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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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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.

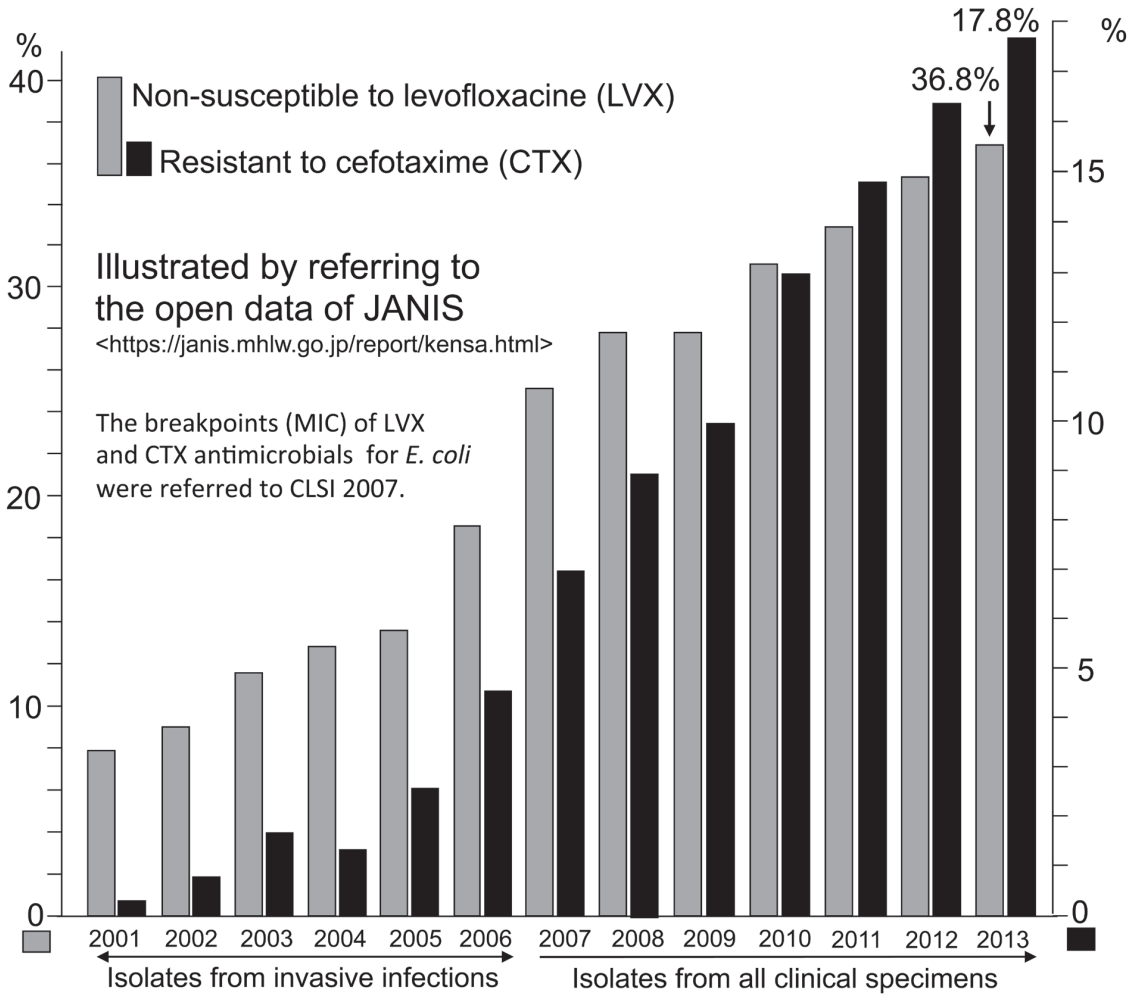

Fig. 1. Rapid rise of clinically isolated *Escherichia coli* that acquired resistance to the third-generation cephalosporins and/or fluoroquinolones (inpatients).

