains utilised were those recommended by CLSI/EUCAST standards.

4 ISOLATES RECOVERED

All isolates were identified to species level wherever possible. For this report, *E. cloacae* complex includes *E. cloacae* , *E. asburiae, and E. kobei.*

A total of 4,952 isolates (46 species, 19 genera) were isolated from patients with bacteraemia. Three genera, *Escherichia coli* (59.7%), *Klebsiella* spp. (18.1%) and *Enterobacter* spp. (8.6%) contributed 86.4% of all isolates. The top ten species according to rank were *E. coli* (59.7%), *K. pneumoniae* (14.7%), *E. cloacae* complex (6.2%), *Proteus mirabilis* (3.7%), *K. oxytoca* (3.3%), *Serratia marcescens* (3.2%), *E. aerogenes* (2.0%), *Salmonella* (non-Typhi) species (1.6%), *Morganella morganii* (1.1%) and *Citrobacter koseri* (1.0%). These ten species comprised 97.4% of all isolates.

Table 4. Isolates recovered

	Total		NSW/ACT	QLD/NT	SA	VIC/TAS	WA
Species	**4952 (%)**		**1099**	**1341**	**563**	**1077**	**872**
Escherichia coli	2954	59.7	61.9	54.4	67.7	56.7	63.2
Klebsiella pneumoniae	727	14.7	12.6	16.8	13.3	14.8	14.9
Enterobacter cloacae	309	6.2	5.5	8.6	3.0	6.6	5.3
Proteus mirabilis	182	3.7	4.5	3.3	3.2	3.2	4.2
Klebsiella oxytoca	163	3.3	3.7	2.2	2.7	4.7	3.1
Serratia marcescens	156	3.2	3.7	4.1	1.8	3.5	1.4
Enterobacter aerogenes	98	2.0	2.3	1.9	1.6	1.9	1.9
Salmonella spp. (non Typhi/Paratyphi)	78	1.6	0.6	2.5	1.1	2.3	0.7
Morganella morganii	54	1.1	1.2	0.9	1.1	1.2	1.1
Citrobacter koseri	51	1.0	0.7	1.5	0.7	0.6	1.5
Citrobacter freundii	38	0.8	0.8	0.7	0.4	1.1	0.6
Salmonella Typhi/Paratyphi	23	0.5	0.5	0.2	0.9	0.4	0.7
Pantoea agglomerans	13	0.3	0.2	0.1	0.5	0.5	0.1
Raoultella ornithinolytica	11	0.2	0.5	0.1	0.4	0.1	0.1
Enterobacter asburiae	11	0.2	0.2	0.2	0.4	0.2	0.2
Other species (total n=31)	84	1.7	1.2	2.3	1.4	2.2	0.9

4.1 ONSET OF BACTERAEMIA

Information on place of onset of bacteraemia was available for 4,784 (97%) episodes. An episode was designated healthcare-onset (HO) if the first positive blood culture was collected >48 h after admission. Overall, 24% of episodes were

HO, although differences were observed with different species. The proportion of HO episodes for the top 12 species is ahown in Table 5:

Table 5. Proportion of Healthcare-onset episodes (top 12 species)

Organism	Total	Community-onset (CO)	Healthcare -onset (HO)	%HO
Escherichia coli	2852	2398	454	15.9%
Klebsiella pneumoniae	704	468	236	33.5%
Enterobacter cloacae	302	157	145	48.0%
Proteus mirabilis	178	135	43	24.2%
Klebsiella oxytoca	158	99	59	37.3%
Serratia marcescens	145	75	70	48.3%
Enterobacter aerogenes	95	47	48	50.5%
Salmonella species (non Typhi)	72	64	8	11.1%
Morganella morganii	51	40	11	21.6%
Citrobacter koseri	50	32	18	36.0%
Citrobacter freundii	38	25	13	34.2%
Salmonella Typhi/Paratyphi	23	23		0.0%
Other species (n=34)	116	74	42	36.2%
All species	4784	3637	1147	24.0%

4.1.1 ONSET VERSUS 30-DAY ALL CAUSE MORTAILTY

The 30-day all-cause mortality was available for 3432 episodes of bacteraemia where onset was known.

Table 6. Onset versus 30-day all-cause Mortality (top 12 species)

	Total			Community-onset			Healthcare-onset			
Organism	N	Mortality (%)		N	Mortality (%)		N	Mortality (%)		P*
Escherichia coli	1986	183	(9.2)	1654	136	(8.2)	332	47	(14.2)	P <0.01
Klebsiella pneumoniae	538	78	(14.5)	351	44	(12.5)	187	34	(18.2)	ns
Enterobacter cloacae	232	27	(11.6)	120	15	(12.5)	112	12	(10.7)	ns
Proteus mirabilis	144	21	(14.6)	109	16	(14.7)	35	5	(14.3)	ns
Klebsiella oxytoca	102	12	(11.8)	69	6	(8.7)	33	6	(18.2)	ns
Serratia marcescens	112	10	(8.9)	55	2	(3.6)	57	8	(14.0)	ns
Enterobacter aerogenes	72	11	(15.3)	34	5	(14.7)	38	6	(15.8)	ns
Salmonella species (non Typhi)	45	1	(2.2)	39	0	(0.0)	6	1	(16.7)	ns
Citrobacter koseri	39	4	(10.3)	25	2	(8.0)	14	2	(14.3)	ns
Morganella morganii	35	1	(2.9)	28	1	(3.6)	7	0	(0.0)	ns
Citrobacter freundii	29	1	(3.4)	19	0	(0.0)	10	1	(10.0)	ns
Salmonella Typhi/Paratyphi	18	0	(0.0)	18	0	(0.0)	0			
All species	3432	360	(10.5)	2572	233	(9.1)	860	127	(14.8)	

* Fisher's exact test for difference in mortality between community- and hospital-onset

5 PATIENT DEMOGRAPHICS

5.1 AGE AND GENDER

Age and gender were available for 4,883 patients. The sex ratio (number of males to 100 females) was 114

Table 7. Gender versus Decade of Life

Decade	Female	Male	Total	M/100F
1	72	119	191	165
2	40	27	67	68
3	131	62	193	47
4	122	87	209	71
5	172	183	355	106
6	286	353	639	123
7	391	568	959	145
8	394	619	1013	157
9	491	472	963	96
10	179	106	285	59
11	6	3	9	50
Total	**2284**	**2599**	**4883**	**114**

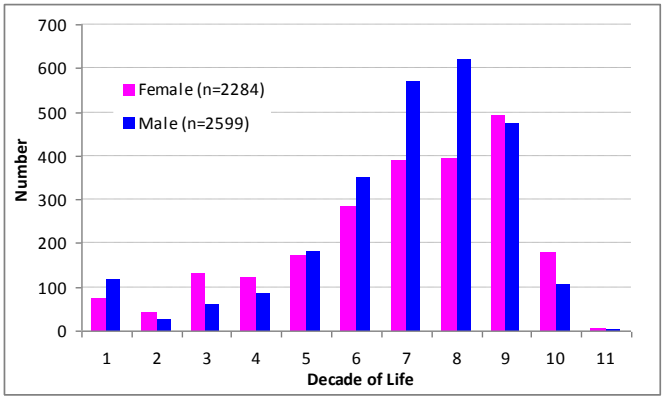


Figure 1. Gender versus Decade of Life

5.2 ABORIGINAL/TORRES STRAIT ISLANDER

Ethnicity (Aboriginal or Torres Strait Islander) was available for 4,165 patient episodes from 21 institutions.

Table 8. Aboriginal or Torres Strait Islander

Region (n)	Isolates	Aboriginal	Torres Strait Islander	Both	ATSI (range across institutions)	
NSW/ACT (4)	908	4			0.4%	(0.0 - 1.6)
QLD/NT (7)	1338	97	18	1	8.7%	(0.0 - 44.4)
SA (2)	232	5			2.2%	(1.1- 7.0)
VIC/TAS (5)	914	8			0.9%	(0.0 – 4.1)
WA (3)	773	46			6.0%	(2.9 - 9.0)
AUS (21)	4165	160	18	1	4.3%	(0.0 - 44.4)

5.3 PRINCIPAL CLINICAL MANIFESTATION

Principal Clinical Manifestation was provided for 3829 patient episodes.

