Review Article

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ESBL genes in *Escherichia coli* in One Health perspective, molecular evidence, and transmission routes

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ABSTRACT

Antimicrobial resistance (AMR) caused by Extended Spectrum β-Lactamase (ESBL)-producing bacteria has emerged as a major global public health threat, involving complex interactions among humans, animals, and the environment. Among ESBL-producing pathogens, *Escherichia coli* is recognized as one of the most important bacteria due to its remarkable genetic adaptability, which facilitates the widespread dissemination of β-lactam resistance genes through horizontal gene transfer mechanisms. This review aims to examine the molecular evidence of ESBL genes in *E. coli*, the characteristics of high-risk clones, mobile genetic elements involved in dissemination, and transmission pathways from a One Health perspective. Evidence from numerous studies demonstrates the predominance of the bla_{CTX-M} gene family, particularly the CTX-M-15 variant, in *E. coli* isolates derived from humans, food-producing animals, companion animals, wildlife, and environmental sources. High-risk clones such as ST131 and ST1193 play a crucial role in the global spread of ESBLs because of their strong colonization capacity, persistence, virulence, and ability to accumulate multiple antimicrobial resistance determinants. Furthermore, the interplay between antimicrobial usage, ecosystem dynamics, and the mobility of genetic elements such as plasmids, transposons, and integrons accelerates the cross-sector dissemination of ESBL-producing *E. coli*. These findings highlight the urgent need for integrated control strategies based on the One Health framework, including molecular surveillance, rational antimicrobial stewardship, and strengthened environmental management, to sustainably mitigate the spread and impact of antimicrobial resistance worldwide.

Introduction

Antimicrobial resistance (AMR) has become one of the most serious global health threats, with an estimated 929,000 deaths reported worldwide in 2019 associated with six major resistant pathogens, namely *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* (Antimicrobial Resistance Collaborators, 2022; Tyasningsih *et al*., 2019). Among these pathogens, *E. coli* is of particular concern due to its widespread distribution in humans, animals, food products, and the environment, making it an important indicator organism in antimicrobial resistance studies. Extended-Spectrum β-Lactamase (ESBL)-producing *E. coli*, together with other members of Enterobacteriaceae, is recognized as one of the major causes of resistance to broad-spectrum β-lactam antibiotics (Wibisono *et al*., 2020a).

Extended-Spectrum β-Lactamase (ESBL) is an enzyme capable of hydrolyzing oxyimino-β-lactam antibiotics, including third-generation cephalosporins, thereby reducing the effectiveness of primary therapies used for severe infections in both human and veterinary medicine. The emergence of ESBL is primarily associated with mutations and acquisition of resistance genes such as bla_{CTX-M}, bla_{TEM}, and bla_{SHV} (Wang *et al*., 2023; Palmeira and Ferreira, 2020). Among these, the bla_{CTX-M} gene family has become globally dominant, particularly the CTX-M-15 variant, which is strongly associated with outbreaks and severe extraintestinal infections in both human and animal populations (Carvalho *et al*., 2020; Matsumura *et al*., 2015). The increasing predominance of CTX-M-type β-lactamases reflects the importance of molecular evidence in understanding the epidemiology and evolution of ESBL genes in *E. coli*.

From a One Health perspective, ESBL-producing *E. coli* represents a cross-ecosystem problem involving humans, animals, and the environ-

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ment. The One Health concept highlights the interconnectedness of these sectors in the emergence and dissemination of resistant bacteria (Agustin *et al*., 2025; Khairullah *et al*., 2025). ESBL-producing bacteria, including *E. coli*, are considered zoonotic pathogens that may be transmitted to humans through the food chain, direct animal contact, and environmental exposure. In addition to causing urinary tract infections, especially in immunocompromised or vulnerable individuals (Ramos *et al*., 2020; Kendek *et al*., 2024), pathogenic *E. coli* strains may also produce toxins that adversely affect human health (Effendi *et al*., 2018; Ansharieta *et al*., 2021).

The spread of ESBL-carrying *E. coli* across humans, animals, and environmental compartments is particularly alarming because plasmid-mediated horizontal gene transfer enables rapid dissemination of resistance genes between bacterial populations (Kawamura *et al*., 2017; Putra *et al*., 2019). The isolation of ESBL-producing *E. coli* from food-producing animals, as well as from hospital and community settings, confirms the role of animals and contaminated environments as important reservoirs and transmission vehicles for resistant bacteria (Mandujano-Hernández *et al*., 2024; Widodo *et al*., 2023).

