FOOD SAFETY

doi: 10.14252/foodsafetyfscj.2017011
Food Safety 2017; Vol. 5, No. 4, 122–150

Review (Invited)

ESBL-producing *Escherichia coli* and Its Rapid Rise among Healthy People

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Since around the 2000s, *Escherichia coli* (*E. coli*) resistant to both oxyimino-cephalosporins and fluoroquinolones has remarkably increased worldwide in clinical settings. The kind of *E. coli* is also identified in patients suffering from community-onset infectious diseases such as urinary tract infections. Moreover, recoveries of multi-drug resistant *E. coli* from the feces of healthy people have been increasingly documented in recent years, although the actual state remains uncertain. These *E. coli* isolates usually produce extended-spectrum β-lactamase (ESBL), as well as acquisition of amino acid substitutions in the quinolone-resistance determining regions (QRDRs) of GyrA and/or ParC, together with plasmid-mediated quinolone resistance determinants such as Qnr, AAC(6')-Ib-cr, and QepA. The actual state of ESBL-producing *E. coli* in hospitalized patients has been carefully investigated in many countries, while that in healthy people still remains uncertain, although high fecal carriage rates of ESBL producers in healthy people have been reported especially in Asian and South American countries. The issues regarding the ESBL producers have become very complicated and chaotic due to rapid increase of both ESBL variants and plasmids mediating ESBL genes, together with the emergence of various "epidemic strains" or "international clones" of *E. coli* and *Klebsiella pneumoniae* harboring transferable-plasmids carrying multiple antimicrobial resistance genes. Thus, the current state of ESBL producers outside hospital settings was overviewed together with the relation among those recovered from livestock, foods, pets, environments and wildlife from the viewpoint of molecular epidemiology. This mini review may contribute to better understanding about ESBL producers among people who are not familiar with the antimicrobial resistance (AMR) threatening rising globally.

Key words: *Escherichia coli*, extended-spectrum β-lactamase (ESBL), food, healthy people, livestock

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Received: 18 August 2017; Accepted: 11 December 2017; Published online: 29 December 2017
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Abbreviations and glossary: AmpC: bacterial cephalosporinase usually produced in Gram-negative bacteria depending on their chromosome; AMR: antimicrobial resistance; CAZ: ceftazidime; Conjugation: direct contact of two separate bacterial cells, and genetic information is usually transferred between the bacterial cells by transmission of plasmid; CVA: clavulanic acid, a β-lactamase inhibitor possessing a β-lactam ring; ESBL: Extended-spectrum β-lactamase, a bacterial enzyme having an ability to hydrolyze the third-generation cephalosporins; FQ: fluoroquinolones including levofloxacin and ciprofloxacin; Inc type: incompatibility type of plasmid that is usually unique to the structure of replication origin of each plasmid; IS*Ecp1*: an insertion sequence usually mediating genes for ESBLs as well as the promoter activity for expression of the ESBL gene, Qnr, AAC(6')-Ib-cr, and QepA; plasmid-mediated quinolone resistance determinants (peptide, enzyme and transporter, respectively); QRDRs: quinolone-resistance determining regions of GyrA (DNA gyrase) and ParC (topoisomerase IV); ST: a sequence type of bacteria usually determined by MLST using the SNPs in 7 house-keeping genes specific for each bacterial species; TEM-1 and SHV-1: plasmid-mediated penicillinases; Tn*3*: transposon 3; UTIs: urinary tract infections

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1. Introduction

Worldwide proliferation of antimicrobial-resistant bacteria has become an urgent global concern[1–3]. Acquisition of antimicrobial resistance in human commensal bacteria such as *Escherichia coli* (*E. coli*) has become a general threat to public health[4], because *E. coli* sometimes causes community-onset infectious diseases including urinary tract infections (UTIs)[5,6] even in healthy people, as well as in hospitalized immuno-compromised patients. Production of extended-spectrum β-lactamases (ESBLs) have also been becoming common in *E. coli* recovered from healthy people worldwide[7–11], and it has become notable that almost all ESBL-producing *E. coli* usually has acquired co-resistance to fluoroquinolones (FQs) and other several clinically important antimicrobials[12–14]. Rapid increase in the isolation of ESBL-producing and FQ-resistant *E. coli* from ill patients admitted to hospital settings has been well investigated and reported from many countries and regions (**Fig. 1**)[15–17], and become one of the emerging public health concerns in 2008[18]. However, the exact conditions of ESBL producers among healthy people leading ordinary lives in the community still remain unclear, despite the fact that ESBL-producing bacteria are dynamically circulating across human, livestock, food, pets, and the environment including wildlife (**Fig. 2**). In particular, potential acquisition of ESBL-producing bacteria from livestock through foods, particularly raw meats, has become one of the general concerns from the viewpoint of food safety and "one health". Thus, the current state of ESBL-producing *E. coli* among healthy people leading ordinary lives in the community was overviewed on the basis of microbial and genetic profiles together with those recovered from livestock, pets, foods, the environment, and wildlife from the pages of recent key publications.

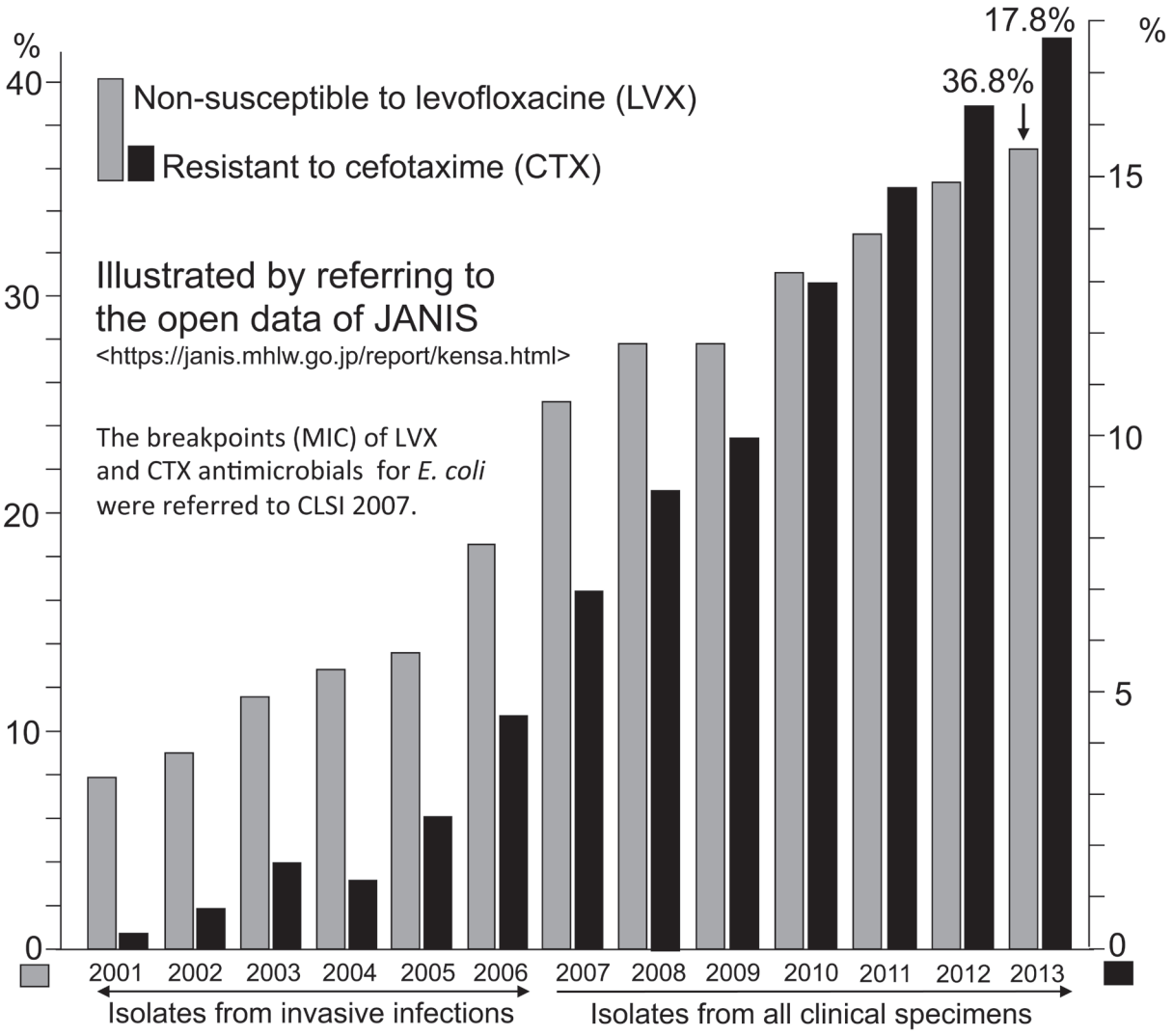

Fig. 1. Rapid rise of clinically isolated *Escherichia coli* that acquired resistance to the third-generation cephalosporins and/or fluoroquinolones (inpatients).

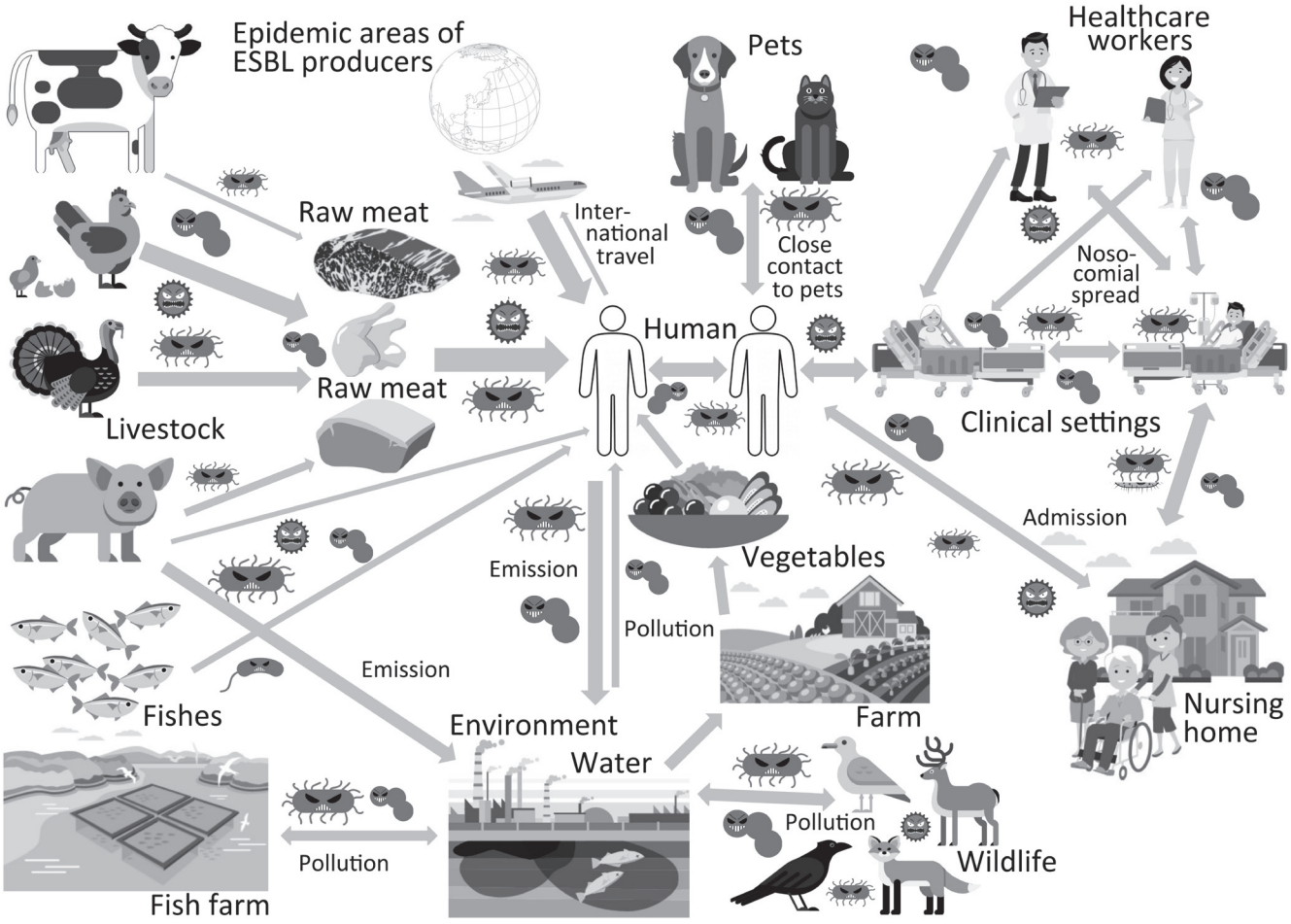

Fig. 2. Possible transmission and circulation of antimicrobial resistant bacteria.

2. What are ESBLs?

2-1 Characteristics of ESBLs and their groups

ESBL is an abbreviation for "extended-spectrum β-lactamase," an enzyme having an ability to hydrolyze the β-lactam ring of broad-spectrum β-lactams such as oxyimino-cephalosporins including cefotaxime, ceftriaxone, and ceftazidime[19]. These antibacterials are the so called "third-generation cephalosporins"[20]. Because, diverse types of ESBLs are usually produced depend on transferable plasmids in various species of Gram-negative bacteria[21–23], the genes for ESBLs can be horizontally transferred to other bacterial species. In the 1980's, TEM-derived ESBLs and SHV-derived ESBLs emerged in Europe[24–26] as variants of TEM-1 and SHV-1 penicillinases[27–29], respectively. In the TEM-derived and SHV-derived ESBLs, several amino acid residues are substituted particularly in the portions that constitute the active center of the enzymes as well as in its Ω-loop region[30,31] on the basis of their ancestral penicillinases. TEM-derived and SHV-derived ESBLs can hydrolyze penicillins and some oxyimino-cephalosporins, but these enzymes hardly hydrolyze cephamycins and carbapenems[32]. TEM-1 penicillinase is well known as the product of *bla* gene that is usually mediated by Tn*3* on various R-plasmids[33]. SHV-1 shows a very high similarity (>90%) to the chromosomal penicillinase of *Klebsiella pneumoniae*[34] on the amino acid sequence level[35], suggesting its origin.

TEM-derived ESBLs were first described as CTX-1, CAZ-1, CTX-2, and CAZ-2, and they were later assigned TEM-3[36], TEM-5, TEM-25, and TEM-8, respectively.

As the second types of plasmid-mediated ESBLs, CTX-M-type ESBLs have been also reported since the 1980's[37]. Initially, CTX-M-type ESBLs were reported to have hydrolytic activity against cefotaxime. Interestingly the CTX-M-type ESBLs usually can effectively hydrolyze also ceftiofur and cefquinome, veterinary broad-spectrum cephalosporins, as well as cefotaxime and ceftriaxone. Unlike the TEM-derived and SHV-derived ESBLs, no prototype having only penicillinase activity has so far been reported yet in the CTX-M-type ESBLs. Since around the 2000s, CTX-M-type ESBLs have become more prevalent worldwide[38] than TEM-derived and SHV-derived ESBLs.

The CTX-M-type ESBLs were initially described as MEN-1[37], and Toho-1[39], and they were later assigned CTX-M-1, and CTX-M-44, respectively. More than 190 variants of CTX-M-type ESBLs have been deposited to the database[40,41] so far. After the emergence of the CTX-M-type β-lactamases, it was reported that *Kluyvera* species, a member of the family *Enterobacteraceae*, intrinsically have unique genes on their chromosome that encode CTX-M-like β-lactamases such as KLUA-1, KLUA-2, KLUC-1 and KLUG-1. For instance, the KLUG-1 of *Kluyvera georgiana* encodes an enzyme highly similar (99%) to the CTX-M-8 in amino acid sequence level[42], that was first identified in *Enterobacteriaceae* isolated from human in Brazil[43] and later found as well in poultry and chicken meat samples worldwide[44,45]. Since the CTX-M-like β-lactamase genes mediated by the chromosome of *Kluyvera* species have little or no promoter activity upstream of the gene, they tend to be silent. Therefore, *Kluyvera* species are usually susceptible to cefotaxime[46–49] despite having intrinsic $bla_{\text{CTX-M}}$-like genes. However, translocation of the chromosomal β-lactamase genes of *Kluyvera* species onto some plasmids by the function of insertion sequences, such as IS*CR1*[50], and IS*Ecp1*[51], having promoter activity confers resistance to oxyimino-cephalosporins through constitutive and multicopy expression of the β-lactamase gene. The types of ESBLs are summarized in **Table 1**.

2-2 Minor groups of ESBL

In addition to the predominant CTX-M-type ESBLs, minor groups of ESBLs such as GES-1[54], VEB-1[55], BES-1[56], SFO-1[57], TLA-1[58], and PSE-2/OXA-10[53,59] have been also reported from ill patients. Like CTX-M-type ESBLs, these minor ESBLs have also a serine residue at the active center of each enzyme, and they belong to class A except for OXA-type ESBLs such as OXA-10 and OXA-11 classified into the class D β-lactamase[60,61]. As for the GES-type and OXA-type β-lactamases, unique variants possessing carbapenemase activity such as GES-5[62,63] and OXA-48[64,65], have emerged in *Enterobacteriaceae*, and the amino acid identities between OXA-10 ESBL and OXA-48 carbapenemase is 44% despite belonging to different clades.

3. Bacterial species as ESBL producers

3-1 Major ESBL-producing bacteria and their increase

The majority of bacterial species producing ESBLs are *E. coli* and *K. pneumoniae*[66]. *Proteus mirabilis*[67], *Klebsiella oxytoca*, and *Citrobacter koseri*[68] producing ESBL have been also identified as causes of clinical outbreaks[69,70]. Since, these bacterial species usually do not produce intrinsic β-lactamases with wide substrate specificity like AmpC[71], production of any of the ESBLs would provide an advantage to survive in clinical and also in some livestock farming environments where considerable amounts of broad-spectrum β-lactams have been consumed. Moreover, many Gram-negative bacterial species including glucose non-fermentative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* have been also identified as ESBL producers[72] even though they usually co-produce various intrinsic broad-spectrum β-lactamases such as AmpC-type β-lactamases[73,74] and OXA-type ones[75], respectively. Emergence of a variety of plasmids carrying multiple antimicrobial resistance genes together with an ESBL gene as the result of recombination and/or fusions of the plasmids, and their widespread growth among diverse bacterial strains and species[76,77] would underlie this phenomenon. Since the genes for ESBL are usually mediated by transferable plasmid, the plasmid mediating ESBL gene often causes an outbreak by spreading among various bacterial species of Gram-negative bacteria (**Fig. 3**). In this case, various different bacterial species harboring genetically and structurally very similar plasmids that mediate the same ESBL gene tend to be isolated from multiple patients admitted to the same patient room or ward of the index case (**Fig. 4**).

