Annual survey of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, 2013

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Up until 2005, national surveillance of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (ESBL-E) was based on diagnostic laboratories referring all isolates to ESR for confirmation. This continuous surveillance ceased in 2005 and was replaced with annual surveys.

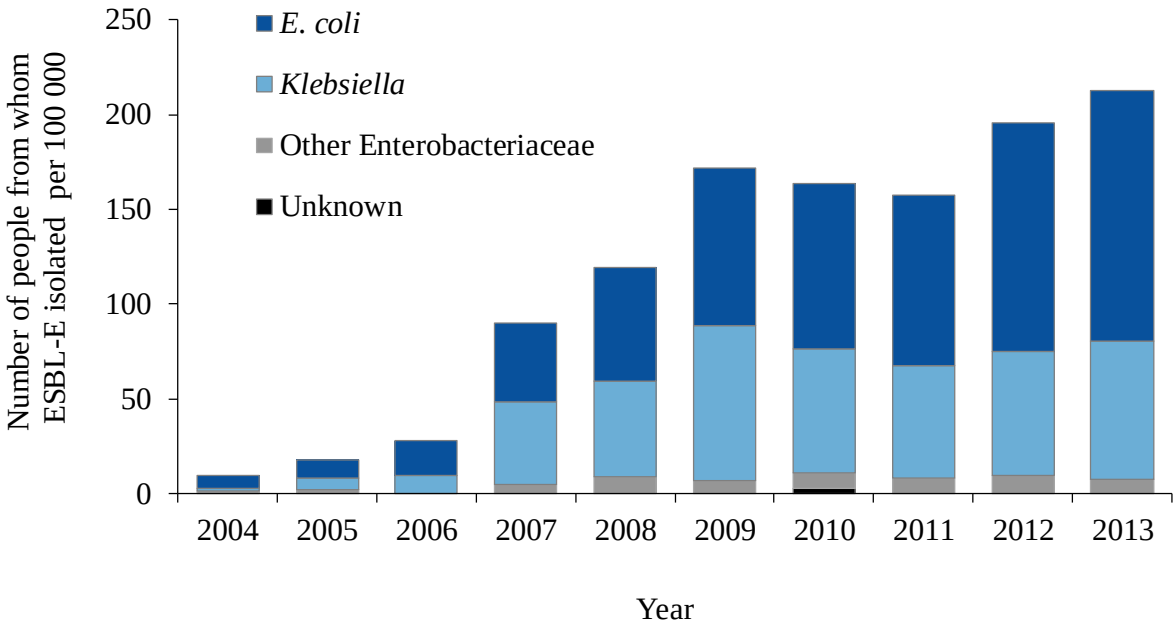
For the 2013 survey, hospital and community microbiology laboratories in New Zealand were asked to refer all ESBL-E isolated during August 2013 to ESR. Laboratories that do not test for ESBL production were asked to refer all Enterobacteriaceae isolates that were non-susceptible to 3rd-generation cephalosporins. The Microbiology Laboratory, North Shore Hospital; Medlab Central, Palmerston North; and the Microbiology Laboratory, Nelson Hospital, referred isolates during a 31-day period between mid-August and the end of September 2013. All remaining laboratories referred ESBL-E during August 2013.

When referring isolates for the survey, laboratories supplied epidemiological data including patient age, geographic location, hospitalisation status, body site from which the ESBL-E was isolated, whether the ESBL-E was causing infection or was from a colonised site, and if the isolate was obtained from a screen or a diagnostic specimen. Laboratories were also asked to provide, where available, information on the susceptibility of the ESBL-E isolates to the following antibiotics: cefoxitin, ciprofloxacin or norfloxacin, co-amoxiclav, co-trimoxazole, ertapenem, fosfomycin, gentamicin, imipenem, meropenem, piperacillin/tazobactam and trimethoprim.