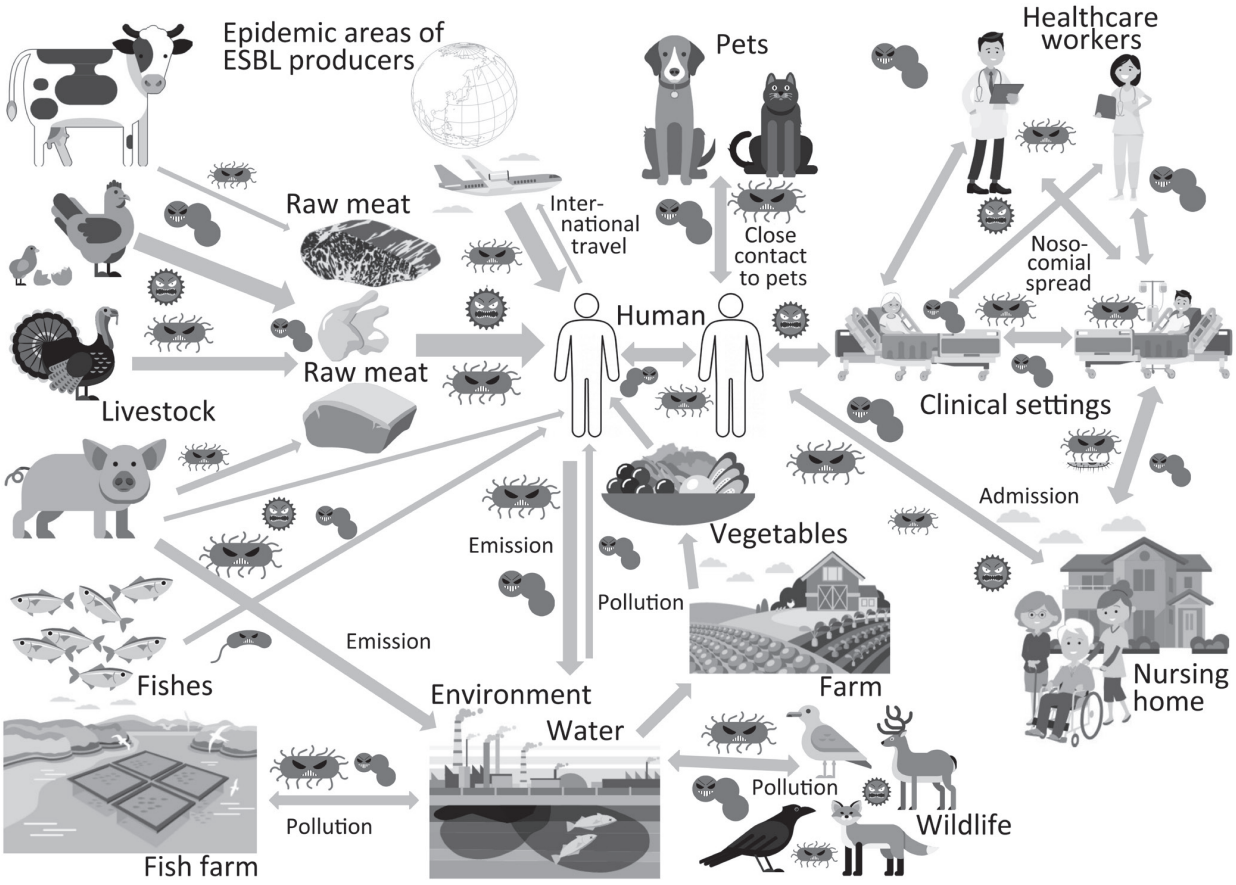

Fig. 2. Possible transmission and circulation of antimicrobial resistant bacteria.

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.

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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

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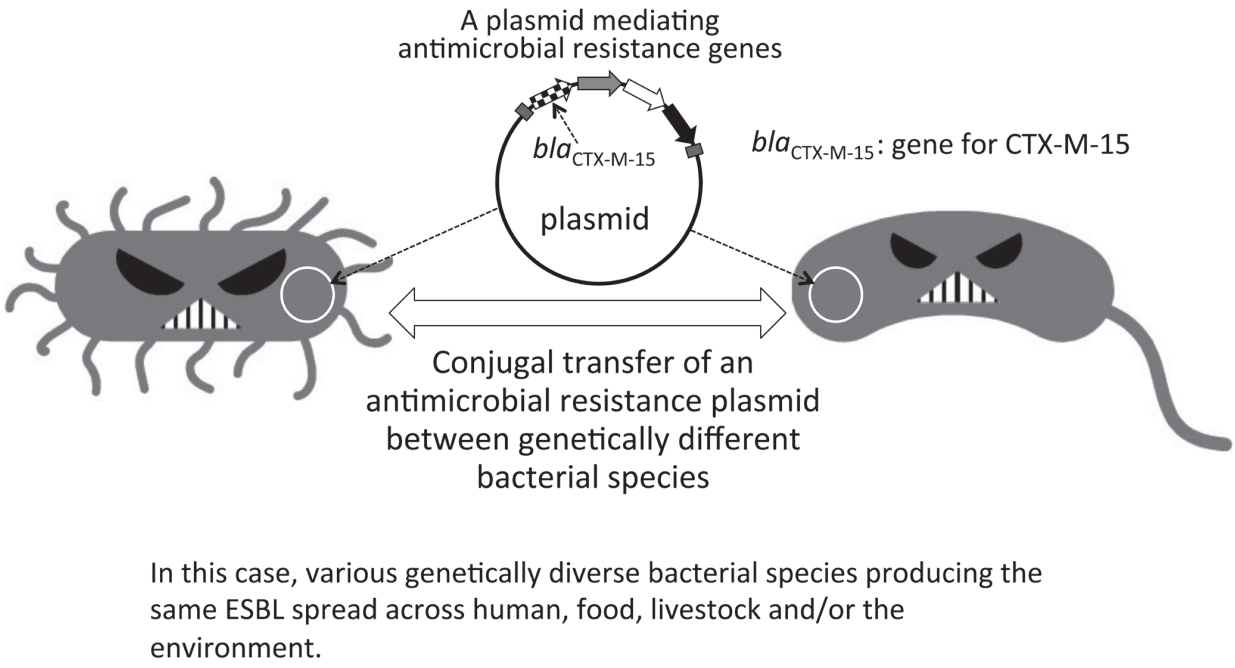

