Annual survey of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, 2014

Kristin Dyet, Rosemary Woodhouse and Helen Heffernan

Antibiotic Reference Laboratory, Institute of Environmental Science and Research Limited (ESR); July 2014.

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 2014 survey, hospital and community microbiology laboratories in New Zealand were asked to refer all ESBL-E isolated during August 2014 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, Whangarei Hospital; Microbiology Laboratory, Hutt Hospital; and Canterbury Southern Community Laboratories referred isolates during a 31-day period between mid-August and mid-October 2014. All remaining laboratories referred ESBL-E during August 2014.

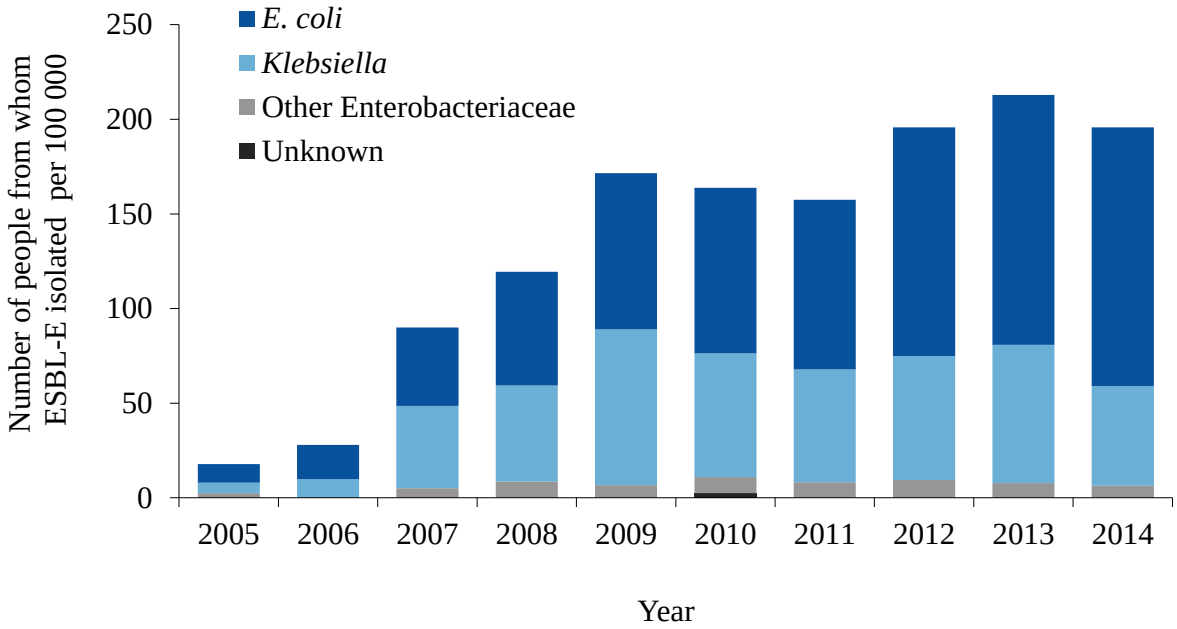
When referring isolates for the survey, laboratories were asked to supply selected epidemiological data, including the patient's date of birth, geographic location, hospitalisation status and history, body site from which the ESBL-E was isolated, whether the ESBL-E was causing infection or was from a 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-lactamases.[3]

During the period of the 2014 survey, ESBL-E were isolated from a total of 736 people, which equates to an annualised incidence rate of 195.7 people with ESBL-E per 100 000 population; an 8.0% decrease on the 2013 rate of 212.8. Figure 1 shows the annual or annualised incidence of ESBL-E over the 10 years 2005 to 2014, and the distribution of ESBLs among *Escherichia coli*, *Klebsiella* species and other Enterobacteriaceae. A notable trend in recent years has been a

decrease in the proportion of ESBL-E that are *Klebsiella* species, and a concomitant increase in the proportion that are *E. coli*. In 2010, 48.1% and 48.0% of ESBL-E included in the survey were *E. coli* and *Klebsiella* species, respectively. By 2014 these proportions had changed to 69.8% *E. coli* and 26.9% *Klebsiella*.