3-2 Enzymatic characteristics of ESBLs and phenotypic features of their producers

Since ESBLs belonging to the class A β-lactamases possess a serine residue at the active center of the enzymes, ESBL activities are effectively blocked by clavulanic acid (CVA) that binds to the serine residue at the active pocket of the ESBLs through forming a stable covalent acyl-intermediate[78]. Therefore, recovery of the effect of some β-lactams such as cefpodoxime and cefotaxime in the presence of CVA is a good indication of ESBL production in *E. coli* and *K. pneumoniae*[79]. However, inhibition activity of sulbactam against CTX-M-type ESBLs is rather weaker than those of CVA and tazobactam[80], and this characteristic is useful in discrimination of CTX-M-type ESBL producers from TEM-derived or SHV-derived ESBL producers in routine laboratory testing. However, CTX-M-190, a new variant of CTX-M-55 belonging to the CTX-M-1 group, showing resistance to both sulbactam and tazobactam has recently been reported from Shanghai[52].

3-3 Initial reports of CTX-M-type ESBLs

FEC-1-producing *E. coli* was first identified in feces of a laboratory dog by a research group of a Japanese pharmaceutical company and documented in 1988[81] prior to the first report of MEN-1 (= CTX-M-1) in 1992[37]; the FEC-1

Table 1. Types and groups of extended-spectrum β-lactamases (ESBLs) and their variants reported from or distributing among *Enterobacteriaceae*

Category	Group/type	Property	β-Lactamase	Reference
TEM-derived or SHV-derived	TEM-derived	Sensitive to inhibitor	TEM-3, TEM-10, and many variants	
		Resistant to inhibitor	TRC-1	Thomson CJ, et al., FEMS Microbiol Lett. 1992; **70**:113–117.
			TEM-35, TEM-36	Saves I, et al., J Biol Chem. 1995; **270**: 18240–18245.
	SHV-derived	Sensitive to inhibitor	SHV-2, SHV-10, SHV-12, and many	
		Resistant to inhibitor	S130G SHV-1 variant	Winkler ML,et al., Antimicrob Agents Chemother. 2015; **59**: 3700–9.
				Sulton D, et al., J Biol Chem. 2005; **280**: 35528–35536.
CTX-M-variant	CTX-M-1 group	Hardly hydrolyze CAZ	CTX-M-1, CTX-M-3, CTX-M-32	
		Can hydrolyze CAZ	CTX-M-15, CTX-M-55	
		Resistant to inhibitors	CTX-M-190	80
	CTX-M-2 group	Hardly hydrolyze CAZ	CTX-M-2, CTX-M-31, Toho-1(=CTX-M-44)	
	CTX-M-9 group	Hardly hydrolyze CAZ	CTX-M-9, CTX-M-14, CTX-M-45	
		Can hydrolyze CAZ	CTX-M-27	
	CTX-M-8/25 group	Hardly hydrolyze CAZ	CTX-M-8, CTX-M-25, CTX-M-39	
Oxacillinase	OXA-type (class D)	ESBL	PSE-2/OXA-10 OXA-11, OXA-405	58
		Carbapenemase	OXA-48, OXA-163, OXA-181, OXA-244, OXA-247	
Other ESBLs	GES	ESBL (GES-5 is carbapenemase)	GES-1	52
	VEB		VEB-1	53
	BES		BES-1	54
	SFO		SFO-1 (very similar to the CTX-M-1 group)	55
	TLA		TLA-1	56

was later found to display an amino acid sequence very similar to CTX-M-type ESBLs belonging to the CTX-M-1 group[82], as well as SFO-1 very similar to the MEN-1[57]. The SFO-1 was first identified in an *Enterobacter cloacae* clinically isolated also in Japan. The genetic information of an extended-spectrum β-lactamase, UOE-1, was first submitted to the databank by a Japanese research group with assigned accession No. AY013478 in 2000. The UOE-1 later assigned CTX-M-15, although the CTX-M-15 has spread worldwide especially in western areas including European countries[38,83]. On the other hands, CTX-M-14 and CTX-M-27 belonging to the CTX-M-9 group were first described in Korea[84] and France[85], respectively, but the nucleotide sequence of $bla_{\text{CTX-M-14}}$ was first submitted to the DNA database in 2000 from the United Kingdom with an accession No. AF252622. The CTX-M-9-group ESBLs have so

doi: 10.14252/foodsafetyfscj.2017011

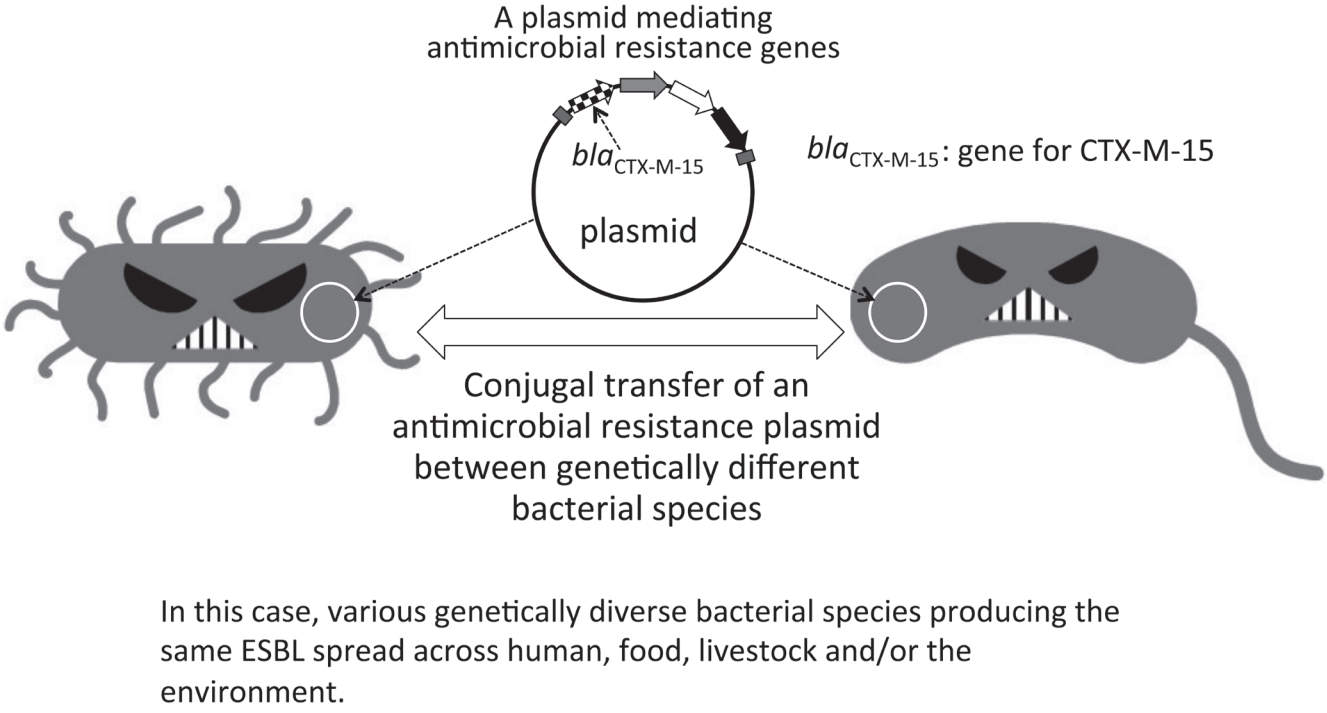

Fig. 3. Transfer of antimicrobial resistance gene-mediating plasmids between genetically different bacteria.

far been often reported from Asian countries[86–88], although CTX-M-15 and CTX-M-14 are now becoming intermixed and epidemic globally[38,89].

3-4 Prevalence of ESBLs and their producers

As described above, *E. coli* and *K. pneumonia* producing TEM-derived or SHV-derived ESBLs have been reported since the 1980s and they became prevalent in the 1990s in many regions including Europe and North America[31,90,91]. However, the producers of CTX-M-type ESBLs have become more prevalent[38,83,87] than those producing TEM-type and SHV-type ESBLs in 2000s worldwide.

CTX-M-type ESBLs have been roughly divided into 4 groups on the basis of the sequence similarity in amino acid residues; e.g. CTX-M-1 group, CTX-M-2 group, CTX-M-9 group, and CTX-M-8/CTX-M-25 group. CTX-M-1, CTX-M-3, CTX-M-15 and CTX-M-55 belong to the CTX-M-1 group, while CTX-M-9, CTX-M-14 and CTX-M-27 belong to the CTX-M-9 group[92,93]. The groups of CTX-M-type ESBLs and their variants are listed in **Table 1**. It is notable that the hydrolytic activities of CTX-M-15, CTX-M-55, and CTX-M-27 against the oxyimino-cephalosporins expand to ceftazidime (CAZ) from cefotaxime[85,94,95].

4. ESBL prevalence among healthy people

4-1 Epidemiology of ESBL producers

The states of colonization by and infections with ESBL producers have been well investigated among hospitalized ill patients[96–98]. However, the actual situation of the fecal carriage of or colonization by ESBL-producing bacteria among healthy people still remains unclear[83,99], though the risk factors for colonizing ESBL producers were investigated[100]. Shortage of the molecular epidemiological data on ESBL producers and exact information about fecal carriage of ESBL producers in healthy people would owe to the difficulty in taking specimens with ethical agreement from each healthy volunteer. Then, we undertook an investigation to understand the state of ESBL producers in healthy people who were engaged mainly in food handling in Japan during 2010 and 2011[8] with the process of "informed consent" because those persons are required to be periodically checked for the fecal carriage of some pathogenic bacteria such as *Salmonella* and *Shigella* spp. under the Japanese Law for Food Safety. According to our result, the isolation frequency of ESBL producers from the feces of healthy people was 3.1% when the test was performed only once using MacConkey agar plates supplemented with 1 mg of cefotaxime per L. However, the isolation frequency elevated to 15.6% when the same tests were recurrently performed more than twice for the same subject. We assume that the number of bacterial cells of ESBL producers in the feces of healthy people would be usually around the lower limit of detection in the routine

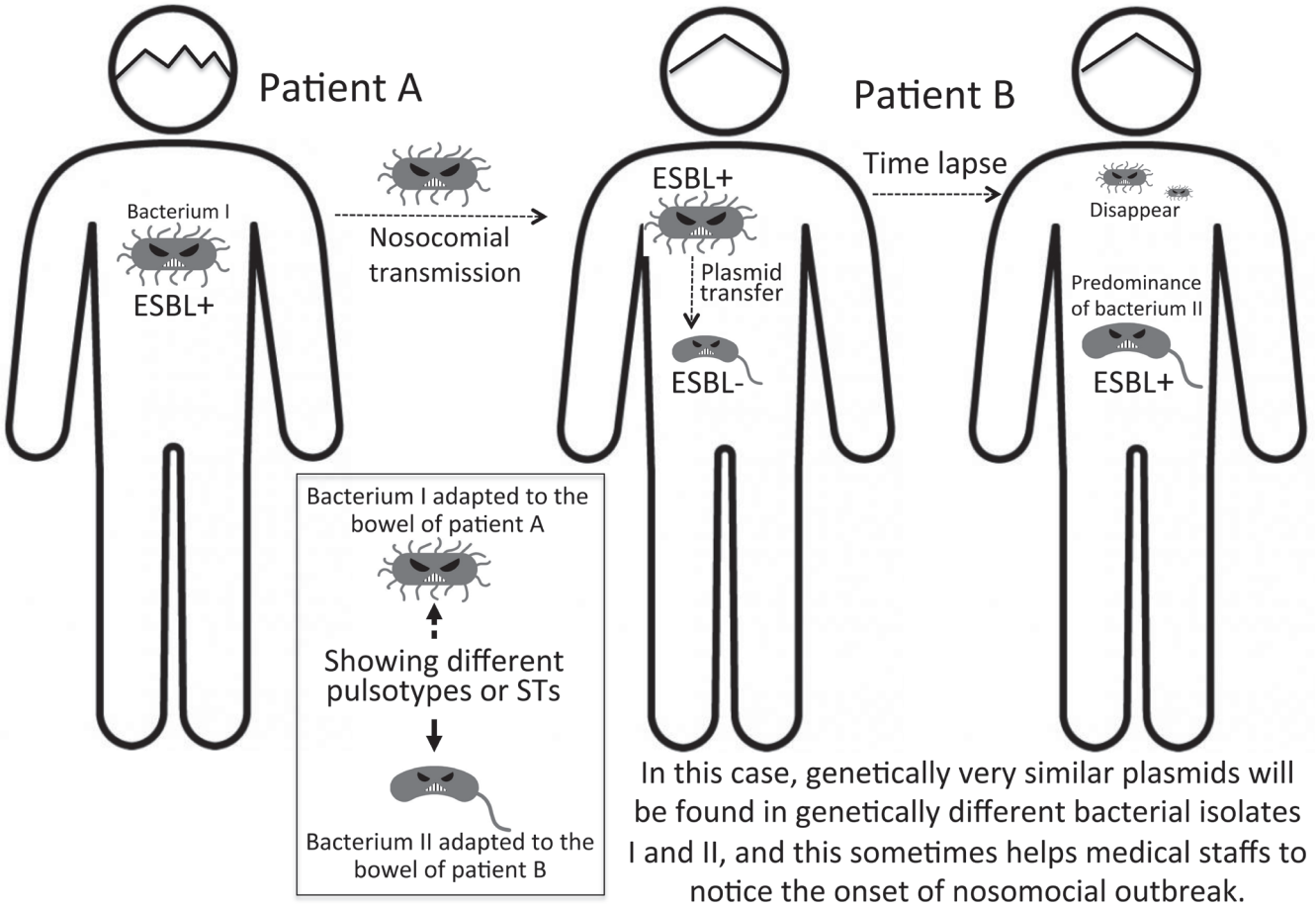

Fig. 4. A case of bacterial outbreak showing different pulsotypes or STs but producing the same ESBL.

microbiology testing we employed. Therefore, false negative results sometimes occur in the screening procedure performed in the investigation. Thus, we speculated that actual fecal carriage of ESBL producers among healthy people in Japan would be above 15% around 2010, a much higher value than the 6.4% obtained by one point investigation in Osaka between July 2009 and June 2010[101].

The isolation frequencies of ESBL producers from healthy adults in Europe were usually lower than 10%[102–106] except for the healthy young children in Spain[107] at the end of 2016, and these values were much lower than those in Asia where the isolation frequencies are usually above 20%[108–113]. The carriage rate of ESBL producers in 2011 was reportedly 20.3% in Korea[114]. Very high isolation frequency above 50% was reported especially from China[115], Thailand[116] and Vietnam[10]. In African countries, the isolation frequencies distributed from 10 to 50%, and a very high isolation frequency (59%) was found in healthy children of the Central African Republic[117]. Various kinds of ESBLs have been identified in healthy people worldwide, and *E. coli* O25-B2-ST131 are often reported from healthy individuals. Genetic properties of ESBLs and ESBL-producing *E. coli* are listed in **Table 2**.

4-2 Stability of ESBL-producing bacteria in the hosts

Since the antimicrobial-resistant bacteria usually pay for fitness costs to keep infections or colonization in their hosts[122,123], they tend to disappear or decrease in the hosts soon or later under the antimicrobial-free condition due to the results of probable survival competition with the wild-type bacterial lineages producing no plasmid-mediated exogenous β-lactamases[123–125]. Moreover, some plasmids that carry antimicrobial resistance genes were also considered to require fitness cost for keeping plasmids in the host bacterial cells[126]. Thus, ESBL producers tend to disappear in the absence of antimicrobial pressure. However, some antimicrobial-resistant bacterial lineages such as *E. coli* O25b:H4-ST131 that have acquired abilities to persist in the human intestine or urinary tract as a kind of adherent-invasive *E. coli* (AIEC)[127] can colonize in their hosts for a long period without any antimicrobial pressure[8]. Furthermore, some combinations of antimicrobial resistance plasmids and bacterial lineages, which can stably accommodate specific

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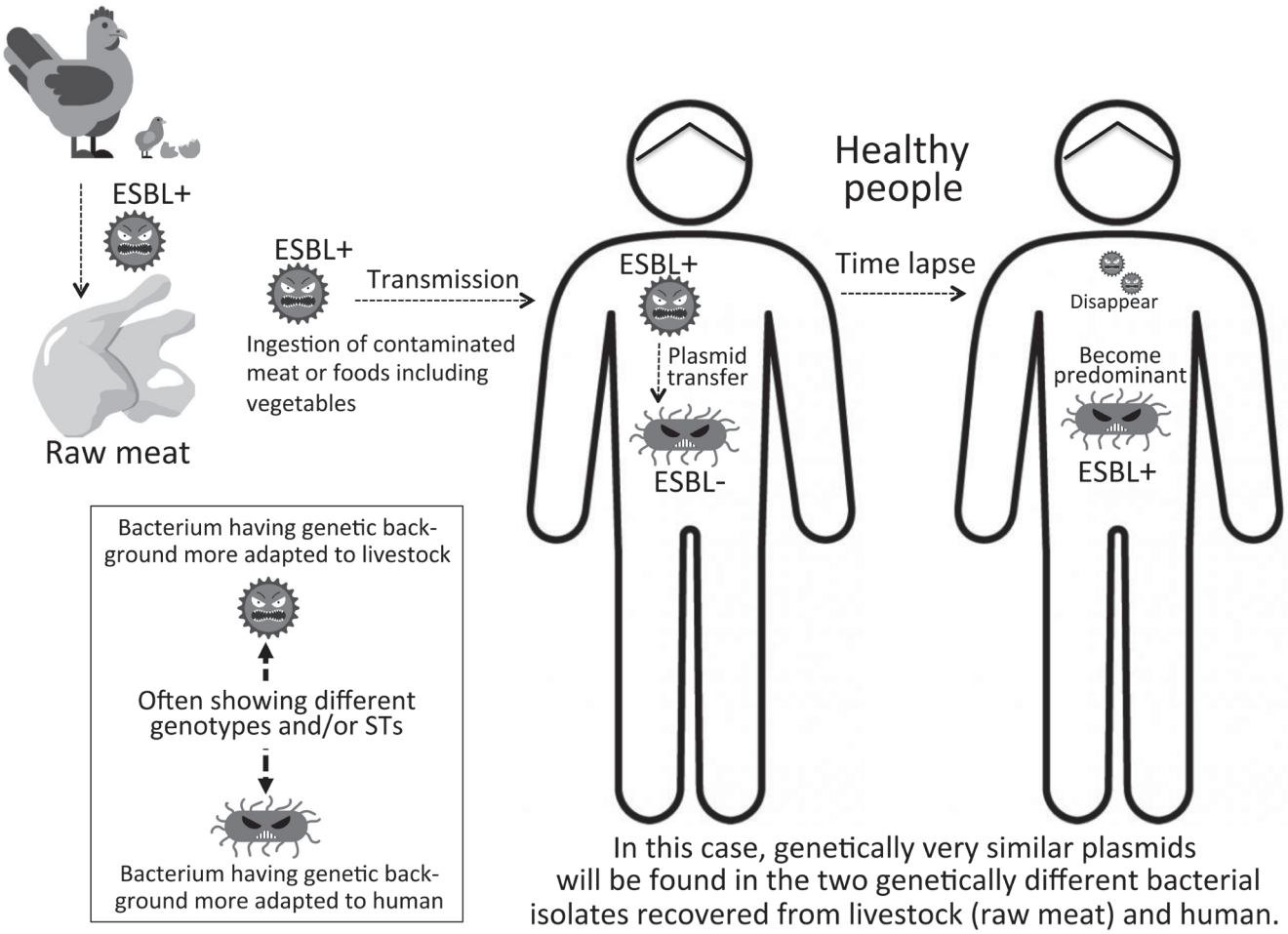


Fig. 5. Probable mechanism underlying the genetic difference between two *E. coli* isolates recovered respectively from livestock (raw meat) and human, that produce the same ESBL.

