

## Review Article

Current epidemiologic features and health dynamics of ESBL-producing *Escherichia coli* in ChinaSayyed Salman<sup>a</sup>, Zeeshan Umar<sup>b</sup>, Yonghong Xiao<sup>a,1,\*</sup><sup>a</sup> Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310000, China<sup>b</sup> Marshall Laboratory of Biomedical Engineering, School of Medicine, Shenzhen University, Shenzhen 510000, China

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## ABSTRACT

Extended-spectrum  $\beta$ -lactamase (ESBL)-producing *Escherichia coli* (*E. coli*) are widespread in China, with occurrences documented in humans, animals, and the environment. The dissemination of ESBL-producing *E. coli* is likely facilitated by the widespread use of antibiotics in human and animal agriculture, the presence of antibiotic-resistant bacteria (ARBs) in animal feces, and close human-animal interactions. Plasmids, particularly those belonging to incompatibility (Inc) group, such as IncF, IncI, and IncH families, play a vital role in facilitating the horizontal gene transfer of ESBL genes across various sectors, from humans to animals and the environment. IS26 and IS1 elements also significantly influences the mobilization and evolution of antibiotic-resistance genes (ARGs), contributing to the spread of ESBL-producing *E. coli*. *bla*<sub>CTX-M-14</sub>, *bla*<sub>CTX-M-15</sub>, and *bla*<sub>CTX-M-55</sub> are prevalent in ESBL-producing *E. coli* across the three domains and are often found in conjunction with other ARGs. Considering these challenges, it is imperative to take proactive measures to prevent the further spread of ARBs. This includes the judicious and responsible use of antibiotics and efforts to minimize contact with animal feces. Sector-specific strategies should be developed to effectively educate and engage relevant personnel in tackling this multifaceted problem. These efforts are vital to combat the dissemination of ESBL-producing *E. coli* and preserve public health.

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## 1. Introduction

The discovery of antibiotics and vaccines has empowered scientists and medical professionals to combat and protect against bacterial infections. However, antibiotics misuse has significantly increased antimicrobial resistance, rendering certain infections nearly untreatable. According to the World Health Organization (WHO), antibiotic resistance poses a significant and formidable challenge to human health, resulting in > 700,000 deaths from bacterial infections annually worldwide [1]. If not adequately addressed, the continued expansion of antibiotic resistance could outstrip other causes of mortality and become the primary contributor to global deaths by 2050. This

development could result in an annual death toll exceeding 10 million people and impose an estimated global economic burden of \$100 trillion [2].

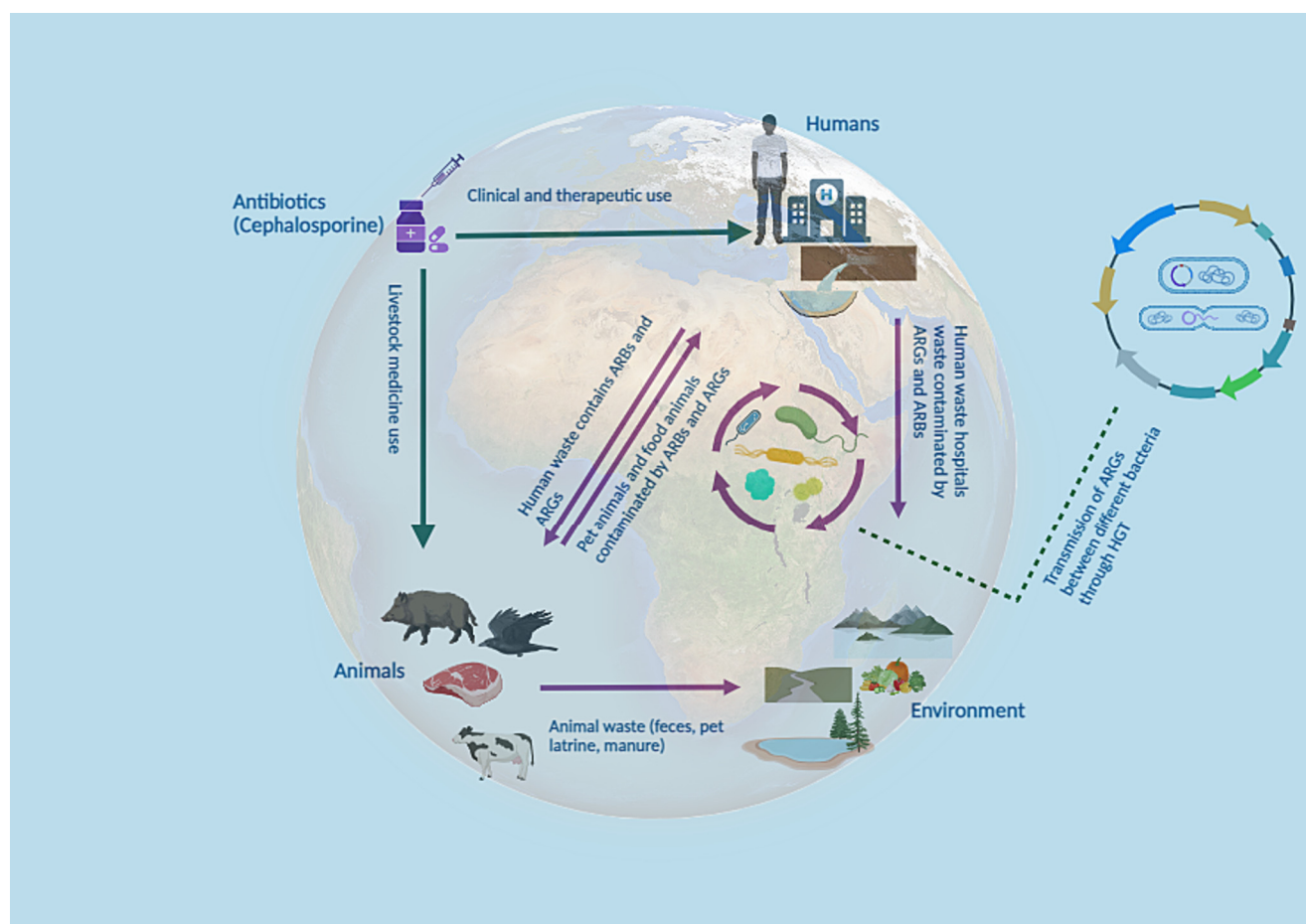
Extended-spectrum  $\beta$ -lactamases (ESBLs) are significant bacterial resistance mechanisms. Extended spectrum  $\beta$ -lactam antibiotics were employed in Western Europe during the emergence of bacterial infections, mainly when the ESBL resistance scenario initially surfaced. Which led to ESBL proliferation in Europe, Asia, and the United States. According to a 2021 UN report, there has been a global surge in the prevalence of ESBL-producing *Escherichia coli* (*E. coli*), increasing from 36% to 47%, compared to 2019 data. Moreover, specific regions in sub-Saharan Africa and southern Asian countries have shown alarmingly high rates of ESBL production, with ~ 50% of *E. coli* strains being ESBL-producing [3].