Fig. 3. Transfer of antimicrobial resistance gene-mediating plasmids between genetically different bacteria.

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

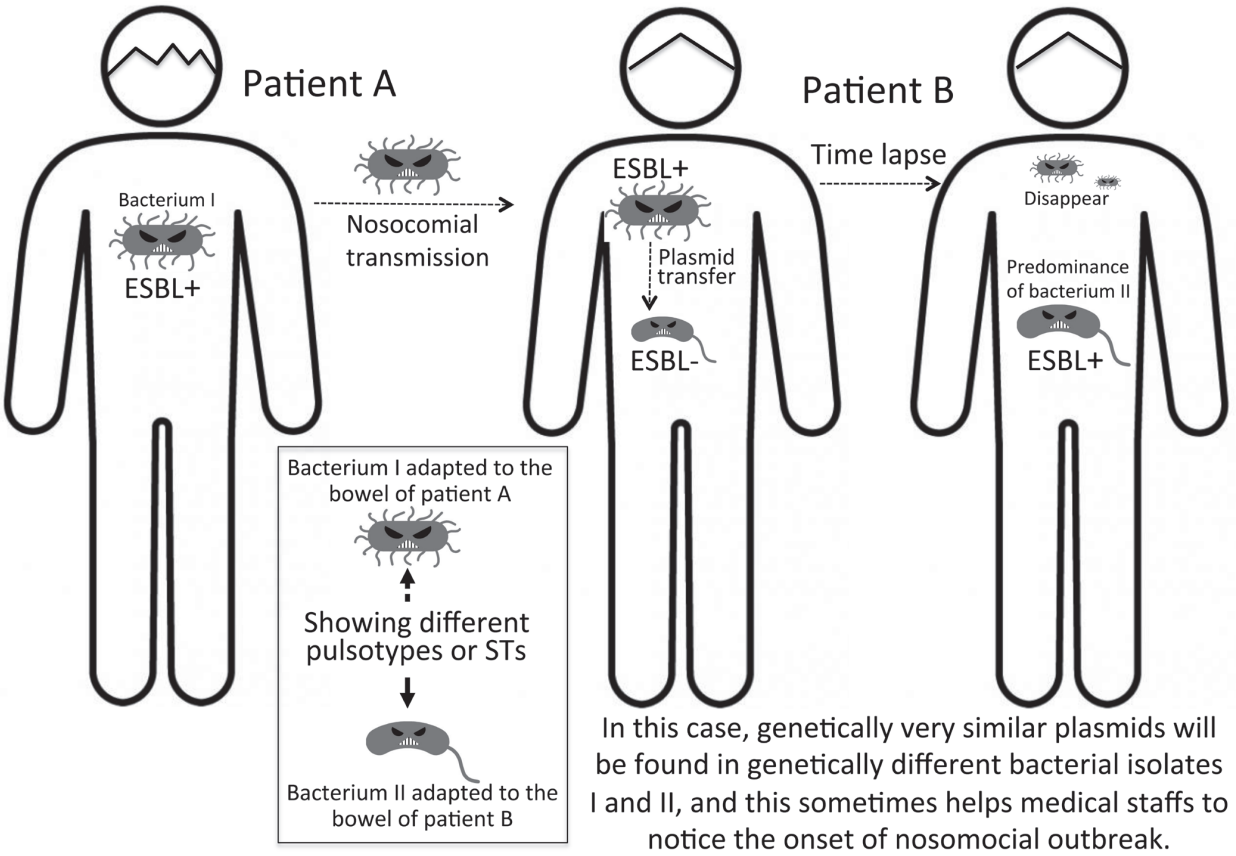

Fig. 4. A case of bacterial outbreak showing different pulsotypes or STs but producing the same ESBL.