R-plasmids, have emerged and spread worldwide, and they are sometimes called "epidemic strain" or "international clone"[128,129]. As for *E. coli*, sequence type 131 (ST131) is the most famous "international clone"[130]. In our recent study, some ESBL-producing *E. coli* lineages O25b:H4-ST131, as well as O1:H6-ST648 and O15:H6-ST345, were able to colonize for more than 3 months in the bowel of healthy people without having antimicrobials[8]. In *K. pneumoniae*, ST13, ST15, ST35, ST37, ST48, ST101, ST147, and ST258 are also regarded to be epidemic lineages as "international clones" possessing multidrug resistance property with producing ESBL as well as plasmid-mediated multiple antimicrobial resistance determinants[131,132]. The combination of *E. coli* ST648 and IncK plasmid mediating $bla_{\text{CTX-M-15}}$ also seemed stable in the human intestine according to our previous study[8], and similar stability was found in the various combinations such as between *E. coli* ST131 and IncF or IncI1-Iγ plasmids[133]. Emergence of "epidemic strains" or "international clones" demonstrating stable combination between specific bacterial lineages and antimicrobial resistance plasmids would well accelerate further global spread of ESBL-producing bacteria belonging to the members of the family *Enterobacteriaceae*[134].

5. Co-transfer of ESBL genes with other antimicrobial resistance genes

Urinary tract infection (UTI) is one of the most common community-acquired infections[4–6], and fosfomycin has become one of the potent antimicrobials in treatment of Gram-negative bacterial infections[135] including UTI[136,137] due to the recent rapid increase in the prevalence of ESBL-producing and fluoroquinolone-resistant *E. coli* in the community as well as in clinical settings worldwide[15,17]. However, the plasmid-mediated fosfomycin resistance gene, *fosA3*, has emerged[138] and spread in both human and animal in several Asian countries[139–141], especially in China[142–144]. This might owe to heavy use of fosfomycin in livestock farming environments in some countries. Thus, it seems natural that ESBL-producing *E. coli* from human

Table 2. Genetic and/or serological characteristics of ESBL-producing *E. coli* recovered outside of health care settings after 2000

Source	City, Country	Item (Year of isolation or publication)	Type of ESBL	Inc type of plasmid	Serotype and/or ST of host *E. coli* [phylo-group] (No. of isolates)	Ref.
Human (Healthy)	City unknown, Lebanon	Healthy infants between 1 and 12 months of age (Jan and May 2013)	CTX-M-9		(15)	118
			CTX-M-9+CTX-M-15		(15)	
			CTX-M-9+CTX-M-15+CTX-M-2		(8)	
			CTX-M types other than M2, M9, and M15		(4)	
	Manouba governorate, North of Tunisia	Elementary school students (during 2012–2013 school year)	CTX-M-1		ST155/CC155(1)	11
					ST58/CC155(1)	
					ST398/CC398(1)	
					ST746(1)	
			CTX-M-15		ST493/CC12(1)	
					ST127(1)	
	Okazaki, Japan	Food Handler (Jan 2010–Dec 2011)	CTX-M-1		OUT (2)	8
			CTX-M-3		O25(1)	
			CTX-M-15		OUT (11), O1(3), O8(3), O78(3), - - - - -	
			CTX-M-55		OUT(1)	
			CTX-M-14		OUT(30), O25(7), O1(5), O153(5), O74(4), -	
			CTX-M-27		O25 (16), - - - -	
			CTX-M-2		OUT(11), O142(3), - - -	
			CTX-M-8		OUT(3), O1(2)	
	Osaka, Japan	Adult volunteers (n = 218) (Jul 2009–Jun 2010)	CTX-M-15		(1)	101
			CTX-M-2		(4)	
			CTX-M-8		(2)	
			CTX-M-14		(4)	

Table 2. (continued)

Source	City, Country	Item (Year of isolation or publication)	Type of ESBL	Inc type of plasmid	Serotype and/or ST of host *E. coli* [phylo-group] (No. of isolates)	Ref.
	Tenri, Japan	Community dwellers (Mar 2011–Mar 2012)	CTX-M-1		ST10[A](1)	119
			CTX-M-15		ST1485[D](12), ST405[D](1), ST2787[B1](1)	
			CTX-M-55		ST59[D](1), ST58[B1](1)	
			CTX-M-2		ST57[D](1), ST2847[D](1), ST3510[B2](1), ST93[A](1)	
			CTX-M-9		ST38[D](1),	
			CTX-M-14		ST38[D] (2), ST405[D] (1), ST648[D] (2), ST69[D] (1), ST70[D] (1), ST131[B2] (2), ST95[B2] (1), ST550[B2] (1) ST93[A](2), ST23[A](2)	
			CTX-M-27		ST131[B2](2), ST716[A](1)	
	Hangzhou, China	Healthy human (2012)	CTX-M-14		CC10[A](3) ST38[D](8) ST131[B2](3) ST648[D](9)	120
			CTX-M-27		ST131[B2](3)	
			CTX-M-3		CC10[A](1)	
			CTX-M-24		ST38[D](1)	
	Shanghai, China	Healthy individuals (May–Jul 2014)	CTX-M-15		(154)	111
			CTX-M-3		(12)	
			CTX-M-55		(7)	
			CTX-M-14		(231)	
			CTX-M-27		(45)	
			CTX-M-65		(18)	
			CTX-M-98		(4)	
			CTX-M-105		(1)	
			CTX-M-64		(8)	
			CTX-M-123		(5)	
			CTX-M-132		(1)	
			CTX-M-137		(1)	

Table 2. (continued)

Source	City, Country	Item (Year of isolation or publication)	Type of ESBL	Inc type of plasmid	Serotype and/or ST of host *E. coli* [phylo-group] (No. of isolates)			Ref.
	Vientiane, Lao People's Democratic Republic	Healthy children ≤6 years of age (Mar–Jun 2011)	CTX-M-15		(10)			109
			CTX-M-55		(13)			
			CTX-M-14		(36)			
			CTX-M-27		(9)			
			CTX-M-64		(5)			
			CTX-M-24		(3)			
			CTX-M-101		(1)			
	7 counties (Stockholm, Gothenburg, et al), Sweden	(Nov 2012–Dec 2013)	CTX-M-1	IncF(45%) IncI1(23%) IncK(5%)	(11)	[A](21)	ST10(7)	102
			CTX-M-15		(43)	[B1] (13)		
						[B2] (24)	ST131(16), H30Rx(6)	
			CTX-M-14		(19)	[D](37)	ST38(10), ST405(4) ST648(2), ST69(3)	
			CTX-M-27		(8)	Singleton(34)		
	Porto, Portugal	Healthy humans (>18 years old, n = 199) (Dec 2013−May 2014)	CTX-M-14	IncK	ST226:[A0](2) ST59:[D1](1)			104
			CTX-M-27	IncF1	ST131:[B2](1)			
	Donostia, Spain	Healthy children 8–16 month-old	CTX-M-1		[A](6), [D](1)			107
			CTX-M-1+TEM-52		[D](1)			
			CTX-M-15		[D](1)			
			CTX-M-15+TEM-52		[D](1)			
			CTX-M-14		[A](2), [B1](1), [D](1)			
			CTX-M-14+SHV-5		[D](1)			
			CTX-M-14+SHV-12		[A](1)			
			CTX-M-22		[D](1)			
			CTX-M-65		[D](1)			
			CTX-M-65+SHV-12		[A](1)			
			SHV-12		[A](5), [B1](1), [D](3)			
			TEM-52		[A](2), [D](2), [B2](2)			

Table 2. (continued)

Source	City, Country	Item (Year of isolation or publication)	Type of ESBL	Inc type of plasmid	Serotype and/or ST of host *E. coli* [phylo-group] (No. of isolates)		Ref.
	Catalonia, Spain	Chicken and pig farm worker (during 2003)	CTX-M-9		O25b:H4 [B2]ST131 (4) Worker		121
			CTX-M-14[4)]		O15:H1[D]ST393(2) Worker O25a:H1[D]ST393(2) Worker O25b:H4[B2]ST131(2) Worker		
			CTX-M-1		O25a:H4[D]ST648(1) Worker		
			CTX-M-15		O25b:H4[B2]ST131(6) Worker		
			CTX-M-32		O25a:H4[D]ST648(2) Worker O25a:HNM[D]ST648(1) Worker		
	4 provinces of the Netherlands	Adults (Aug and Dec 2011)	CTX-M-24		ST131[B2](1)		9
			CTX-M-15		ST38(2), ST648(2), ST131(1), - - -		
			CTX-M-14		ST10(1), ST38(1), ST58(1), ST69(1), ST414(1), ST1982(1), ST5039(1), ST648(1), - - -		
			CTX-M-24		ST38(1), ST58(1)		
	Amsterdam, the Netherlands	Adults (≥18 years old) (Jun–Nov 2011)	CTX-M-15		(59)	MLST showed 47 different STs ST131(21) ST10(18)/ CC10(26) ST38(9)	105
			CTX-M-15+TEM-52		(1)		
			CTX-M-1		(25)		
			CTX-M-1+SHV-12		(1)		
			CTX-M-3		(4)		
			CTX-M-55		(3)		
			CTX-M-32		(3)		
			CTX-M-2		(2)		
			CTX-M-14		(18)		
			CTX-M-14+OXA-48		(1)		
			CTX-M-9		(4)		
			CTX-M-27		(5)		
			CTX-M-9 group		(1)		
			CTX-M		(2)		
			CTX-M-21, -22		(4)		

UTIs would be found to harbor *fosA3*-mediating plasmids in high frequency in China[145]. Moreover, FosA3 producers have also been spreading outside of Asia[146–150]. Therefore, further prevalence of *fosA3* among the ESBL-producing *E. coli* showing resistance to fluoroquinolones, which are mostly *E. coli* ST131 subclones, *H30*[151,152] and *H30*Rx[153] clades, should be more carefully monitored in days to come within the community, especially in UTI patients[154].

6. Potential source of ESBL genes found in healthy people

6-1 Potential source of ESBL genes and their producers

It has been assumed that the environment such as drinking water is one of the potential sources of ESBL producers in developing countries where no reliable waterworks and sewage systems have been equipped[155–158]. In those countries, various antimicrobial-resistant bacteria including ESBL producers have been recovered even from drinking water[155,157,159] and vegetables[160]. The origins of ESBL producers in drinking water were speculated to be the sewage or drainage from human and livestock[161–165]. Moreover, similarity in genetic backgrounds of ESBL-producing *E. coli* isolates recovered from human and foods suggests their close evolutional relatedness[166]. Nevertheless, the genetic lineages of ESBL producers from healthy people are sometimes different from those recovered from livestock and foods[167]. For instance, *E. coli* O25b:H4-ST131 is the most prevalent epidemic lineage as ESBL producers in human[88,104], but this type is still relatively rare in livestock and foods[45,168]. Therefore, it is speculated that the majority of ESBL producers colonizing in livestock are not the direct origin of ESBL producers recovered from healthy people and outpatients. However, some of the ESBL-producing *E. coli* lineages such as ST10, ST38, ST69, ST405, ST410, and ST648 have so far been identified in both livestock and human, suggesting their probable transmission across livestock and human[8,120,121,169,170].

6-2 Probable acquisition of ESBL-producing *E. coli* via foods

Like other microbial pathogens, some of the ESBL-producing *E. coli* lineages have become a kind of zoonotic microbes transmitted from livestock to human via direct contact[171,172] or foods including raw meats. Moreover, raw milks are also reportedly contaminated with ESBL producers[173,174], though drinking of non-sterilized raw milk is prohibited in many countries. Among the livestock meats, it is well known that raw chicken meat is often contaminated with ESBL producers[167,169,175] also in Japan[45,176], because ESBL-producing *E. coli* usually colonizes in the intestine of livestock including poultry[177]. Some broad-spectrum cephalosporins such as ceftiofur and cefquinome have been approved and prescribed as veterinary medicines for cattle and porcine, but these agents are not approved for poultry in Japan. As for the CTX-M-type ESBLs, CTX-M-2-producing and CTX-M-8-producing *E. coli* were often found in Brazil from both chicken and human[43,178,179]. These findings would suggest probable transmission of the CTX-M-producers from chicken to human, and possibly abroad via export of chicken meat[180]. However, although CTX-M-type ESBLs belonging to CTX-M-1 group such as CTX-M-1 and CTX-M-15 were predominantly found in *E. coli* isolated from domestic chicken meat in our previous investigation, few CTX-M-14 and CTX-M-27 (**Table 3**), that are prevalent in human in Japan and surrounding Asian countries, were found in retail chicken meat in Japan[45]. Moreover, ESBL-producing *E. coli* O25b:H4-ST131 which are dominant in human as an *E. coli* epidemic clone was relatively rare in the chicken meat[189] (**Table 3**). These findings may suggest low implication of chicken meat contaminated with ESBL-producing *E. coli* in the recent rapidly increasing prevalence of ESBL producers found in human in Japan and elsewhere. However, plasmid transfer between different bacterial lineages adapted to chicken and human[143] (**Figs. 3 and 5**), respectively, and translocation of mobile genetic element mediating the ESBL genes[190] between different Inc-type plasmids (**Fig. 6**) should be considered in more accurate evaluation of the influence of ESBL producers in foods on the increasing colonization of ESBL producers in human.

6-3 International travel as a probable risk for acquisition of ESBL producers

Since the 2000s, international travel to the regions where antimicrobial-resistant bacteria are prevalent has been gradually recognized as one of the probable risks of acquisition of ESBL producers[191–193]. Among the countries and regions, the risk of acquisition of ESBL producers during travel was reported to be highest in southern Asian countries including India[194], followed by west and northern African countries[195–197]. Among the travel-acquired ESBL producers, more than 10% of them still colonized ESBL producers at 12 months after their travel[198].

6-4 Transfer of ESBL producers between pets and human

ESBL-producing *E. coli* has been increasingly reported from dogs and cats[199,200], and the antimicrobial-resistance determinants and the genotypes of *E. coli* isolates from the

Table 3. Characteristics of ESBL-producing *E. coli* from meats and vegetables

City, Country	Sample (Study period)	ESBL type (Number of isolates)	Serological/genetical characteristic of each ESBL producer [phylo-group] (No. of isolates)	Ref.
Aichi, Japan	Retail chicken meat (Jan–Oct 2010)	CTX-M-2(22)	OUT:HUT(6), OUT:H-(6), OUT:H18(2), O8:H21(1), O25:H4(1), O25:HUT(1), O27:HUT(1), O153:HUT(1), O166:H45(1), OUT:H18(2)	45
		CTX-M-1(5)	O1:H-(2), O18:H-(1), OUT:H11(1), OUT:HUT(1)	
		CTX-M-3(2)	OUT:H42(1), H8:H21(1)	
		CTX-M-15(5)	OUT:UHT(3), OUT:H-(1), O8:H9(1)	
		CTX-M-8(8)	O8:H21(1), O8:HUT(1), O18:H7(1), O25:H4(1), OUT:H21(1), OUT:H42(1), OUT:H51(1), OUT:HUT(1)	
		CTX-M-8+TEM-135(1)	O8:H-(1)	
		SHV-2(1)	O78:HUT(1)	
		SHV-12(7)	OUT:H-(1), O20:H-(1), OUT:H4(1), O25:H4(1), OUT:H42(1), OUT:HUT(1), OUT:H10	
		TEM-52(1)	O8:H21(1)	
Shenzhen, China	Fresh pork and chicken samples purchased from wet markets that sell fresh and unprocessed meat products (Nov 2012–May 2013)	CTX-M-55(8) CTX-M-15(4) CTX-M-14(2) CTX-M-123(1)	Chicken ST155[B1](2), ST156[B1](1), ST-not determined[D](1), ST90[A](1), ST2509[A](1) Pork ST156[B1](2), ST162[B1](1), ST88[A](2), ST101[B1](1), ST1196[B1](1), ST789[A](1), ST5037[B1](1)	143
Guangzhou City, China	Raw pork and cooked pork products (Sep–Nov 2013)	CTX-M-1(1) CTX-M-1+SHV(1) CTX-M-9(1) TEM(4)		181
Ho Chi Minh City, Vietnam	Food samples (chicken meat, pork, beef, and fish) (Oct 2012–Mar 2014)	CTX-M-9 group (110) CTX-M-1 group (102) SHV-12 (3)	Chicken(44), Pork(41), Beef(12), Fish(13) Chicken(62), Pork(15), Beef(10), Fish(15) Chicken(1), Beef(2)	182
Hatay region, Turkey,	Chicken meat (Feb–Jun 2012)	CTX-M-1(39)	[D1](30), [D2](2), [A0](3), [A1](1), [B1](3)	183
		CTX-M-1+TEM-1b(10)	[D1](7), [D2](2), [A0](1)	
		CTX-M-1+TEM-1b + SHV-5(1)	[D1](1)	
		CTX-M-3(3)	[D1](2), [A0](1)	
		CTX-M-15(4)	[D1](2), [D2](2)	
		CTX-M-15+SHV-12(1)	[D2](1)	
		SHV-12(1)	[D1](1)	
		SHV-12+TEM-1b(1)	[B1](1)	
		TEM-1b (2)	[B1](1), D1(1)	
	Beef (Feb–Jun 2012)	CTX-M-3(1)	[D1](1)	
		CTX-M-15+TEM-1b(1)	[B1](1)	

Table 3. (continued)