At ESR, all isolates referred for the survey were confirmed as ESBL positive by the Clinical and Laboratory Standards Institute's (CLSI's) phenotypic confirmatory disc test,[1] or a double-disc synergy test with cefotaxime, ceftazidime, cefpodoxime and cefepime as substrates.[2] In addition, the cefoxitin susceptibility of all isolates was determined by the CLSI disc susceptibility test.[1] Any cefoxitin non-susceptible isolates of species that do not have intrinsic chromosomally mediated AmpC β-lactamase were tested by PCR for the genes encoding plasmid-mediated AmpC β-lactamase.[3]

During the period of the 2013 survey, ESBL-E were isolated from a total of 793 people, which equates to an annualised incidence rate of 212.8 people with ESBL-E per 100 000 population; an 8.7% increase on the 2012 rate of 195.7. Figure 1 shows the annual or annualised incidence of ESBL-E over the 10 years 2004 to 2013, and the distribution of ESBLs among *Escherichia coli*, *Klebsiella* species and other Enterobacteriaceae.

Figure 1. ESBL-producing Enterobacteriaceae incidence rates, 2004-2013



Data for 2004 and 2005 are based on continuous surveillance of all ESBL-E isolations. Data for 2006 to 2013 are annualised and based on 4-week or 1-month surveys conducted in these years. The 2006 survey only included urinary *E. coli* and *Klebsiella*, therefore the data for 2006 is not directly comparable with that for other years. The category 'Unknown' in 2010 represents people identified with an ESBL-E during the survey period but from whom no isolate was referred to ESR and the species was not reported.

The 793 ESBL-E isolates referred in 2013 comprised 492 (62.0%) *E. coli*, 272 (34.3%) *Klebsiella* species, 15 (1.9%) *Enterobacter* species, 6 (0.8%) *Citrobacter* species, 5 (0.6%) *Proteus* species, 2 (0.3%) *Serratia* species, and 1 (0.1%) non-typhoidal *Salmonella* (*S.* Stanley). Thirty-one patients had two different ESBL-producing species and one patient had three species.

The patients from whom ESBL-E were isolated were categorised as hospital patients if they were in a healthcare facility (including emergency department, outpatient clinic or long-term care facility) when ESBL-E were isolated or had been in a healthcare facility in the previous three months. All other patients were categorised as community patients. The majority of the ESBL-E (60.2%, 456 of the 757 patients for whom the information was reported) were isolated from patients categorised as hospital patients. Among these 456 hospital patients, 393 (86.2%) were reported to be or have been in a public hospital, 58 (12.7%) in a long-term care facility, and 5 (1.1%) in a private hospital. A larger proportion of the ESBL-producing *Klebsiella* than *E. coli* were isolated from patients categorised as hospital patients (76.0% vs 50.5%). These proportions of hospital patients are similar to those recorded in the 2012 and 2011 surveys, but lower than the proportions recorded in earlier surveys: for example in the 2010 survey, 83.1% of all ESBL-E, and 95.4% of ESBL-producing *Klebsiella*, were isolated from hospital patients.

61.2% of the patients with ESBL-E were ≥65 years of age, 35.4% were 15-64 years old and 3.4% were ≤14 years old. The annualised incidence rates in these three age groups were 916.0, 114.1 and 36.4 per 100 000, respectively. ESBL-producing *Klebsiella* were more likely to be

isolated from older patients than ESBL-producing *E. coli*, with 76.0% of *Klebsiella* isolated from patients ≥65 years of age compared with 53.3% of *E. coli*.

Information on whether the ESBL-E was causing infection or from a colonised site was reported for 88.2% of the patients with ESBL-E, of whom 42.6% were considered to have an ESBL-E infection. Table 1 compares the distribution of species, hospital and community patients, and isolation sites for ESBL-E from infected sites with those from colonised sites. In surveys in previous years, this analysis has usually shown that ESBL-producing *Klebsiella* were more likely to be isolated from colonised sites than *E. coli*, and that ESBL-E from hospital patients were more likely to be isolated from colonised sites than ESBL-E from community patients. These observations are likely to have reflected the screening that occurs in hospitals as part of measures to control the transmission of ESBL-E, and the fact that ESBL-producing *Klebsiella* were more likely than ESBL-producing *E. coli* to be associated with hospital patients.