In addition to their presence in humans, ESBLs have been detected in nonhuman sources, such as animals and the environment (Fig. 1). The first ESBL genotypes were initially identified in *E. coli* from a dog in Japan in 1988, with a focus on a strain that produced the CTX-M-3 enzyme. Research on ESBL genes in aquatic environments has been conducted worldwide. For example, studies have been conducted on *E. coli* in various rivers, including the Mur River in Europe (specifically, Austria) [4], the Yamato River in Asia (Japan) [5] and

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**Fig. 1.** Diagrammatic representation of the transmissions of extended-spectrum  $\beta$ -lactamase (ESBL) genes among humans, animals, and the environment. Abbreviation: ARGs, antibiotic-resistance genes; ARBs, antibiotic-resistance bacteria; HGT, horizontal gene transfer.

the Asi (Orontes) river in Turkey [6]. The most commonly identified ESBL genotypes in these studies were *bla*<sub>CTX-M-1</sub> and *bla*<sub>CTX-M-9</sub>.

## 2. ESBLs historical findings and classification

Research on antibiotic resistance began with the discovery of  $\beta$ -lactamases in an *E. coli* strain, originally termed *Bacillus coli*, in England in 1940 [7]. In 1965, the initial description of  $\beta$ -lactamases on “resistance factor (R-factors)” was made. However, only a limited subset of these enzymes was associated with transferable penicillinase on R<sub>TEM</sub>, now commonly referred to as TEM-1 [7]. After TEM-1, SHV-1 (for sulfhydryl variable) is the next most prevalent plasmid-based  $\beta$ -lactamase, commonly found in *Klebsiella pneumoniae* (*K. pneumoniae*) and *E. coli*. Although SHV-1 is usually chromosomally encoded in most *K. pneumoniae* isolates, it is typically plasmid-mediated in *E. coli* [8]. TEM-1 and SHV-1 emerged after the introducing of first and second-generation cephalosporins. Other ESBL genotypes such as CTX-M (named for its preferential hydrolytic activity against cefotaxime, with CTX as its acronym and M for Munich), OXA type, and more uncommon enzymes such as BEL-1 (Belgium), PER (Pseudomonas extended resistance), BES-1 (Brazil), VEB (Vietnam ESBL), and SFO-1 (*Serratia fonticola*) are typical of either SHV or TEM types and are produced by Gram-negative organisms [9].

Based on molecular structural classification,  $\beta$ -lactamases in Group 2 are divided into Classes A and D. Within this group, the Subgroup 2be belongs to ESBLs and includes enzyme families such as TEM-2, TEM-30, SHV-3, SHV-10, CTX-M (group), BEL-1, BES-1, SFO-1, TLA-1, TLA-2, PER, and VEB. These ESBLs can hydrolyze one or more

oxymino- $\beta$ -lactams, including cefotaxime, ceftazidime, and aztreonam, while retaining activity against penicillins and cephalosporins. Other subgroups in Group 2 include 2br, which comprises TEM-30, TEM-31 (IRT-2 and IRT-1), and SHV-10; 2ber, which comprises TEM-50 (CMT-1); 2ce which contains RTG-4 (CARB-10); and 2d, which includes various OXA enzymes such as OXA-1 and OXA-10. Subgroup 2de contains OXA-11 and OXA-15, 2df includes OXA-23 and OXA-48, 2e comprises CepA, and 2f consists of KPC-2, IMI-1, and SME-1 enzymes. Enzymes in subgroup 2f exhibit increased hydrolysis of carbapenems, oxymino- $\beta$ -lactams, and cephamycins [10].

## 3. ESBLs epidemiology in patients and the health population of China

ESBL-producing *E. coli* strains first emerged in China in the early 1990s [11]. These strains are now prevalent in both community and healthcare settings, exhibiting variations based on geographic location and the site of infection. Although their distribution is not restricted to humans; these strains are also widely distributed in animals and the environment (Table 1) [12–59]. A significant increase was observed in the rates of ESBL-producing *E. coli* isolates from intraabdominal infections (IAIs), which increased from 36.1% between 2002 and 2003 to 68.1% between 2010 and 2011 ( $P < 0.001$ ). Similarly, the prevalence of ESBL-producing *E. coli* in healthcare-associated isolates exhibited an upward trend, increasing from 52.2% from 2002 to 2003 to 70.0% from 2010 to 2011 ( $P = 0.001$ ). In community-associated isolates, ESBL production rates increased from 19.1% from 2002 to 2003 to 61.6 % from 2010 to 2011 ( $P < 0.001$ ) [60]. During a