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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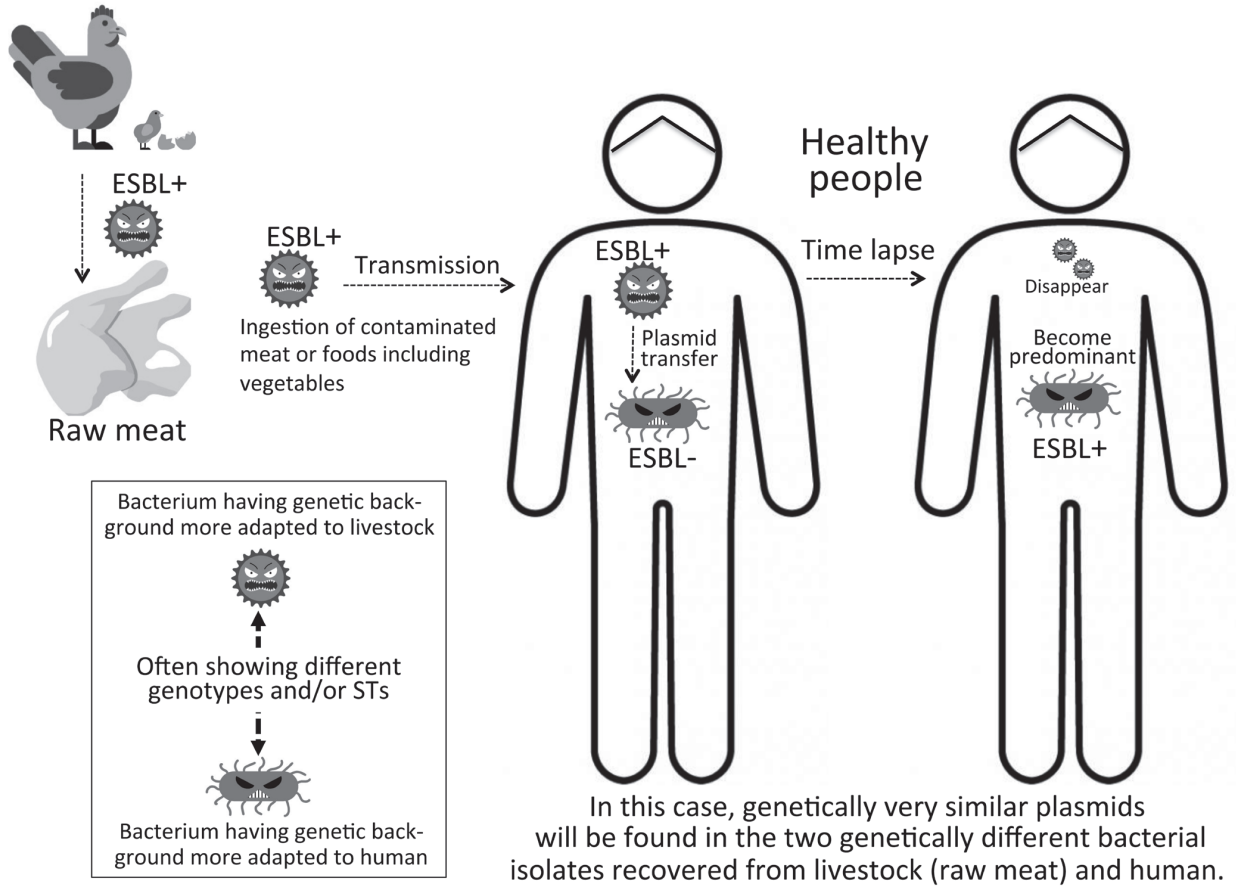

Fig. 5. Probable mechanism underlying the genetic difference between two *E. coli* isolates recovered respectively from livestock (raw meat) and human, that produce the same ESBL.