However, these species and patient type differences were less evident in 2013, with 66.4% of ESBL-producing *Klebsiella* and 53.1% of ESBL-producing *E. coli* being isolated from colonised sites, and almost equal proportions of hospital and community patients being colonised rather than infected with ESBL-E. The latter finding is due to ESBL-E being detected in community patients during screening pre- or on-admission to a healthcare facility, rather than any extensive screening of patients in the community.

Table 1. Comparison of ESBL-producing Enterobacteriaceae from infected and colonised sites, 2013[1]

	Number (row %)	
	ESBL-E from infected sites (n=298)	**ESBL-E from colonised sites** (n=401)
Species:		
E. coli	202 (46.9)	229 (53.1)
Klebsiella species	81 (33.6)	160 (66.4)
other species	15 (55.6)	12 (44.4)
Isolated from:		
hospital patients[2]	172 (41.7)	241 (58.4)
community patients[2]	114 (42.2)	156 (57.8)
Isolation site:		
CSF/blood	15 (100)	0
skin and soft tissue	8 (57.1)	6 (42.9)
respiratory tract	5 (50.0)	5 (50.0)
urine	267 (82.9)	55 (17.1)
screening site	0	335 (100)
other	3 (100)	0

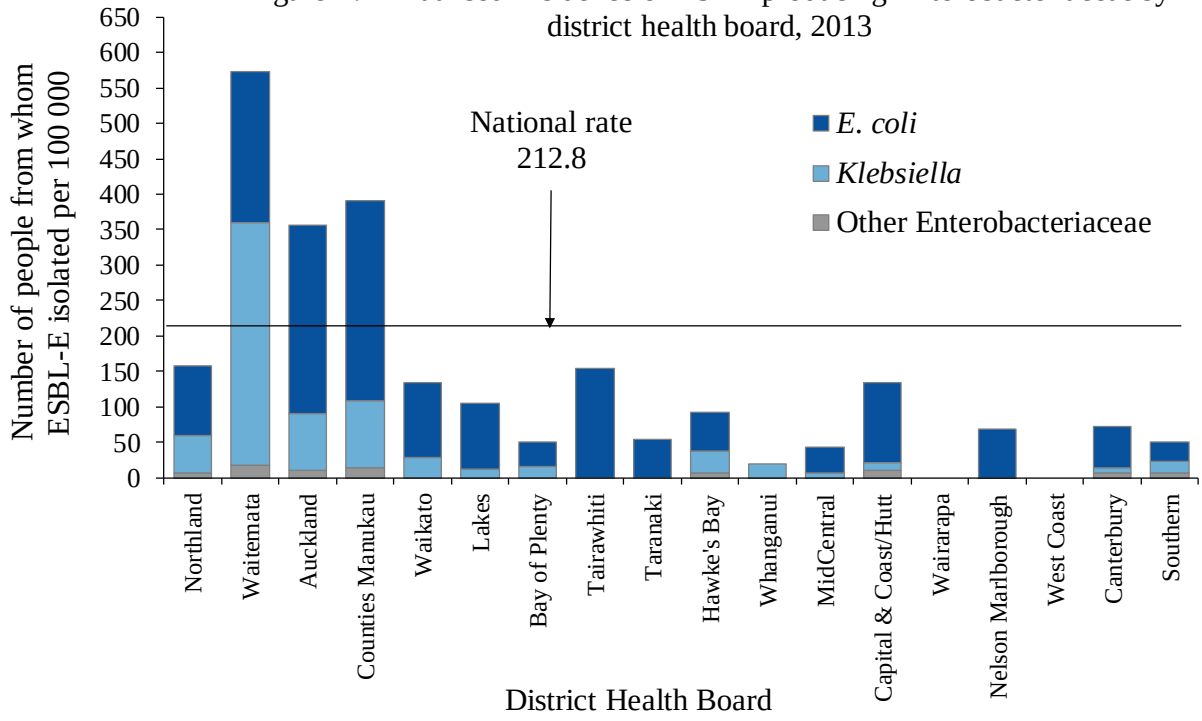
1 Information on whether the ESBL-E was isolated from an infected or colonised site was reported for 699 of the 793 isolates. The remaining 94 isolates are not included in the analyses in this table. Of these 94 isolates, 82 were from urine.