**Table 1**Prevalence of extended-spectrum  $\beta$ -lactamases (ESBLs) in animals and the environment in China.

Region/province	Source	ESBL / no. isolates	Distribution of major genotypes/sequence types (STs) and their percentage (%)	References
<b>Meat (animals ready for food) and other ready-to-eat food</b>				
East, West, North, and South China	Ready-to-eat food	22 / 1,118	<i>bla</i> <sub>CTX-M</sub> (13.4%) and <i>bla</i> <sub>OXA</sub> (7.9%)	[12]
Guangzhou City, Guangdong Province	Ready-to-eat food product	64 / 720	<i>bla</i> <sub>CTX-M-15</sub> (1.6%)	[13]
Shaanxi Province	Retail food	140 / 659	<i>bla</i> <sub>CTX-M-1</sub> (28.8%), <i>bla</i> <sub>CTX-M-2</sub> (3.4%), and <i>bla</i> <sub>CTX-M-9</sub> (67.8%)	[14]
Anhui Province	Chicken	100 / 202	<i>bla</i> <sub>CTX-M</sub> (19.8%)	[15]
Guangdong Province	Chicken / ducks	74 / 247	<i>bla</i> <sub>CTX-M</sub> (29.9%)	[16]
Henan Province	Chicken	31 / 51	<i>bla</i> <sub>CTX-M</sub> (51.7%)	[17]
North and South China	Chicken	128 / 696	<i>bla</i> <sub>CTX-M</sub> (75%)	[18]
Northeast and South China	Chicken	191 / 195	<i>bla</i> <sub>CTX-M-15</sub> (34.8%) and <i>bla</i> <sub>CTX-M-65</sub> (21%)	[19]
Shandong Province	Chicken	142 / 160	<i>bla</i> <sub>CTX-M-15</sub> (39.4%) and <i>bla</i> <sub>CTX-M-65</sub> (29.5%)	[20]
South China	Ducks	123 / 230	<i>bla</i> <sub>CTX-M</sub> (87.8%)	[21]
Sichuan Province and Chongqing Municipality	Cattle meat	102 / 222	<i>bla</i> <sub>CTX-M</sub> (9.5%)	[22]
Different geographic areas of China	Healthy food animals	111 / 896	<i>bla</i> <sub>CTX-M-14</sub> (36%), <i>bla</i> <sub>CTX-M-55</sub> (26.1%), and <i>bla</i> <sub>CTX-M-65</sub> (19.8%)	[23]
<b>Livestock</b>				
Heilongjiang Province	Pigs	198 / 458	<i>bla</i> <sub>CTX-M-55</sub> (52.6%), <i>bla</i> <sub>CTX-M-15</sub> (28.9%), and <i>bla</i> <sub>CTX-M-14</sub> (58.7%)	[24]
Guangdong Province	Pigs	36 / 125	<i>bla</i> <sub>CTX-M-9</sub> (75%) and <i>bla</i> <sub>CTX-M-1</sub> (61.1%)	[25]
Guangxi Zhuang Autonomous Region, China	Swine	22 / 72	<i>bla</i> <sub>CTX-M-14</sub> (59.4%) and <i>bla</i> <sub>CTX-M-123</sub> (37.5%)	[26]
Guizhou Province	Swine	38 / 47	<i>bla</i> <sub>CTX-M-9</sub> (29.8%), <i>bla</i> <sub>CTX-M-1</sub> (10.6%), and <i>bla</i> <sub>DHA</sub> (17%)	[27]
16 different provinces in China	Cattle (mastitic cows)	153 / 1,252	<i>bla</i> <sub>CTX-M-15</sub> (78.5%)	[28]
Jiangsu Province, China	Swine	78 / 197	<i>bla</i> <sub>CTX-M-15</sub> (69%), and <i>bla</i> <sub>CTX-M-55</sub> (29%)	[29]
Northwest China	Sheep	67	<i>bla</i> <sub>CTX-M-55</sub> (61.5%) and <i>bla</i> <sub>CTX-M-15</sub> (19.2%)	[30]
Shaanxi and Gansu Provinces	Swine	44 / 456	<i>bla</i> <sub>CTX-M</sub> (90.9%)	[31]
Different geographic areas of China	Cows feces	284 / 290	<i>bla</i> <sub>CTX-M-14</sub> (24.1%), <i>bla</i> <sub>CTX-M-15</sub> (21.4%), and <i>bla</i> <sub>CTX-M-17</sub> (19.3%)	[32]
Different geographic areas of China	Pigs / poultry / ducks	777 / 2,815	<i>bla</i> <sub>CTX-M-14</sub> (22.6%), <i>bla</i> <sub>CTX-M-55</sub> (23.9%), and <i>bla</i> <sub>CMY</sub> (10.1%)	[33]
Shandong Province	Pigs	42 / 100	<i>bla</i> <sub>CTX-M-14</sub> (29.4%), <i>bla</i> <sub>CTX-M-55</sub> (32.4%), and <i>bla</i> <sub>CTX-M-15</sub> (20.6%)	[34]
Tai'an City, Shandong Province	Swine manure	42 / 180	<i>bla</i> <sub>CTX-M</sub> (86%)	[35]
Sichuan Province	Swine feces	15 / 18	<i>bla</i> <sub>CTX-M-1</sub> (86.6%)	[36]
<b>Companion animals</b>				
Shandong Province	Companion animals	34 / 79	<i>bla</i> <sub>CTX-M</sub> (60.8%)	[37]
Beijing Municipality	Pets (dogs and cats)	90 / 127	<i>bla</i> <sub>CTX-M</sub> (34.6%) and <i>bla</i> <sub>CMY</sub> (9%)	[38]
Northeastern China	Pets (dogs and cats) and working dogs	219 / 554	<i>bla</i> <sub>CTX-M</sub> (68%)	[39]
Shaanxi Province	Sick dogs	89 / 165	<i>bla</i> <sub>CTX-M</sub> (87.5%) and <i>bla</i> <sub>CMY-2</sub> (7.5%)	[40]
South China	Pets (cats and dogs)	97 / 99	<i>bla</i> <sub>CTX-M-14</sub> (46.8%) and <i>bla</i> <sub>CTX-M-55</sub> (25%)	[41]
Tai'an City, Shandong Province	Companion dogs	3 / 118	<i>bla</i> <sub>CTX-M-15</sub> (2.5%)	[42]
Yangzhou City, Jiangsu Province	Stray dogs	80 / 156	<i>bla</i> <sub>CTX-M-15</sub> (37.5%) and <i>bla</i> <sub>CTX-M-55</sub> (36.2%)	[43]
Hong Kong Special Administrative Region, China	Wild rodent	68 / 965	<i>bla</i> <sub>CTX-M-1</sub> (52.1%) and <i>bla</i> <sub>CTX-M-9</sub> (44.9%)	[44]
Sichuan Province	Giant pandas	4 / 4	<i>bla</i> <sub>CTX-M-55</sub> and <i>bla</i> <sub>CTX-M-105</sub> (4/4)	[45]
Hunan Province	Zoo animals	23 / 93	<i>bla</i> <sub>CTX-M-55</sub> (34.8%), <i>bla</i> <sub>CTX-M-14</sub> (26.0%), <i>bla</i> <sub>CTX-M-27</sub> (21.7%), and <i>bla</i> <sub>CTX-M-15</sub> (13.0%)	[46]
<b>Environments</b>				
Tai'an City, Shandong Province	Well water	4 / 100 (wells)	<i>bla</i> <sub>CTX-M-15</sub> (4%) and <i>bla</i> <sub>CTX-M-27</sub> (1%)	[47]
Tai'an City, Shandong Province	Spring water	13 / 50	<i>bla</i> <sub>CTX-M-14</sub> (31.3%), <i>bla</i> <sub>CTX-M-15</sub> (37.5%), and <i>bla</i> <sub>CTX-M-55</sub> (18.7%)	[48]
Laiwu City, Shandong Province	Drinking water wells and pit latrines wastewater	63 / 200	<i>bla</i> <sub>CTX-M-14</sub> (17.4%) and <i>bla</i> <sub>CTX-M-15</sub> (42.8%)	[49]
Guantao County, Hebei Province	Rural water	18 / 24	<i>bla</i> <sub>CTX-M</sub> (25.8%)	[50]
Northwest China	Rivers and lakes	76 / 2,686	<i>bla</i> <sub>CTX-M-14</sub> (46%) and <i>bla</i> <sub>CTX-M-123</sub> (19.7%)	[51]
Taizhou City, Zhejiang Province	Wastewater treatment plants (WWTPs)	18 / 18	<i>bla</i> <sub>CTX-M-14</sub> (50%) and <i>bla</i> <sub>CTX-M-15</sub> (61.1%)	[52]
Shandong Province	Pig forms, surrounding environment (rivers, wells, lakes, and sediments)	88 / 231	<i>bla</i> <sub>CTX-M-14</sub> (39.7%), <i>bla</i> <sub>CTX-M-55</sub> (11.3%), and <i>bla</i> <sub>CTX-M-65</sub> (22.7%)	[53]
Tai'an City, Shandong Province	Pig feces and rivers in the surrounding	57 / 300	<i>bla</i> <sub>CTX-M-14</sub> (38.7%), <i>bla</i> <sub>CTX-M-15</sub> (54.8%) and <i>bla</i> <sub>TEM-52</sub> (6.5%)	[54]
Hangzhou City, Zhejiang Province	Environmental water, swine, healthy humans	86 / 139	<i>bla</i> <sub>CTX-M-1</sub> group (23%) and <i>bla</i> <sub>CTX-M-9</sub> group (71.2%)	[55]
Western China	Swine / human feces	120 / 447	<i>bla</i> <sub>CTX-M-15</sub> (18.3%), <i>bla</i> <sub>CTX-M-55</sub> (12.5%), <i>bla</i> <sub>SHV-2</sub> (14.1%), and <i>bla</i> <sub>CMY-2</sub> (49.1%)	[56]
Xinjiang Uygur Autonomous Region	Cow's milk / surrounding environment	149 / 766	<i>bla</i> <sub>CTX-M</sub> (97.3%)	[57]
Jinan City, Shandong Province	Chicken surrounding / river	29 / 258	<i>bla</i> <sub>CTX-M</sub> (51.7%)	[58]
Shandong Province	Pig's feces and surrounding environment	6 / 10 forms	<i>bla</i> <sub>CTX-M-14</sub> (26.8%) and <i>bla</i> <sub>CTX-M-15</sub> (26%)	[59]