Transmission pathways of ESBL-producing *E. coli* are highly complex and occur through both direct and indirect routes. These include nosocomial infections, gastrointestinal colonization, international traveler mobility, agricultural activities, wastewater systems, poultry production, and wildlife reservoirs (Husna *et al*., 2023; Bréchet *et al*., 2014). Migratory birds have been identified as potential long-distance carriers, with reported prevalence rates of 17% in Pakistan and 17.3%–38.18% in Bangladesh (Mohsin *et al*., 2017). Likewise, aquatic animals such as fish and shrimp may act as reservoirs of antimicrobial resistance genes, posing risks through the consumption of raw seafood (Sultan *et al*., 2022). Environmental contamination through hospital waste, wastewater treatment plant discharges, and agricultural runoff further contributes to the circulation of ESBL genes into natural ecosystems (Silva *et al*., 2019).

The prevalence of ESBL-producing *E. coli* remains high globally. In Southeast Asia, including Indonesia, studies reported that 15.8% of beef cattle fecal isolates carried the CTX-M gene, while 5.21% of dairy cattle rectal swab isolates were ESBL-positive, including CTX-M and TEM gene carriers (Sukmawinata, 2015; Sudarwanto *et al*., 2016). In South America, prevalence rates reached 43% in cattle and 47% in dogs (Benavides *et al*., 2021). Globally, approximately 25.4% of individuals carry ESBL-producing *E. coli* in their intestinal tract, with prevalence rates of 23.4% in healthy communities and 27.7% in healthcare facilities (Ng *et al*., 2025). Similar findings have been reported in pet animals and livestock, including Bangladesh, where the prevalence reached 41.2% (Bezabih *et al*., 2021; Salgado-Caxito *et al*., 2021; Rahaman *et al*., 2025). Therefore, this review aimed to comprehensively discuss the molecular evidence of ESBL genes in *E. coli*, highlight the role of high-risk clones and mobile genetic elements, and explore the major transmission routes from a One Health perspective.

HIGH-RISK *E. coli* clones

High-risk *E. coli* clones are a subgroup of *E. coli* that exhibit a remarkable ability to spread antibioresistance and cause serious disease. Table 1 summarizes the major high-risk *E. coli* clones implicated in the global dissemination of ESBL genes across human, animal, and environmental sectors within the One Health framework. The most frequently reported lineages are ST131, ST69, ST10, ST405, ST38, ST95, ST648, ST73, and ST1193, which have been detected in hospital- and community-associated infections (Manges *et al*., 2019; Shaik *et al*., 2017; Mazumder *et al*., 2021; Peirano *et al*., 2022). *E. coli* clones are characterized by several key features, namely, global distribution, recognition of multiple antimicrobial resistance determinants, colonization ability and long persistence in the host (>6 months), effective transmission between hosts, increased pathogenicity and fitness, and the ability to cause recurrent or severe infections (Kocsis *et al*., 2022). *E. coli* clones are not only found in human clinical settings but can also circulate in animals and the environment. *E. coli* exhibits high genomic plasticity, enabling the acquisition of resistance genes through plasmids, integrons, and other genetic elements, contributing to the evolution of diverse clones with complex resistance profiles (Abdalla *et al*., 2025).

High-risk clones are generally identified based on whole genome sequencing (WGS) analysis, which reveals specific genetic patterns, including the presence of resistance genes such as CTX-M, NDM carbapenemase genes, OXA-48, and mutations in antibiotic targets such as fluoroquinolones (Mendes *et al*., 2022; Benulič *et al*., 2020). Several *E. coli* clones have been identified as high-risk clones internationally based on their widespread distribution and association with high levels of resistance, particularly in clinical isolates. The most dominant clone globally is ST131. ST131 is a prime example of a high-risk clone and has been recorded as dominant in multiple countries (Li *et al*., 2023). This clone typically belongs to the B2 phylogroup and is frequently associated with

Table 1. Major high-risk *E. coli* clones associated with ESBL dissemination in a One Health perspective.

Clone / Sequence Type (ST)	Main characteristics	Resistance profile / Key genes	Main sources	Clinical and One Health significance	References
ST131	Most globally dominant high-risk clone; phylogroup B2; high colonization and persistence	CTX-M, especially CTX-M-15 and CTX-M-27; fluoroquinolone resistance	Humans, environment, and animals	Major cause of recurrent UTI, bloodstream infections, nosocomial and community outbreaks	(Li *et al*., 2023; Chen *et al*., 2019; Mathers *et al*., 2015)
ST1193	Emerging globally important clone; strong virulence and gut persistence	Fluoroquinolone resistance; ESBL genes	Mainly humans and community infections	Important in community-acquired infections and therapeutic failure	(Pitout *et al*., 2023; Mazumder *et al*., 2022)
ST69	Widely distributed extraintestinal pathogenic clone	ESBL-associated genes and multidrug resistance	Humans and animals	Associated with UTI and invasive infections	(Manges *et al*., 2019; Shaik *et al*., 2017)
ST10	Broad ecological distribution	CTX-M and other ESBL genes	Humans, livestock, and environment	Important clone in cross-sector transmission	(Kocsis *et al*., 2022)
ST73	Highly pathogenic lineage	ESBL and fluoroquinolone resistance	Humans and companion animals	Frequently associated with UTI	(Pitout *et al*., 2023)
ST405	Internationally disseminated clone	CTX-M, carbapenemase-associated resistance	Humans and hospitals	Important hospital-associated MDR clone	(Mazumder *et al*., 2021)
ST648	Zoonotic and environmental distribution	ESBL and carbapenem resistance	Humans, poultry, and environment	One Health transmission concern	(Shaik *et al*., 2017)
ST155	Cross-sector clone	CTX-M-15 dominant	Humans, poultry, and environment	Supports inter-sector spread	(Acharya *et al*., 2025)
ST2179	Poultry-associated dominant clone	ESBL-producing lineage	Poultry	Important reservoir in animal sector	(Acharya *et al*., 2025)