Table 1 footnotes continued on next page

2 Patients were categorised as hospital patients if they were in a healthcare facility (including emergency department, outpatient clinic or long-term care facility) when ESBL-E was isolated or had been in a healthcare facility in the previous three months. All other patients were categorised as community patients. Patient categorisation not known for 12 infected patients and 4 colonised patients.

Figure 2 shows the annualised incidence of ESBL-E in each district health board (DHB). There are very marked geographic differences in incidence rates, with rates in the three DHBs in the greater Auckland area, Waitemata (572.0 per 100 000), Counties Manukau (391.0) and Auckland (356.5) DHBs, being 3.7, 2.5 and 2.3 times greater than the highest rate in any other DHB (154.2 in Tairawhiti). It is notable that not only did Waitemata DHB have the highest incidence rate of ESBL-E, but, in contrast to almost all other areas, the incidence of ESBL-producing *Klebsiella* (343.6 per 100 000) was considerably higher than that of ESBL-producing *E. coli* (211.3).

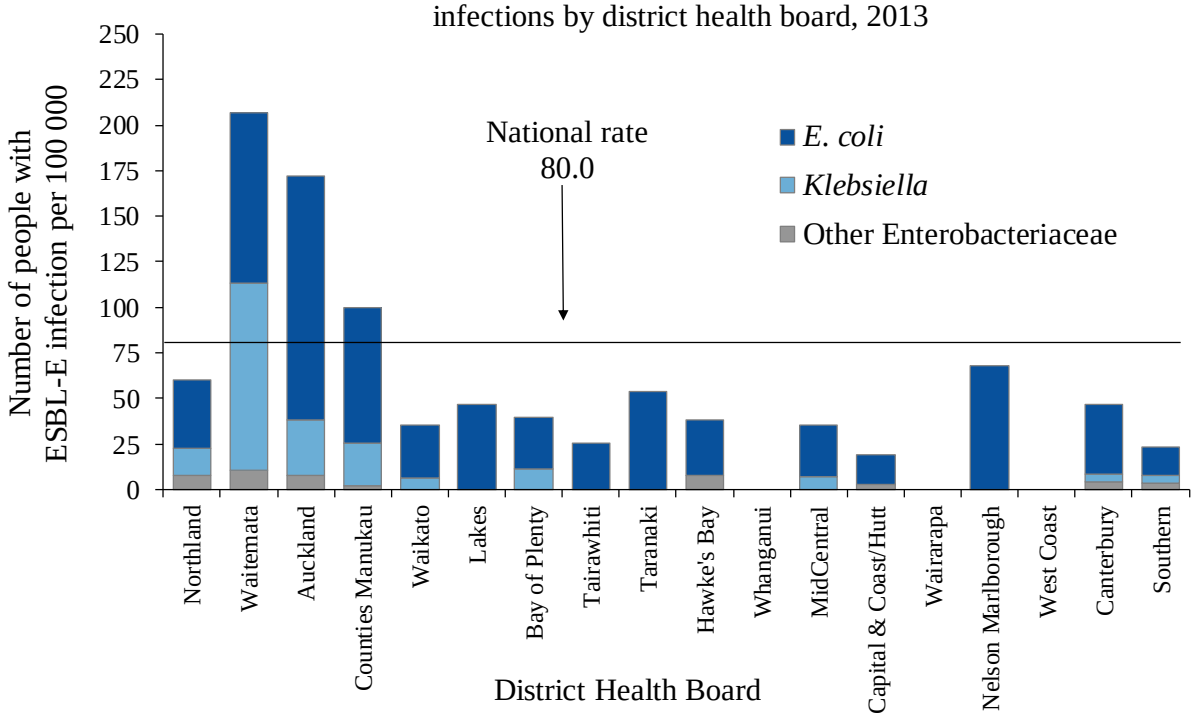
Figure 2. Annualised incidence of ESBL-producing Enterobacteriaceae by district health board, 2013