Table 9. Principal Clinical Manifestation

Principal Clinical Manifestation	Total	Male	Female	P*
Urinary tract infection	1676	766	910	p <0.01
Biliary tract infection (including cholangitis)	556	345	211	p <0.01
No focus (e.g. febrile neutropenia)	536	316	220	p <0.01
Intra-abdominal infection other than biliary tract	405	238	167	0.01 < p <0.05
Other clinical syndrome	276	159	117	ns
Device-related infection without metastatic focus	244	135	109	ns
Skin and skin structure	94	69	25	p <0.01
Device-related infection with metastatic focus	19	13	6	ns
Osteomyelitis/septic arthritis	17	9	8	ns
Unknown	6	2	4	
All	**3829**	**2052**	**1777**	

* Fisher's exact test for difference between males and females

5.4 LENGTH OF STAY POST BACTERAEMIC EPISODE

Length of stay (post bacteraemia) was available for 3,919 episode

Table 10. Length of Stay Post Bacteraemic Episode

Length of Stay (days)	Total (%)		Median
< 7	1769	(45.1)	4
7 - 14	1213	(31.0)	9
15 - 30	588	(15.0)	19
31 - 60	265	(6.8)	41
> 60	84	(2.1)	84
	3919		**7 days**

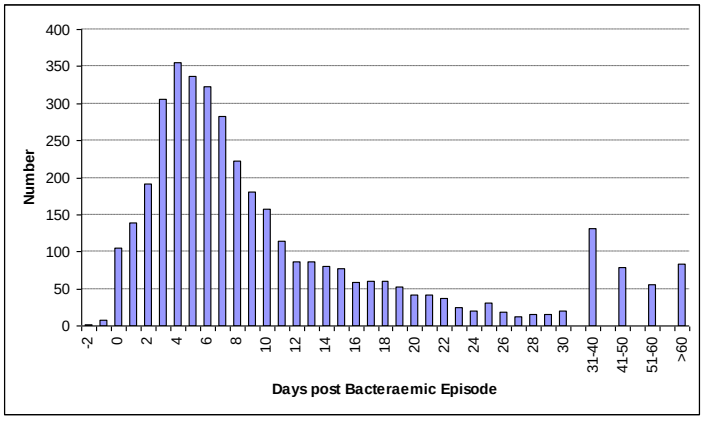


*Figure 2. Length of Stay Post Bacteraemic Episode **

* A negative value indicates that the blood culture was taken at least 24 hours prior to patient admission

5.5 PRINCIPAL ANTIMICROBIAL TREATMENT AND 30-DAY ALL-CAUSE MORTALITY

The top five principal antimicrobial treatments for the top 10 species vs 30-day all-cause mortality (where both treatment and outcome are known) is shown in Table 9. The principal antimicrobial treatment was included in the table if used for more than one bacteraemic episode for species recovered.

Table 11. Top Five Principal Antimicrobial Treatments versus 30-day all-cause Mortality

Species	Antimicrobial Agent	Number	(% of n)	Died	(% mortality)
Escherichia coli	Ceftriaxone	529	(28.4)	31	(5.9)
(n=1862)	Piperacillin-tazobactam	528	(28.4)	52	(9.8)
	Meropenem	207	(11.1)	18	(8.7)
	Ampicillin	150	(8.1)	8	(5.3)
	Ciprofloxacin	90	(4.8)	1	(1.1)
	Other	303	(16.3)	23	(7.6)
	Not treated	55	(3.0)	37	(67.3)
Klebsiella pneumoniae	Piperacillin-tazobactam	196	(39.8)	24	(12.2)
(n=493)	Ceftriaxone	109	(22.1)	9	(8.3)
	Meropenem	69	(14.0)	5	(7.2)
	Ciprofloxacin	26	(5.3)	1	(3.8)
	Cefazolin	13	(2.6)	0	(0.0)
	Other	68	(13.8)	19	(27.9)
	Not treated	12	(2.4)	10	(83.3)
Enterobacter cloacae	Meropenem	132	(63.8)	13	(9.8)
(n=207)	Piperacillin-tazobactam	27	(13.0)	4	(14.8)
	Ciprofloxacin	20	(9.7)	1	(5.0)
	Ceftriaxone	6	(2.9)	2	
	Gentamicin	5	(2.4)	0	
	Other	16	(7.7)	3	(18.8)
	Not treated	1	(0.5)	1	
Proteus mirabilis	Piperacillin-tazobactam	39	(28.7)	6	(15.4)
(n=136)	Ceftriaxone	29	(21.3)	5	(17.2)
	Ampicillin	23	(16.9)	0	(0.0)
	Meropenem	12	(8.8)	0	(0.0)
	Ciprofloxacin	8	(5.9)	0	
	Other	18	(13.2)	0	(0.0)
	Not treated	7	(5.1)	7	
Serratia marcescens	Meropenem	63	(65.6)	1	(1.6)
(n=96)	Ciprofloxacin	13	(13.5)	0	(0.0)
	Piperacillin-tazobactam	7	(7.3)	2	
	Cefepime	5	(5.2)	2	
	Gentamicin	3	(3.1)	0	
	Other	4	(4.2)	0	
	Not treated	1	(1.0)	1	
Klebsiella oxytoca	Piperacillin-tazobactam	36	(38.3)	2	(5.6)
(n=94)	Ceftriaxone	26	(27.7)	2	(7.7)
	Meropenem	12	(12.8)	2	(16.7)
	Ciprofloxacin	7	(7.4)	1	
	Amoxycillin-clavulanate	3	(3.2)	0	

Species	Antimicrobial Agent	Number	(% of n)	Died	(% mortality)
	Other	8	(8.5)	0	
	Not treated	2	(2.1)	1	
Enterobacter aerogenes **(n=69)**	Meropenem	38	(55.1)	4	(10.5)
	Piperacillin-tazobactam	9	(13.0)	3	
	Ciprofloxacin	6	(8.7)	1	
	Cefepime	6	(8.7)	0	
	Ceftriaxone	3	(4.3)	0	
	Other	6	(8.7)	1	
	Not treated	1	(1.4)	1	
Salmonella **species (non Typhi) (n=38)**	Ceftriaxone	27	(71.1)	0	
	Ciprofloxacin	4	(10.5)	0	
	Piperacillin-tazobactam	2	(5.3)	0	
	Ampicillin	1	(2.6)	0	
	Gentamicin	1	(2.6)	0	
	Other	4	(10.5)	0	
	Not treated	1	(2.3)	0	
Citrobacter koseri **(n=34)**	Ceftriaxone	10	(29.4)	0	(0.0)
	Piperacillin-tazobactam	10	(29.4)	1	(10.0)
	Meropenem	6	(17.6)	2	
	Ciprofloxacin	3	(8.8)	0	
	Gentamicin	2	(5.9)	0	
	Other	3	(8.8)	1	
Morganella morganii **(n=31)**	Meropenem	13	(41.9)	0	(0.0)
	Ciprofloxacin	7	(22.6)	0	
	Piperacillin-tazobactam	5	(16.1)	0	
	Other	6	(19.4)	1	
Citrobacter freundii **(n=29)**	Meropenem	19	(65.5)	1	(5.3)
	Ciprofloxacin	3	(10.3)	0	
	Piperacillin-tazobactam	2	(6.9)	0	
	Cefepime	2	(6.9)	0	
	Other	3	(10.3)	0	
Salmonella **Typhi/Paratyphi (n=17)**	Ceftriaxone	16	(94.1)	0	(0.0)
	Amoxycillin	1	(5.9)	0	

6 SUSCEPTIBILITY TESTING RESULTS

Overall percentages of resistance or non-susceptibility for *E. coli*, *Klebsiella* spp. (*K. pneumoniae* and *K. oxytoca*) and *Enterobacter* spp. (*E. cloacae* and *E. aerogenes*) are shown in Section 7.1 and the Appendix. Appendix 1 shows the details of percentages susceptible, intermediate and resistant for each antibiotic and all species. 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 IN INDICATOR SPECIES (NATIONAL PRIORITY)

For Table 12 to Table 25, the percentage resistant/non-susceptible is presented for both CLSI and EUCAST criteria respectabilty.