Figure 1. ESBL-producing Enterobacteriaceae incidence rates, 2005-2014



Data for 2005 are based on continuous surveillance of all ESBL-E isolations. Data for 2006 to 2014 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 736 ESBL-E isolates referred in 2014 comprised 514 (69.8%) *E. coli*, 198 (26.9%) *Klebsiella* species, 12 (1.6%) *Enterobacter* species, 5 (0.7%) *Proteus mirabilis*, 4 (0.5%) *Citrobacter* species, 1 (0.1%) *Escherichia hermannii*, 1 (0.1%) *Kluyvera ascorbata*, and 1 (0.1%) *Morganella morganii*. Thirteen patients had two different ESBL-producing 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 was 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 (57.5%, 407 of the 708 patients for whom the information was reported) were isolated from patients categorised as hospital patients. Among these 407 hospital patients, 347 (85.3%) were reported to be or have been in a public hospital, 42 (10.3%) in a long-term care facility, 17 (4.2%) in a private hospital, and the type of healthcare facility was unknown for the remaining hospital patient. A larger proportion of the ESBL-producing *Klebsiella* than *E. coli* were isolated from patients categorised as hospital patients (78.3% vs 46.9%). These proportions of hospital patients are similar to those recorded since 2011, 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.

59.0% of the patients with ESBL-E were ≥65 years of age, 35.2% were 15-64 years old and 5.7% were ≤14 years old. The annualised incidence rates in these three age groups were 800.7, 105.3 and 55.3 per 100 000, respectively. ESBL-producing *Klebsiella* were more likely to be isolated from older patients than ESBL-producing *E. coli*, with 72.2% of *Klebsiella* isolated from patients ≥65 years of age compared with 53.9% of *E. coli*.

Information on whether the ESBL-E was causing infection or was from a colonised site was reported for 86.3% of the patients with ESBL-E, of whom 56.5% were reported 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 previous years, this analysis has usually shown that ESBL-producing *E. coli* were more likely to be isolated from infected sites than colonised sites and vice versa for *Klebsiella*. However in 2014, the proportions of ESBL-producing *E. coli* and *Klebsiella* that were isolated from infected sites were very similar (57.2% and 57.8%, respectively). As has been observed in previous years, the proportion (52.0%) of the ESBL-E from hospital patients that were from colonised sites was greater than the proportion (34.6%) of ESBL-E from community patients that were from colonised sites. This difference is likely to reflect the screening that occurs in hospitals as part of measures to control the transmission of ESBL-E.

Table 1. Comparison of ESBL-producing Enterobacteriaceae from infected and colonised sites, 2014[1]

	Number (row %)	
	ESBL-E from infected sites (n=359)	**ESBL-E from colonised sites** (n=276)
Species:		
E. coli	255 (57.2)	191 (42.8)
Klebsiella species	96 (57.8)	70 (42.2)
other species	8 (34.8)	15 (65.2)
Isolated from:		
hospital patients[2]	167 (48.0)	181 (52.0)
community patients[2]	176 (65.4)	93 (34.6)
Isolation site:[3]		
CSF/blood	13 (100)	0
skin and soft tissue	10 (83.3)	2 (16.7)
respiratory tract	3 (75.0)	1 (25.0)
urine	330 (96.5)	12 (3.5)
screening site	0	257 (100)
other	3 (60.0)	2 (40.0)

1 Information on whether the ESBL-E was isolated from an infected or colonised site was reported for 635 of the 736 isolates. The remaining 101 isolates are not included in the analyses in this table. Among these 101 isolates, 88 were from urine.