10-year investigation, the prevalence of ESBL-producing *E. coli* in bloodstream infections (BSIs) fluctuated: the rates were 68.9% in 2004 to 2005, 73.2% from 2007 to 2008, 67.9% from 2009 to 2010, 72.6% from 2011 to 2012, and 58.4% from 2013 to 2014 [61]. According to most recent data, ESBL-producing *E. coli* accounts for 38.07% of community-acquired urinary tract infections (CA-UTIs) across various regions of China, including the northeastern, northern, central, western, and eastern areas. They are also responsible for 40.98% of BSIs in the southeastern region of China [62,63].

The emergence of CTX-M-producing *E. coli* strains in China was documented in 1997 [64]. Initially, *E. coli* strains carrying *bla*<sub>CTX-M-9</sub>, *bla*<sub>CTX-M-13</sub>, and *bla*<sub>CTX-M-14</sub> genotypes were isolated from hospital patients, often coexisting with *bla*<sub>SHV-12</sub>. A novel variant (*bla*<sub>SHV-8</sub>) was later discovered coexist with the *bla*<sub>CTX-M-14</sub> genotype [64,65]. Subsequent studies reported a high prevalence (62.3%) of *E. coli* strains carrying CTX-M group in patients with IAIs across China, along with *bla*<sub>SHV</sub> (5.39%). Among these, the most frequent genotypes were *bla*<sub>CTX-M-15</sub> (28.7%), followed by *bla*<sub>CTX-M-55</sub> (16.2%). A smaller proportion exhibited *bla*<sub>CTX-M-123</sub> and *bla*<sub>CTX-M-82</sub> genotypes [66]. In Shandong Province, a similarly high prevalence (62.8%) of the CTX-M group was observed in various hospitals. The most common genotype was *bla*<sub>CTX-M-14</sub> (57.7%), followed by *bla*<sub>CTX-M-55</sub> (23.4%) and *bla*<sub>CTX-M-15</sub> (15.4%). Multilocus sequence typing (MLST) analysis revealed that most strains belonged to ST131 (13.1%), followed by ST405 (9.5%) and ST69 (7.5%) [67]. For instance, CA-UTIs caused by *E. coli* in various regions showed a high prevalence of *bla*<sub>CTX-M-14</sub> genotypes, with an incidence rate of 31.8 %. Other genotypes such as *bla*<sub>CTX-M-55</sub> (23.4%), *bla*<sub>CTX-M-15</sub> (17.5%), and *bla*<sub>CTX-M-27</sub>, were also prevalent [63]. High-risk clones ST131 and ST1193 of ESBL-producing *E. coli* had a high carriage rate of the CTX-M group among healthy children within the community, along with the dominant ESBL genotype *bla*<sub>CTX-M-14</sub>, indicating severe community-wide dissemination of ESBL genes [68]. Moreover, samples from Jiangsu Province showed a high prevalence of *bla*<sub>CTX-M-55</sub>, associated with the *E. coli* clone ST8369, suggesting ongoing community dissemination [69]. Recent studies have also reported an increased dominance of the CTX-M group in *E. coli* strains causing BSIs. A 3-year study in eastern China found a high prevalence of *bla*<sub>CTX-M-14</sub>, *bla*<sub>CTX-M-55</sub>, *bla*<sub>CTX-M-15</sub>, and *bla*<sub>CTX-M-27</sub> [62]. Similarly, a high prevalence of sequence types (STs) ST1193, ST95, ST73, ST69, and ST131 has been reported among ESBL-producing *E. coli* in neonates across China [70]. Lastly, a screening conducted in a Hanzhou district hospital revealed that 100.0% of the samples tested positive for ESBLs, with 36.1% belonging to ST131 *E. coli* clones. The most dominant ESBL genotypes were *bla*<sub>CTX-M-27</sub> and *bla*<sub>CTX-M-55</sub> (25.0%), followed by *bla*<sub>CTX-M-14</sub> (22.2%) and *bla*<sub>CTX-M-15</sub> (16.7%) [71].

Various factors facilitate the transmission of ESBL genes among humans. One key mechanism is CTX-M plasmid-mediated genes, notably prevalent among the community population harboring ESBL-producing *E. coli*. For example, CTX-M-15 undergoes transfer via conjugation *in vitro*, originating from donor bacteria [72]. Further investigation has highlighted that the horizontal gene transfer of  $\beta$ -lactamase genes is primarily mediated by incompatibility (Inc) plasmids such as IncK and IncF that encode genes responsible for multidrug resistance (MDR). Moreover, *ISAbal-bla*<sub>ADC-162-*trpA*</sub> and *ISEcp1-bla*<sub>CT14-IS903-*bla*<sub>CMY-2-bla</sub>-*sugE*</sub> in *E. coli* implies the transmission of *bla*<sub>ADC-162</sub> and *bla*<sub>CMY-2</sub> genes via IncF plasmids. These sequences suggest the potential for widespread outbreaks linked to these genotypes [73]. Conversely, a study from Southern China indicated that the dissemination of *bla*<sub>CTX-M-55</sub> genotypes among human populations was facilitated by IncI1 and IncFII plasmids and mobile elements such as *ISEcp1* and *IS26*.

Most plasmid-mediated *bla*<sub>CTX-M-55</sub> gene-carrying strains belong to the high-risk ST1193 clone. These factors have been identified as primary contributors to the widespread distribution and prevalence of *bla*<sub>CTX-M-55</sub> genotypes [74]. Further adding to the complexity, *bla*<sub>CTX-M-55</sub>

carries the  $\Delta$ IS26- $\Delta$ ISEcp1-*bla*<sub>CTX-M-55</sub>- $\Delta$ orf477- $\Delta$ Tn2 structure in community isolates. These genes have been identified in the IncHI2/ST3 plasmid in *E. coli* ST8369; *ISEcp1* indicates that the gene might be transferred from chromosome to plasmid and subsequent community dissemination [69]. Shao et al. recently found that a significant proportion (83.3%) of clinical ESBL-producing *E. coli* isolates from Eastern China harbored IncF family-associated plasmids. Further analysis revealed *ISEcp1* (36.1%) and *IS903B* (19.4%) elements in these isolates. Single nucleotide polymorphism (SNP) analysis established that seven isolates exhibited genetic variations indicative of a common clone [71]. Most plasmids found in isolates from community and health populations showed similar insertion sequences and nearly identical plasmid profiles, suggesting significant dissemination of ESBL genes in both populations. The high prevalence of the *bla*<sub>CTX-M-55</sub> gene may be associated with these factors.