Data for the Capital & Coast and Hutt District Health Boards (DHBs) are combined as 'Capital & Coast/Hutt', and data for the Canterbury and South Canterbury DHBs are combined as 'Canterbury'.

Some of the apparent differences in ESBL-E rates between DHBs evident in Figure 2 could be due to differences in screening policies between DHBs. Figure 3 shows the annualised DHB incidence rates for ESBL-E that were isolated from infections only. The three DHBs with the highest rates of ESBL-E isolations (Waitemata, Counties Manukau and Auckland, Figure 2) also had the highest rates of ESBL-E infection. Waitemata DHB had the highest rates of both ESBL-E isolations and infections.

Figure 3. Annualised incidence of ESBL-producing Enterobacteriaceae infections by district health board, 2013



Data for the Capital & Coast and Hutt District Health Boards (DHBs) are combined as 'Capital & Coast/Hutt', and data for the Canterbury and South Canterbury DHBs are combined as 'Canterbury'.

The proportions of the ESBL-E isolates that would be categorised as ESBL screen positive, cefotaxime resistant and ceftazidime resistant, on the basis of interpreting cefotaxime and ceftazidime zones of inhibition according to the 2013 CLSI standards,[1] are shown in Table 2. 99.5% of the ESBL-producing *E. coli, Klebsiella* and *Proteus mirabilis* isolates were categorised as cefotaxime resistant, but only 57.8% of these isolates were categorised as ceftazidime resistant, presumably due to CTX-M-type ESBLs being prevalent. Similarly, 96.2% of the species other than *E. coli, Klebsiella* and *P. mirabilis* were categorised as cefotaxime resistant, but only 73.1% were ceftazidime resistant.

Table 2. Cefotaxime and ceftazidime susceptibility of ESBL-producing Enterobacteriaceae, 2013

Species	Number (%) of ESBL-producing Enterobacteriaceae (n=793)							
	Cefotaxime				Ceftazidime			
	S[1]	I[1]	R[1]	Screen positive[2]	S	I	R	Screen positive
E. coli, Klebsiella and *P. mirabilis* n=767	2 (0.3)	2 (0.3)	763 (99.5)	766 (99.9)	212 (27.6)	112 (14.6)	443 (57.8)	648 (84.5)
Other species n=26	0	1 (3.8)	25 (96.2)	26 (100)	6 (23.1)	1 (3.8)	19 (73.1)	24 (92.3)

1 S, susceptible; I, intermediate; R, resistant; based on cefotaxime and ceftazidime zone diameters interpreted according to the 2013 CLSI interpretive standards (see reference 1 below).
2 ESBL screen positive according to the 2013 CLSI interpretive standards, that is, cefotaxime zone diameter ≤27 mm, ceftazidime zone diameter ≤22 mm.

The ESBL-producing *E. coli, Klebsiella, Proteus, Salmonella, Citrobacter amalonaticus, Citrobacter farmeri* and *Citrobacter koseri* isolates that were cefoxitin non-susceptible were tested for the genes encoding plasmid-mediated AmpC β-lactamases. Fourteen (2.8%) of the 492 ESBL-producing *E. coli* had a plasmid-mediated AmpC β-lactamase: 10 CMY-2-like types and 4 DHA types. One (0.4%) of the 272 ESBL-producing *Klebsiella* had a plasmid-mediated AmpC β-lactamase: a DHA type. Genes encoding plasmid-mediated AmpC β-lactamases were not found in the other species tested.