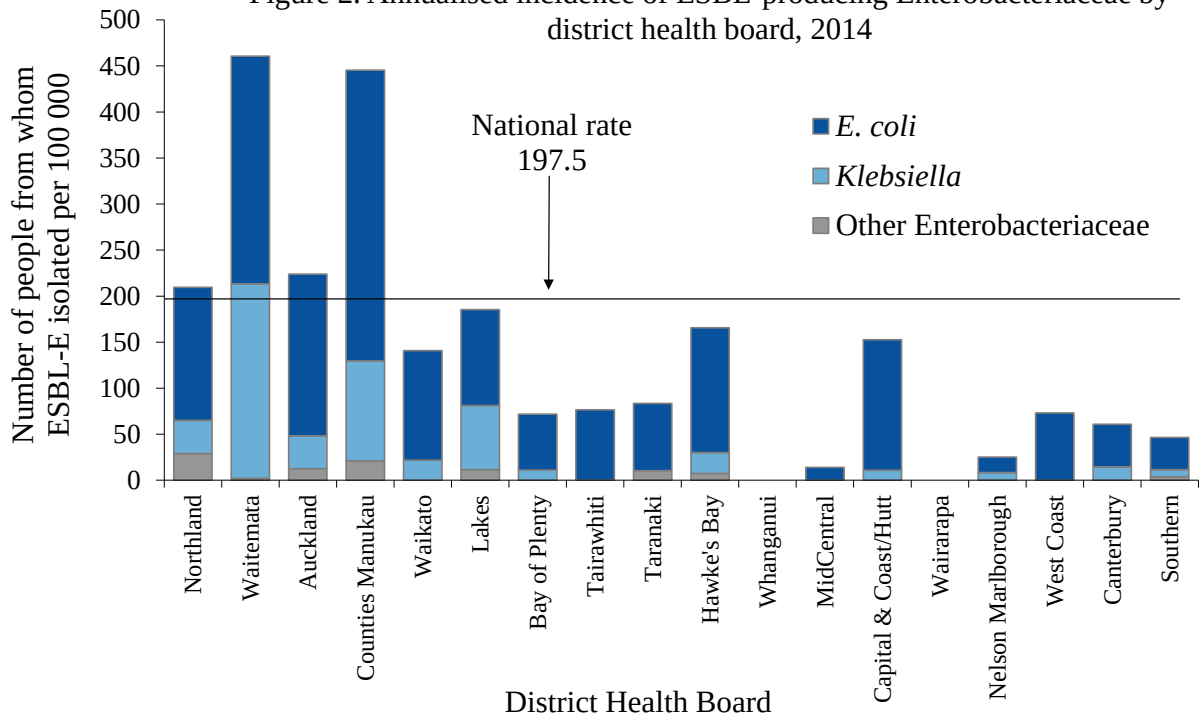
Table 1 footnotes continued on next page

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 16 infected patients and 2 colonised patients.

3 Site not reported for two of the ESBL-E from colonised sites.

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 Waitemata (460.7 per 100 000) and Counties Manukau (445.4) DHBs being at least twice the rate in any other DHB. 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* (211.2 per 100 000) was similar to that of ESBL-producing *E. coli* (247.4).

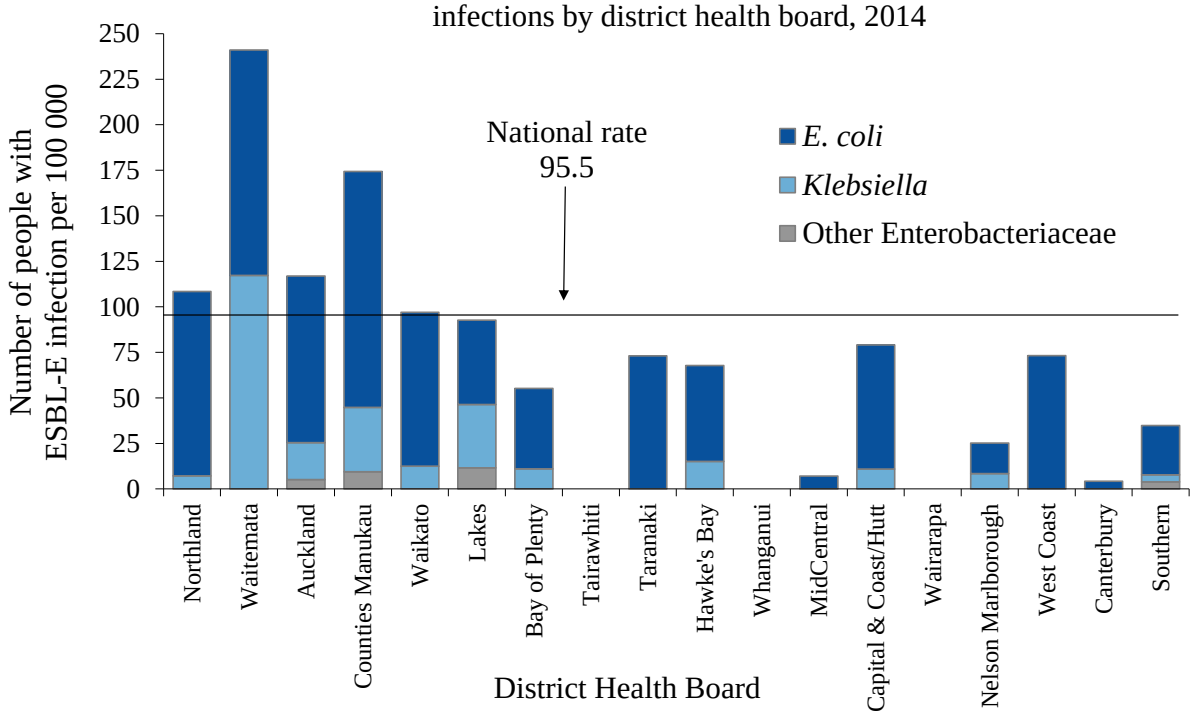
Figure 2. Annualised incidence of ESBL-producing Enterobacteriaceae by district health board, 2014