#### 4. Epidemiology and transmission of ESBL *E. coli* in the environment and food

Antibiotic-resistance bacteria (ARBs) and antibiotic-resistance genes (ARGs) are pervasive in various environments, including farms, urban areas, medical facilities, wastewater treatment plants (WWTPs), and water discharge points. Infected animals such as poultry and products from food animals such as meat and milk serve as sources for disseminating resistance genes. Similarly, using swine waste, such as manure, to enhance agricultural soil fertility has been identified as a significant contributor to environmental contamination [75]. *E. coli*, commonly found in the intestinal tract and as a member of coliform bacteria, can infiltrate and contaminate the surrounding environment, emerging as a notable environmental contaminant. For instance, a study on the prevalence of ESBL-producing *E. coli* in environmental water revealed a reservoir of ESBLs (12.5%) in river water [55]. Furthermore, ESBL-producing *E. coli* (4.0%) has emerged in water from wells in eastern China [47], while rivers and lakes in northwest China, particularly in Shaanxi Province, continue to serve as significant reservoirs of ESBL-producing *E. coli* [51]. Despite ongoing contamination of rivers and other water reservoirs by humans and animals alike, a small proportion of spring wells have displayed notable ESBL-producing *E. coli* incidence (81.3%), particularly in those near commercial areas [48]. Similarly, animal formation, including poultry and pig farming, can contaminate nearby rivers or act as a disseminator of ARGs. ESBL-producing *E. coli* exhibits 90% similarity to samples from nearby rivers [58]. In addition to these water sources, the food chain plays a pivotal role in disseminating ESBLs in the environment. A significant prevalence of ESBL-producing *E. coli* has been reported across various regions of China, including the eastern, western, northern, and southern parts. Remarkably, all isolates exhibited MDR, with most bacterial strains identified as ESBL-producing *E. coli*, isolated from sources such as meat, cold noodles, salad, and pasteurized milk [12,14].

The genotypic scenario of ESBL-producing *E. coli* exhibits a prevailing genotypic landscape in the environment, with the CTX-M group being particularly prominent. A comparative study reported a notable increase in the CTX-M group (14.4%), with the most prevalent genotypes being *bla*<sub>CTX-M-14</sub>, *bla*<sub>CTX-M-15</sub>, and *bla*<sub>CTX-M-55</sub>. This study revealed that CC10 is commonly found across animals, humans, and the environment. ST131, ST648, and ST38 have also been detected in environmental water and human samples, indicating their wide distribution [55]. Similarly, data from rivers, lakes, springs, and well water revealed a high prevalence of ESBL genotypes of *E. coli*, including *bla*<sub>CTX-M-15</sub>, *bla*<sub>CTX-M-14</sub>, *bla*<sub>CTX-M-55</sub>, and *bla*<sub>CTX-M-27</sub>. Furthermore, high-risk clones, such as ST131 in well and spring water and ST10 and ST131 in lakes and rivers, underscore the significance of these environments as reservoirs [48,51]. Nearby pit latrines may contaminate well water in rural areas. Specifically, 22 well water isolates (95.6%) and 37 pit latrine wastewater isolates (92.5%) carried



*bla*<sub>CTX-M</sub> genes along with the *bla*<sub>TEM-1</sub> genotype. The phylogenetic profile of ESBL-producing *E. coli* from well water and pit latrine also showed similarities, with 39.1% and 26.1% of *E. coli* from well water belonging to Groups A and B1, respectively, compared to 32.5% and 22.5% from wastewater. These findings prove that pit latrine contamination impacts well water [49]. In some regions of China, reports have indicated substantial amounts of ESBL-producing *E. coli* in urban wastewater, significantly contributing to environmental ESBL spread through river discharge. A high prevalence of the CTX-M group, mainly *bla*<sub>CTX-M-14</sub> and *bla*<sub>CTX-M-15</sub> genotypes carried by the same STs (ST155 and ST405), has also been observed in this context [52]. Zou et al. comprehensively demonstrated the interconnectedness of animals, humans, and the environment in disseminating resistance genes. The CTX-M-9 group was the most frequently observed, with ST10 being common across all source samples. The most prevalent genotype was *bla*<sub>CTX-M-14</sub>, followed by *bla*<sub>CTX-M-65</sub>, *bla*<sub>CTX-M-55</sub>, *bla*<sub>CTX-M-15</sub>, *bla*<sub>CTX-M-27</sub>, and *bla*<sub>CTX-M-3</sub>. Pig feces and various environmental sources, including human waste, bird feces, river water, river sediment, and vegetables, predominantly carried the *bla*<sub>CTX-M-14</sub> gene. Drinking water, soil, and outlet sediment exhibit a higher occurrence of *bla*<sub>CTX-M-65</sub>, whereas *bla*<sub>CTX-M-55</sub> is prevalent in *E. coli* [53]. The food chain also plays a pivotal role in disseminating ARGs in humans and the environment. In particular, ready-to-eat meat has been identified as a significant source within the food chain. A study conducted in a local market found ESBL-producing *E. coli* strains in 64 of 720 ready-to-eat meat and vegetable samples. Various resistance genes, including *bla*<sub>SHV</sub> (9.4%), *bla*<sub>TEM</sub> (7.8%), *bla*<sub>CTX-M-15</sub> (1.6%), and *bla*<sub>CTX-M-9</sub> (1.6%), were prevalent in these samples [13]. Another study across different regions in China reported ESBL-producing *E. coli* strains in ready-to-eat food, including meat, noodles, and roasted meat. *bla*<sub>TEM</sub> was the most frequently identified  $\beta$ -lactam resistance gene, occurring in 43.6% of the strains. After *bla*<sub>TEM</sub>, the *bla*<sub>CTX-M</sub> gene was detected in 13.4% of the strains, and the *bla*<sub>OXA</sub> gene was detected in 7.9%. Among *bla*<sub>CTX-M</sub> genotypes, *bla*<sub>CTX-M-14</sub>, *bla*<sub>CTX-M-55</sub>, *bla*<sub>CTX-M-15</sub>, *bla*<sub>CTX-M-65</sub>, *bla*<sub>CTX-M-132</sub>, and *bla*<sub>CTX-M-32</sub> were the most commonly identified [12].