fluoroquinolone resistance and the production of extended-spectrum β-lactamases such as CTX-M. The C1-M27 subclade of ST131 has also been reported globally and has been shown to play a significant role in the spread of the β-lactamase CTX-M-27 (Chen *et al*., 2019). The ST131 clone exhibits substantial genetic diversification with multiple clades and subclades, suggesting continuous evolution through the acquisition of chromosomal and plasmid mutations that extend its resistance to multiple antibiotic classes (Mathers *et al*., 2015).

The emerging clone ST1193 has emerged as an increasingly important high-risk clone, particularly in community-acquired infections, and contains a potent combination of resistance genes and virulence factors. This clone is often resistant to fluoroquinolones and can persist in the gut for extended periods. In addition to ST131 and ST1193, several other clones have also been identified as high-risk clones, although their prevalence varies by geographic location and isolate source (Pitout *et al*., 2023). These clones include ST10, ST69, ST73, ST405, ST410, ST457, and several other clones frequently associated with ESBL production, carbapenem resistance, or other combinations of resistance profiles (Kocsis *et al*., 2022; Al Mir, 2020).

Based on cross-sector surveillance results using Whole Genome Sequencing, of the 100 ESBL-producing *E. coli* isolates analyzed, the majority still showed sensitivity to imipenem (98%), meropenem (94%), and tigecycline (94%), but six isolates from poultry were identified as resistant to colistin with MIC values ≥ 4 µg/mL. Genomic analysis revealed a high level of genetic diversity with the discovery of 56 sequence types (STs), including three novel STs. The ST131 clone was the most dominant with seven isolates originating from humans and the environment, followed by ST2179 with six isolates all originating from poultry, and ST155 with five isolates found in humans, poultry, and the environment (Acharya *et al*., 2025). All eight *E. coli* phylogroups were detected, with 86% of the isolates belonging to phylogroups A, B1, B2, and D. Of the total isolates, 98 carried the CTX-M gene, with the CTX-M-15 allele being the most dominant (76%). AmpC-type ESBL genes were detected in four isolates and OXA-type β-lactamases in six isolates, while the NDM-5 carbapenemase gene was found in two imipenem-resistant human isolates. The coexistence of more than one β-lactamase gene was reported in 26% of isolates, reflecting the accumulation of resistance determinants in a single strain and strengthening the evidence of the spread of ESBL *E. coli* clones across human, animal, and environmental sectors in a One Health perspective (Soncini *et al*., 2022).

The presence of these clones strengthens the evidence for cross-sectoral transmission, which increases the risk of resistant infections spreading from animals to humans and vice versa. *E. coli*, as a gut commensal and a major pathogen, especially in urinary tract infections, becomes particularly dangerous when carrying ESBL genes because the resulting infections are associated with increased morbidity, mortality, and healthcare burden (Ramos *et al*., 2020). These data confirm that ESBL *E. coli* clones are not just a local resistance problem, but a global One Health threat involving animals, humans, and the environment through interconnected transmission pathways. The impact of the presence of *E. coli* clones that have spread globally, such as ST131-H30R and ST1193-H64, which exhibit high levels of antimicrobial resistance, significantly limits therapeutic options and potentially reduces treatment success (Mazumder *et al*., 2022; García-Meniño *et al*., 2022; de Cueto *et al*., 2017). According to Silva *et al*. (2023), *E. coli* clones that are pandemic globally and high-risk zoonotic clones have been reported in various types of food-producing animals, and a number of these clones are known to have spread across ecologies, including the environment and human populations.