City, Country	Sample (Study period)	ESBL type (Number of isolates)	Serological/genetical characteristic of each ESBL producer [phylo-group] (No. of isolates)	Ref.
Sweden	Frozen chicken meat fillets (Sep–Nov 2010)	CTX- M-1(4) Mediated by IncI2 plasmid	ST117(1), ST1640(2), ST2183(1)	184
Tilburg, the Netherlands	Chicken meat (17 Aug–30 Oct 2009)	CTX-M-1(50) CTX-M-2(4) CTX-M-14(2) CTX-M-15(1) Other CTX-M(4) TEM-52(12) SHV-2(1) SHV-12(12)		167
Utrecht, the Netherlands	Chicken breasts (2010)	CTX-M-1(46) CTX-M-2(4) TEM-20(2) TEM-52(38) SHV-2(3) SHV-12(15)	ST10(4) ST23(4) ST57(1) ST117(1) ST354(1)	169
Greifswald & Berlin, Germany	Chicken breasts and legs (between 16 and 26 Aug 2011, and between 24 Oct and 15 Nov 2011)	CTX-M-1(77) CTX-M-2(6) CTX-M-65(1) SHV-2(1) SHV-2A(4) SHV-12(82) TEM-52(16) CTX-M-1+TEM-52(1)	phylogenetic group A strain was confirmed in different samples from three supermarket chains	185
Tilbury, UK	non-EU raw chicken meat imported into the UK (Aug–Oct 2008)	CTX-M-2(42) CTX-M-8(38) CTX-M-2+ CMY(2)	[A](5), [B1](14), [B2](3), D(20) [A](15), [B1](9), [D](14) [A](1), [D](1)	186
Palermo, Italy	Retail chicken meat (May 2013–Apr 2015)	CTX-M-1 g (1) CTX-M-9 g (1) CTX-M-2 g (1) CTX-M-15 (2)	ST131*H30*R(3) ST131*H30*Rx(2)	168

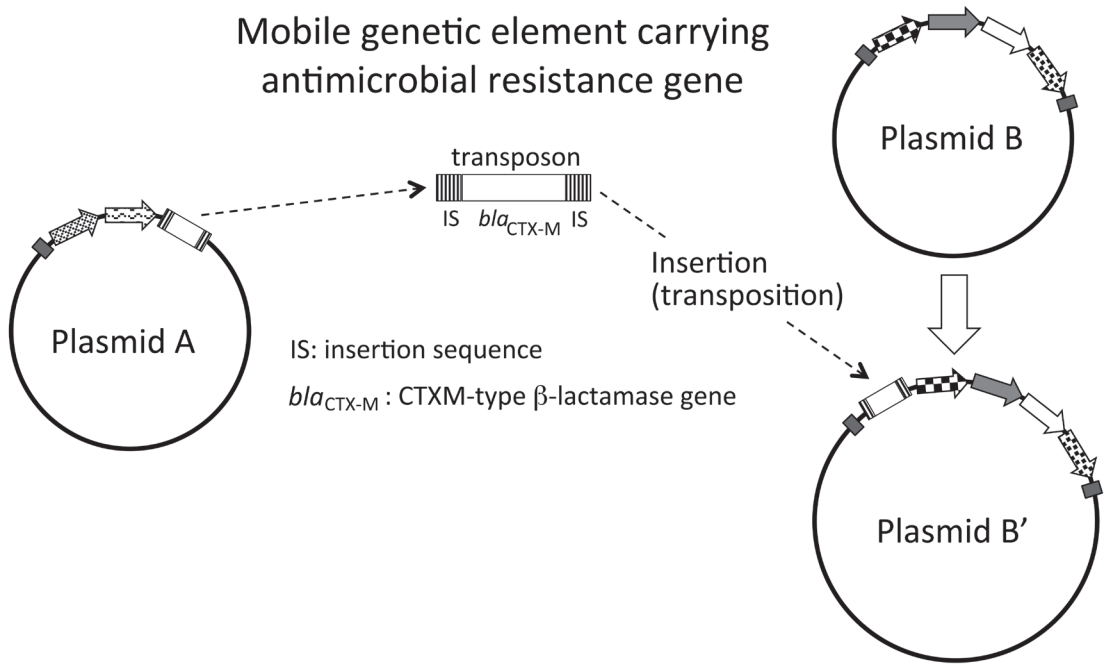
Table 3. (continued)

City, Country	Sample (Study period)	ESBL type (Number of isolates)	Serological/genetical characteristic of each ESBL producer [phylo-group] (No. of isolates)	Ref.
Zürich, Switzerland	Vegetables imported from the Dominican Republic, India, Thailand, and Vietnam (Jul and Aug 2014)	From Dominican Republic	ST131 [B2](1), ST405/CC405 [D] (1)	160
		CTX-M-15(2)		
		CTX-M-14(1)	ST38/CC38 [D] (1)	
		CTX-M-65(1)	ST167/CC10 [A] (1)	
		SHV-12(1)	ST1656 [B1] (1)	
		From India	ST410/CC23 [A](1), ST4681[B1](1)	
		CTX-M-15(8)	ST1881 [B1] (1), ST155/CC155 [B1] (1) ST443/CC205 [B1] (1), ST4682 [B1] (1) ST4684 [B1] (1), ST641/CC86 [A] (1)	
		CTX-M-1(1)	ST155/CC155 [B1] (1)	
		CTX-M-14(1)	ST38/CC38 [D] (1)	
		From Thailand	ST58/CC155[B1](1), ST4679[B1](1)	
		CTX-M-14(3)	ST3696[A](1)	
		CTX-M-55(5)	ST167/CC10[A](1) ST393/CC31[D](1) ST48/CC10 [A](1) ST4680 [B1] (1) ST226/CC226 [A] (1)	
		From Vietnam	ST10/CC10 [A] (1)	
		CTX-M-55(1)		
		CTX-M-65(2)	ST58/CC155 [B1] (1), ST4683[B1] (1)	
Rio de Janeiro, Brazil	Sixteen frozen chicken carcasses (Aug 2010–Apr 2011)	CTX-M-2(16)	[D] (7), [B1] (5), [A] (4)	187
		CTX-M-8(7)	[B1] (5), [D](2)	
		CTX-M-15(1)	[B1] (1)	
		CTX-M-2+CMY-2(1)	[D] (1)	
		CTX-M-8+CMY-2(1)	[A] (1)	
São Paulo, Brazil	Chicken meat (Mar 2011–Jul 2013)	CTX-M-2(2)		188
		CTX-M-8(1)		

pets have considerable similarity to those from human[201–203]. *E. coli* O25:H4-ST131 is often recovered from clinical human specimens, and this lineage is sometimes isolated from companion animals[204], suggesting its probable transmission from human to pets or vice-versa. Companion animals would receive ESBL producers through their foods[205] as well as from their owner, and could keep the microbes in their intestine for a long period as a reservoir[206,207]. Thus, carriage of antimicrobial-resistant microbes in companion animals should be carefully monitored especially in those living with elderly people[208].

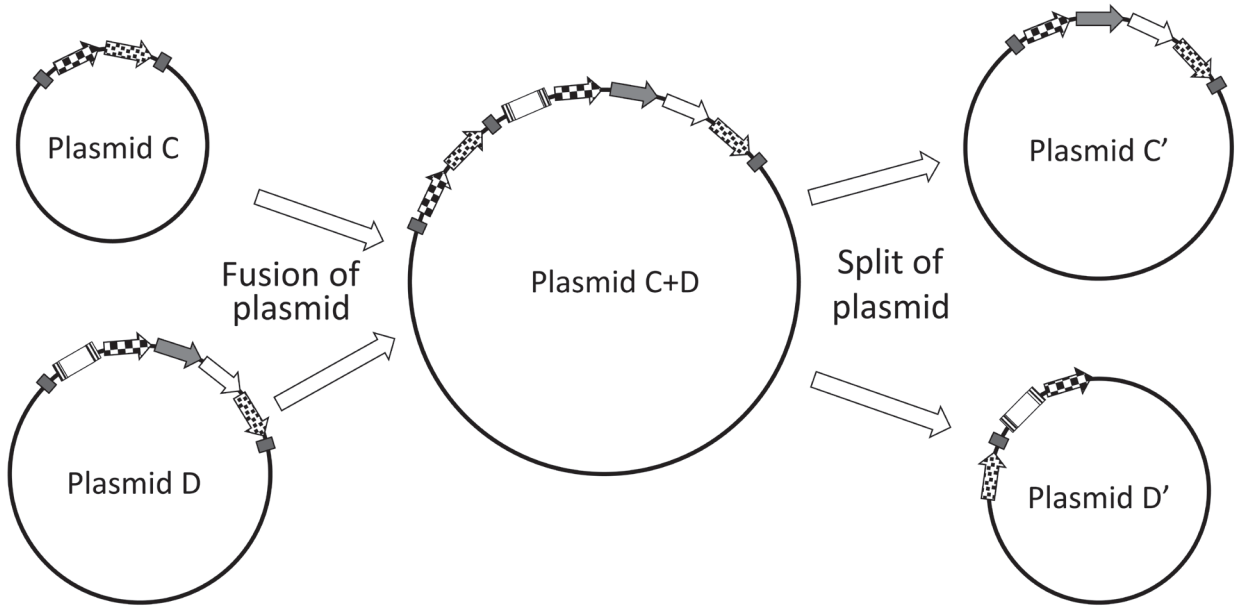
7. Emission of ESBL producers into the environment and wildlife

As described above, water of rivers and lakes have been reportedly polluted with ESBL producers even in some high-income countries[209,210] as well as in many developing countries because of the sewage or drainage emissions into rivers from households, hospitals and livestock farming settings.



Antimicrobial resistance genes often transpose onto other plasmids with different Inc-type by the help of transposons and/or insertion sequences (IS). Thus the simple comparison of plasmids sometimes has no meaning to speculates the nosocomial spread of bacteria depend on the plasmid profiles.

Fig. 6. Translocation of antimicrobial resistance mobile genetic element between plasmids.



The sizes of plasmid sometimes change by fusion and split of plasmids, and this make it difficult to estimate the genetic relations of plasmids mediating similar antimicrobial resistant genetic determinants by comparing the plasmid sizes.

Fig. 7. Fusion and split of antimicrobial resistance plasmids.

Moreover, ESBL producers were recovered from drinking water even in France[211]. Furthermore, recoveries of ESBL producers from wildlife such as birds[212–214], boars and *Barbary macaques*[215], red deer and wild small mammals[216], and raccoon[217,218] have been increasingly documented from many countries. The wildlife colonized by ESBL producers would work as incubators and reservoirs of antimicrobial-resistant microbes including ESBL producers in the environments surrounding the human community, and this would become one of the human public health concerns[219]. The ESBL producers in the feces of wildlife would indeed contrarily pollute the river water, drinking water, vegetables, and livestock, and this would subsequently augment the fecal carriage of ESBL producers in companion animals and ordinary citizens as a result of environmental circulation of ESBL-producing *Enterobacteriaceae*. Thus, close monitoring regarding ESBL producers in environmental water and wildlife would become more important than ever, and wild small animals could contribute as good sentinels to the monitoring of AMR in the environment[220].

8. Important viewpoints in molecular epidemiological investigation of ESBL producers

As described above, the genetic lineages of ESBL producers are often different between livestock and human[45], and the plasmids mediating ESBL genes have been sometimes different between farm animals and human[221]. These findings indeed provide evidence denying the possible transfer of ESBL producers from livestock to human via foods. However, the IncI1 plasmids often found in the *E. coli* lineages adapted to chicken[222] may well be transferred to the human type *E. coli* lineages such as serotypes O1, O16 and O25 belonging to ST131 in the human intestinal environment[223], a speculation supported by experiment[224] and investigation[225]. This speculation might be corroborated by the findings that multiple bacterial species or lineages producing the same ESBL are sometimes recovered from the same healthy individual[8–10] (**Figs. 4 and 5**). Therefore, simple comparison of bacterial genetic lineages such as ST would have little meaning in the retroactive investigation into the transmission pathway and the origin of ESBL-producing *E. coli* recovered from human. To overcome this limitation, genetic analyses of each plasmid mediating ESBL gene would be very useful. For this purpose, typing of the incompatibility (Inc) group of each plasmid, as well as the sequence typing of plasmid (pMLST) would be of value. Comparative analyses of overall organization of ORFs on the plasmids would also become very useful, because, even if the O-serotypes or STs are different between 2 ESBL producers from livestock and human, the fundamental genetic structure of the plasmids mediating ESBL gene would be kept after the transfer of the plasmid from the *E. coli* lineages intimate to animal bowel into the *E. coli* lineages adapted to human intestine. Thus, possible transfer of plasmids carrying ESBL genes between the *E. coli* lineages adapted to animal and human, respectively, should be considered in the exact molecular epidemiological investigations of ESBL-producing bacteria (**Fig. 5**).

Even if both ST of *E. coli* isolate and the Inc-type of plasmid mediating ESBL gene are different between 2 *E. coli* isolates recovered independently from livestock and human despite the fact that both the isolates harbor the same ESBL gene such as $bla_{\text{CTX-M-15}}$, the comparative analysis of the structure of mobile genetic elements or integrative and conjugative elements (ICE)[226] mediating various $bla_{\text{CTX-M}}$ genes, together with IS*Ecp1*, IS*CR1* containing *orf513*, and *orf477*, would be helpful to assess the genetic relatedness of the $bla_{\text{CTX-M}}$ genes identified in 2 different *E. coli* isolates independently recovered from different origins (**Figs. 4 and 5**). Actually, although such comparative analyses have been made[69,227], fusion and split of plasmids mediating various antimicrobial resistance genes make it difficult to perform comparative analyses of plasmids (**Figs. 6 and 7**).

9. Conclusion

As well as livestock and their raw meat, ready-to eat sandwiches and vegetables have also been reportedly contaminated with ESBL-producing *E. coli* in Algeria and Korea[228,229], although contamination of fruits and vegetables with ESBL producers are not found in Switzerland and the UK[230,231]. Various genetic variants of ESBLs have emerged in both human and livestock, and they are usually mediated by a variety of transferable plasmids with different Inc-types, such as IncF, IncA/C, IncK, IncN and IncI1, that have accumulated multiple antimicrobial resistance genes including *aac*, *aad*, and *aph* for aminoglycoside resistance, *qnr*, *aac(6')-Ib-cr*, and *qep* for quinolone resistance, and *fosA* for fosfomycin resistance; however, coexistence of ESBL genes and *mcr-1* for colistin resistance on the same plasmid is still rare at present. The genetic environments surrounding the ESBL genes have become very complicated and diverse[232] through recurrent rearrangements in and around the antimicrobial resistance genetic elements. Moreover, the genetic elements mediating antimicrobial resistance genes can translocate onto separate plasmids possessing different genetic backbones, and the plasmids with different Inc-types fuse each other or split into daughter plasmids. Furthermore, the genetic lineages of *E. coli* harboring the plasmids that

mediate ESBL genes have become multifarious. As for the ESBL-producing *E. coli*, their STs are indeed often different between human and livestock. For instance, *E. coli* O25b-B2-ST131 are often isolated from human clinical samples, but this type of *E. coli* isolates is rarely found in livestock and foods. Contrarily, some STs, such as ST10, ST38, ST69 and ST648, are shared by both human and animal, and are sometimes found in raw meat. Therefore, these STs might well work as a shuttle of the plasmids mediating ESBL genes between livestock and human via foods. Since the ESBL producers are still emitting from both human facilities and livestock farming settings into the natural environment[164,165,233], the antimicrobial-resistant microbes would contrarily transmit from the environment to human[234]. Moreover, various bacterial species belonging to the family *Enterobacteriaceae* including *E. coli* producing AmpC-type cephalosporinases having wider substrate specificity to cephamycins than class A enzymes[235], have also been recovered from vegetables[236,237]. As they become prevalent, ESBL producers sometimes cause severe bacteremia[238] and pneumonia[239] even in the community. Therefore, we must take a much close look at the trend of ESBL producers in both the human community and the environment including livestock farming environments from "one health" perspective[176,240,241].

Acknowledgements

We thank S. Kumagai for his important suggestions and are grateful to the Food Safety Commission of Japan for its assistance in writing the manuscript.