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)	

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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)			

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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

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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)	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
		CTX-M-15(4)		
		CTX-M-14(2)		
		CTX-M-123(1)		
Guangzhou City, China	Raw pork and cooked pork products (Sep–Nov 2013)	CTX-M-1(1)		181
		CTX-M-1+SHV(1)		
		CTX-M-9(1)		
		TEM(4)		
Ho Chi Minh City, Vietnam	Food samples (chicken meat, pork, beef, and fish) (Oct 2012–Mar 2014)	CTX-M-9 group (110)	Chicken(44), Pork(41), Beef(12), Fish(13)	182
		CTX-M-1 group (102)	Chicken(62), Pork(15), Beef(10), Fish(15)	
		SHV-12 (3)	Chicken(1), Beef(2)	
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

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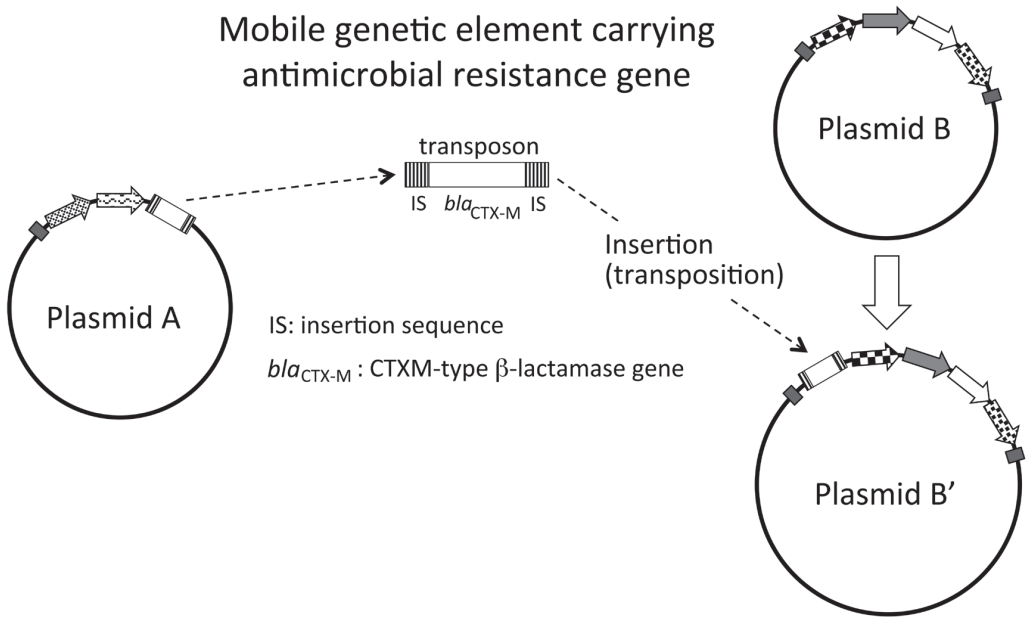
Table 3. (continued)

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].

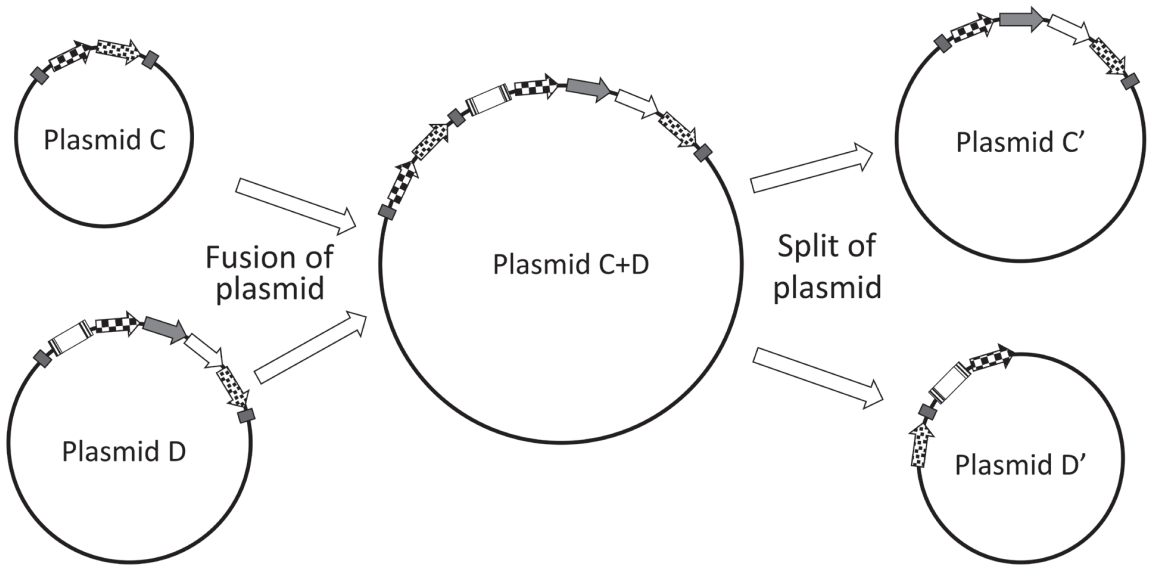
7. Emission of ESBL producers into the environment and wildlife

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.

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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].

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