Molecular evidence of esbl genes in *E. coli*

Extended-spectrum β-lactamase-producing Enterobacterales (ESBL-PE) are a group of bacteria that have developed resistance to various important antibiotics, including penicillins, cephalosporins, and monobactams, due to their ability to produce β-lactamase enzymes (Castanheira *et al*., 2021; Prayudi *et al*., 2023). These enzymes work by hydrolyzing the β-lactam ring, thereby eliminating the drug's antibacterial activity and reducing the effectiveness of clinical therapy, given that β-lactam antibiotics are widely used to treat infections caused by both Gram-positive and Gram-negative bacteria. ESBL-PE generally exhibits cross-resistance patterns to other antibiotic classes, such as fluoroquinolones, trimethoprim, and tetracyclines. ESBL-producing *E. coli* is one of the most frequently reported species and plays a significant role in the rise in cases of multiresistant infections (Mai and Espinoza, 2023). Table 2 demonstrates that CTX-M remains the most globally dominant ESBL gene, particularly in animal-associated isolates, while TEM predominates in several human clinical studies, indicating sector-specific molecular variation.

Comparison of ESBL phenotypes and genotypes in *E. coli* isolates from humans, animals, and the environment indicates a close relationship in antibiotic resistance patterns (Muleme *et al*., 2023). The emergence of ESBL variants, such as the CTX-M, SHV, and TEM genes, with distinct genetic signatures in environmental isolates indicates the evolutionary dynamics and exchange of resistance genes (Yu *et al*., 2024). These findings confirm that ESBL-producing *E. coli* are not only found in humans but also

Table 2. Molecular evidence of ESBL genes in *E. coli* across humans, animals, and environmental sources.

Country / Region	Source / Host	No. of isolates	ESBL prevalence / Confirmation	Dominant ESBL genes detected	Key findings	References
Malaysia	Broiler chicken farms	97	–	CTX-M (62.9%) and TEM (45.4%)	High prevalence in poultry-associated isolates	(Lemlem *et al*., 2023)
Egypt	Dogs and cats	167	35.5% ESBL-positive	Not specified	Companion animals act as potential reservoirs	(Kabay and Fındık, 2025)
South Korea	Dogs	56	–	CTX-M (73.2%)	High CTX-M carriage in companion animals	(Choi *et al*., 2023)
Global meta-data	Companion animals	–	16.20%	Predominantly CTX-M	Highest prevalence in pets compared to wildlife	(Di Marcantonio *et al*., 2025)
Global meta-data	Livestock and food	–	14.60%	Predominantly CTX-M	Important source in food chain transmission	(Di Marcantonio *et al*., 2025)
Global meta-data	Wildlife	–	7.00%	–	Lowest prevalence among sectors	(Di Marcantonio *et al*., 2025)
Nigeria (SE)	Human clinical samples	44*	–	TEM (93.2%), CTX-M (20.5%), and SHV (2.3%)	TEM gene highly dominant in human isolates	(Egwu *et al*., 2023)
United Kingdom	Human samples	27	88.8% phenotypically confirmed	–	Very high ESBL confirmation rate	(Ibrahim *et al*., 2023)
Nigeria	Human isolates	200	35.0% ESBL-positive	TEM, SHV, and CTX-M	Most isolates from nosocomial infections	(Nwafia *et al*., 2019)

Note: *estimated from percentage denominator in the study.

widely distributed in animals and the environment, reflecting cross-sectoral relationships and supporting the One Health concept in the spread of antimicrobial resistance. The CTX-M gene variant is reported to be the most dominant ESBL-encoding gene globally, in both humans and animals (Fonseca *et al*., 2022; Paulitsch-Fuchs *et al*., 2022).

According to Lemlem *et al*. (2023), in Malaysia a total of 97 *E. coli* isolates taken from broiler chicken farm samples, 62.9% of isolates have been detected CTX-M gene, while the percentage of the presence of TEM gene shows a percentage of 45.4%. Based on research by Kabay and Fındık (2025), in Egypt *E. coli* isolates obtained from dogs and cats showed a fairly high prevalence of ESBL production, from a total of 167 *E. coli* isolates analyzed, 35.5% of ESBL-positive *E. coli* isolates were confirmed as ESBL producers through confirmatory phenotypic tests. According to Choi *et al*. (2023), that in South Korea, the CTX-M gene was detected in 73.2% (41 of 56 bla_{CTX-M} carrier isolates) taken from dog isolates in *E. coli* bacteria. These findings indicate that ESBL-producing *E. coli* are commonly found in companion animals such as dogs and cats, potentially acting as reservoirs of antibiotic-resistant bacteria, which have important implications for animal and public health. According to Di Marcantonio *et al*. (2025), the prevalence of ESBL-producing *E. coli* in companion animals was 16.2%, followed by livestock and food sources at 14.6%, while the lowest prevalence was observed in wildlife at 7.0%.