A comparative analysis between human waste and well water, showed the FIB replicon in 50% of wastewater and 60% of well water samples. FIA and IncI1 replicons were also detected in the same samples. Seven samples from both sources displayed 100% genetic similarity through enterobacterial repetitive intergenic consensus (ERIC)-polymerase chain reaction (PCR) fingerprints, suggests a potential transmission pathway from wastewater to the well [49]. Recent studies have provided insights into the prevalence of ESBL-producing *E. coli* among hospital personnel and the environment. Genomic investigations revealed that positive samples harbored *bla*<sub>CTX-M</sub> genes. In contrast, five samples demonstrated a significant resemblance, as determined by SNP analyses, indicating a common origin. These samples were collected from diverse sources, including patients, staff members, and the environment. Furthermore, *bla*<sub>CTX-M</sub> genes exhibited a wide diversity and were detected in multiple locations within the chromosome and various plasmids. The identified *bla*<sub>CTX-M</sub>-bearing plasmid lineages were found in numerous STs across the surveillance, staff, and clinical collections. A more detailed analysis of *ISEcp1*-*bla*<sub>CTX-M</sub> transposition units provides insights into their transmission mechanisms. This study provides evidence supporting the acquisition of chromosomal copies of *bla*<sub>CTX-M</sub> genes from distinct plasmid lineages and the transfer of *bla*<sub>CTX-M-55</sub> from an ST1193 chromosome to a smaller mobilizable plasmid. These findings raise concerns about potential community contamination and the environment outside the hospital [76].

## 5. Epidemiology and transmission of ESBL *E. coli* in animals

ESBL emergence in China's poultry sector began around 2004 [18]. Subsequently, there has been a notable increase in the occurrence of

ESBL-producing *E. coli* in the Chinese poultry sector, with prevalence rates from 63.8% in 2016 to 67.0% in 2019 [77]. Similarly, the frequency of ESBL-producing *E. coli* in animal populations, particularly in dairy and swine, has significantly increased: 19.5% in dairy animals and 75.4% in swine [57,78]. In addition to farm animals, a high prevalence of ESBL-producing *E. coli* (42.7%) has been reported in zoo wildlife, including peacocks, gibbon monkeys, alpaca, Phoenicopteridae, black hat hanging monkeys, swan, squirrel monkeys, and guinea fowl [46]. Recent findings from Shandong Province reveal that ESBL-producing *E. coli* in companion animals, such as cats and dogs, reaches as high as 43.0%, encompassing healthy and diseased animals [37]. Most studies have consistently reported a notable prevalence of ESBL-producing *E. coli* in the animal sector, indicating the widespread distribution of *E. coli* [15,16]. These findings highlight the potential for transmitting ARGs from animals to humans and the broader environment.

ESBL genotypes in the animal sector exhibit considerable variability among distinct animal species. Notably, specific genotypes have been consistently identified in certain poultry sectors within central China [17]. For instance, *bla*<sub>TEM</sub> ( $\beta$ -lactamase) + *bla*<sub>CTX-M</sub> (74.4%) and *bla*<sub>CTX-M</sub> + *bla*<sub>SHV-12</sub> (3.0%) genotypes are frequently observed. Among the *bla*<sub>CTX-M</sub> group, *bla*<sub>CTX-M-55</sub> (48.4%) was the most common genotype, followed by *bla*<sub>CTX-M-14</sub> (11.0%) and *bla*<sub>CTX-M-15</sub> (8.0%) [77]. Mastitic cows also harbor ESBL genotypes, with the *bla*<sub>CTX-M</sub> group being predominant, particularly with *bla*<sub>CTX-M-15</sub>. However, many ESBL producing strains found to carry either *bla*<sub>TEM</sub> or *bla*<sub>SHV</sub> genes individually or coharboring [57], suggesting that mastitic cows can be vectors for disseminating resistance genes into the surrounding environment. The same ESBL genotypes, such as *bla*<sub>CTX-M-14</sub>, *bla*<sub>CTX-M-15</sub>, *bla*<sub>CTX-M-17</sub>, and *bla*<sub>CTX-M-55</sub>, have been detected in fecal and meat samples, often associated with high-risk clones, such as ST398 (ST398cplx) and ST7130, indicating ARGs dissemination [22]. Sheep, similar to cows, exhibit a significant occurrence of *bla*<sub>CTX-M</sub> and *bla*<sub>TEM</sub> ( $\beta$ -lactamase) genotypes in ESBL-producing *E. coli* strains responsible for causing diarrhea. These strains also carry high-risk *E. coli* clones, including ST10, ST23, ST44, and ST58. [30]. In a comparative analysis of food animals, including swine, chickens, and cattle, the *bla*<sub>TEM</sub> ( $\beta$ -lactamase) genotype exhibited the highest frequency (99.2%), followed by *bla*<sub>SHV</sub> ( $\beta$ -lactamase) (2.6%) and *bla*<sub>CTX-M</sub> (34.2%), as the most prevalent ESBL genotypes. ST48 was frequent among all pigs, cattle, and chickens. Within the CTX-M group, *bla*<sub>CTX-M-55</sub> was the most prevalent genotype (77%) [78]. Dogs, both pets and strays, have also been documented as carriers of ESBL-producing *E. coli*. For instance, Liu et al. observed a high prevalence of *bla*<sub>CTX-M</sub>, *bla*<sub>TEM-1</sub> (broad spectrum), and *bla*<sub>OXA-48</sub> genotypes in diseased dogs, whereas Sun et al. found that *bla*<sub>CTX-M-15</sub>, *bla*<sub>CTX-M-55</sub>, and *bla*<sub>CMY</sub> were the dominant genotypes in stray dogs [42,43]. Wild animals like pandas and rats can exhibit ESBL-producing *E. coli*. These organisms have demonstrated a significant frequency of ESBL genotypes. A recent study has revealed *bla*<sub>CTX-M</sub> and *bla*<sub>CMY</sub> genes in giant pandas, whereas wild rodents, including brown and black rats, exhibit a high prevalence of *bla*<sub>CTX-M-1</sub> and nine groups [45].

In China, studies have proposed that ESBL genes, notably *bla*<sub>CTX-M</sub>, may have originated from *Kluyvera* spp. through multiple mobilization events or the mutation of other *bla*<sub>CTX-M-1</sub> group genes, such as *bla*<sub>CTX-M-3</sub> and *bla*<sub>CTX-M-15</sub>. This hypothesis is supported by observed spacer region variations between the right inverted repeats and *bla*<sub>CTX-M-1</sub> group genes. For instance, isolates from the same source exhibited different spacer lengths. These include 127 bp upstream of *bla*<sub>CTX-M-3</sub>, 48 or 127 bp upstream of *bla*<sub>CTX-M-15</sub>, and 45, 48, or 127 bp upstream of *bla*<sub>CTX-M-55</sub>. Distinct intergenic regions between *bla*<sub>CTX-M-55</sub> genes and the *ISEcp1* insertion sequence provide further evidence of gene dissemination [79]. Some studies have noted the *bla*<sub>CTX-M</sub> genotype in chickens, ducks, and pets, indicating a common origin and potential transmission between these animals via humans through plasmids. The predominant CTX-M types were detected in pet and poultry iso-