Table 12. Ampicillin

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	673	730	379	610	524	2916
	%I	1.2 / -	2.3 / -	1.3 / -	2.6 / -	2.3 / -	2.0 / -
	%R	51.3 / 52.5	51.9 / 54.2	41.7 / 43.0	50.8 / 53.4	52.1 / 54.4	50.2 / 52.2
***Salmonella* species (non Typhi/Paratyphi)**	n	7	34	6	25	6	78
	%I	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -
	%R	0.0 / 0.0	5.9 / 5.9	33.3 / 33.3	8.0 / 8.0	0.0 / 0.0	7.7 / 7.7
***S.* Typhi/Paratyphi**	n	5	3	5	4	6	23
	%I	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -
	%R	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0

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 13. Amoxycillin-clavulanate

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	673	730	378	610	524	2915
	%I	14.3 /	13.6 /	8.5 /	13.6 /	13.7 /	13.1 /
	%R	5.9 /	8.9 /	4.2 /	6.1 /	6.9 /	6.7 /
K. pneumoniae	n	134	223	75	159	124	715
	%I	3.0 /	6.3 /	6.7 /	9.4 /	1.6 /	5.6 /
	%R	1.5 /	3.1 /	2.7 /	7.5 /	5.6 /	4.2 /
K. oxytoca	n	40	29	15	51	26	161
	%I	5.0 /	6.9 /	0.0 /	0.0 /	11.5 /	4.3 /
	%R	5.0 /	13.8 /	6.7 /	7.8 /	7.7 /	8.1 /
***Salmonella* species (non Typhi/Paratyphi)**	n	7	34	6	25	6	78
	%I	0.0 /	0.0 /	0.0 /	0.0 /	0.0 /	0.0 /
	%R	0.0 /	0.0 /	16.7 /	0.0 /	0.0 /	1.3 /
***S.* Typhi/Paratyphi**	n	5	3	5	4	6	23
	%I	0.0 /	0.0 /	0.0 /	0.0 /	0.0 /	0.0 /
	%R	0.0 /	0.0 /	0.0 /	0.0 /	0.0 /	0.0 /

* For EUCAST interpretation, the clavulanate is fixed at 2 mg/L, rather than a 2:1 ratio used in CLSI guidelines. As all cards used have a 2:1 ratio of clavulanate no EUCAST category has been applied.

Comments: Intermediate susceptibility or resistance to amoxycillin-clavulanate is intrinsic in *Enterobacter* spp., 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* spp. due to higher levels of natural ß-lactamases.

Table 14. Ticarcillin-clavulanate

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	673	730	379	609	524	2915
	%R	7.7 / 21.5	8.6 / 16.7	6.6 / 17.4	8.0 / 17.7	9.2 / 17.7	8.1 / 18.3
K. pneumoniae	n	134	224	75	159	124	716
	%R	3.0 / 3.7	4.5 / 8.9	6.7 / 10.7	10.1 / 17.0	5.6 / 7.3	5.9 / 9.6
E. cloacae	n	60	115	17	71	44	307
	%R	30.0 / 35.0	20.0 / 24.3	29.4 / 29.4	21.1 / 23.9	20.5 / 27.3	22.8 / 27.0
K. oxytoca	n	40	29	15	51	26	161
	%R	7.5 / 10.0	20.7 / 20.7	6.7 / 6.7	7.8 / 7.8	11.5 / 19.2	10.6 / 12.4
E. aerogenes	n	25	26	9	21	16	97
	%R	24.0 / 28.0	11.5 / 15.4	33.3 / 44.4	38.1 / 42.9	43.8 / 43.8	27.8 / 32.0
***Salmonella* species (non Typhi/Paratyphi)**	n	7	34	6	25	6	78
	%R	0.0 / 0.0	0.0 / 0.0	16.7 / 33.3	0.0 / 4.0	0.0 / 0.0	1.3 / 3.8
***S.* Typhi/Paratyphi**	n	5	3	5	4	6	23
	%R	0.0 / 0.0	0.0 / 0.0.	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0

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

Table 15. Piperacillin-tazobactam

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	673	730	379	589	523	2894
	%R	1.9 / 5.1	3.4 / 6.4	2.9 / 4.5	2.5 / 6.6	4.6 / 7.8	3.0 / 6.2
K. pneumoniae	n	134	224	75	158	124	715
	%R	1.5 / 3.0	2.7 / 7.1	6.7 / 9.3	7.0 / 10.1	4.8 / 5.6	4.2 / 7.0
E. cloacae	n	60	115	17	68	44	304
	%R	18.3 / 28.3	15.7 / 19.1	17.6 / 29.4	17.6 / 20.6	15.9 / 15.9	16.8 / 21.4
K. oxytoca	n	40	29	15	49	26	159
	%R	10.0 / 10.0	20.7 / 24.1	6.7 / 6.7	8.2 / 8.2	15.4 / 15.4	11.9 / 12.6
E. aerogenes	n	25	26	9	21	16	97
	%R	16.0 / 24.0	11.5 / 15.4	11.1 / 33.3	23.8 / 38.1	43.8 / 43.8	20.6 / 28.9
***Salmonella* species (non Typhi/Paratyphi)**	n	7	34	6	24	6	77
	%R	0.0 / 0.0	0.0 / 0.0	0.0 / 16.7	0.0 / 0.0	0.0 / 0.0	0.0 / 1.3
***S.* Typhi/Paratyphi**	n	5	3	5	4	6	23
	%R	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0

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

Table 16. Cefazolin

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	640	708	379	442	276	2445
	%R	20.5 / -	19.4 / -	14.2 / -	21.9 / -	18.5 / -	19.2 / -
K. pneumoniae	n	127	217	75	117	63	599
	%R	3.1 / -	12.0 / -	9.3 / -	17.9 / -	3.2 / -	10.0 / -
E. cloacae	n	58	114	17	59	21	269
	%R	87.9 / -	95.6 / -	100 / -	98.3 / -	95.2 / -	94.8 / -
K. oxytoca	n	38	29	15	42	16	140
	%R	52.6 / -	62.1 / -	53.3 / -	66.7 / -	81.3 / -	62.1 / -
E. aerogenes	n	25	24	9	15	10	83
	%R	76.0 / -	66.7 / -	88.9 / -	86.7 / -	90.0 / -	78.3 / -
***Salmonella* species (non Typhi/Paratyphi)**	n	7	31	6	19	2	65
	%R	0.0 / -	0.0 / -	16.7 / -	0.0 / -	0.0 / -	1.5 / -
***S.* Typhi/Paratyphi**	n	3	3	5	4	3	18
	%R	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -

Comments: Interpretation based on MIC range available on Vitek/Phoenix cards, which currently do not match those of the CLSI breakpoints published in 2013. For this analysis, susceptible was defined as ≤ 4mg/L, Resistant as ≥8 mg/L (no intermediate range). Resistance to cefazolin, representative of first generation cephalosporins, is common in *E. coli* and *Klebsiella* spp. *Enterobacter* spp. are intrinsically resistant due to natural ß-lactamases.

Table 17. Cefoxitin

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	673	730	379	610	524	2916
	%R	3.0 / -	4.1 / -	1.3 / -	2.1 / -	3.1 / -	2.9 / -
K. pneumoniae	n	135	223	75	159	124	716
	%R	0.7 / -	4.5 / -	4.0 / -	8.2 / -	2.4 / -	4.2 / -
K. oxytoca	n	40	29	15	51	26	161
	%R	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -
***Salmonella* species (non Typhi/Paratyphi)**	n	7	34	6	25	6	78
	%R	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -
***S.* Typhi/Paratyphi**	n	5	3	5	4	6	23
	%R	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -

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* spp. have an intrinsic AmpC β-lactamase, they will test as resistant or intermediate

Table 18. Ceftriaxone

Species		NSW*/ACT	QLD/NT	SA*	VIC/TAS	WA	Australia
E. coli	n	673	730	379	610	524	2916
	%NS	9.7 / 9.7	5.6 / 5.6	5.6 / 5.6	10.0 / 10.0	6.3 / 6.3	7.6 / 7.6
K. pneumoniae	n	135	224	75	159	124	717
	%NS	2.2 / 2.2	7.1 / 7.1	1.3 / 1.3	12.6 / 12.6	4.0 / 4.0	6.3 / 6.3
E. cloacae	n	60	115	17	71	44	307
	%NS	33.3 / 33.3	23.5 / 23.5	29.4 / 29.4	26.8 / 26.8	20.5 / 20.5	26.0 / 26.0
K. oxytoca	n	40	29	15	51	26	161
	%NS	7.5 / 7.5	13.8 / 13.8	0.0 / 0.0	7.8 / 7.8	3.8 / 3.8	7.4 / 7.4
E. aerogenes	n	25	26	9	21	16	97
	%NS	24.0 / 24.0	15.4 / 15.4	44.4 / 44.4	33.3 / 33.3	43.8 / 43.8	28.9 / 28.9
***Salmonella* species (non Typhi/Paratyphi)**	n	7	34	6	25	6	78
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0
***S.* Typhi/Paratyphi**	n	5	3	5	4	6	23
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0

* Ceftriaxone concentration range (Phoenix™ cards) unable to differentiate the intermediate from the susceptible category; for this report some ceftriaxone-intermediate isolates may be called sensitive.