According to Egwu *et al*. (2023), PCR analysis of human clinical samples in Southeastern Nigeria showed that 41 (93.2%) of ESBL-producing *E. coli* isolates carried the TEM gene, 9 (20.5%) of CTX-M, and 1 (2.3%) of SHV. According to Ibrahim *et al*. (2023), in the UK, testing results showed that 24 of 27 *E. coli* isolates (88.8%) isolated from human samples were phenotypically confirmed as ESBL-producing. According to Nwafia *et al*. (2019) in Nigeria, of a total of 200 *E. coli* isolates analyzed, 70 isolates (35.0%) were confirmed as ESBL producers, most of which, 53 isolates (75.7%), originated from nosocomial human infections. Genetic detection showed that the bla_{TEM}, bla_{SHV}, and bla_{CTX-M} genes were found in 66 isolates (94%). The distribution of identified ESBL genes included CTX-M in 26 isolates (37.14%), TEM in 7 isolates (10.0%), and SHV in 2 isolates (2.86%).

Genetic elements that facilitate spread

The emergence and spread of ESBL-producing *E. coli* is the result of complex, interconnected interactions between humans, animals, and the environment (Aworh *et al*., 2025; Fatokun *et al*., 2024). Selection pressure from the irrational use of antibiotics, particularly third-generation cephalosporins in human healthcare, plays a significant role in maintaining and expanding resistant bacterial populations, primarily through nosocomial transmission (Zamudio *et al*., 2024). This creates opportunities for ESBL-carrying bacteria to persist and spread within healthcare facilities, then spread to the community through various transmission routes (Castañeda-Barba *et al*., 2024; Cho *et al*., 2023). Table 3 illustrates the major sectors involved in the dissemination of ESBL genes and highlights the central role of mobile genetic elements, particularly plasmids, integrons, and transposons, in facilitating horizontal gene transfer.

In the livestock context, intensive production systems encourage selection for resistance through the use of antibiotics as prophylactic, therapeutic, and growth-promoting agents (Matheou *et al*., 2025; Trinchera *et al*., 2025). The livestock environment provides a conducive ecosystem for the persistence of resistant bacteria and the exchange of genetic material. Plasmids, transposons, and integrons act as the primary vectors that carry and transfer ESBL genes between bacteria, both within and across species (Motlhalamme *et al*., 2024; Ahmad *et al*., 2023). Through horizontal gene transfer mechanisms, resistance genes spread rapidly and efficiently within microbial populations (Xu *et al*., 2024; Liu *et al*., 2022).

Environmental factors amplify these dynamics, particularly through wastewater contamination, agricultural runoff, and antibiotic residues from industrial agriculture (Selvarajan *et al*., 2022; Apreja *et al*., 2022). Polluted environments serve as genetic recombination hotspots, where bacteria from different sources meet, facilitating the exchange of ESBL-carrying plasmids, integrons, and transposons (Gillieatt and Coleman, 2024; Smyth, 2023; Ahmad *et al*., 2022). These conditions make environmental ecosystems important reservoirs for resistance genes that can re-enter the food chain or infect humans and other animals.

Wildlife and companion animals also act as links between reservoirs (Ribeiro *et al*., 2024; Motlhalamme *et al*., 2024). Exposure to resistant bacteria through contaminated water and the environment allows wildlife to reflect resistance levels in natural ecosystems and act as vectors for transmission (Cho *et al*., 2023; Olaru *et al*., 2023). Meanwhile, the close interaction between humans and companion animals opens up opportunities for bidirectional resistance gene flow. These pathways emphasize that ESBL spread cannot be understood in isolation but rather requires a One Health approach that integrates human, animal, and environmental health aspects in efforts to control antimicrobial resistance.

Mutations and adaptations in esbl genes

β-lactam antibiotics are a group of antimicrobials that work by inhibiting bacterial cell wall biosynthesis by binding to penicillin-binding proteins (PBPs) (Dabhi *et al*., 2024; Martin *et al*., 2022; Ealand *et al*., 2018). PBP enzymes play a crucial role in the formation of peptidoglycan cross-links, which provide structural strength to bacterial cell walls (Zavala, 2018). Inhibition of PBP activity disrupts cell wall stability, leading to bacterial lysis and eventual death. The effectiveness of β-lactam antibiotics is highly dependent on the integrity of the β-lactam ring, a key structural component in binding to PBPs (Cho *et al*., 2014). Table 4 summarizes the key molecular events involved in ESBL-mediated resistance, beginning with the inhibition of penicillin-binding proteins by β-lactam antibiotics and followed by enzymatic hydrolysis through β-lactamases.

Table 3. Genetic elements and ecological factors facilitate the spread of ESBL genes in *E. coli* from a One Health perspective.