References

1. Williams DN. Antimicrobial resistance: are we at the dawn of the post-antibiotic era? *J R Coll Physicians Edinb*. 2016; **46**: 150–156. PMID: 27959347 doi: 10.4997/JRCPE.2016.302
2. Spellberg B, Bartlett JG, Gilbert DN. The future of antibiotics and resistance. *N Engl J Med*. 2013; **368**: 299–302. PMID: 23343059 doi: 10.1056/NEJMp1215093
3. Bajaj P, Singh NS, Virdi JS. *Escherichia coli* β-Lactamases: What Really Matters. *Front Microbiol*. 2016; **7**: 417. PMID: 27065978 doi: 10.3389/fmicb.2016.00417
4. van der Starre WE, van Nieuwkoop C, Paltansing S, et al. Risk factors for fluoroquinolone-resistant *Escherichia coli* in adults with community-onset febrile urinary tract infection. *J Antimicrob Chemother*. 2011; **66**: 650–656. PMID: 21123286 doi: 10.1093/jac/dkq465
5. Walker E, Lyman A, Gupta K, Mahoney MV, Snyder GM, Hirsch EB. Clinical management of an increasing threat: Outpatient urinary tract infections due to multidrug-resistant uropathogens. *Clin Infect Dis*. 2016; **63**: 960–965. PMID: 27313263 doi: 10.1093/cid/ciw396
6. Chin TL, McNulty C, Beck C, MacGowan A. Antimicrobial resistance surveillance in urinary tract infections in primary care. *J Antimicrob Chemother*. 2016; **71**: 2723–2728. PMID: 27353470 doi: 10.1093/jac/dkw223
7. Pitout JD, Nordmann P, Laupland KB, Poirel L. Emergence of *Enterobacteriaceae* producing extended-spectrum β-lactamases (ESBLs) in the community. *J Antimicrob Chemother*. 2005; **56**: 52–59. PMID: 15917288 doi: 10.1093/jac/dki166
8. Nakane K, Kawamura K, Goto K, Arakawa Y. Long-term colonization by bla_{CTX-M}-harboring *Escherichia coli* in healthy Japanese people engaged in food handling. *Appl Environ Microbiol*. 2016; **82**: 1818–1827. PMID: 26746714 doi: 10.1128/AEM.02929-15
9. van Hoek AH, Schouls L, van Santen MG, Florijn A, de Greeff SC, van Duijkeren E. Molecular characteristics of extended-spectrum cephalosporin-resistant *Enterobacteriaceae* from humans in the community. *PLoS One*. 2015; **10**: e0129085. PMID: 26029910
10. Bui TM, Hirai I, Ueda S, et al. Carriage of *Escherichia coli* producing CTX-M-type extended-spectrum β-lactamase in healthy Vietnamese individuals. *Antimicrob Agents Chemother*. 2015; **59**: 6611–6614. PMID: 26195526 doi: 10.1128/AAC.00776-15
11. Ferjani S, Saidani M, Hamzaoui Z, et al. Community fecal carriage of broad-spectrum cephalosporin-resistant *Escherichia coli* in Tunisian children. *Diagn Microbiol Infect Dis*. 2017; **87**: 188–192. PMID: 27856044 doi: 10.1016/j.diagmicrobio.2016.03.008
12. Cerquetti M, Giufrè M, García-Fernández A, et al. Ciprofloxacin-resistant, CTX-M-15-producing *Escherichia coli* ST131 clone in extraintestinal infections in Italy. *Clin Microbiol Infect*. 2010; **16**: 1555–1558. PMID: 20121822 doi: 10.1111/j.1469-0691.2010.03162.x
13. Blanco J, Mora A, Mamani R, et al. National survey of *Escherichia coli* causing extraintestinal infections reveals the spread of drug-resistant clonal groups O25b:H4-B2-ST131, O15:H1-D-ST393 and CGA-D-ST69 with high virulence gene content in Spain. *J Antimicrob Chemother*. 2011; **66**: 2011–2021. PMID: 21669946 doi: 10.1093/jac/dkr235
14. Kim SY, Park YJ, Johnson JR, Yu JK, Kim YK, Kim YS. Prevalence and characteristics of *Escherichia coli* sequence type 131 and its *H30* and *H30*Rx subclones: a multicenter study from Korea. *Diagn Microbiol Infect Dis*. 2016; **84**: 97–101. PMID: 26643062 doi: 10.1016/j.diagmicrobio.2015.10.016
15. Talan DA, Takhar SS, Krishnadasan A, et al. EMERGEncy ID Net Study Group. Fluoroquinolone-resistant and extended-spectrum β-lactamase-producing *Escherichia coli* infections in patients with pyelonephritis, United States(1). *Emerg Infect Dis*. 2016; **22**: 1594–1603. doi: 10.3201/eid2209.160148
16. Weissman SJ, Hansen NI, Zaterka-Baxter K, Higgins RD, Stoll BJ. Emergence of antibiotic resistance-associated clones among *Escherichia coli* recovered from newborns with early-onset sepsis and meningitis in the United States, 2008–2009. *J Pediatric Infect Dis Soc*. 2016; **5**: 269–276. PMID: 26407251
17. Peirano G, Pitout JD. Fluoroquinolone-resistant *Escherichia coli* sequence type 131 isolates causing bloodstream infections in a canadian region with a centralized laboratory system: rapid emergence of the *H30*-Rx sublineage. *Antimicrob Agents Chemother*. 2014; **58**: 2699–2703. PMID: 24566175 doi: 10.1128/AAC.00119-14

18. Pitout JD, Laupland KB. Extended-spectrum β-lactamase-producing *Enterobacteriaceae*: an emerging public-health concern. *Lancet Infect Dis*. 2008; **8**: 159–166. PMID: 18291338 doi: 10.1016/S1473-3099(08)70041-0
19. Jacoby GA, Carreras I. Activities of β-lactam antibiotics against *Escherichia coli* strains producing extended-spectrum β-lactamases. *Antimicrob Agents Chemother*. 1990; **34**: 858–862. PMID: 2193623 doi: 10.1128/AAC.34.5.858
20. Farber B, Moellering RC Jr. The third generation cephalosporins. *Bull N Y Acad Med*. 1982; **58**: 696–710. PMID: 6762896
21. Paul GC, Gerbaud G, Bure A, Philippon AM, Pangon B, Courvalin P. TEM-4, a new plasmid-mediated β-lactamase that hydrolyzes broad-spectrum cephalosporins in a clinical isolate of *Escherichia coli*. *Antimicrob Agents Chemother*. 1989; **33**: 1958–1963. PMID: 2692515 doi: 10.1128/AAC.33.11.1958
22. Jacoby GA, Sutton L. Properties of plasmids responsible for production of extended-spectrum β-lactamases. *Antimicrob Agents Chemother*. 1991; **35**: 164–169. PMID: 1849707 doi: 10.1128/AAC.35.1.164
23. Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: a clinical update. *Clin Microbiol Rev*. 2005; **18**: 657–686. PMID: 16223952 doi: 10.1128/CMR.18.4.657-686.2005
24. Knothe H, Shah P, Krcmery V, Antal M, Mitsuhashi S. Transferable resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical isolates of *Klebsiella pneumoniae* and *Serratia marcescens*. *Infection*. 1983; **11**: 315–317. PMID: 6321357 doi: 10.1007/BF01641355
25. Brun-Buisson C, Legrand P, Philippon A, Montravers F, Ansquer M, Duval J. Transferable enzymatic resistance to third-generation cephalosporins during nosocomial outbreak of multiresistant *Klebsiella pneumoniae*. *Lancet*. 1987; **2**: 302–306. PMID: 2886766 doi: 10.1016/S0140-6736(87)90891-9
26. Philippon A, Ben Redjeb S, Fournier G, Ben Hassen A. Epidemiology of extended spectrum β-lactamases. *Infection*. 1989; **17**: 347–354. PMID: 2689354
27. Arlet G, Rouveau M, Fournier G, Lagrange PH, Philippon A. Novel, plasmid-encoded, TEM-derived extended-spectrum β-lactamase in *Klebsiella pneumoniae* conferring higher resistance to aztreonam than to extended-spectrum cephalosporins. *Antimicrob Agents Chemother*. 1993; **37**: 2020–2023. PMID: 8239625 doi: 10.1128/AAC.37.9.2020
28. Du Bois SK, Marriott MS, Amyes SG. TEM- and SHV-derived extended-spectrum β-lactamases: relationship between selection, structure and function. *J Antimicrob Chemother*. 1995; **35**: 7–22. PMID: 7768784 doi: 10.1093/jac/35.1.7
29. Liakopoulos A, Mevius D, Ceccarelli D. A review of SHV extended-spectrum β-lactamases: neglected yet ubiquitous. *Front Microbiol*. 2016; **7**: 1374. PMID: 27656166
30. Kurokawa H, Yagi T, Shibata N, Shibayama K, Kamachi K, Arakawa Y. A new SHV-derived extended-spectrum β-lactamase (SHV-24) that hydrolyzes ceftazidime through a single-amino-acid substitution (D179G) in the -loop. *Antimicrob Agents Chemother*. 2000; **44**: 1725–1727. PMID: 10817740 doi: 10.1128/AAC.44.6.1725-1727.2000
31. Bush K. Extended-spectrum β-lactamases in North America, 1987-2006. *Clin Microbiol Infect*. 2008; **14** (Suppl 1): 134–143. PMID: 18154537 doi: 10.1111/j.1469-0691.2007.01848.x
32. Sirot D. Extended-spectrum plasmid-mediated β-lactamases. J Antimicrob Chemother. 1995; 36 Suppl A: 19–34.
33. Jeong YS, Lee JC, Kang HY, et al. Epidemiology of nalidixic acid resistance and TEM-1- and TEM-52-mediated ampicillin resistance of *Shigella sonnei* isolates obtained in Korea between 1980 and 2000. *Antimicrob Agents Chemother*. 2003; **47**: 3719–3723. PMID: 14638472 doi: 10.1128/AAC.47.12.3719-3723.2003
34. Arakawa Y, Ohta M, Kido N, Fujii Y, Komatsu T, Kato N. Close evolutionary relationship between the chromosomally encoded β-lactamase gene of *Klebsiella pneumoniae* and the TEM β-lactamase gene mediated by R plasmids. *FEBS Lett*. 1986; **207**: 69–74. PMID: 3533626 doi: 10.1016/0014-5793(86)80014-X
35. Mercier J, Levesque RC. Cloning of SHV-2, OHIO-1, and OXA-6 β-lactamases and cloning and sequencing of SHV-1 β-lactamase. *Antimicrob Agents Chemother*. 1990; **34**: 1577–1583. PMID: 2221867 doi: 10.1128/AAC.34.8.1577
36. Petit A, Gerbaud G, Sirot D, Courvalin P, Sirot J. Molecular epidemiology of TEM-3 (CTX-1) β-lactamase. *Antimicrob Agents Chemother*. 1990; **34**: 219–224. PMID: 2327769 doi: 10.1128/AAC.34.2.219
37. Barthélémy M, Péduzzi J, Bernard H, Tancrède C, Labia R. Close amino acid sequence relationship between the new plasmid-mediated extended-spectrum β-lactamase MEN-1 and chromosomally encoded enzymes of *Klebsiella oxytoca*. *Biochim Biophys Acta*. 1992; **1122**: 15–22. PMID: 1633193 doi: 10.1016/0167-4838(92)90121-S
38. Cantón R, Coque TM. The CTX-M β-lactamase pandemic. *Curr Opin Microbiol*. 2006; **9**: 466–475. PMID: 16942899 doi: 10.1016/j.mib.2006.08.011
39. Ishii Y, Ohno A, Taguchi H, Imajo S, Ishiguro M, Matsuzawa H. Cloning and sequence of the gene encoding a cefotaxime-hydrolyzing class A β-lactamase isolated from *Escherichia coli*. *Antimicrob Agents Chemother*. 1995; **39**: 2269–2275. PMID: 8619581 doi: 10.1128/AAC.39.10.2269
40. <http://www.lahey.org/Studies/>.
41. <https://www.ncbi.nlm.nih.gov/pathogens/submit-beta-lactamase/>.
42. Poirel L, Kämpfer P, Nordmann P. Chromosome-encoded Ambler class A β-lactamase of *Kluyvera georgiana*, a probable progenitor of a subgroup of CTX-M extended-spectrum β-lactamases. *Antimicrob Agents Chemother*. 2002; **46**: 4038–4040. PMID: 12435721 doi: 10.1128/AAC.46.12.4038-4040.2002
43. Bonnet R, Sampaio JL, Labia R, et al. A novel CTX-M β-lactamase (CTX-M-8) in cefotaxime-resistant *Enterobacteriaceae* isolated in Brazil. *Antimicrob Agents Chemother*. 2000; **44**: 1936–1942. PMID: 10858358 doi: 10.1128/AAC.44.7.1936-1942.2000
44. Ferreira JC, Penha Filho RA, Andrade LN, Berchieri A Jr, Darini AL. IncI1/ST113 and IncI1/ST114 conjugative plasmids carrying $bla_{CTX-M-8}$ in *Escherichia coli* isolated from poultry in Brazil. *Diagn Microbiol Infect Dis*. 2014; **80**: 304–306. PMID: 25284375 doi: 10.1016/j.diagmicrobio.2014.09.012
45. Kawamura K, Goto K, Nakane K, Arakawa Y. Molecular epidemiology of extended-spectrum β-lactamases and *Escherichia coli* isolated from retail foods including chicken meat in Japan. *Foodborne Pathog Dis*. 2014; **11**: 104–110. PMID: 24093132 doi: 10.1089/fpd.2013.1608

46. Decousser JW, Poirel L, Nordmann P. Characterization of a chromosomally encoded extended-spectrum class A β-lactamase from *Kluyvera cryocrescens*. *Antimicrob Agents Chemother*. 2001; **45**: 3595–3598. PMID: 11709346 doi: 10.1128/AAC.45.12.3595-3598.2001
47. Stock I. Natural antimicrobial susceptibility patterns of *Kluyvera ascorbata* and *Kluyvera cryocrescens* strains and review of the clinical efficacy of antimicrobial agents used for the treatment of *Kluyvera* infections. *J Chemother*. 2005; **17**: 143–160. PMID: 15920899 doi: 10.1179/joc.2005.17.2.143
48. Carter JE, Evans TN. Clinically significant *Kluyvera* infections: a report of seven cases. *Am J Clin Pathol*. 2005; **123**: 334–338. PMID: 15716228 doi: 10.1309/61XP4KTLJYWM5H35
49. Stone ND, O'Hara CM, Williams PP, McGowan JE Jr, Tenover FC. Comparison of disk diffusion, VITEK 2, and broth microdilution antimicrobial susceptibility test results for unusual species of *Enterobacteriaceae*. *J Clin Microbiol*. 2007; **45**: 340–346. PMID: 17135429 doi: 10.1128/JCM.01782-06
50. Arduino SM, Roy PH, Jacoby GA, Orman BE, Pineiro SA, Centron D. $bla_{CTX\text{-}M\text{-}2}$ is located in an unusual class 1 integron (In35) which includes Orf513. *Antimicrob Agents Chemother*. 2002; **46**: 2303–2306. PMID: 12069995 doi: 10.1128/AAC.46.7.2303-2306.2002
51. Saladin M, Cao VT, Lambert T, et al. Diversity of CTX-M β-lactamases and their promoter regions from *Enterobacteriaceae* isolated in three Parisian hospitals. *FEMS Microbiol Lett*. 2002; **209**: 161–168. PMID: 12007800
52. Shen Z, Ding B, Bi Y, et al. CTX-M-190, a Novel β-lactamase resistant to tazobactam and sulbactam, identified in an *Escherichia coli* clinical isolate. *Antimicrob Agents Chemother*. 2016; **61**: e01848–e16. PMID: 27821452
53. Kiratisin P, Apisarnthanarak A, Laesripa C, Saifon P. Molecular characterization and epidemiology of extended-spectrum-β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates causing health care-associated infection in Thailand, where the CTX-M family is endemic. *Antimicrob Agents Chemother*. 2008; **52**: 2818–2824. PMID: 18505851 doi: 10.1128/AAC.00171-08
54. Poirel L, Le Thomas I, Naas T, Karim A, Nordmann P. Biochemical sequence analyses of GES-1, a novel class A extended-spectrum β-lactamase, and the class 1 integron In52 from Klebsiella pneumoniae. *Antimicrob Agents Chemother*. 2000; **44**: 622–632. PMID: 10681329 doi: 10.1128/AAC.44.3.622-632.2000
55. Poirel L, Naas T, Guibert M, Chaibi EB, Labia R, Nordmann P. Molecular and biochemical characterization of VEB-1, a novel class A extended-spectrum β-lactamase encoded by an *Escherichia coli* integron gene. *Antimicrob Agents Chemother*. 1999; **43**: 573–581. PMID: 10049269
56. Bonnet R, Sampaio JL, Chanal C, et al. A novel class A extended-spectrum β-lactamase (BES-1) in *Serratia marcescens* isolated in Brazil. *Antimicrob Agents Chemother*. 2000; **44**: 3061–3068. PMID: 11036023 doi: 10.1128/AAC.44.11.3061-3068.2000
57. Matsumoto Y, Inoue M. Characterization of SFO-1, a plasmid-mediated inducible class A β-lactamase from *Enterobacter cloacae*. *Antimicrob Agents Chemother*. 1999; **43**: 307–313. PMID: 9925524
58. Silva J, Aguilar C, Ayala G, et al. TLA-1: a new plasmid-mediated extended-spectrum β-lactamase from Escherichia coli. *Antimicrob Agents Chemother*. 2000; **44**: 997–1003. PMID: 10722503 doi: 10.1128/AAC.44.4.997-1003.2000
59. Arlet G, Philippon A. Construction by polymerase chain reaction and use of intragenic DNA probes for three main types of transferable β-lactamases (TEM, SHV, CARB) [corrected]. [corrected] *FEMS Microbiol Lett*. 1991; **66**: 19–25. Erratum in: FEMS Microbiol Lett 1991; 68:125. PMID: 1936934
60. Evans BA, Amyes SG. OXA β-lactamases. *Clin Microbiol Rev*. 2014; **27**: 241–263. PMID: 24696435 doi: 10.1128/CMR.00117-13
61. Antunes NT, Fisher JF. Acquired Class D β-Lactamases. *Antibiotics (Basel)*. 2014; **3**: 398–434. (Basel). PMID: 27025753
62. Vourli S, Giakkoupi P, Miriagou V, Tzelepi E, Vatopoulos AC, Tzouvelekis LS. Novel GES/IBC extended-spectrum β-lactamase variants with carbapenemase activity in clinical enterobacteria. *FEMS Microbiol Lett*. 2004; **234**: 209–213. PMID: 15135524
63. Jeong SH, Bae IK, Kim D, et al. First outbreak of *Klebsiella pneumoniae* clinical isolates producing GES-5 and SHV-12 extended-spectrum β-lactamases in Korea. *Antimicrob Agents Chemother*. 2005; **49**: 4809–4810. PMID: 16251340 doi: 10.1128/AAC.49.11.4809-4810.2005
64. Poirel L, Héritier C, Tolün V, Nordmann P. Emergence of oxacillinase-mediated resistance to imipenem in *Klebsiella pneumoniae*. *Antimicrob Agents Chemother*. 2004; **48**: 15–22. PMID: 14693513 doi: 10.1128/AAC.48.1.15-22.2004
65. Leonard DA, Bonomo RA, Powers RA. Class D β-lactamases: a reappraisal after five decades. *Acc Chem Res*. 2013; **46**: 2407–2415. PMID: 23902256 doi: 10.1021/ar300327a
66. Curello J, MacDougall C. Beyond susceptible and resistant, Part II: treatment of infections due to Gram-negative organisms producing extended-spectrum β-lactamases. *J Pediatr Pharmacol Ther*. 2014; **19**: 156–164. PMID: 25309145
67. Nagano N, Shibata N, Saitou Y, Nagano Y, Arakawa Y. Nosocomial outbreak of infections by Proteus mirabilis that produces extended-spectrum CTX-M-2 type β-lactamase. *J Clin Microbiol*. 2003; **41**: 5530–5536. PMID: 14662935 doi: 10.1128/JCM.41.12.5530-5536.2003
68. Muta T, Tsuruta N, Seki Y, et al. A nosocomial outbreak due to novel CTX-M-2-producing strains of *Citrobacter koseri* in a hematological ward. *Jpn J Infect Dis*. 2006; **59**: 69–71. PMID: 16495644
69. Kim JY, Park YJ, Kim SI, Kang MW, Lee SO, Lee KY. Nosocomial outbreak by *Proteus mirabilis* producing extended-spectrum β-lactamase VEB-1 in a Korean university hospital. *J Antimicrob Chemother*. 2004; **54**: 1144–1147. PMID: 15546971 doi: 10.1093/jac/dkh486
70. Lowe C, Willey B, O'Shaughnessy A, et al. Mount Sinai Hospital Infection Control Team Outbreak of extended-spectrum β-lactamase-producing *Klebsiella oxytoca* infections associated with contaminated handwashing sinks(1). *Emerg Infect Dis*. 2012; **18**: 1242–1247. PMID: 22841005 doi: 10.3201/eid1808.111268
71. Nomura K, Yoshida T. Nucleotide sequence of the *Serratia marcescens* SR50 chromosomal *ampC* β-lactamase gene. *FEMS Microbiol Lett*. 1990; **58**: 295–299. PMID: 2227364