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

Table 19. Ceftazidime

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	673	730	379	607	524	2913
	%NS	5.5 / 8.9	3.2 / 4.7	2.6 / 5.3	5.3 / 8.9	3.2 / 6.3	4.1 / 6.9
K. pneumoniae	n	135	224	75	159	124	717
	%NS	2.2 / 2.2	3.1 / 7.6	2.7 / 2.7	11.3 / 11.9	4.0 / 4.8	4.9 / 6.6
E. cloacae	n	60	115	17	71	44	307
	%NS	30.0 / 31.7	20.9 / 23.5	11.8 / 29.4	25.4 / 28.2	18.2 / 22.7	22.8 / 26.4
K. oxytoca	n	40	29	15	50	26	160
	%NS	2.5 / 2.5	3.4 / 3.4	0.0 / 0.0	0.0 / 2.0	0.0 / 0.0	1.2 / 1.9
E. aerogenes	n	25	26	9	21	16	97
	%NS	24.0 / 28.0	15.4 / 15.4	44.4 / 44.4	33.3 / 38.1	43.8 / 43.8	28.9 / 30.9
***Salmonella* species (non Typhi/Paratyphi)**	n	7	34	6	25	6	78
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0
***S.* Typhi/Paratyphi**	n	5	3	5	4	6	23
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0

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

Table 20. Cefepime

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	671	730	379	609	524	2913
	%NS	4.9 / 8.0	1.5 / 3.4	3.4 / 4.7	4.8 / 8.4	3.2 / 5.0	3.5 / 6.0
K. pneumoniae	n	135	224	75	159	124	717
	%NS	2.2 / 2.2	2.7 / 5.4	0.0 / 1.3	5.7 / 10.7	1.6 / 2.4	2.8 / 5.0
E. cloacae	n	60	115	17	71	44	307
	%NS	1.7 / 6.7	4.3 / 12.2	11.8 / 17.6	5.6 / 12.7	2.3 / 13.6	4.2 / 11.7
K. oxytoca	n	40	29	15	51	26	161
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	2.0 / 2.0	0.0 / 0.0	0.6 / 0.6
E. aerogenes	n	25	26	9	21	16	97
	%NS	0.0 / 4.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 1.0
***Salmonella* species (non Typhi/Paratyphi)**	n	7	34	6	25	6	78
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0
***S.* Typhi/Paratyphi**	n	5	3	5	4	6	23
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0

Comments: %NS includes SDD category for CLSI interpretation. In *E. coli* and *Klebsiella* spp. non-susceptibility to cefepime is suggestive of mixed or hyperproduction of extended-spectrum ß-lactamases. In *Enterobacter* spp. non-susceptibility is suggestive of the presence of acquired extended-spectrum ß-lactamases

Table 21. Meropenem

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	673	730	379	609	524	2915
	%NS	0.1 / 0.1	0.3 / 0.3	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.1 / 0.1
K. pneumoniae	n	135	224	75	159	124	717
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	2.5 / 2.5	0.8 / 0.0	0.7 / 0.6
E. cloacae	n	60	115	17	71	44	307
	%NS	1.7 / 1.7	7.0 / 7.0	5.9 / 5.9	2.8 / 2.8	2.3 / 0.0	4.2 / 3.9
K. oxytoca	n	40	29	15	51	26	161
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0
E. aerogenes	n	25	26	9	21	16	97
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0
***Salmonella* species (non Typhi/Paratyphi)**	n	7	34	6	25	6	78
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0
***S.* Typhi/Paratyphi**	n	5	3	5	4	6	23
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.04

Comments: Non-susceptibility in Enterobacteriaceae suggests the possible presence of carbapenemases. However, isolates that contain ESBL or de-repressed AmpC enzymes and have decreased permeability may have meropenem MICs elevated above wild-type.

Table 22. Ciprofloxacin

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	673	730	379	609	524	2915
	%NS	12.2 /13.2	7.5 / 8.4	9.0 / 10.6	10.5 / 11.0	12.8 / 13.9	10.4 / 11.3
K. pneumoniae	n	135	224	75	159	124	717
	%NS	1.5 / 3.7	4.9 / 6.2	12.0 / 13.3	5.0 / 11.9	2.4 / 4.8	4.6 / 7.5
E. cloacae	n	60	115	17	71	44	307
	%NS	6.7 / 6.7	0.0 / 4.3	11.8 / 11.8	5.6 / 9.9	0.0 / 0.0	3.3 / 5.9
K. oxytoca	n	40	29	15	51	26	161
	%NS	2.5 / 2.5	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.6 / 0.6
E. aerogenes	n	25	26	9	21	16	97
	%NS	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	4.8 / 9.5	0.0 / 0.0	1.0 / 2.1
***Salmonella* species ***	n	7	34	6	25	6	78
(non Typhi/Paratyphi)	%NS	0.0 / 0.0	2.9 / 2.9	16.7 / 16.7	8.0 / 8.0	0.0 / 0.0	5.1 / 5.1
***S.* Typhi/Paratyphi ***	n	5	3	5	4	6	23
	%NS	80.0 / 80.0	33.3 / 33.3	0.0 / 0.0	50.0 / 50.0	66.7 / 66.7	47.8 / 47.8

* Ciprofloxacin concentration range available on the cards used restricts ability to accurately determine susceptible CLSI/EUCAST) and intermediate (CLSI) categories for *Salmonella* species.

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

Table 23. Gentamicin

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	673	730	379	609	524	2915
	%R	10.1 / 10.1	5.8 / 6.0	6.6 / 6.6	8.5 / 8.5	7.4 / 7.6	7.8 / 7.9
K. pneumoniae	n	135	224	75	159	124	717
	%R	2.2 / 2.2	4.0 / 4.0	5.3 / 5.3	5.0 / 5.7	2.4 / 2.4	3.8 / 3.9
E. cloacae	n	60	115	17	71	44	307
	%R	10.0 / 15.0	9.6 / 9.6	11.8 / 11.8	7.0 / 8.5	0.0 / 0.0	7.8 / 9.1
K. oxytoca	n	40	29	15	51	26	161
	%R	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	3.8 / 3.8	0.6 / 0.6
E. aerogenes	n	25	26	9	21	16	97
	%R	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0
***Salmonella* species**	n	7	34	6	25	6	78
(non Typhi/Paratyphi)	%R	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	4.0 / 4.0	0.0 / 0.0	1.3 / 1.3
***S.* Typhi/Paratyphi**	n	5	3	5	4	6	23
	%R	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0

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

Table 24. Trimethoprim

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	673	708	379	610	437	2807
	%R	29.3 / 34.5	29.5 / 29.8	16.1 / 19.0	28.5 / 28.7	26.3 / 26.3	26.9 / 28.7
K. pneumoniae	n	135	217	75	159	104	690
	%R	8.9 / 10.4	18.0 / 19.4	10.7 / 17.3	20.8 / 22.0	4.8 / 5.8	14.1 / 15.9
E. cloacae	n	60	114	17	71	40	302
	%R	21.7 / 25.0	27.2 / 27.2	17.6 / 17.6	14.1 / 16.9	7.5 / 7.5	19.9 / 21.2
K. oxytoca	n	40	29	15	51	23	158
	%R	5.0 / 7.5	6.9 / 6.9	0.0 / 0.0	2.0 / 2.0	0.0 / 0.0	3.2 / 3.8
E. aerogenes	n	25	24	9	21	15	94
	%R	0.0 / 0.0	0.0 / 0.0	11.1 / 11.1	9.5 / 9.5	0.0 / 0.0	3.2 / 3.2
***Salmonella* species (non Typhi/Paratyphi)**	n	7	31	6	25	5	74
	%R	0.0 / 0.0	6.5 / 6.5	0.0 / 0.0	4.0 / 4.0	0.0 / 0.0	4.1 / 4.1
***S.* Typhi/Paratyphi**	n	5	3	5	4	4	21
	%R	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0

Comments: Trimethoprim resistance is the result of mutations in the gene encoding dihydrofolate reductase (DHFR) or acquisition of a gene encoding a new low affinity DHFR.