Sector / Reservoir	Key facilitating factors	Main genetic elements	Mechanism of spread	One Health significance	References
Human healthcare	Irrational antibiotic use, especially third-generation cephalosporins; nosocomial transmission	Plasmids, integrons, and transposons	Horizontal gene transfer, clonal spread in hospitals and communities	Maintains resistant strains and facilitates spillover into the community	(Zamudio *et al*., 2024; Castañeda-Barba *et al*., 2024; Cho *et al*., 2023)
Livestock production	Prophylactic, therapeutic, and growth-promoting antibiotic use; intensive farming	Plasmids, transposons, and integrons	Intra- and interspecies gene transfer	Major reservoir for resistant bacteria entering food chain	(Matheou *et al*., 2025; Trinchera *et al*., 2025; Ahmad *et al*., 2023)
Environment	Wastewater contamination, agricultural runoff, and antibiotic residues	ESBL-carrying plasmids, integrons, and transposons	Genetic recombination hotspots, horizontal gene exchange	Environmental reservoir and recirculation source	(Selvarajan *et al*., 2022; Apreja *et al*., 2022; Gillieatt and Coleman, 2024)
Wildlife	Exposure to contaminated water and habitats	Mobile genetic elements acquired from environment	Passive carriage and ecological dissemination	Indicator and vector of environmental AMR spread	(Ribeiro *et al*., 2024; Olaru *et al*., 2023)
Companion animals	Close human contact	Shared plasmids and ESBL genes	Bidirectional transmission	Human-animal bridge for resistance flow	(Motlhalamme *et al*., 2024; Cho *et al*., 2023)

The most dominant bacterial resistance mechanism to β-lactam antibiotics is the production of β-lactamase enzymes (Martin *et al*., 2022; Alfei and Schito, 2022). This enzyme is capable of hydrolyzing the amide bond in the β-lactam ring, thus altering the antibiotic's structure and losing its affinity for PBPs. Consequently, the β-lactam antibiotic becomes inactive and fails to inhibit bacterial cell wall synthesis (Dabhi *et al*., 2024; Abbas *et al*., 2022). β-lactamase production is a highly efficient defense mechanism and is commonly found in pathogenic Gram-negative bacteria (Gauba and Rahman, 2023; Alam *et al*., 2022).

Based on similarities in amino acid sequence and catalytic mechanisms, β-lactamases are classified into four main classes: A, B, C, and D (Avery *et al*., 2022; Pongchaikul and Mongkolsuk, 2022). Class A, C, and D β-lactamases are serine hydrolase enzymes that use serine residues in the active site to attack the β-lactam ring and form a covalent acyl-enzyme intermediate (Palzkill, 2018). In contrast, class B β-lactamases are metallo-β-lactamases that require one or two zinc ions as cofactors to activate water molecules, which directly participate in the hydrolysis process, bypassing the formation of an acyl-enzyme intermediate (Kaderabkova *et al*., 2022).

Class A β-lactamases play a significant role in the development of antibiotic resistance because they are often encoded by mobile plasmids (Palzkill, 2018). The presence of plasmids allows the β-lactamase-encoding gene to transfer between bacteria through conjugation, allowing rapid and widespread spread of resistance (Fang *et al*., 2024). Class A enzymes generally exhibit high hydrolytic activity against early-generation penicillins and cephalosporins, resulting in decreased effectiveness of these antibiotics in clinical therapy (Philippon *et al*., 2022).

Class A β-lactamases have a structure composed of β and α/β domains, with the active site located between the two domains (Eiamphungporn *et al*., 2018; Philippon *et al*., 2016). The catalytic process involves several conserved amino acid residues. The Ser70 residue functions as the primary nucleophile, attacking the carbonyl amide bond of the β-lactam ring (Agarwal *et al*., 2023; Salahuddin *et al*., 2018). The formation of the acyl-enzyme intermediate is stabilized by other residues such as Ser130, Asn132, and Ala237 through hydrogen bonding interactions (Minasov *et al*., 2002; Wang *et al*., 2006). The next step is desilation, which involves the activation of a water molecule by the Glu166 residue, releasing the hydrolyzed antibiotic from the enzyme's active site (Wong, 2022; Kaderabkova *et al*., 2022).

Extended-Spectrum β-Lactamase is a variant of class A β-lactamase that undergoes structural changes due to genetic mutations in specific residues around the active site, particularly in the omega loop region (Yi *et al*., 2016). These mutations do not alter core residues essential for catalysis, but instead increase the flexibility and volume of the enzyme's active site. These changes enable ESBL enzymes to accommodate and hydrolyze extended-spectrum β-lactam antibiotics, particularly third-generation cephalosporins such as cefotaxime and ceftazidime, which were previously relatively stable to hydrolysis by conventional β-lactamases (Palzkill, 2018; Paterson and Bonomo, 2005).

Esbl gene

Extended-Spectrum β-Lactamase (ESBL) genes are the primary genetic determinants responsible for bacterial resistance to β-lactam antibiotics, particularly broad-spectrum cephalosporins. The three most frequently reported ESBL gene families are cefotaximase (CTX-M), temoneira (TEM), and sulfhydryl variable (SHV), whose presence has been widely detected in pathogenic bacterial isolates, particularly Enterobacteriaceae (Wibisono *et al*., 2020b; Faridah *et al*., 2023). Table 5 summarizes the three major ESBL gene families, namely CTX-M, TEM, and SHV, which are the principal molecular determinants of β-lactam resistance in *E. coli*.