72. Nagano N, Nagano Y, Cordevant C, Shibata N, Arakawa Y. Nosocomial transmission of CTX-M-2 β-lactamase-producing *Acinetobacter baumannii* in a neurosurgery ward. *J Clin Microbiol*. 2004; **42**: 3978–3984. PMID: 15364979 doi: 10.1128/JCM.42.9.3978-3984.2004

73. Knott-Hunziker V, Petursson S, Jayatilake GS, Waley SG, Jaurin B, Grundström T. Active sites of β-lactamases. The chromosomal β-lactamases of *Pseudomonas aeruginosa* and *Escherichia coli*. *Biochem J*. 1982; **201**: 621–627. PMID: 6807285 doi: 10.1042/bj2010621

74. Bou G, Martínez-Beltrán J. Cloning, nucleotide sequencing, and analysis of the gene encoding an AmpC β-lactamase in *Acinetobacter baumannii*. *Antimicrob Agents Chemother*. 2000; **44**: 428–432. PMID: 10639377 doi: 10.1128/AAC.44.2.428-432.2000

75. Brown S, Young HK, Amyes SG. Characterisation of OXA-51, a novel class D carbapenemase found in genetically unrelated clinical strains of *Acinetobacter baumannii* from Argentina. *Clin Microbiol Infect*. 2005; **11**: 15–23. PMID: 15649299 doi: 10.1111/j.1469-0691.2004.01016.x

76. Yang L, Yang L, Lü DH, et al. Co-prevalance of PMQR and 16S rRNA methylase genes in clinical *Escherichia coli* isolates with high diversity of CTX-M from diseased farmed pigeons. *Vet Microbiol*. 2015; **178**: 238–245. PMID: 26013416 doi: 10.1016/j.vetmic.2015.05.009

77. Mathers AJ, Peirano G, Pitout JD. The role of epidemic resistance plasmids and international high-risk clones in the spread of multidrug-resistant *Enterobacteriaceae*. *Clin Microbiol Rev*. 2015; **28**: 565–591. PMID: 25926236 doi: 10.1128/CMR.00116-14

78. Chen CC, Herzberg O. Inhibition of β-lactamase by clavulanate. Trapped intermediates in cryocrystallographic studies. *J Mol Biol*. 1992; **224**: 1103–1113. Erratum in: J Mol Biol 1992; 226:285. PMID: 1569569 doi: 10.1016/0022-2836(92)90472-V

79. Tenover FC, Raney PM, Williams PP, et al. Project ICARE Evaluation of the NCCLS extended-spectrum β-lactamase confirmation methods for Escherichia coli with isolates collected during Project ICARE. *J Clin Microbiol*. 2003; **41**: 3142–3146. PMID: 12843054 doi: 10.1128/JCM.41.7.3142-3146.2003

80. Faheem M, Rehman MT, Danishuddin M, Khan AU. Biochemical characterization of CTX-M-15 from *Enterobacter cloacae* and designing a novel non-β-lactam-β-lactamase inhibitor. *PLoS One*. 2013; **8**: e56926. PMID: 23437273 doi: 10.1371/journal.pone.0056926

81. Matsumoto Y, Ikeda F, Kamimura T, Yokota Y, Mine Y. Novel plasmid-mediated β-lactamase from *Escherichia coli* that inactivates oxyimino-cephalosporins. *Antimicrob Agents Chemother*. 1988; **32**: 1243–1246. PMID: 3056257 doi: 10.1128/AAC.32.8.1243

82. <https://www.ncbi.nlm.nih.gov/nuccore/AB098539.1>.

83. Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum β-lactamases in the community: toward the globalization of CTX-M. *Clin Microbiol Rev*. 2013; **26**: 744–758. PMID: 24092853 doi: 10.1128/CMR.00023-13

84. Pai H, Choi EH, Lee HJ, Hong JY, Jacoby GA. Identification of CTX-M-14 extended-spectrum β-lactamase in clinical isolates of *Shigella sonnei, Escherichia coli*, and *Klebsiella pneumoniae* in Korea. *J Clin Microbiol*. 2001; **39**: 3747–3749. PMID: 11574608 doi: 10.1128/JCM.39.10.3747-3749.2001

85. Bonnet R, Recule C, Baraduc R, et al. Effect of D240G substitution in a novel ESBL CTX-M-27. *J Antimicrob Chemother*. 2003; **52**: 29–35. PMID: 12775683 doi: 10.1093/jac/dkg256

86. Ho PL, Yeung MK, Lo WU, et al. Predominance of pHK01-like incompatibility group FII plasmids encoding CTX-M-14 among extended-spectrum β-lactamase-producing *Escherichia coli* in Hong Kong, 1996-2008. *Diagn Microbiol Infect Dis*. 2012; **73**: 182–186. PMID: 22521053 doi: 10.1016/j.diagmicrobio.2012.03.009

87. Zhao WH, Hu ZQ. Epidemiology and genetics of CTX-M extended-spectrum β-lactamases in Gram-negative bacteria. *Crit Rev Microbiol*. 2013; **39**: 79–101. PMID: 22697133

88. Matsumura Y, Johnson JR, Yamamoto M, et al. Kyoto–Shiga Clinical Microbiology Study Group Kyoto-Shiga Clinical Microbiology Study Group CTX-M-27- and CTX-M-14-producing, ciprofloxacin-resistant *Escherichia coli* of the *H30* subclonal group within ST131 drive a Japanese regional ESBL epidemic. *J Antimicrob Chemother*. 2015; **70**: 1639–1649. PMID: 25687644

89. Bush K. Proliferation and significance of clinically relevant β-lactamases. *Ann N Y Acad Sci*. 2013; **1277**: 84–90. PMID: 23346859

90. Arlet G, Brami G, Décrè D, et al. Molecular characterisation by PCR-restriction fragment length polymorphism of TEM β-lactamases. *FEMS Microbiol Lett*. 1995; **134**: 203–208. PMID: 8586268

91. Mulvey MR, Bryce E, Boyd D, et al. Canadian Hospital Epidemiology Committee, Canadian Nosocomial Infection Surveillance Program, Health Canada Ambler class A extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella* spp. in Canadian hospitals. *Antimicrob Agents Chemother*. 2004; **48**: 1204–1214. PMID: 15047521 doi: 10.1128/AAC.48.4.1204-1214.2004

92. D'Andrea MM, Arena F, Pallecchi L, Rossolini GM. CTX-M-type β-lactamases: a successful story of antibiotic resistance. *Int J Med Microbiol*. 2013; **303**: 305–317. PMID: 23490927 doi: 10.1016/j.ijmm.2013.02.008

93. Qi C, Pilla V, Yu JH, Reed K. Changing prevalence of *Escherichia coli* with CTX-M-type extended-spectrum β-lactamases in outpatient urinary *E. coli* between 2003 and 2008. *Diagn Microbiol Infect Dis*. 2010; **67**: 87–91. PMID: 20227224 doi: 10.1016/j.diagmicrobio.2009.12.011

94. Baraniak A, Fiett J, Hryniewicz W, Nordmann P, Gniadkowski M. Ceftazidime-hydrolysing CTX-M-15 extended-spectrum β-lactamase (ESBL) in Poland. *J Antimicrob Chemother*. 2002; **50**: 393–396. PMID: 12205064 doi: 10.1093/jac/dkf151

95. Kiratisin P, Apisarnthanarak A, Saifon P, Laesripa C, Kitphati R, Mundy LM. The emergence of a novel ceftazidime-resistant CTX-M extended-spectrum β-lactamase, CTX-M-55, in both community-onset and hospital-acquired infections in Thailand. *Diagn Microbiol Infect Dis*. 2007; **58**: 349–355. PMID: 17449211 doi: 10.1016/j.diagmicrobio.2007.02.005

96. Alevizakos M, Karanika S, Detsis M, Mylonakis E. Colonisation with extended-spectrum β-lactamase-producing *Enterobacteriaceae* and risk for infection among patients with solid or haematological malignancy: a systematic review and meta-analysis. *Int J Antimicrob Agents*. 2016; **48**: 647–654. PMID: 27746102 doi: 10.1016/j.ijantimicag.2016.08.021
97. Stapleton PJ, Murphy M, McCallion N, Brennan M, Cunney R, Drew RJ. Outbreaks of extended spectrum β-lactamase-producing *Enterobacteriaceae* in neonatal intensive care units: a systematic review. *Arch Dis Child Fetal Neonatal Ed*. 2016; **101**: F72–F78. PMID: 26369370
98. Wragg R, Harris A, Patel M, Robb A, Chandran H, McCarthy L. Extended spectrum β lactamase (ESBL) producing bacteria urinary tract infections and complex pediatric urology. *J Pediatr Surg*. 2017; **52**: 286–288. PMID: 27894763 doi: 10.1016/j.jpedsurg.2016.11.016
99. Adler A, Katz DE, Marchaim D. The continuing plague of extended-spectrum β-lactamase-producing *Enterobacteriaceae* infections. *Infect Dis Clin North Am*. 2016; **30**: 347–375. PMID: 27208763 doi: 10.1016/j.idc.2016.02.003
100. Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal colonization with extended-spectrum β-lactamase-producing *Enterobacteriaceae* and risk factors among healthy individuals: A systematic review and meta-analysis. *Clin Infect Dis*. 2016; **63**: 310–318. PMID: 27143671 doi: 10.1093/cid/ciw283
101. Luvsansharav UO, Hirai I, Niki M, et al. Prevalence of fecal carriage of extended-spectrum β-lactamase-producing *Enterobacteriaceae* among healthy adult people in Japan. *J Infect Chemother*. 2011; **17**: 722–725. PMID: 21359543 doi: 10.1007/s10156-011-0225-2
102. Ny S, Löfmark S, Börjesson S, et al. Community carriage of ESBL-producing *Escherichia coli* is associated with strains of low pathogenicity: a Swedish nationwide study. *J Antimicrob Chemother*. 2017; **72**: 582–588. PMID: 27798205 doi: 10.1093/jac/dkw419
103. Ebrahimi F, Mózes J, Mészáros J, et al. Asymptomatic faecal carriage of ESBL producing enterobacteriaceae in Hungarian healthy individuals and in long-term care applicants: A shift towards CTX-M producers in the community. *Infect Dis (Lond)*. 2016; **48**: 557–559. (Lond). PMID: 26982242 doi: 10.3109/23744235.2016.1155734
104. Rodrigues C, Machado E, Fernandes S, Peixe L, Novais Â. An update on faecal carriage of ESBL-producing *Enterobacteriaceae* by Portuguese healthy humans: detection of the H30 subclone of B2-ST131 *Escherichia coli* producing CTX-M-27. *J Antimicrob Chemother*. 2016; **71**: 1120–1122. PMID: 26747102 doi: 10.1093/jac/dkv443
105. Reuland EA, Al Naiemi N, Kaiser AM, et al. Prevalence and risk factors for carriage of ESBL-producing *Enterobacteriaceae* in Amsterdam. *J Antimicrob Chemother*. 2016; **71**: 1076–1082. PMID: 26755493 doi: 10.1093/jac/dkv441
106. Ulstad CR, Solheim M, Berg S, Lindbæk M, Dahle UR, Wester AL. Carriage of ESBL/AmpC-producing or ciprofloxacin non-susceptible *Escherichia coli* and *Klebsiella* spp. in healthy people in Norway. *Antimicrob Resist Infect Control*. 2016; **5**: 57. PMID: 28018582
107. Fernández-Reyes M, Vicente D, Gomariz M, et al. High rate of fecal carriage of extended-spectrum-β-lactamase-producing *Escherichia coli* in healthy children in Gipuzkoa, northern Spain. *Antimicrob Agents Chemother*. 2014; **58**: 1822–1824. PMID: 24395224 doi: 10.1128/AAC.01503-13
108. Sun Q, Tärnberg M, Zhao L, et al. Varying high levels of faecal carriage of extended-spectrum β-lactamase producing *Enterobacteriaceae* in rural villages in Shandong, China: implications for global health. *PLoS One*. 2014; **9**: e113121. PMID: 25405340
109. Stoesser N, Xayaheuang S, Vongsouvath M, et al. Colonization with *Enterobacteriaceae* producing ESBLs in children attending pre-school childcare facilities in the Lao People's Democratic Republic. *J Antimicrob Chemother*. 2015; **70**: 1893–1897. PMID: 25681128
110. Zhang H, Zhou Y, Guo S, Chang W. High prevalence and risk factors of fecal carriage of CTX-M type extended-spectrum β-lactamase-producing *Enterobacteriaceae* from healthy rural residents of Taian, China. *Front Microbiol*. 2015; **6**: 239. PMID: 25870591 doi: 10.3389/fmicb.2015.00239
111. Ni Q, Tian Y, Zhang L, et al. Prevalence and quinolone resistance of fecal carriage of extended-spectrum β-lactamase-producing *Escherichia coli* in 6 communities and 2 physical examination center populations in Shanghai, China. *Diagn Microbiol Infect Dis*. 2016; **86**: 428–433. PMID: 27681363 doi: 10.1016/j.diagmicrobio.2016.07.010
112. Babu R, Kumar A, Karim S, et al. Faecal carriage rate of extended-spectrum β-lactamase-producing *Enterobacteriaceae* in hospitalised patients and healthy asymptomatic individuals coming for health check-up. *J Glob Antimicrob Resist*. 2016; **6**: 150–153. PMID: 27530858 doi: 10.1016/j.jgar.2016.05.007
113. Çakir Erdoğan D, Cömert F, Aktaş E, Köktürk F, Külah C. Fecal carriage of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella* spp. in a Turkish community. *Turk J Med Sci*. 2017; **47**: 172–179. PMID: 28263486 doi: 10.3906/sag-1512-9
114. Ko YJ, Moon HW, Hur M, Park CM, Cho SE, Yun YM. Fecal carriage of extended-spectrum β-lactamase-producing *Enterobacteriaceae* in Korean community and hospital settings. *Infection*. 2013; **41**: 9–13. PMID: 22723075 doi: 10.1007/s15010-012-0272-3
115. Li B, Sun JY, Liu QZ, Han LZ, Huang XH, Ni YX. High prevalence of CTX-M β-lactamases in faecal *Escherichia coli* strains from healthy humans in Fuzhou, China. *Scand J Infect Dis*. 2011; **43**: 170–174. PMID: 21128708 doi: 10.3109/00365548.2010.538856
116. Boonyasiri A, Tangkoskul T, Seenama C, Saiyarin J, Tiengrim S, Thamlikitkul V. Prevalence of antibiotic resistant bacteria in healthy adults, foods, food animals, and the environment in selected areas in Thailand. *Pathog Glob Health*. 2014; **108**: 235–245. PMID: 25146935 doi: 10.1179/2047773214Y.0000000148
117. Farra A, Frank T, Tondeur L, et al. High rate of faecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae in healthy children in Bangui, Central African Republic. Clin Microbiol Infect. 2016; 22: 891.e1-891.e4.
118. Hijazi SM, Fawzi MA, Ali FM, Abd El Galil KH. Multidrug-resistant ESBL-producing *Enterobacteriaceae* and associated risk factors in community infants in Lebanon. *J Infect Dev Ctries*. 2016; **10**: 947–955. PMID: 27694727 doi: 10.3855/jidc.7593

119. Nakamura A, Komatsu M, Noguchi N, et al. Analysis of molecular epidemiologic characteristics of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* colonizing feces in hospital patients and community dwellers in a Japanese city. *J Infect Chemother*. 2016; **22**: 102–107. PMID: 26705747 doi: 10.1016/j.jiac.2015.11.001

120. Hu YY, Cai JC, Zhou HW, et al. Molecular typing of CTX-M-producing *escherichia coli* isolates from environmental water, swine feces, specimens from healthy humans, and human patients. *Appl Environ Microbiol*. 2013; **79**: 5988–5996. PMID: 23892737 doi: 10.1128/AEM.01740-13

121. Cortés P, Blanc V, Mora A, et al. Isolation and characterization of potentially pathogenic antimicrobial-resistant *Escherichia coli* strains from chicken and pig farms in Spain. *Appl Environ Microbiol*. 2010; **76**: 2799–2805. PMID: 20228098 doi: 10.1128/AEM.02421-09

122. Andersson DI, Levin BR. The biological cost of antibiotic resistance. *Curr Opin Microbiol*. 1999; **2**: 489–493. PMID: 10508723 doi: 10.1016/S1369-5274(99)00005-3

123. Andersson DI, Hughes D. Antibiotic resistance and its cost: is it possible to reverse resistance? *Nat Rev Microbiol*. 2010; **8**: 260–271. PMID: 20208551

124. Linkevicius M, Anderssen JM, Sandegren L, Andersson DI. Fitness of *Escherichia coli* mutants with reduced susceptibility to tigecycline. *J Antimicrob Chemother*. 2016; **71**: 1307–1313. PMID: 26851608 doi: 10.1093/jac/dkv486

125. López-Rojas R, McConnell MJ, Jiménez-Mejías ME, Domínguez-Herrera J, Fernández-Cuenca F, Pachón J. Colistin resistance in a clinical *Acinetobacter baumannii* strain appearing after colistin treatment: effect on virulence and bacterial fitness. *Antimicrob Agents Chemother*. 2013; **57**: 4587–4589. PMID: 23836165 doi: 10.1128/AAC.00543-13

126. Humphrey B, Thomson NR, Thomas CM, et al. Fitness of *Escherichia coli* strains carrying expressed and partially silent IncN and IncP1 plasmids. *BMC Microbiol*. 2012; **12**: 53. PMID: 22475035 doi: 10.1186/1471-2180-12-53

127. Martinez-Medina M, Mora A, Blanco M, et al. Similarity and divergence among adherent-invasive *Escherichia coli* and extraintestinal pathogenic *E. coli* strains. *J Clin Microbiol*. 2009; **47**: 3968–3979. PMID: 19828750 doi: 10.1128/JCM.01484-09

128. Phan MD, Forde BM, Peters KM, et al. Molecular characterization of a multidrug resistance IncF plasmid from the globally disseminated *Escherichia coli* ST131 clone. *PLoS One*. 2015; **10**: e0122369. PMID: 25875675 doi: 10.1371/journal.pone.0122369

129. Hrabák J, Empel J, Bergerová T, et al. International clones of *Klebsiella pneumoniae* and *Escherichia coli* with extended-spectrum β-lactamases in a Czech hospital. *J Clin Microbiol*. 2009; **47**: 3353–3357. PMID: 19710276 doi: 10.1128/JCM.00901-09