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 two DHBs with the highest rates of ESBL-E isolations (Waitemata and Counties Manukau, Figure 2) also had the highest rates of ESBL-E infection. Waitemata DHB had the highest rates of both ESBL-E isolations and infections.

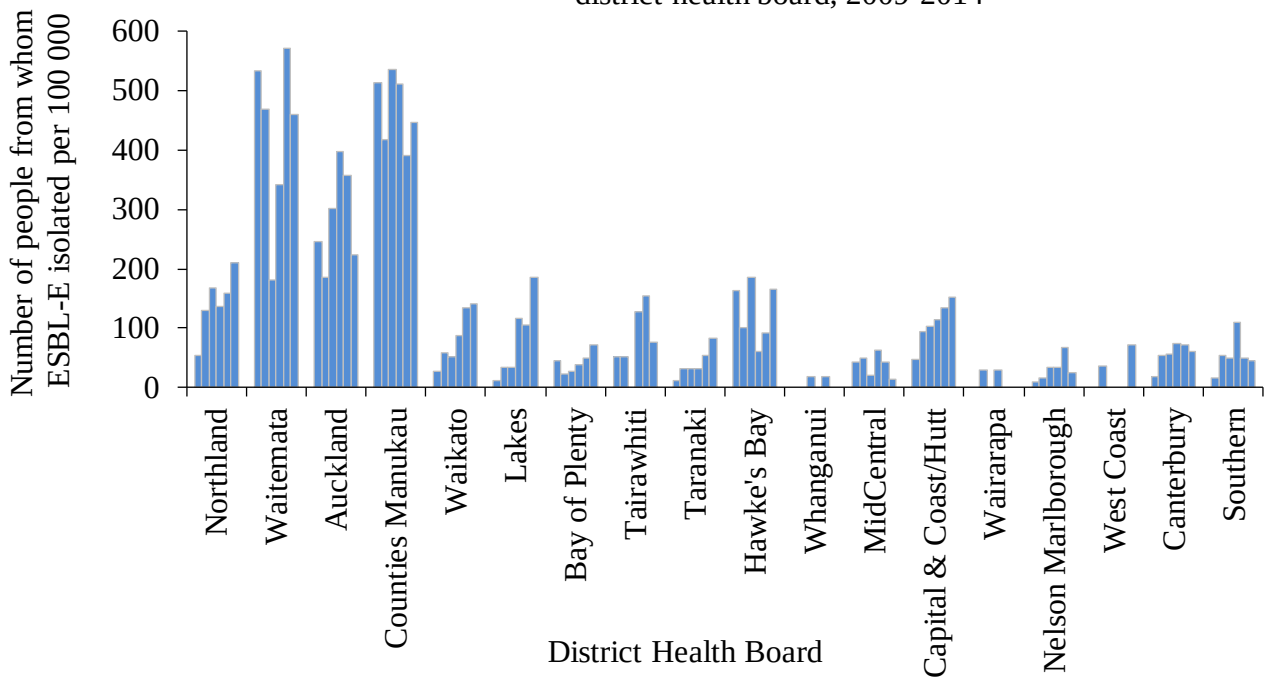
Figure 3. Annualised incidence of ESBL-producing Enterobacteriaceae infections by district health board, 2014



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'.

Over the six-year period 2009 to 2014, there were statistically significant increases in the incidence of ESBL-E in 5 of the 18 DHB/DHB combinations analysed. These DHBs were, ordered from the DHB with the highest increase to that with the smallest increase: Lakes, Northland, Waikato, Capital & Coast/Hutt and Taranaki (Figure 4).