The SHV gene was initially associated with resistance to penicillin and early-generation cephalosporins, but some variants have undergone structural mutations that broaden the spectrum of their enzymatic activity. The β-lactamase enzyme produced by the SHV gene is capable of hydrolyzing third-generation cephalosporin antibiotics, such as cefotaxime and ceftazidime, thereby reducing the effectiveness of these antibiotics (Sulaiman *et al*., 2025). Mutations in the SHV-1 gene contribute to the emergence of ESBL phenotypes capable of overcoming broad-spectrum cephalosporins (Bharadwaj *et al*., 2022).

The CTX-M gene is currently reported to be the most dominant ESBL group globally. There are over 130 CTX-M enzyme variants grouped into five main clusters: CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, and CTX-M-25. Among these groups, CTX-M-15 is the most frequently found type in both hospital and community settings (Ghenea *et al*., 2022). The CTX-M gene is most commonly detected in *E. coli*, characterized by its hydrophilic nature and high affinity for cephalosporins, particularly cefotaxime, which is the basis for the name CTX (Wibisono *et al*., 2021). In addition to conferring resistance to β-lactams, plasmids carrying the CTX-M gene often carry additional resistance genes to other antibiotic classes, such as aminoglycosides, tetracyclines, sulfonamides, and trimethoprim. This allows for co-resistance, simultaneous gene expression, and cross-selection under antibiotic pressure. Most CTX-M-producing isolates also exhibit resistance to fluoroquinolones, further narrowing effective therapeutic options (Lahlaoui *et al*., 2014).

The TEM gene is a major contributor to β-lactam resistance in

Table 4. Molecular mechanisms, mutations, and adaptive changes in ESBL genes associated with β-lactam resistance in *E. coli*.

Component / Mechanism	Molecular description	Key residues / Elements	Functional impact	References
β-lactam antibiotics mode of action	Inhibit bacterial cell wall synthesis by binding to PBPs and preventing peptidoglycan cross-linking	β-lactam ring and PBPs	Causes cell wall instability, lysis, and bacterial death	(Dabhi *et al*., 2024; Martin *et al*., 2022; Cho *et al*., 2014)
β-lactamase-mediated resistance	Hydrolysis of β-lactam ring amide bond	β-lactamase enzyme	Inactivates antibiotic and prevents PBP binding	(Abbas *et al*., 2022; Gauba and Rahman, 2023)
Class A β-lactamase	Serine hydrolase enzyme; plasmid-mediated	Ser70, Ser130, Asn132, Ala237, and Glu166	Major mechanism of plasmid-borne resistance	(Palzkill, 2018; Fang *et al*., 2024)
Class B β-lactamase	Metallo-β-lactamase requiring Zn^{2+} ions	Zinc-dependent catalytic site	Direct hydrolysis via activated water molecule	(Kaderabkova *et al*., 2022)
Catalytic acylation	Initial nucleophilic attack on β-lactam ring	Ser70	Formation of acyl-enzyme intermediate	(Agarwal *et al*., 2023; Salahuddin *et al*., 2018)
Intermediate stabilization	Hydrogen bond stabilization	Ser130, Asn132, and Ala237	Stabilizes hydrolysis complex	(Minasov *et al*., 2002; Wang *et al*., 2006)
Deacylation / hydrolysis release	Water activation and release of hydrolyzed antibiotic	Glu166	Completes antibiotic inactivation	(Wong, 2022; Kaderabkova *et al*., 2022)
ESBL adaptive mutations	Mutations around active site, especially omega loop	Omega loop region	Enlarges active site and increases flexibility	(Yi *et al*., 2016)
Extended-spectrum adaptation	Enables hydrolysis of 3rd-generation cephalosporins	Mutated active-site architecture	Resistance to cefotaxime and ceftazidime	(Palzkill, 2018; Paterson and Bonomo, 2005)

Table 5. Major ESBL gene families in *E. coli* and their resistance characteristics.

ESBL gene family	Main variants / Clusters	Main antibiotic targets hydrolyzed	Key characteristics	Clinical significance	References
CTX-M	CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, CTX-M-25; CTX-M-15 dominant	Third-generation cephalosporins, especially cefotaxime and ceftazidime	Most globally dominant ESBL family; plasmid-mediated; frequently co-harbors resistance genes to aminoglycosides, tetracyclines, sulfonamides, and trimethoprim	Major driver of multidrug resistance in hospital and community settings	(Ghenea *et al*., 2022; Wibisono *et al*., 2021; Lahlaoui *et al*., 2014)
TEM	TEM-1, TEM-2, and TEM-3	Penicillins, first-generation cephalosporins; mutated variants hydrolyze extended-spectrum cephalosporins	Highly prevalent in Gram-negative bacteria; TEM-1 found in >90% of ampicillin-resistant *E. coli*	Important contributor to classical β-lactam resistance and ESBL evolution	(Lima *et al*., 2020; Ghafourian *et al*., 2015; Rostinawati *et al*., 2025)
SHV	SHV-1 and mutated ESBL variants	Penicillins, early cephalosporins, and third-generation cephalosporins after mutation	Initially narrow-spectrum; structural mutations expand hydrolytic activity	Associated with emergence of ESBL phenotype in Enterobacteriaceae	(Sulaiman *et al*., 2025; Bharadwaj *et al*., 2022)