Table 25. Nitrofurantoin

Species		NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
E. coli	n	671	730	379	610	524	2914
	%R	1.2 / 1.2	1.8 / 1.8	1.6 / 1.6	0.7 / 0.7	1.7 / 1.7	1.4 / 1.4
K. pneumoniae	n	135	223	75	159	124	716
	%R	38.5 / -	37.2 / -	50.7 / -	34.6 / -	28.2 / -	36.7 / -
E. cloacae	n	60	114	17	71	44	306
	%R	23.3 / -	16.7 / -	58.8 / -	18.3 / -	11.4 / -	19.9 / -
K. oxytoca	n	40	29	15	51	26	161
	%R	0.0 / -	3.4 / -	6.7 / -	2.0 / -	3.8 / -	2.5 / -
E. aerogenes	n	25	26	9	21	16	97
	%R	48.0 / -	53.8 / -	55.6 / -	57.1 / -	50.0 / -	52.6 / -
***Salmonella* species (non Typhi/Paratyphi)**	n	7	34	6	25	6	78
	%R	14.3 / -	2.9 / -	16.7 / -	12.0 / -	0.0 / -	7.7 / -
***S.* Typhi/Paratyphi**	n	5	3	5	4	6	23
	%R	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -	0.0 / -

* For EUCAST interpretative breakpoints apply for *E. coli* only

Comments: Nitrofurantoin resistance in *K. pneumoniae* is mostly attributable to the resistance breakpoint falling within the wild-type distribution.

6.2 MAJOR RESISTANCES – MOLECULAR STUDIES

6.2.1 EXTENDED-SPECTRUM β-LACTAMASES

Extended-spectrum ß-lactamases (ESBLs) 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 appeared: the presence of ESBLs in *Enterobacter* species, and the emergence of specific types of ESBLs (so-called CTX-M enzymes) in *E. coli* strains in the community. The latter is part of a global epidemic. It is unclear what is driving this community expansion of CTX-M ESBLs in Australia, as third-generation cephalosporins are not widely used in that setting. It is likely to be driven by cross-resistance and co-resistance to agents used in community practice. There is also increasing recognition of ESBLs becoming established in long-term care facilities in Australia. ESBLs are important because they compromise the efficacy of third-generation cephalosporins which have been such a useful therapeutic alternative for infections in patients presenting from the community, as evidenced by the freuqncy with which ceftriaxone was used for treatment in this survey. ESBL-harbouring strains frequently possess co-resistance to other non β-lactam agents. This can result in delays in the use of effective empiric therapy, with a lack of available oral options for treatment resulting in excess hospitalisation, and in the setting of sepsis, increased mortality.

Most ESBL-producing strains will be captured/recognised using the CLSI/EUCAST ceftriaxone "susceptible" breakpoint of 1 mg/L. The "susceptible" breakpoint of 4 mg/L for ceftazidime is less sensitive for ESBL detection, but an MIC > 1mg/L is more sensitive. **Isolates with either ceftriaxone or ceftazidime MICs above 1 mg/L were selected for 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. However, due to card range limitations, **isolates with a cefepime MIC > 1mg/L were selected for molecular testing**.

Molecular testing involved 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, from 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 that 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 classified as carrying an ESBL in this report*. All CTX-M genes encode ESBLs, as do plasmid-borne AmpC genes effectively.

Table 26. Presumptive and Confirmed Extended-spectrum β-lactamase Production

Species	NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
Escherichia coli	680	731	381	611	551	2954
ESBL phenotype	73	46	26	64	37	246
Ceftriaxone > 1 mg/L	9.6%	5.6%	5.5%	10.0%	5.8%	7.4%
Ceftazidime > 1 mg/L	8.8%	4.7%	5.2%	8.8%	5.8%	6.8%
Either of above	10.7%	6.3%	6.8%	10.5%	6.7%	8.3%
Confirmed						
any ESBL* (No. received)	58/68	39/45	15/22	57/64	28/36	197/235
CTX-M types	50	26	13	54	27	170
plasmid-borne AmpC	8	13	2	3	1	27
SHV	2	2	0	0	0	4
Klebsiella pneumoniae	138	225	75	159	130	727
ESBL phenotype	3	18	2	20	6	49
Ceftriaxone > 1 mg/L	2.2%	7.1%	1.3%	12.6%	3.8%	6.2%
Ceftazidime > 1 mg/L	2.2%	7.6%	2.7%	11.9%	4.6%	6.5%
Either of above	2.2%	8.0%	2.7%	12.6%	4.6%	6.7%
Confirmed						
any ESBL* (No. received)	2/2	13/18	2/2	17/20	4/6	38/48

Species	NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
CTX-M types	2	12	1	13	3	31
plasmid-borne AmpC	0	0	1	1	2	4
TEM	2	10	2	14	2	30
Klebsiella oxytoca	41	29	15	51	27	163
ESBL phenotype	3	4	0	4	1	12
Ceftriaxone > 1 mg/L	7.3%	13.8%	0.0%	7.8%	3.7%	7.4%
Ceftazidime > 1 mg/L	2.4%	3.4%	0.0%	0.0%	0.0%	1.2%
Either of above	7.3%	13.8%	0.0%	7.8%	3.7%	7.4%
Confirmed						
any ESBL* (No. received)	1/3	1/4	-	0/4	0/1	2/12 †
CTX-M types	1	0	-	0	0	1
SHV	0	1	-	0	0	1
Proteus mirabilis	49	44	18	34	37	182
ESBL phenotype	2	0	1	1	0	4
Ceftriaxone > 1 mg/L	4.1%	0.0%	5.6%	0.0%	0.0%	1.6%
Ceftazidime > 1 mg/L	2.0%	0.0%	0.0%	2.9%	0.0%	1.1%
Either of above	4.1%	0.0%	5.6%	2.9%	0.0%	2.2%
Confirmed						
any ESBL* (No. received)	2/2	-	1/1	0/1	-	3/4
CTX-M types	1	-	1	0	-	2
plasmid-borne AmpC	1	-	0	0	-	1
TEM	1	-	1	0	-	2

* Strains may possess more than one type of ESBL gene
† See text for explanantion of low proportion of ESBL

Based on the tests performed in this study, ESBLs were more common among *E. coli* (6.7% confirmed) and *K. pneumoniae* (5.2% confirmed). For *Enterobacter* species with cefepime MIC > 1 mg/L, 15/33 *E. cloacae* (45%, 4.9% overall) and 0/1 *E. aerogenes* contained an ESBL. Of identified ESBLs, *E. cloacae* contained the following types: TEM and SHV-types (n=5), CTX-M group 1 and TEM (n=4), CTX-M group 9 only (n=3), and TEM only (n=3).

The majority (83%) of *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, have borderline resistance to cefepime, but remain susceptible to ceftazidime. This pattern is not typical of other types of ESBL.

There was a notable presence of CTX-M enzymes in *E. coli.* One hundred and seventy of 197 (86%) confirmed ESBLs had CTX-M types; CTX-M group 1 (n=97), CTX-M group 9 (n=72), and CTX-M group 1 + CTX-M group 9 (n=1)). Over half of the *E. coli* with CTX-M group 1 types were found to belong to the O25b-ST131 clone, all were CTX-M-15-like (n=52) or CTX-M-3-like (n=2). O25b-ST131 accounted for 66% (88/133) of *E. coli* ESBL phenotypes that were ciprofloxacin resistant (MIC >1 mg/L), and only 2% (2/84) of ciprofloxacin susceptible ESBL phenotypes. Among *K. pneumoniae* with confirmed ESBLs, 31/38 (82%) contained CTX-M types; CTX-M group 1 (n=28) and CTX-M group 9 (n=3).

ESBL phenotypes were significantly more likely to be found among healthcare- than community-onset episodes of *E. coli* (p=0.0017) and *E. cloacae* (p =0.0003) bacteraemia compared to all other species combined (Fisher's exact test). No significant difference was noted among *K. pneumoniae* (P=0.3475) for healthcare- versus community-onset.