130. Giedraitienė A, Vitkauskienė A, Pavilonis A, et al. Prevalence of O25b-ST131 clone among *Escherichia coli* strains producing CTX-M-15, CTX-M-14 and CTX-M-92 β-lactamases. *Infect Dis (Lond)*. 2017; **49**: 106–112. PMID: 27563748 doi: 10.1080/23744235.2016.1221531

131. Rodrigues C, Machado E, Ramos H, Peixe L, Novais Â. Expansion of ESBL-producing *Klebsiella pneumoniae* in hospitalized patients: a successful story of international clones (ST15, ST147, ST336) and epidemic plasmids (IncR, IncFIIK). *Int J Med Microbiol*. 2014; **304**: 1100–1108. PMID: 25190354 doi: 10.1016/j.ijmm.2014.08.003

132. Marcade G, Brisse S, Bialek S, et al. The emergence of multidrug-resistant *Klebsiella pneumoniae* of international clones ST13, ST16, ST35, ST48 and ST101 in a teaching hospital in the Paris region. *Epidemiol Infect*. 2013; **141**: 1705–1712. PMID: 23034125 doi: 10.1017/S0950268812002099

133. Day MJ, Rodríguez I, van Essen-Zandbergen A, et al. Diversity of STs, plasmids and ESBL genes among *Escherichia coli* from humans, animals and food in Germany, the Netherlands and the UK. *J Antimicrob Chemother*. 2016; **71**: 1178–1182. PMID: 26803720 doi: 10.1093/jac/dkv485

134. Nordberg V, Quizhpe Peralta A, Galindo T, et al. High proportion of intestinal colonization with successful epidemic clones of ESBL-producing *Enterobacteriaceae* in a neonatal intensive care unit in Ecuador. *PLoS One*. 2013; **8**: e76597. PMID: 24146896 doi: 10.1371/journal.pone.0076597

135. Reffert JL, Smith WJ. Insights from the Society of Infectious Diseases Pharmacists Fosfomycin for the treatment of resistant gram-negative bacterial infections. *Pharmacotherapy*. 2014; **34**: 845–857. PMID: 24782335

136. Matthews PC, Barrett LK, Warren S, et al. Oral fosfomycin for treatment of urinary tract infection: a retrospective cohort study. *BMC Infect Dis*. 2016; **16**: 556. PMID: 27729016

137. Veve MP, Wagner JL, Kenney RM, Grunwald JL, Davis SL. Comparison of fosfomycin to ertapenem for outpatient or step-down therapy of extended-spectrum β-lactamase urinary tract infections. *Int J Antimicrob Agents*. 2016; **48**: 56–60. PMID: 27234673 doi: 10.1016/j.ijantimicag.2016.04.014

138. Wachino J, Yamane K, Suzuki S, Kimura K, Arakawa Y. Prevalence of fosfomycin resistance among CTX-M-producing *Escherichia coli* clinical isolates in Japan and identification of novel plasmid-mediated fosfomycin-modifying enzymes. *Antimicrob Agents Chemother*. 2010; **54**: 3061–3064. PMID: 20404116 doi: 10.1128/AAC.01834-09

139. Lee SY, Park YJ, Yu JK, et al. Prevalence of acquired fosfomycin resistance among extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* clinical isolates in Korea and IS*26*-composite transposon surrounding *fosA3*. *J Antimicrob Chemother*. 2012; **67**: 2843–2847. PMID: 22893681 doi: 10.1093/jac/dks319

140. Tseng SP, Wang SF, Kuo CY, et al. Characterization of fosfomycin resistant extended-spectrum β-lactamase-producing *Escherichia coli* isolates from human and pig in Taiwan. *PLoS One*. 2015; **10**: e0135864. PMID: 26280832

141. Sato N, Kawamura K, Nakane K, Wachino J, Arakawa Y. First detection of fosfomycin resistance gene *fosA3* in CTX-M-producing *Escherichia coli* isolates from healthy individuals in Japan. *Microb Drug Resist*. 2013; **19**: 477–482. PMID: 23909549 doi: 10.1089/mdr.2013.0061

142. Hou J, Huang X, Deng Y, et al. Dissemination of the fosfomycin resistance gene *fosA3* with CTX-M β-lactamase genes and *rmtB* carried on IncFII plasmids among *Escherichia coli* isolates from pets in China. *Antimicrob Agents Chemother*. 2012; **56**: 2135–2138. PMID: 22232290 doi: 10.1128/AAC.05104-11

143. Xie M, Lin D, Chen K, Chan EW, Yao W, Chen S. Molecular characterization of *Escherichia coli* strains isolated from retail meat that harbor bla_{CTX-M} and *fosA3* genes. *Antimicrob Agents Chemother*. 2016; **60**: 2450–2455. PMID: 26856843 doi: 10.1128/AAC.03101-15

144. Chan J, Lo WU, Chow KH, Lai EL, Law PY, Ho PL. Clonal diversity of *Escherichia coli* isolates carrying plasmid-mediated fosfomycin resistance gene *fosA3* from livestock and other animals. *Antimicrob Agents Chemother*. 2014; **58**: 5638–5639. PMID: 24982077 doi: 10.1128/AAC.02700-14

145. Cao XL, Shen H, Xu YY, et al. High prevalence of fosfomycin resistance gene *fosA3* in bla_{CTX-M}-harbouring *Escherichia coli* from urine in a Chinese tertiary hospital during 2010-2014. *Epidemiol Infect*. 2017; **145**: 818–824. PMID: 27938421 doi: 10.1017/S0950268816002879

146. Alrowais H, McElheny CL, Spychala CN, et al. Fosfomycin resistance in *Escherichia coli*, Pennsylvania, USA. *Emerg Infect Dis*. 2015; **21**: 2045–2047. PMID: 26488485 doi: 10.3201/eid2111.150750

147. Mendes AC, Rodrigues C, Pires J, et al. Importation of fosfomycin resistance *fosA3* gene to Europe. *Emerg Infect Dis*. 2016; **22**: 346–348. PMID: 26812028 doi: 10.3201/eid2202.151301

148. Villa L, Guerra B, Schmoger S, et al. IncA/C plasmid carrying bla_{NDM-1}, bla_{CMY-16}, and *fosA3* in a *Salmonella enterica* serovar Corvallis strain isolated from a migratory wild bird in Germany. *Antimicrob Agents Chemother*. 2015; **59**: 6597–6600. PMID: 26169417 doi: 10.1128/AAC.00944-15

149. Sennati S, Riccobono E, Di Pilato V, et al. pHN7A8-related multiresistance plasmids ($bla_{CTX-M-65}$, *fosA3* and *rmtB*) detected in clinical isolates of *Klebsiella pneumoniae* from Bolivia: intercontinental plasmid dissemination? *J Antimicrob Chemother*. 2016; **71**: 1732–1734. PMID: 26903279 doi: 10.1093/jac/dkv506

150. Cunha MP, Lincopan N, Cerdeira L, et al. Coexistence of CTX-M-2, CTX-M-55, CMY-2, FosA3 and QnrB19 in extraintestinal pathogenic *Escherichia coli* from poultry in Brazil. *Antimicrob Agents Chemother*. 2017; **61**: e02474–e16. PMID: 28167554 doi: 10.1128/AAC.02474-16

151. Johnson JR, Tchesnokova V, Johnston B, et al. Abrupt emergence of a single dominant multidrug-resistant strain of *Escherichia coli*. *J Infect Dis*. 2013; **207**: 919–928. PMID: 23288927 doi: 10.1093/infdis/jis933

152. Colpan A, Johnston B, Porter S, et al. VICTORY (Veterans Influence of Clonal Types on Resistance: Year 2011) Investigators Escherichia coli sequence type 131 (ST131) subclone H30 as an emergent multidrug-resistant pathogen among US veterans. *Clin Infect Dis*. 2013; **57**: 1256–1265. PMID: 23926176 doi: 10.1093/cid/cit503

153. Banerjee R, Robicsek A, Kuskowski MA, et al. Molecular epidemiology of *Escherichia coli* sequence type 131 and Its H30 and H30-Rx subclones among extended-spectrum-β-lactamase-positive and -negative *E. coli* clinical isolates from the Chicago Region, 2007 to 2010. *Antimicrob Agents Chemother*. 2013; **57**: 6385–6388. PMID: 24080662 doi: 10.1128/AAC.01604-13

154. Matsumura Y, Pitout JD, Gomi R, et al. Global *Escherichia coli* sequence type 131 clade with $bla_{CTX-M-27}$ gene. *Emerg Infect Dis*. 2016; **22**: 1900–1907. PMID: 27767006 doi: 10.3201/eid2211.160519

155. De Boeck H, Miwanda B, Lunguya-Metila O, et al. ESBL-positive Enterobacteria isolates in drinking water. *Emerg Infect Dis*. 2012; **18**: 1019–1020. PMID: 22608263 doi: 10.3201/eid1806.111214

156. Zhang H, Zhou Y, Guo S, Chang W. Prevalence and characteristics of extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* isolated from rural well water in Taian, China, 2014. *Environ Sci Pollut Res Int*. 2015; **22**: 11488–11492. PMID: 25821088

157. Abera B, Kibret M, Mulu W. Extended-spectrum β-lactamases and antibiogram in *Enterobacteriaceae* from clinical and drinking water sources from Bahir Dar City, Ethiopia. *PLoS One*. 2016; **11**: e0166519. PMID: 27846254 doi: 10.1371/journal.pone.0166519

158. Amaya E, Reyes D, Paniagua M, et al. Antibiotic resistance patterns of *Escherichia coli* isolates from different aquatic environmental sources in León, Nicaragua. *Clin Microbiol Infect*. 2012; **18**: E347–E354. PMID: 22738232 doi: 10.1111/j.1469-0691.2012.03930.x

159. Talukdar PK, Rahman M, Rahman M, et al. Antimicrobial resistance, virulence factors and genetic diversity of *Escherichia coli* isolates from household water supply in Dhaka, Bangladesh. *PLoS One*. 2013; **8**: e61090. PMID: 23573295 doi: 10.1371/journal.pone.0061090

160. Zurfluh K, Nüesch-Inderbinen M, Morach M, Zihler Berner A, Hächler H, Stephan R. Extended-spectrum-β-lactamase-producing *Enterobacteriaceae* isolated from vegetables imported from the Dominican Republic, India, Thailand, and Vietnam. *Appl Environ Microbiol*. 2015; **81**: 3115–3120. PMID: 25724954 doi: 10.1128/AEM.00258-15

161. Diwan V, Chandran SP, Tamhankar AJ, Stålsby Lundborg C, Macaden R. Identification of extended-spectrum β-lactamase and quinolone resistance genes in *Escherichia coli* isolated from hospital wastewater from central India. *J Antimicrob Chemother*. 2012; **67**: 857–859. PMID: 22267239 doi: 10.1093/jac/dkr564

162. Korzeniewska E, Harnisz M. β-lactamase-producing *Enterobacteriaceae* in hospital effluents. *J Environ Manage*. 2013; **123**: 1–7. PMID: 23563146 doi: 10.1016/j.jenvman.2013.03.024

163. Conte D, Palmeiro JK, da Silva Nogueira K, et al. Characterization of CTX-M enzymes, quinolone resistance determinants, and antimicrobial residues from hospital sewage, wastewater treatment plant, and river water. *Ecotoxicol Environ Saf*. 2017; **136**: 62–69. PMID: 27816836 doi: 10.1016/j.ecoenv.2016.10.031

164. Gao L, Tan Y, Zhang X, et al. Emissions of *Escherichia coli* carrying extended-spectrum β-lactamase resistance from pig farms to the surrounding environment. *Int J Environ Res Public Health*. 2015; **12**: 4203–4213. PMID: 25893997 doi: 10.3390/ijerph120404203

165. von Salviati C, Laube H, Guerra B, Roesler U, Friese A. Emission of ESBL/AmpC-producing *Escherichia coli* from pig fattening farms to surrounding areas. *Vet Microbiol*. 2015; **175**: 77–84. PMID: 25465658 doi: 10.1016/j.vetmic.2014.10.010

166. Wang J, Stephan R, Power K, Yan Q, Hächler H, Fanning S. Nucleotide sequences of 16 transmissible plasmids identified in nine multidrug-resistant *Escherichia coli* isolates expressing an ESBL phenotype isolated from food-producing animals and healthy humans. *J Antimicrob Chemother*. 2014; **69**: 2658–2668. PMID: 24920651 doi: 10.1093/jac/dku206

167. Overdevest I, Willemsen I, Rijnsburger M, et al. Extended-spectrum β-lactamase genes of *Escherichia coli* in chicken meat and humans, The Netherlands. *Emerg Infect Dis*. 2011; **17**: 1216–1222. PMID: 21762575 doi: 10.3201/eid1707.110209

168. Ghodousi A, Bonura C, Di Carlo P, van Leeuwen WB, Mammina C. Extraintestinal pathogenic *Escherichia coli* sequence type 131 *H30*-R and *H30*-Rx subclones in retail chicken meat, Italy. *Int J Food Microbiol*. 2016; **228**: 10–13. PMID: 27082892 doi: 10.1016/j.ijfoodmicro.2016.04.004

169. Cohen Stuart J, van den Munckhof T, Voets G, Scharringa J, Fluit A, Hall ML. Comparison of ESBL contamination in organic and conventional retail chicken meat. *Int J Food Microbiol*. 2012; **154**: 212–214. PMID: 22260927 doi: 10.1016/j.ijfoodmicro.2011.12.034

170. Wu G, Day MJ, Mafura MT, et al. Comparative analysis of ESBL-positive *Escherichia coli* isolates from animals and humans from the UK, The Netherlands and Germany. *PLoS One*. 2013; **8**: e75392. PMID: 24086522 doi: 10.1371/journal.pone.0075392

171. Dahms C, Hübner NO, Kossow A, Mellmann A, Dittmann K, Kramer A. Occurrence of ESBL-producing *Escherichia coli* in livestock and farm workers in Mecklenburg-Western Pomerania, Germany. *PLoS One*. 2015; **10**: e0143326. PMID: 26606146 doi: 10.1371/journal.pone.0143326

172. Pohjola L, Nykäsenoja S, Kivistö R, et al. Zoonotic public health hazards in backyard chickens. *Zoonoses Public Health*. 2016; **63**: 420–430. PMID: 26752227 doi: 10.1111/zph.12247

173. Skočková A, Bogdanovičoá K, Koláčková I, Karpíšková R. Antimicrobial-resistant and extended-spectrum β-lactamase-producing *Escherichia coli* in raw cow's milk. *J Food Prot*. 2015; **78**: 72–77. PMID: 25581180 doi: 10.4315/0362-028X.JFP-14-250

174. Odenthal S, Akineden Ö, Usleber E. Extended-spectrum β-lactamase producing *Enterobacteriaceae* in bulk tank milk from German dairy farms. *Int J Food Microbiol*. 2016; **238**: 72–78. PMID: 27592073 doi: 10.1016/j.ijfoodmicro.2016.08.036

175. Agersø Y, Aarestrup FM, Pedersen K, Seyfarth AM, Struve T, Hasman H. Prevalence of extended-spectrum cephalosporinase (ESC)-producing *Escherichia coli* in Danish slaughter pigs and retail meat identified by selective enrichment and association with cephalosporin usage. *J Antimicrob Chemother*. 2012; **67**: 582–588. PMID: 22207594 doi: 10.1093/jac/dkr507

176. Yamamoto S, Asakura H, Igimi S. Recent trends for the prevalence and transmission risk of extended spectrum β-lactamases (ESBL) producing bacteria in foods. *Shokuhin Eiseigaku Zasshi*. 2017; **58**: 1–11. (in Japanese). PMID: 28260727 doi: 10.3358/shokueishi.58.1

177. Michael GB, Kaspar H, Siqueira AK, et al. Extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* isolates collected from diseased food-producing animals in the GERM-Vet monitoring program 2008-2014. *Vet Microbiol*. 2017; **200**: 142–150. PMID: 27634182 doi: 10.1016/j.vetmic.2016.08.023

178. Ferreira JC, Penha Filho RA, Andrade LN, Berchieri A Jr, Darini AL. Detection of chromosomal *bla*$_{(CTX\text{-}M\text{-}2)}$ in diverse *Escherichia coli* isolates from healthy broiler chickens. *Clin Microbiol Infect*. 2014; **20**: O623–O626. PMID: 24438126 doi: 10.1111/1469-0691.12531

179. Peirano G, Asensi MD, Pitondo-Silva A, Pitout JD. Molecular characteristics of extended-spectrum β-lactamase-producing *Escherichia coli* from Rio de Janeiro, Brazil. *Clin Microbiol Infect*. 2011; **17**: 1039–1043. PMID: 21722255 doi: 10.1111/j.1469-0691.2010.03440.x

180. Warren RE, Ensor VM, O'Neill P, et al. Imported chicken meat as a potential source of quinolone-resistant *Escherichia coli* producing extended-spectrum β-lactamases in the UK. *J Antimicrob Chemother*. 2008; **61**: 504–508. PMID: 18222958 doi: 10.1093/jac/dkm517

181. Li L, Ye L, Yu L, Zhou C, Meng H. Characterization of extended spectrum β-lactamase producing enterobacteria and methicillin-resistant *Staphylococcus aureus* isolated from raw pork and cooked pork products in south China. *J Food Sci*. 2016; **81**: M1773–M1777. PMID: 27232438 doi: 10.1111/1750-3841.13346

182. Nguyen P, Nguyen TA, Le TH, et al. Dissemination of extended-spectrum β-lactamase- and AmpC β-lactamase-producing *Escherichia coli* within the food distribution system of Ho Chi Minh City, Vietnam. *BioMed Res Int*. 2016; **2016**: 8182096. PMID: 26989692 doi: 10.1155/2016/8182096

183. Pehlivanlar Önen S, Aslantaş Ö, Şebnem Yılmaz E, Kürekci C. Prevalence of β-Lactamase Producing *Escherichia coli* from Retail Meat in Turkey. *J Food Sci*. 2015; **80**: M2023–M2029. PMID: 26256548 doi: 10.1111/1750-3841.12984

184. Börjesson S, Egervärn M, Lindblad M, Englund S. Frequent occurrence of extended-spectrum β-lactamase- and transferable ampc β-lactamase-producing *Escherichia coli* on domestic chicken meat in Sweden. *Appl Environ Microbiol*. 2013; **79**: 2463–2466. PMID: 23354705 doi: 10.1128/AEM.03893-12

185. Kola A, Kohler C, Pfeifer Y, et al. High prevalence of extended-spectrum-β-lactamase-producing *Enterobacteriaceae* in organic and conventional retail chicken meat, Germany. *J Antimicrob Chemother*. 2012; **67**: 2631–2634. PMID: 22868643 doi: 10.1093/jac/dks295