For the first time in 2013, laboratories referring ESBL-E isolates for the survey were asked to provide, if tested, the susceptibility of the isolates to the following antibiotics: cefoxitin, ciprofloxacin or norfloxacin, co-amoxiclav, co-trimoxazole, ertapenem, fosfomycin, gentamicin, imipenem, meropenem, piperacillin/tazobactam and trimethoprim. The results are shown in Table 3. There were high rates of fluoroquinolone, gentamicin and co-trimoxazole/ trimethoprim resistance among ESBL-E. While fosfomycin susceptibility was only reported for 190 of the total 793 isolates, the rate of resistance was low at 4.2% for all isolates and 2.5% among ESBL-producing *E. coli*.

Table 3. Antimicrobial susceptibility of ESBL-producing Enterobacteriaceae, 2013[1]

Antimicrobial	Number isolates with results reported[2]	Percent								
		E. coli			*Klebsiella*			All isolates		
		S[3]	I[3]	R[3]	S	I	R	S	I	R
Co-amoxiclav	484	52.2	21.8	26.1	35.3	17.3	47.5	46.7	19.6	33.7
Piperacillin-tazobactam	166	90.5	5.3	4.2	75.8	17.7	6.5	83.7	9.6	6.6
Cefoxitin	499	89.9	4.6	5.5	96.0	1.3	2.7	89.2	3.4	7.4
Ertapenem	397	99.6	0.0	0.4	98.3	0.9	0.9	99.0	0.3	0.8
Imipenem	193	100	0.0	0.0	100	0.0	0.0	100	0.0	0.0
Meropenem	240	99.4	0.0	0.6	98.3	0.0	1.7	99.2	0.0	0.8
Ciprofloxacin	370	39.8	1.5	58.7	50.5	19.6	29.9	44.1	6.8	49.2
Norfloxacin	421	32.6	1.4	66.0	62.4	12.0	25.6	42.8	4.5	52.7
Gentamicin	636	55.8	0.0	44.2	42.9	0.0	57.1	51.3	0.2	48.6
Co-trimoxazole	413	29.4	0.7	69.9	12.8	0.9	86.3	24.5	0.7	74.8
Trimethoprim	493	29.8	0.3	69.9	8.4	0.0	91.6	23.7	0.2	76.1
Fosfomycin	190	97.5	0.0	2.5	93.8	0.0	6.3	95.8	0.0	4.2

1 Based on data supplied by laboratories referring isolates for the survey.
2 Total number of ESBL-E isolates with susceptibility to the antibiotic reported.
3 S, susceptible; I, intermediate; R, resistant.

Note: To provide additional phenotypic and molecular epidemiological information on ESBL-E in New Zealand, a subset of 353 clinical isolates was selected for further analysis. This analysis included full quantitative testing of susceptibility to an extended range of antibiotics, such as fosfomycin, mecillinam and tigecycline; identification of the ESBL type; and molecular typing, including the identification of multilocus sequence type (ST) 131 among ESBL-producing *E. coli*. The results of this further analysis will be published at https://surv.esr.cri.nz/antimicrobial/esbl.php.

References

1 Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; twenty-third informational supplement. Wayne (PA): CLSI; 2013. CLSI document M100-S23.

2 Jarlier V, Nicolas MH, Fournier G, et al. Extended-broad spectrum ß-lactamases conferring transferable resistance to newer ß-lactam agents in Enterobacteriaceae: hospital prevalence and susceptibility patterns. Rev Infect Dis 1988; 10: 867-78.

3 Perez-Perez FJ, Hanson ND. Detection of plasmid-mediated AmpC beta-lactamase genes in clinical isolates by using multiplex PCR. J Clin Microbiol 2002; 40: 2153-62.