Figure 4. Annualised incidence of ESBL-producing Enterobacteriaeceae by district health board, 2009-2014



The series of bars for each DHB represent the individual years 2009 to 2014 from left to right. Data for the Capital & Coast and Hutt 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 were categorised as ESBL screen positive, cefotaxime resistant and ceftazidime resistant, on the basis of interpreting cefotaxime and ceftazidime zones of inhibition according to the 2014 CLSI standards,[1] are shown in Table 2. 98.9% of the ESBL-producing *E. coli, Klebsiella* and *P. mirabilis* isolates were categorised as cefotaxime resistant, but only 50.5% of these isolates were categorised as ceftazidime resistant, presumably due to CTX-M-type ESBLs being prevalent. Similarly, 100.0% of the species other than *E. coli, Klebsiella* and *P. mirabilis* were categorised as cefotaxime resistant, but only 73.7% were ceftazidime resistant.

Table 2. Cefotaxime and ceftazidime susceptibility of ESBL-producing Enterobacteriaceae, 2014

Species	Number (%) of ESBL-producing Enterobacteriaceae (n=736)							
	Cefotaxime				Ceftazidime			
	S[1]	I[1]	R[1]	Screen positive[2]	S	I	R	Screen positive
E. coli, Klebsiella and *P. mirabilis* n=717	4 (0.6)	4 (0.6)	709 (98.9)	714 (99.6)	239 (33.3)	116 (16.2)	362 (50.5)	562 (78.4)
Other species n=19	0	0	19 (100)	19 (100)	3 (15.8)	2 (10.5)	14 (73.7)	18 (94.7)

1 S, susceptible; I, intermediate; R, resistant; based on cefotaxime and ceftazidime zone diameters interpreted according to the 2014 CLSI interpretive standards (see reference 1 below).
2 ESBL screen positive according to the 2014 CLSI interpretive standards, that is, cefotaxime zone diameter ≤27 mm, ceftazidime zone diameter ≤22 mm.

The ESBL-producing *E. coli, Klebsiella, Citrobacter koseri, E. hermannii, K. ascorbata* and *P. mirabilis* isolates that were cefoxitin non-susceptible were tested for the genes encoding plasmid-mediated AmpC β-lactamases. Seven (1.4%) of the 514 ESBL-producing *E. coli* had a plasmid-mediated AmpC β-lactamase: five CMY-2-like types and two DHA types. Two (1.0%) of the 191 ESBL-producing *K. pneumoniae* had a plasmid-mediated AmpC β-lactamase: both DHA types. Genes encoding plasmid-mediated AmpC β-lactamases were not found in the other species tested.

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 275 of the total 736 isolates, the rate of resistance was low at 2.6% for all isolates and 1.6% among ESBL-producing *E. coli*.

Table 3. Antimicrobial susceptibility of ESBL-producing Enterobacteriaceae, 2014[1]

Antimicrobial	Number of 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	556	51.4	18.6	30.0	32.9	25.0	42.1	45.7	20.0	34.4
Piperacillin-tazobactam	101	82.5	1.8	15.8	80.5	7.3	12.2	81.2	5.0	13.9
Cefoxitin	547	87.1	3.9	9.0	89.9	6.5	3.6	85.9	4.6	9.5
Ertapenem	461	100.0	0.0	0.0	97.0	0.8	2.3	99.1	0.2	0.7
Imipenem	85	98.5	0.0	1.5	100.0	0.0	0.0	98.8	0.0	1.2
Meropenem	255	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0	0.0
Ciprofloxacin	378	32.6	4.3	63.0	47.6	11.9	40.5	36.8	6.9	56.4
Norfloxacin	412	33.1	2.7	64.2	57.9	11.2	30.8	40.3	5.3	54.4
Gentamicin	630	64.9	0.7	34.4	38.9	1.3	59.9	57.6	0.8	41.6
Co-trimoxazole	353	27.0	1.9	71.0	7.8	0.0	92.2	22.4	1.4	76.2
Trimethoprim	508	22.9	0.3	76.8	4.9	0	95.1	18.1	0.2	81.7
Fosfomycin	275	97.8	0.5	1.6	95.2	0.0	4.8	97.1	0.4	2.6

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.

References

1 Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; twenty-fourth informational supplement. Wayne (PA): CLSI; 2014. CLSI document M100-S24.

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.