6.2.2 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 six 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 27. Presumptive plasmid-borne AmpC ß-lactamase Production

Species	NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
Escherichia coli	673	730	379	610	524	2916
Cefoxitin ≥ 32 mg/L	20 (3.0%) [0.8% - 7.6%]	30 (4.1%) [1.9% - 9.8%]	5 (1.3%) [0.0% - 2.2%]	13 (2.1%) [0.0% - 2.5%]	16 (3.1%) [2.3% - 7.0%]	84 (2.9%) [0.0% - 9.8%]
Confirmed (no. received)	8/18	13/30	2/5	3/12	1/16	27/81
bla_{CMY-2}	8	10	2	3	0	23
bla_{DHA-1}	0	3	0	0	1	4
Klebsiella pneumoniae	135	223	75	159	124	716
Cefoxitin ≥ 32 mg/L	1 (0.7%) [0.0% - 2.9%]	10 (4.5%) [0.0% - 7.1%]	3 (4.0%) [0.0% - 4.5%]	13 (8.2%) [0.0% - 17.1%]	3 (2.4%) [0.0% - 3.8%]	30 (4.2%) [0.0% - 17.1%]
Confirmed (no. received)	0/1	0/9	1/2	1/10	2/2	4/24
bla_{DHA-1}	0	0	1	1	1	3
bla_{CMY-2}	0	0	0	0	1	1
Proteus mirabilis	49	44	18	34	35	180
Cefoxitin ≥ 32 mg/L	1 (2.0%) [0.0% - 14.3%]	1 (2.3%) [0.0% - 10.0%]	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.1%) [0.0% - 14.3%]
Confirmed (no. received)	1/1	0/1				1/2
bla_{CMY-4}	1	0				1

The proportions of *E. coli* and *K. pneumoniae* with elevated cefoxitin MICs were low. Only 33% (27/81) of cefoxitin-resistant *E. coli* and 14% (4/29) of *K. pneumoniae* that were available for molecular confirmation were confirmed to contain plasmid-borne AmpC. bla_{CMY-2} was found in 76% (25/33) of isolates with plasmid-borne AmpC genes. A high proportion (16/23, 70%) of *E. coli* with bla_{CMY-2} belonged to phylogenetic group D. Carbapenamase genes (bla_{IMP-4}, n=1; bla_{KPC-2}, n=3) were detected in four of the cefoxitin-resistant *K. pneumoniae* from Victoria that did not have plasmid-borne AmpC genes. One E. coli with a cefoxitin MIC = 16 mg/L (intermediate) also contained bla_{DHA-1}.

6.2.3 CARBAPENEMASES

Fourteen (0.3%) isolates from 12 patients were found to harbour a carbapenemase gene. bla_{IMP-4} was detected in nine strains (*E. cloacae* (4), *Citrobacter* spp., (2) *E. coli* (1), *S. marcescens* (1), *K. pneumoniae* (1); bla_{KPC-2} was detected in three *K. pneumoniae* isolates (two patients, one with two bacteraemic episodes); and bla_{NDM-7} in one patient with two bacteraemic episodes. Nine of 11 isolates with confirmed metallo-β-lactamases also contained plasmid-mediated quinolone resistance genes (*aac(6')Ib-cr* alone or with *qnrA* or *qnrB*).

Table 28. Carbapenemases and Associated Resistance genes

Gene	State	Species	Meropenem MIC (mg/L)	ESBL Types [a]	PMQR [b]	16S rRNA methylases
***bla*$_{IMP-4}$**	ACT	*C. freundii* (n=1)	8	- [c]	*aac(6')Ib-cr*	-
		C. amalonaticus (n=1)	≥16	TEM	*qnrB*	-
	NSW	*E. cloacae* (n=1)	≥16	TEM, SHV	*aac(6')Ib-cr, qnrB*	-
	QLD	*E. coli* (n=1)	≥16	TEM	-	-
		E. cloacae (n=2)	≥16	TEM	*aac(6')Ib-cr, qnrA*	-
		E. cloacae (n=1)	≥16	TEM, SHV	*aac(6')Ib-cr, qnrB*	-
	VIC	*K. pneumoniae* (n=1)	4	TEM, SHV, CTX-M-15	*aac(6')Ib-cr, qnrB*	-
		S. marcescens (n=1)	≥16	TEM	-	-
***bla*$_{KPC-2}$**	VIC	*K. pneumoniae* (n=1)	≥16	SHV	-	-
		K. pneumoniae (n=2) [d]	≥16	TEM, SHV	-	-
***bla*$_{NDM-7}$**	QLD	*E. cloacae* (n=2) [d]	≥16	TEM, CTX-M-15	*aac(6')Ib-cr, qnrB*	-

[a] TEM types, SHV types, CTX-M types, pAmpC
[b] *aac(6')Ib-cr*, Qnr, efflux (*qepA*, *opxAB*)
[c] not detected
[d] One patient, two admissions

6.2.4 QUINOLONE RESISTANCE

Quinolone resistance is most commonly due to mutations in DNA gyrase and topoisomerase IV. More recently plasmid-mediated quinolone resistance (PMQR) has emerged in Enterobacteriaceae. PMQR may be due to the presence of qnr genes (*qnrA*, *qnrB*, *qnrS*, q*nrC*, *qnrD*), *aac(6')-Ib-cr*, encoding for a variant aminoglycoside acetyltransferase enzyme; or genes encoding for efflux pumps (*qepA*, *oqxAB*).

Table 29. Plasmid-mediated quinolone resistance

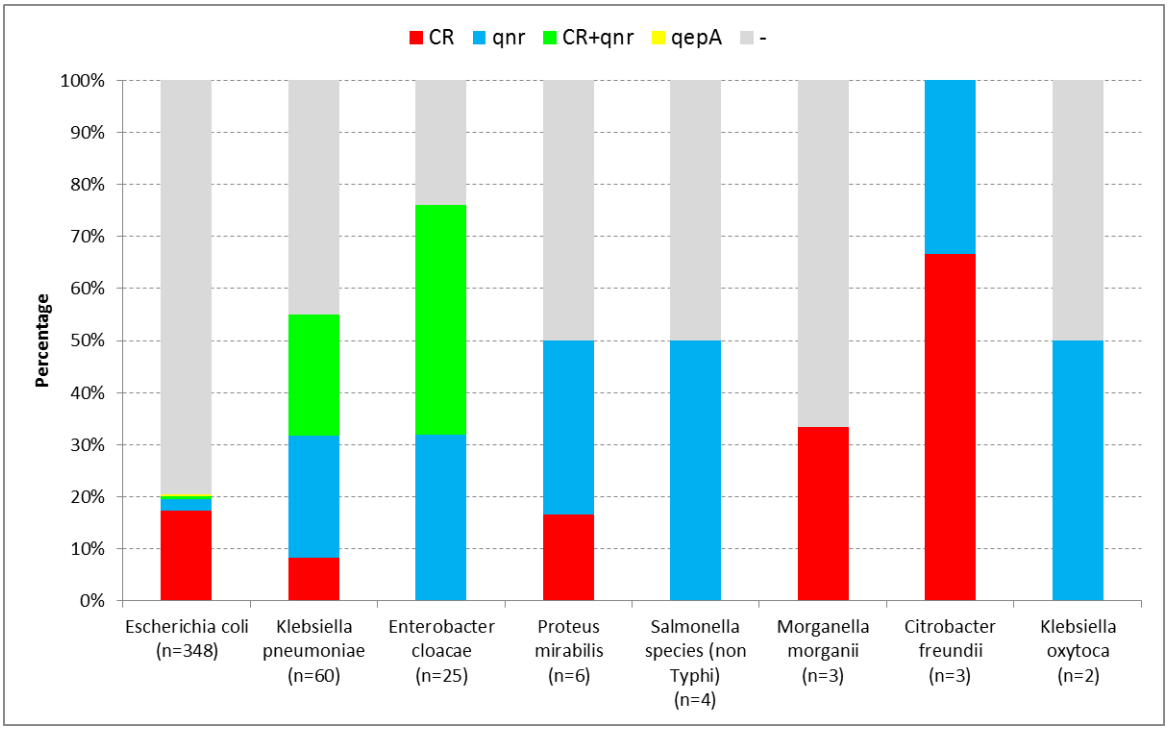
Species	NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
Escherichia coli	100	68	43	75	82	368
Ciprofloxacin >0.25 mg/L*	14.7% [9.2 - 17.8]	9.3% [5.3 - 11.5]	11.2% [9.1 - 13.0]	12.3% [6.3 - 19.1]	14.9% [13.6 - 16.8]	12.4% [5.3 - 19.1]
Confirmed (no. received)	20/91	13/66	3/36	22/75	13/79	71/347 **[20.5%]**
aac(6')-Ib-cr	17	12	3	19	9	60
qnrS	2	0	0	1	3	6
qnrA	0	0	0	1	0	1
qnrB	0	1	0	0	0	1
aac(6')-Ib-cr + qnrS	0	0	0	0	1	1
aac(6')-Ib-cr + qnrA	1	0	0	0	0	1
QepA	0	0	0	1	0	1
Klebsiella pneumoniae	8	17	12	22	9	68
Ciprofloxacin >0.25 mg/L*	5.8% [0.0 – 10.7]	7.6% [0.0 – 27.3]	16.0% [9.1 - 20.0]	13.8% [6.7 – 25.7]	6.9% [0.0 – 9.4]	9.4% [0.0 – 27.3]
Confirmed (no. received)	2/7	14/17	2/9	11/19	4/8	33/60 **[55.0%]**
aac(6')-Ib-cr	1	1	1	1	1	5
qnrB	0	7	0	2	0	9
qnrS	0	1	0	2	2	5
aac(6')-Ib-cr + qnrB	1	5	1	6	1	14