186. Dhanji H, Murphy NM, Doumith M, et al. Cephalosporin resistance mechanisms in *Escherichia coli* isolated from raw chicken imported into the UK. *J Antimicrob Chemother*. 2010; **65**: 2534–2537. PMID: 20889530 doi: 10.1093/jac/dkq376

187. Botelho LA, Kraychete GB, Costa e Silva JL, et al. Widespread distribution of CTX-M and plasmid-mediated AmpC β-lactamases in *Escherichia coli* from Brazilian chicken meat. *Mem Inst Oswaldo Cruz*. 2015; **110**: 249–254. PMID: 25946250

188. Casella T, Rodríguez MM, Takahashi JT, et al. Detection of *bla*$_{CTX\text{-}M}$-type genes in complex class 1 integrons carried by *Enterobacteriaceae* isolated from retail chicken meat in Brazil. *Int J Food Microbiol*. 2015; **197**: 88–91. PMID: 25576985 doi: 10.1016/j.ijfoodmicro.2014.12.001

189. Mora A, Herrera A, Mamani R, et al. Recent emergence of clonal group O25b:K1:H4-B2-ST131 *ibeA* strains among *Escherichia coli* poultry isolates, including CTX-M-9-producing strains, and comparison with clinical human isolates. *Appl Environ Microbiol*. 2010; **76**: 6991–6997. PMID: 20817805 doi: 10.1128/AEM.01112-10

190. Dhanji H, Doumith M, Hope R, Livermore DM, Woodford N. IS*Ecp1*-mediated transposition of linked $bla_{CTX-M-3}$ and bla_{TEM-1b} from the IncI1 plasmid pEK204 found in clinical isolates of *Escherichia coli* from Belfast, UK. *J Antimicrob Chemother*. 2011; **66**: 2263–2265. PMID: 21795257 doi: 10.1093/jac/dkr310

191. Hawkey PM. Prevalence and clonality of extended-spectrum β-lactamases in Asia. *Clin Microbiol Infect*. 2008; **14** (Suppl 1): 159–165. PMID: 18154540 doi: 10.1111/j.1469-0691.2007.01855.x

192. Laupland KB, Church DL, Vidakovich J, Mucenski M, Pitout JD. Community-onset extended-spectrum β-lactamase (ESBL) producing *Escherichia coli*: importance of international travel. *J Infect*. 2008; **57**: 441–448. PMID: 18990451 doi: 10.1016/j.jinf.2008.09.034

193. Tängdén T, Cars O, Melhus A, Löwdin E. Foreign travel is a major risk factor for colonization with *Escherichia coli* producing CTX-M-type extended-spectrum β-lactamases: a prospective study with Swedish volunteers. *Antimicrob Agents Chemother*. 2010; **54**: 3564–3568. PMID: 20547788 doi: 10.1128/AAC.00220-10

194. Barreto Miranda I, Ignatius R, Pfüller R, et al. High carriage rate of ESBL-producing *Enterobacteriaceae* at presentation and follow-up among travellers with gastrointestinal complaints returning from India and Southeast Asia. *J Travel Med*. 2016; **23**: tav024. PMID: 26858272 doi: 10.1093/jtm/tav024

195. Östholm-Balkhed A, Tärnberg M, Nilsson M, Nilsson LE, Hanberger H, Hällgren A. Travel Study Group of Southeast Sweden Travel-associated faecal colonization with ESBL-producing *Enterobacteriaceae*: incidence and risk factors. *J Antimicrob Chemother*. 2013; **68**: 2144–2153. PMID: 23674762 doi: 10.1093/jac/dkt167

196. Solé M, Pitart C, Oliveira I, et al. Extended spectrum β-lactamase-producing *Escherichia coli* faecal carriage in Spanish travellers returning from tropical and subtropical countries. *Clin Microbiol Infect*. 2014; **20**: O636–O639. PMID: 24528474 doi: 10.1111/1469-0691.12592

197. von Wintersdorff CJ, Penders J, Stobberingh EE, et al. High rates of antimicrobial drug resistance gene acquisition after international travel, The Netherlands. *Emerg Infect Dis*. 2014; **20**: 649–657. PMID: 24655888 doi: 10.3201/eid2004.131718

198. Arcilla MS, van Hattem JM, Haverkate MR, et al. Import and spread of extended-spectrum β-lactamase-producing *Enterobacteriaceae* by international travellers (COMBAT study): a prospective, multicentre cohort study. *Lancet Infect Dis*. 2017; **17**: 78–85. PMID: 27751772 doi: 10.1016/S1473-3099(16)30319-X

199. Rubin JE, Pitout JD. Extended-spectrum β-lactamase, carbapenemase and AmpC producing *Enterobacteriaceae* in companion animals. *Vet Microbiol*. 2014; **170**: 10–18. PMID: 24576841 doi: 10.1016/j.vetmic.2014.01.017

200. Pomba C, Rantala M, Greko C, et al. Public health risk of antimicrobial resistance transfer from companion animals. *J Antimicrob Chemother*. 2017; **72**: 957–968. PMID: 27999066

201. Falgenhauer L, Imirzalioglu C, Ghosh H, et al. Circulation of clonal populations of fluoroquinolone-resistant CTX-M-15-producing *Escherichia coli* ST410 in humans and animals in Germany. *Int J Antimicrob Agents*. 2016; **47**: 457–465. PMID: 27208899 doi: 10.1016/j.ijantimicag.2016.03.019

202. Guo S, Wakeham D, Brouwers HJ, et al. Human-associated fluoroquinolone-resistant *Escherichia coli* clonal lineages, including ST354, isolated from canine feces and extraintestinal infections in Australia. *Microbes Infect*. 2015; **17**: 266–274. PMID: 25576024 doi: 10.1016/j.micinf.2014.12.016

203. Valentin L, Sharp H, Hille K, et al. Subgrouping of ESBL-producing Escherichia coli from animal and human sources: an approach to quantify the distribution of ESBL types between different reservoirs. *Int J Med Microbiol*. 2014; **304**: 805–816. PMID: 25213631 doi: 10.1016/j.ijmm.2014.07.015

204. Ewers C, Grobbel M, Stamm I, et al. Emergence of human pandemic O25:H4-ST131 CTX-M-15 extended-spectrum-β-lactamase-producing *Escherichia coli* among companion animals. *J Antimicrob Chemother*. 2010; **65**: 651–660. PMID: 20118165 doi: 10.1093/jac/dkq004

205. Seiffert SN, Carattoli A, Tinguely R, Lupo A, Perreten V, Endimiani A. High prevalence of extended-spectrum β-lactamase, plasmid-mediated AmpC, and carbapenemase genes in pet food. *Antimicrob Agents Chemother*. 2014; **58**: 6320–6323. PMID: 25092703 doi: 10.1128/AAC.03185-14

206. Meireles D, Leite-Martins L, Bessa LJ, et al. Molecular characterization of quinolone resistance mechanisms and extended-spectrum β-lactamase production in *Escherichia coli* isolated from dogs. *Comp Immunol Microbiol Infect Dis*. 2015; **41**: 43–48. PMID: 25999092 doi: 10.1016/j.cimid.2015.04.004

207. Wedley AL, Dawson S, Maddox TW, et al. Carriage of antimicrobial resistant *Escherichia coli* in dogs: Prevalence, associated risk factors and molecular characteristics. *Vet Microbiol*. 2017; **199**: 23–30. PMID: 28110781 doi: 10.1016/j.vetmic.2016.11.017

208. Blom A, Ahl J, Månsson F, Resman F, Tham J. The prevalence of ESBL-producing *Enterobacteriaceae* in a nursing home setting compared with elderly living at home: a cross-sectional comparison. *BMC Infect Dis*. 2016; **16**: 111. PMID: 26944857 doi: 10.1186/s12879-016-1430-5

209. Zurfluh K, Hächler H, Nüesch-Inderbinen M, Stephan R. Characteristics of extended-spectrum β-lactamase- and carbapenemase-producing *Enterobacteriaceae* Isolates from rivers and lakes in Switzerland. *Appl Environ Microbiol*. 2013; **79**: 3021–3026. PMID: 23455339 doi: 10.1128/AEM.00054-13

210. Dhanji H, Murphy NM, Akhigbe C, et al. Isolation of fluoroquinolone-resistant O25b:H4-ST131 *Escherichia coli* with CTX-M-14 extended-spectrum β-lactamase from UK river water. *J Antimicrob Chemother*. 2011; **66**: 512–516. PMID: 21172781 doi: 10.1093/jac/dkq472

211. Madec JY, Haenni M, Ponsin C, Kieffer N, Rion E, Gassilloud B. Sequence type 48 *Escherichia coli* carrying the $bla_{CTX-M-1}$ IncI1/ST3 plasmid in drinking water in France. *Antimicrob Agents Chemother*. 2016; **60**: 6430–6432. PMID: 27550353 doi: 10.1128/AAC.01135-16

212. Parker D, Sniatynski MK, Mandrusiak D, Rubin JE. Extended-spectrum β-lactamase producing *Escherichia coli* isolated from wild birds in Saskatoon, Canada. *Lett Appl Microbiol*. 2016; **63**: 11–15. PMID: 27214496

213. Stedt J, Bonnedahl J, Hernandez J, et al. Carriage of CTX-M type extended spectrum β-lactamases (ESBLs) in gulls across Europe. *Acta Vet Scand*. 2015; **57**: 74. PMID: 26526188 doi: 10.1186/s13028-015-0166-3

214. Guenther S, Grobbel M, Beutlich J, et al. CTX-M-15-type extended-spectrum β-lactamases-producing *Escherichia coli* from wild birds in Germany. *Environ Microbiol Rep*. 2010; **2**: 641–645. PMID: 23766249 doi: 10.1111/j.1758-2229.2010.00148.x

215. Bachiri T, Bakour S, Ladjouzi R, Thongpan L, Rolain JM, Touati A. High rates of CTX-M-15-producing Escherichia coli and Klebsiella pneumoniae in wild boars and Barbary macaques in Algeria. *J Glob Antimicrob Resist*. 2017; **8**: 35–40. PMID: 27984780 doi: 10.1016/j.jgar.2016.10.005

216. Alonso CA, González-Barrio D, Tenorio C, Ruiz-Fons F, Torres C. Antimicrobial resistance in faecal *Escherichia coli* isolates from farmed red deer and wild small mammals. Detection of a multiresistant *E. coli* producing extended-spectrum β-lactamase. *Comp Immunol Microbiol Infect Dis*. 2016; **45**: 34–39. PMID: 27012919 doi: 10.1016/j.cimid.2016.02.003

217. Jardine CM, Janecko N, Allan M, et al. Antimicrobial resistance in *Escherichia coli* isolates from raccoons (*Procyon lotor*) in Southern Ontario, Canada. *Appl Environ Microbiol*. 2012; **78**: 3873–3879. PMID: 22447599 doi: 10.1128/AEM.00705-12

218. Bondo KJ, Pearl DL, Janecko N, et al. Epidemiology of antimicrobial resistance in *Escherichia coli* isolates from raccoons (*Procyon lotor*) and the environment on swine farms and conservation areas in Southern Ontario. *PLoS One*. 2016; **11**: e0165303. PMID: 27829035

219. Carroll D, Wang J, Fanning S, McMahon BJ. Antimicrobial resistance in wildlife: implications for public health. *Zoonoses Public Health*. 2015; **62**: 534–542. PMID: 25639901

220. Furness LE, Campbell A, Zhang L, Gaze WH, McDonald RA. Wild small mammals as sentinels for the environmental transmission of antimicrobial resistance. *Environ Res*. 2017; **154**: 28–34. PMID: 28013185 doi: 10.1016/j.envres.2016.12.014

221. de Been M, Lanza VF, de Toro M, et al. Dissemination of cephalosporin resistance genes between *Escherichia coli* strains from farm animals and humans by specific plasmid lineages. *PLoS Genet*. 2014; **10**: e1004776. PMID: 25522320 doi: 10.1371/journal.pgen.1004776

222. Fischer EA, Dierikx CM, van Essen-Zandbergen A, et al. The IncI1 plasmid carrying the $bla_{CTX\text{-}M\text{-}1}$ gene persists in in vitro culture of a *Escherichia coli* strain from broilers. *BMC Microbiol*. 2014; **14**: 77. PMID: 24666793 doi: 10.1186/1471-2180-14-77

223. Zurfluh K, Glier M, Hächler H, Stephan R. Replicon typing of plasmids carrying $bla_{CTX\text{-}M\text{-}15}$ among *Enterobacteriaceae* isolated at the environment, livestock and human interface. *Sci Total Environ*. 2015; **521-522**: 75–78. PMID: 25828415 doi: 10.1016/j.scitotenv.2015.03.079

224. Smet A, Rasschaert G, Martel A, et al. In situ ESBL conjugation from avian to human *Escherichia coli* during cefotaxime administration. *J Appl Microbiol*. 2011; **110**: 541–549. PMID: 21143712 doi: 10.1111/j.1365-2672.2010.04907.x

225. Rashid H, Rahman M. Possible transfer of plasmid mediated third generation cephalosporin resistance between *Escherichia coli* and *Shigella sonnei* in the human gut. *Infect Genet Evol*. 2015; **30**: 15–18. PMID: 25461693 doi: 10.1016/j.meegid.2014.11.023

226. Toleman MA, Walsh TR. Combinatorial events of insertion sequences and ICE in Gram-negative bacteria. *FEMS Microbiol Rev*. 2011; **35**: 912–935. PMID: 21729108 doi: 10.1111/j.1574-6976.2011.00294.x

227. Kiiru J, Butaye P, Goddeeris BM, Kariuki S. Analysis for prevalence and physical linkages amongst integrons, IS*Ecp1*, IS*CR1*, Tn*21* and Tn*7* encountered in *Escherichia coli* strains from hospitalized and non-hospitalized patients in Kenya during a 19-year period (1992-2011). *BMC Microbiol*. 2013; **13**: 109. PMID: 23682924 doi: 10.1186/1471-2180-13-109

228. Yaici L, Haenni M, Métayer V, et al. Spread of ESBL/AmpC-producing *Escherichia coli* and *Klebsiella pneumoniae* in the community through ready-to-eat sandwiches in Algeria. *Int J Food Microbiol*. 2017; **245**: 66–72. PMID: 28135647 doi: 10.1016/j.ijfoodmicro.2017.01.011

229. Kim HS, Chon JW, Kim YJ, Kim DH, Kim MS, Seo KH. Prevalence and characterization of extended-spectrum-β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in ready-to-eat vegetables. *Int J Food Microbiol*. 2015; **207**: 83–86. PMID: 26001064 doi: 10.1016/j.ijfoodmicro.2015.04.049

230. Randall LP, Lodge MP, Elviss NC, et al. Evaluation of meat, fruit and vegetables from retail stores in five United Kingdom regions as sources of extended-spectrum β-lactamase (ESBL)-producing and carbapenem-resistant *Escherichia coli*. *Int J Food Microbiol*. 2017; **241**: 283–290. PMID: 27821357 doi: 10.1016/j.ijfoodmicro.2016.10.036

231. Nüesch-Inderbinen M, Zurfluh K, Peterhans S, Hächler H, Stephan R. Assessment of the prevalence of extended-spectrum β-lactamase-producing *Enterobacteriaceae* in ready-to-eat salads, fresh-cut fruit, and sprouts from the Swiss market. *J Food Prot*. 2015; **78**: 1178–1181. PMID: 26038909 doi: 10.4315/0362-028X.JFP-15-018

232. Dhanji H, Patel R, Wall R, et al. Variation in the genetic environments of $bla_{(CTX\text{-}M\text{-}15)}$ in *Escherichia coli* from the faeces of travellers returning to the United Kingdom. *J Antimicrob Chemother*. 2011; **66**: 1005–1012. PMID: 21393166 doi: 10.1093/jac/dkr041

233. Korzeniewska E, Harnisz M. Extended-spectrum β-lactamase (ESBL)-positive *Enterobacteriaceae* in municipal sewage and their emission to the environment. *J Environ Manage*. 2013; **128**: 904–911. PMID: 23886578 doi: 10.1016/j.jenvman.2013.06.051

234. Huijbers PM, Blaak H, de Jong MC, Graat EA, Vandenbroucke-Grauls CM, de Roda Husman AM. Role of the environment in the transmission of antimicrobial resistance to humans: A Review. *Environ Sci Technol*. 2015; **49**: 11993–12004. PMID: 26355462 doi: 10.1021/acs.est.5b02566

235. Philippon A, Slama P, Dény P, Labia R. at al. A Structure-based classification of Class A β-lactamases, a broadly diverse family of enzymes. *Clin Microbiol Rev*. 2016; **29**: 29–57. PMID: 26511485 doi: 10.1128/CMR.00019-15

236. Njage PM, Buys EM. Quantitative assessment of human exposure to extended spectrum and AmpC β-lactamases bearing *E. coli* in lettuce attributable to irrigation water and subsequent horizontal gene transfer. *Int J Food Microbiol*. 2017; **240**: 141–151. PMID: 27789039 doi: 10.1016/j.ijfoodmicro.2016.10.011

237. van Hoek AH, Veenman C, van Overbeek WM, Lynch G, de Roda Husman AM, Blaak H. Prevalence and characterization of ESBL- and AmpC-producing *Enterobacteriaceae* on retail vegetables. *Int J Food Microbiol*. 2015; **204**: 1–8. PMID: 25828704 doi: 10.1016/j.ijfoodmicro.2015.03.014

238. Peirano G, van der Bij AK, Gregson DB, Pitout JD. Molecular epidemiology over an 11-year period (2000 to 2010) of extended-spectrum β-lactamase-producing *Escherichia coli* causing bacteremia in a centralized Canadian region. *J Clin Microbiol*. 2012; **50**: 294–299. PMID: 22162555 doi: 10.1128/JCM.06025-11

239. Prina E, Ranzani OT, Polverino E, et al. Risk factors associated with potentially antibiotic-resistant pathogens in community-acquired pneumonia. *Ann Am Thorac Soc*. 2015; **12**: 153–160. PMID: 25521229 doi: 10.1513/AnnalsATS.201407-305OC

240. Sikkema R, Koopmans M. One Health training and research activities in Western Europe. *Infect Ecol Epidemiol*. 2016; **6**: 33703. PMID: 27906121 doi: 10.3402/iee.v6.33703

241. Asokan GV, Asokan V. Bradford Hill's criteria, emerging zoonoses, and One Health. *J Epidemiol Glob Health*. 2016; **6**: 125–129. PMID: 26589252 doi: 10.1016/j.jegh.2015.10.002