lates. Specifically, isolates from ducks contained F2:A:B- and IncN plasmid types, whereas pet-originating isolates had F2:A:B- or F33:A:B- plasmid types, with structural similarities. The dissemination of *rmtB* and *bla*<sub>CTX-M</sub> genes in *E. coli* isolates from poultry and pets is attributed to similar F2:A:B and F33:A:B-plasmids [16]. Moreover, the rapid transmission of *bla*<sub>CTX-M-55</sub> in animals can also be attributed to plasmid-mediated mechanisms. Zhang et al. found that IncN and IncFII plasmids are involved in the dissemination. The genetic architecture of the *bla*<sub>CTX-M-55</sub> gene, particularly IS26-ΔISEcp1-*bla*<sub>CTX-M-55-orf477</sub> (similar to that discussed earlier in ESBL in patients and the health population of China) reveals three separate spacer sequences located between the ISEcp1 and *bla*<sub>CTX-M-55</sub> genes, providing valuable insights into the mechanisms governing the dissemination of this gene [80]. Outer membrane vesicles are also considered a factor facilitating the dissemination of *bla*<sub>CTX-M-55</sub>. The horizontal gene transfer of *bla*<sub>CTX-M-55</sub> on the IncI2 plasmid is facilitated by outer membrane vesicles in avian-derived *E. coli* [81]. The *bla*<sub>CTX-M-55</sub> genotype is predominantly present in animal populations, and recent studies have also identified this gene in humans. With the concept of One health in mind, it is anticipated that this genotype will continue to spread, posing significant challenges for researchers in terms of epidemic control.

## 6. Intersectoral transmission of ESBLs between humans, animals, and the environment

Many associated factors among humans, animals, and the environment permit the dissemination of various pathogens and facilitate the transmission of mobile genetic elements carrying ARGs (Fig. 2). Soil, water, livestock, and plant foods are directly or indirectly exposed to antibiotics due to agricultural use or contamination. In China, the spread of ESBL-producing *E. coli*, specifically those within the CTX-M group, has been documented across humans, animals, and the environment. Investigation into the transmission of ESBL genotypes by *E. coli* between animals and humans using MLST and ERIC profiling has revealed that humans and animals exhibit similar ESBL genes and profiles of antibiotic resistance [34]. ESBL genotypes, including *bla*<sub>CTX-M-14</sub>, *bla*<sub>CTX-M-15</sub>, and *bla*<sub>CTX-M-55</sub>, observed among individuals in community and hospital settings [67], are also detected in the environment, particularly in rivers and lakes [51]. Furthermore, identical ESBL genotypes, such as *bla*<sub>CTX-M-14</sub>, *bla*<sub>CTX-M-15</sub>, and *bla*<sub>CTX-M-55</sub> in poultry farms and the adjacent rivers suggest potential transmission of these genotypes across different sectors [58].

Similarly, the transmission of high-risk clone STs, notably ST131, predominantly occurs among humans, primarily within hospital patient populations [70], and in environmental contexts, mainly through water sources [50]. This serves as the primary medium for dissemination. A comparative analysis of ESBL-producing *E. coli* within these domains employing molecular homology via phylogenetic grouping, pulsed-field gel electrophoresis (PFGE), and MLST has revealed a commonality in *E. coli* isolates across humans and environmental water sources. Four STs, (B2-ST131, D-ST648, D-ST38, and A-CC10) are consistently identified in these isolates. These strains share the same genes, such as *bla*<sub>CTX-M</sub> [55]. Moreover, ST10 transmission among animal populations [51] and the environment could facilitate intersectoral transmission. Several studies have reported ST10 across various sample types, including pig feces, wastewater, drinking water, river water, and river sediment. Furthermore, PFGE analysis has indicated that plasmid and ST10 the high risk clone may represent the essential mechanism of *bla*<sub>CTX-M</sub> gene dissemination in the area. Multiple groups, each comprising two or more isolates, have been identified, often containing isolates from diverse environmental sources [53]. A comparative analysis between human and avian samples has also found a high degree of genetic similarity. MLST and SNP analyses have demonstrated genetic similarity and ST156, ST155, ST10, ST167, and ST226 in human and chicken samples [82].

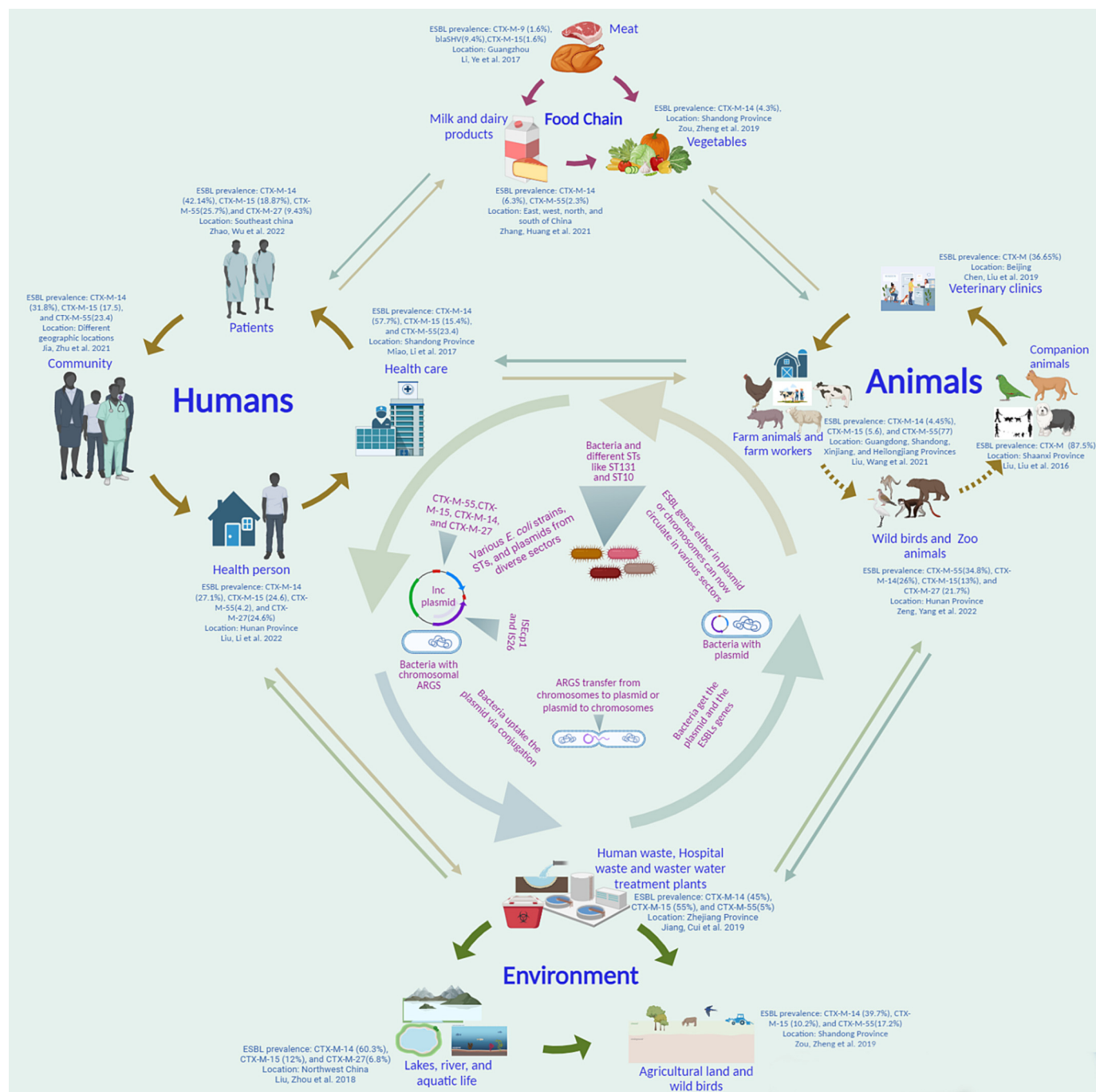
The spread of ARGs among *E. coli* isolates in food-producing animals has been observed due to the cotransferability of *oqxAB* and *bla*<sub>CTX-M</sub> genes mainly carried on IncF plasmids [83]. However, the widespread distribution of ESBL genes in the environment setting can be attributed to intratransmission dynamics. One study has shed light on the role of pit latrines, wastewater, and neighboring well water contributing to the dispersal of ESBL genotypes. This research unveils identical ESBL genes belonging to phylogenetic groups A and B1, and plasmid replicon types FIB (occurring at 60.1%) and replicon IncI1 (occurring at 43.5%). Furthermore, extensive dispersion of ESBL-producing *E. coli* isolates has been confirmed through genetic relatedness analysis, employing ERIC-PCR fingerprints [49].