Species	NSW/ACT	QLD/NT	SA	VIC/TAS	WA	Australia
Enterobacter cloacae	6	10	3	8	1	28
Ciprofloxacin >0.25 mg/L*	10.0% [0.0 – 18.2]	8.7% [0.0 – 27.3]	15.8% [0.0 – 30.0]	11.3% [0.0 – 25.0]	2.2% [0.0 - 4.8]	9.0% [0.0 – 30.0]
Confirmed (no. received)	4/6	8/10	2/2	4/6	1/1	19/25 **[76.0%]**
qnrA	0	0	0	2	1	3
qnrS	1	0	2	0	0	3
qnrB	0	2	0	0	0	2
aac(6')-Ib-cr + *qnrA*	3	2	0	2	0	7
aac(6')-Ib-cr + *qnrB*	0	4	0	0	0	4

* Isolates with ciprofloxacin MIC <=0.5 mg/L were excluded from followup due to Phoenix NMIC/ID-80 card range limitation

The proportion and type of PMQR determinant found among isolates with ciprofloxacin MIC >0.25 mg/L varied among the different species (Figure 2). *Aac(6')-Ib-cr*, with or without Qnr, was dominant, and was present in six of the species.

Figure 3. Proportion of Plasmid-mediated quinolone resistance genes among species with ciprofloxacin MIC >0.25 mg/L



CR = *aac(6')-Ib-cr*; qnr = qnrA, qnrB or qnrS

- = no PMQR detected; resistance likely due to mutations in DNA gyrase and topoisomerase IV

6.2.5 *Escherichia coli* SEQUENCE TYPE 131

Sequence type 131 (O25b-ST131) is the predominant *E. coli* lineage among extraintestinal pathogenic *E. coli* worldwide. ST131 isolates are commonly reported to produce ESBLs, such as CTX-M-15, and almost all ST-131 with CTX-M-15 are resistant to fluoroquinolones.

Most of the strains with an ESBL phenotype harboured genes of the CTX-M type (170/218, 78%). Over half (54/98) of the *E. coli* with CTX-M group 1 types (CTX-M-15 like) were found to belong to the O25b-ST131 lineage. O25b-ST131 accounted for 67% (88/132) of *E. coli* ESBL phenotypes that were ciprofloxacin resistant (MIC >1 mg/L), and only 2% (2/86) of ciprofloxacin susceptible ESBL phenotypes. Ninety-four percent (88/90) and 57% (51/90) of O25b-ST131 with an ESBL phenotype were associated with *H30* and *H30*-Rx subclones, respectively, which have a reported association with more antibiotic resistances and greater virulence potential.[12] The *H30*-Rx subclone of ST131 often carried $bla_{CTX\text{-}M\text{-}15}$ and *aac(6')-Ib-cr.* As expected, > 99% of *E. coli* isolates received that were associated with the O25b-ST131 clone belonged to phylogenetic group B2.

Table 30. E. coli O25b-ST131 clone and ESBL phenotype

ESBL Type	N	*O25b-ST131*	*Non-O25b-ST131*
ESBL Phenotype	**218**	**90**	**128**
CTX-M types	170	88 (52%)	82 (48%)
CTX-M-15 like	98	54	44
H30 (*H30*-Rx) subclones	53 (50)	53 (50)	0 (0)
Non CTX-M-15 like	72	34	38
H30 (*H30*-Rx) subclones	34 (0)	33 (0)	1 (0)
Non CTX-M types	48	2 (4%)	46 (96%)
H30 (*H30*-Rx) subclones	2 (0)	2 (1)	0 (0)
ESBL with ciprofloxacin MIC > 1 mg/L	132	88 (67%)	44 (33%)
H30 (*H30*-Rx) subclones	89 (51)	88 (51)	1 (0)
ESBL with ciprofloxacin MIC ≤ 1 mg/L	86	2 (2%)	84 (98%)
H30 (*H30*-Rx) subclones	0 (0)	0 (0)	0 (0)

* includes one strain with both CTX-M group-1 and CTX-M group-9 enzymes

6.3 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 ESBL phenoptyp (MIC >1 mg/L to ceftriaxone or ceftazidime) which were resistant to other drug classes is shown in Table 22:

Table 31. Co-resistance percentages in strains with ESBL phenotype

Species	ESBL Phenotype Category	Ciprofloxacin	Gentamicin	Trimethoprim
Escherichia coli (n=246)	%I	1.6%	1.2%	0.4%
	%R	58.1%	41.1%	60.5%
Klebsiella pneumoniae (n=49)	%I	22.4%	2.0%	0.0%
	%R	44.9%	44.9%	89.1%

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

6.4 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.

Only isolates where the full range of antimicrobial agents were tested are included for multi-drug resistance determination. Note: Some institutions had either supressed reporting of cefazolin or used panels that did not include this agent. The agents included/excluded for each species are listed in the legend after Table 43.

Table 32. Multiple acquired resistance in Escherichia coli [a]

	Non-multi-resistant						Multi-resistant											
Region	**Total**	**0**	**1**	**2**	**3**	**%**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**%**
NSW/ACT	636	261	121	120	45	86.0%	33	14	19	16	2	4	1					14.0%
QLD/NT	708	294	137	145	55	89.1%	29	14	18	6	8	2						10.9%
SA	378	202	70	56	22	92.6%	7	6	8	4	3							7.4%
VIC/TAS	433	181	82	68	38	85.2%	25	11	16	6	5		1					14.8%
WA	276	127	52	47	22	89.9%	9	8	5	4	1	1						10.1%
Total	*2431*	*1065*	*462*	*436*	*182*	*88.2%*	*103*	*53*	*66*	*36*	*19*	*7*	*2*					*11.8%*

Table 33. Multiple acquired resistance in Klebsiella pneumoniae [b]

	Non-multi-resistant						Multi-resistant										
Region	**Total**	**0**	**1**	**2**	**3**	**%**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**%**
NSW/ACT	126	76	40	6	1	97.6%				1		1	1				2.4%
QLD/NT	217	112	66	20	2	92.2%	3	4	6	3	1						7.8%
SA	75	34	24	10	3	94.7%	1	2			1						5.3%
VIC/TAS	117	63	27	7	3	85.5%	3	7	1	1		1		2	2		14.5%
WA	63	45	13	3	1	99.4%			1								1.6%
Total	*598*	*330*	*170*	*46*	*10*	*93.0%*	*7*	*13*	*8*	*5*	*2*	*2*	*1*	*2*	*2*		*7.0%*

Table 34. Multiple acquired resistance in Enterobacter cloacae [c]

	Non-multi-resistant						Multi-resistant						
Region	**Total**	**0**	**1**	**2**	**3**	**%**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**%**
NSW/ACT	60	29	10	2	9	83.3%	5	4	1					16.7%
QLD/NT	114	58	28	4	9	86.8%	7	5	1	1	1			13.2%
SA	17	5	6	1	3	88.2%			1		1			11.8%
VIC/TAS	68	43	7	4	6	88.2%	3	2	1	1	1			11.8%
WA	40	27	4	2	5	95.0%	1	1						5.0%
Total	*299*	*162*	*55*	*13*	*32*	*87.6%*	*16*	12	*4*	*2*	3			*12.4%*

Table 35. Multiple acquired resistance in Proteus mirabilis [a]

		Non-multi-resistant					Multi-resistant										
Region	**Total**	**0**	**1**	**2**	**3**	**%**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**%**
NSW/ACT	46	1	25	12	5	93.5%	2				1							6.5%
QLD/NT	42	1	21	13	3	90.5%	3	1										9.5%
SA	18	4	7	5	1	94.4%							1					5.6%
VIC/TAS	26		15	7	2	92.3%	2											7.7%
WA	18	2	10	4	1	94.4%	1											5.6%
Total	*150*	*8*	*78*	*41*	*12*	*92.7%*	*8*	*1*			*1*		*1*					*7.3%*

Table 36. Multiple acquired resistance in Klebsiella oxytoca [b]

		Non-multi-resistant					Multi-resistant									
Region	**Total**	**0**	**1**	**2**	**3**	**%**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**%**
NSW/ACT	38	16	16	3	1	94.7%	2										5.3%
QLD/NT	29	9	13	2	2	89.7%	3										10.3%
SA	15	7	6	1	1	100%											0.0%
VIC/TAS	41	13	23	2	1	95.1%	2										4.9%
WA	16	3	11	2		100%											0.0%
Total	*139*	*48*	*69*	*10*	*5*	*95.0%*	*7*										*5.0%*

Table 37. Multiple acquired resistance in Serratia marcescens [c]

		Non-multi-resistant					Multi-resistant							
Region	**Total**	**0**	**1**	**2**	**3**	**%**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**%**
NSW/ACT	41		39	2		100%								0.0%
QLD/NT	54		51	2	1	100%								0.0%
SA	10		9	1		100%								0.0%
VIC/TAS	28	1	26			96.4%			1					3.6%
WA	9		9			100%								0.0%
Total	*142*	*1*	*134*	*5*	*1*	*99.3%*			*1*					*0.7%*

Table 38. Multiple acquired resistance in Enterobacter aerogenes [c]

		Non-multi-resistant					Multi-resistant							
Region	**Total**	**0**	**1**	**2**	**3**	**%**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**%**
NSW/ACT	25	10	9	1	3	92.0%	2							8.0%
QLD/NT	24	9	12	1	1	95.8%	1							4.2%
SA	9	3	1	1	2	77.8%	2							22.2%
VIC/TAS	21	4	9	2	3	85.7%	3							14.3%
WA	15	3	5		5	86.7%	2							13.3%
Total	94	29	36	5	14	*89.4%*	10							*10.6%*

Table 39. Multiple acquired resistance in Salmonella species (non-Typhi/Paratyphi) [a]

		Non-multi-resistant					Multi-resistant										
Region	Total	0	1	2	3	%	4	5	6	7	8	9	10	11	12	13	14	%
NSW/ACT	7	6	1			100%												0.0%
QLD/NT	31	27	3	1		100%												0.0%
SA	6	3	2		1	100%												0.0%
VIC/TAS	19	15	2	1		94.7%	1											5.3%
WA	2	2				100%												0.0%
Total	65	53	8	2	1	*98.5%*	1											*1.5%*

Table 40. Multiple acquired resistance in Morganella morganii [c]

		Non-multi-resistant					Multi-resistant							
Region	Total	0	1	2	3	%	4	5	6	7	8	9	10	%
NSW/ACT	13		10	2	1	100%								0.0%
QLD/NT	12		11	1		100%								0.0%
SA	6	2	4			100%								0.0%
VIC/TAS	11		8	1	2	100%								0.0%
WA	8	1	6	1		100%								0.0%
Total	50	3	39	5	3	*100%*								*0.0%*

Table 41. Multiple acquired resistance in Citrobacter koseri [c]

		Non-multi-resistant					Multi-resistant							
Region	Total	0	1	2	3	%	4	5	6	7	8	9	10	%
NSW/ACT	8	8				100%								0.0%
QLD/NT	20	18	1			95.0%		1						5.0%
SA	4	4				100%								0.0%
VIC/TAS	6	6				100%								0.0%
WA	11	10	1			100%								0.0%
Total	49	46	2			*98.0%*		1						*2.0%*

Table 42. Multiple acquired resistance in Citrobacter freundii [c]

		Non-multi-resistant					Multi-resistant							
Region	Total	0	1	2	3	%	4	5	6	7	8	9	10	%
NSW/ACT	9	5		2	1	88.9%			1					11.1%
QLD/NT	10	6	2	1		90.0%		1						10.0%
SA	2	1		1		100%								0.0%
VIC/TAS	9	6	1			77.8%	1		1					22.2%
WA	4	4				100%								0.0%
Total	34	22	3	4	1	*88.2%*	1	1	*2*					*11.8%*

Table 43. Multiple acquired resistance in Salmonella Typhi/Paratyphi [a]

		Non-multi-resistant					Multi-resistant										
Region	**Total**	**0**	**1**	**2**	**3**	**%**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**%**
NSW/ACT	3		3			100%												0.0%
QLD/NT	3	3				100%												0.0%
SA	5	5				100%												0.0%
VIC/TAS	4	2	2			100%												0.0%
WA	3	1	2			100%												0.0%
Total	18	11	7			*100%*												*0.0%*

Legend: (Tables 32 to 43)

[a] **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.

[b] **Antibiotics included**: amoxycillin-clavulanate, piperacillin-tazobactam, cefazolin, cefoxitin, ceftriaxone, ceftazidime, cefepime, gentamicin, amikacin, ciprofloxacin, nitrofurantoin, trimethoprim, meropenem
Antibiotics excluded: ampicillin, ticarcillin-clavulanate, tobramycin, norfloxacin, nalidixic acid, sulfamethoxazole-trimethoprim

[c] **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

6.5 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, patient throughput, patient complexity and local antibiotic use patterns very much determine the types of resistance likely to be observed.

2. Although data have been collected from 25 large laboratories across Australia, it is unclear how representative the sample is of Australia as a whole, i.e. what proportion of the population are served by these laboratories. Further it is likely that the proportion of the population served differs across the jurisdictional groupings used in this report.

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APPENDIX 1. SUSCEPTIBILITY RESULTS BY REGION

Summary reports for all species can be accessed by following the snapshot or pdf hyperlink. You will need the snapshot viewer (free download) for the snp file. National reports provide summary susceptbility data (number and percent (if more than 10 isolates) using both CLSI and EUCAST interpretative guidelines for all species isolated. Where more than ten isolates this data is seperated into regional summaries.

National Reports	
Amikacin.snp	Amikacin.pdf
Amoxicillin-clavulanate.snp	Amoxicillin-clavulanate.pdf
Ampicillin.snp	Ampicillin.pdf
Cefazolin.snp	Cefazolin.pdf
Cefepime.snp	Cefepime.pdf
Cefoxitin.snp	Cefoxitin.pdf
Ceftazidime.snp	Ceftazidime.pdf
Ceftriaxone.snp	Ceftriaxone.pdf
Ciprofloxacin.snp	Ciprofloxacin.pdf
Gentamicin.snp	Gentamicin.pdf
Meropenem.snp	Meropenem.pdf
Nitrofurantoin.snp	Nitrofurantoin.pdf
Norfloxacin.snp	Norfloxacin.pdf
Piperacillin-tazobactam.snp	Piperacillin-tazobactam.pdf
Ticarcillin-clavulanate.snp	Ticarcillin-clavulanate.pdf
Tobramycin.snp	Tobramycin.pdf
Trimethoprim.snp	Trimethoprim.pdf

Regional Reports	
Amikacin.snp	Amikacin.pdf
Amoxicillin-clavulanate.snp	Amoxicillin-clavulanate.pdf
Ampicillin.snp	Ampicillin.pdf
Cefazolin.snp	Cefazolin.pdf
Cefepime.snp	Cefepime.pdf
Cefoxitin.snp	Cefoxitin.pdf
Ceftazidime.snp	Ceftazidime.pdf
Ceftriaxone.snp	Ceftriaxone.pdf
Ciprofloxacin.snp	Ciprofloxacin.pdf
Gentamicin.snp	Gentamicin.pdf
Meropenem.snp	Meropenem.pdf
Nitrofurantoin.snp	Nitrofurantoin.pdf
Norfloxacin.snp	Norfloxacin.pdf
Piperacillin-tazobactam.snp	Piperacillin-tazobactam.pdf
Ticarcillin-clavulanate.snp	Ticarcillin-clavulanate.pdf
Tobramycin.snp	Tobramycin.pdf
Trimethoprim.snp	Trimethoprim.pdf

APPENDIX 2. ANTIBIOTIC PROFILES BY FREQUENCY

Only isolates where the full range of antimicrobial agents were tested are included in the profiles. The regional antibiotic profiles for the top 12 species can be accessed by following the hyperlinks. Profiles are generated using CLSI guidelines.

Citrobacter freundii.snp	*Citrobacter freundii*.pdf
Citrobacter koseri.snp	*Citrobacter koseri*.pdf
Enterobacter aerogenes.snp	*Enterobacter aerogenes*.pdf
Enterobacter cloacae.snp	*Enterobacter cloacae*.pdf
Escherichia coli.snp	*Escherichia coli*.pdf
Klebsiella oxytoca.snp	*Klebsiella oxytoca*.pdf
Klebsiella pneumoniae.snp	*Klebsiella pneumoniae*.pdf
Morganella morganii.snp	*Morganella morganii*.pdf
Proteus mirabilis.snp	*Proteus mirabilis*.pdf
Salmonella spp. (non-Typhi/Paratyphi).snp	*Salmonella* spp. (nonTyphi/Paratyphi).pdf
Salmonella Typhi/Paratyphi.snp	*Salmonella* Typhi/Paratyphi.pdf
Serratia marcescens.snp	*Serratia marcescens*.pdf