However, plasmid F33:A:B is a mobilization vehicle for the plasmid-mediated resistance gene. IS26 and IS1294 elements carried by the same plasmid possess the capacity to capture and mobilize ARGs. After the conjugation assay, these elements could also acquire fragments from other plasmids carrying genes related to plasmid replication, stability, or unknown functions. This mechanism represents an efficient means for disseminating resistance genes [84]. Studies have also reported that the plasmid might broaden its repertoire of resistance genes during the conjugation phase [85]. Specific plasmids, such as IncHI2/ST3 coharboring ESBL genotypes along with *mcr-1* and *oqxAB*, can expedite horizontal gene transfer, potentially contributing to the dissemination of ESBL genotypes [86]. Specifically, the IncHI2 plasmid with ΔIS26-*bla*<sub>CTX-M-14</sub>-ΔIS903B insertion sequence in *E. coli* ST6802 and ST48 isolates from swine waste has been identified as highly conjugative and genetically stable, suggesting the potential transmission of ESBL genotypes from animals to environmental reservoirs [87].

Insertion sequences, such as ISEcp1-mediated transposition, have played a vital role in spreading *bla*<sub>CTX-M-64</sub> genes among various plasmids and chromosomes. The Tn1721-like structure mobilizes *bla*<sub>CTX-M-27</sub> carrying genes within Enterobacteriaceae, particularly in *E. coli* and *Salmonella* spp. [88,89]. Interestingly, when examining *bla*<sub>CTX-M-27</sub> in F24:A:B1(IncF) plasmids within *E. coli* isolates from swine, Tn3-like transposon is interrupted by the Tn2 region. This interruption, facilitated by Tn2, has contributed significantly to the dissemination of the *bla*<sub>CTX-M-27</sub> gene and also stabilized the plasmid [90]. An in-depth investigation into plasmids revealed that IncI1 and IncF18:A:B1 plasmids from avian *E. coli* isolates exhibit a mosaic mobile resistance region (MRR). This region consists of various transposons flanked by IS26 elements, carrying a combination of antibiotic resistance and virulence determinants. IS26 and IS1 elements have emerged as pivotal components in the assembly and evolution of MRRs within plasmids. These elements played a role in the mobility of virulence determinants, underscoring their importance in disseminating resistance genes and virulence determinants [91]. Plasmids such as F18:A:B1 are adept at facilitating horizontal gene transfer and clonal spread. The dissemination of *bla*<sub>CTX-M-55</sub>, alongside the cooccurrences of other resistance genes such as *tetA*, *floR*, *fosA3*, *aadA5*, *CmlA*, and *InuF*, intensifies the selection of resistance traits and expedites the transmission of *bla*<sub>CTX-M-55</sub> in *E. coli* [92]. Studies frequently report the clonal transmission of *bla*<sub>CTX-M-55</sub>-positive *E. coli* across three domains: humans, animals, and the environment. This transmission is often accompanied by the simultaneous transfer of *fosA*, *mcr*, *bla*<sub>NDM</sub>, and *tet(X)* genes. The widespread presence of IncI1 and IncI2 in various hosts from diverse sources indicates that this specific plasmid region facilitates the extensive dissemination of *bla*<sub>CTX-M-55</sub>-positive *E. coli* [93].

## 7. Conclusion

ESBL-producing *E. coli* has become a widespread concern in China, with its presence in humans, animals, and the environment. The dissemination of ESBL-producing *E. coli* is enhanced by various physical



**Fig. 2.** Intersectoral transmission of ESBP genes, such as the CTX-M group, among humans, animals, and the environment. *bla*<sub>CTX-M</sub> genotypes from different geographic locations transfer intersectorally. The Inc plasmid and IS26 and IS1 elements are prevalent in all sectors. These elements are crucial in the mobilization and evolution of ARGs. Abbreviations: ESBP, extended-spectrum  $\beta$ -lactamase; ARGs, antibiotic-resistance genes; STs, sequence types; ESBP, Extended-spectrum  $\beta$ -lactamase; *E. coli*, *Escherichia coli*; Inc, incompatibility.

and genetic factors, significantly contributing to its proliferation. Physical factors play a substantial role in this scenario. These factors encompass extensive antibiotic use in human and animal agriculture, leading to the selection of antibiotic-resistant strains. ARBs in animal feces also serve as a reservoir for the further spread of ESBP-producing *E. coli*. Furthermore, the close contact between humans and animals, especially in agricultural settings, facilitates the transmission of these bacteria. On the genetic front, the dissemination of ESBP genes is greatly influenced by STs and the transmission of plasmids. In particular, plasmids play a pivotal role, as they serve as a significant mechanism for the horizontal gene transfer of ESBP genes. This genetic

exchange accelerates the spread of antibiotic resistance. The consequences of the widespread dissemination of ESBP-producing *E. coli* are profound. This renders infections caused by these bacteria challenging to manage due to their resistance to commonly used antibiotics. As a result, the healthcare system faces increasing difficulties in treating such infections, leading to a higher burden on patients and healthcare providers. In light of these challenges, it is imperative to implement measures to mitigate the dissemination of ESBP-producing *E. coli*. These measures include the prudent and judicious use of antibiotics in human healthcare and animal agriculture. Adopting practices that minimize exposure to animal feces, such as improved



hygiene and waste management, can help curb the spread of these bacteria. In conclusion, the widespread presence of ESBL-producing *E. coli* in China demands a comprehensive and multifaceted approach. Addressing both physical and genetic factors and tailoring strategies to individual sectors can mitigate the dissemination of these ARBs and safeguard public health.

### Conflict of interest statement

The authors declare that there are no conflicts of interest.

### Author contributions

**Sayyed Salman:** Data curation, Writing – original draft. **Zeeshan Umar:** Writing – review & editing. **Yonghong Xiao:** Supervision, Conceptualization, Methodology.

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