Gram-negative bacteria. TEM β-lactamase enzymes belong to a family of enzymes capable of degrading β-lactam antibiotics, such as penicillins and cephalosporins. Some TEM variants are classified as ESBLs, with the main strains being TEM-1, TEM-2, and TEM-3 (Lima *et al*., 2020). TEM-1 is the most common variant, with more than 90% of ampicillin-resistant *E. coli* isolates known to carry the TEM-1 gene (Ghafourian *et al*., 2015). Functionally, TEM-1 has the ability to hydrolyze penicillin and first-generation cephalosporins, thus playing a significant role in mediating resistance to conventional β-lactam antibiotics. The role of TEM-1 in resistance to penicillin and early-generation cephalosporins has been widely recognized in various research reports (Rostinawati *et al*., 2025). Resistance to third-generation cephalosporins develops further when mutations occur in the TEM-1, TEM-2, or SHV-1 genes, resulting in new β-lactamase enzymes with a broader spectrum of activity (Bharadwaj *et al*., 2022).

Global health impact and implications of one health

The presence of ESBL-producing *E. coli* has a significant global health impact because it plays a role in serious, difficult-to-treat infections across a wide range of clinical and community settings. The high prevalence of ESBL-producing *E. coli* in humans, animals, and the environment demonstrates the widespread distribution of resistance genes such as CTX-M, TEM, and SHV across One Health sectors (Rahaman *et al*., 2025). The bacteria's ability to produce ESBL enzymes leads to failure of broad-spectrum β-lactam antibiotic therapy and increases the burden of disease due to more severe infections and prolonged hospital stays (Rawat and Nair, 2010). A global meta-analysis indicates that these ESBL genes are not only present in human clinical isolates but are also consistently reported in food production animals and environmental sources such as water and wastewater, expanding the resistance reservoir beyond healthcare facilities and human communities (Ramatla *et al*., 2023).

Antimicrobial resistance is a complex, cross-sectoral problem, requiring integrated policies and responses that include controlling antibiotic use in medicine and animal husbandry, as well as improving environmental sanitation practices to prevent the rise in multiresistant infections (Salam *et al*., 2023). A One Health approach is crucial to reduce the public health impact of ESBL-producing *E. coli* and improve prevention and therapy strategies, as without multilateral intervention, the transmission of antimicrobial resistance is expected to continue to exacerbate the global disease burden (Khairullah *et al*., 2025).

ESBL transmission monitoring and control strategy

Strategies for monitoring and controlling the transmission of ESBL-producing *E. coli* should be based on a multisectoral approach encompassing human, animal, and environmental compartments, in accordance with the One Health principle (Miltgen *et al*., 2022). Molecular evidence suggests that ESBL genes can reside on various types of plasmids capable of moving between strains and species, leading to complex and dynamic transmission pathways across ecological compartments (Ghorbani-Dalini *et al*., 2015). Genomic-based surveillance, including the use of whole-genome sequencing, is essential for identifying the distribution of resistance genes, high-risk clones, and transmission pathways across sectors, allowing these data to map transmission patterns and assess the effectiveness of interventions (Gilchrist *et al*., 2015). Coordinated national and international monitoring is needed to establish a comprehensive database, enabling early detection of increasing ESBL prevalence and rapid response to outbreaks or cross-border spread (Alenzi *et al*., 2026). Control interventions also include strict antibiotic use policies in the clinical and livestock sectors, improved sanitation and waste management, and public education programs to reduce inappropriate antibiotic use (Acharya *et al*., 2025). This approach not only curbs the spread of ESBL genes but also reduces cross-transfer between humans, animals, and the environment, helping to minimize the greater public health risks posed by antimicrobial resistance.

Conclusion

ESBL-producing *E. coli* is a key determinant of β-lactam antibiotic resistance. Molecular evidence indicates that ESBL genes, particularly CTX-M with the CTX-M-15 variant, have been widely distributed in various reservoirs and are often associated with high-risk *E. coli* clones that have the capacity to adapt and spread globally. The presence of these clones in humans, animals, and the environment confirms that ESBL resistance is not a sectoral phenomenon, but rather a complex, cross-ecosystem problem. The spread of ESBL *E. coli* is accelerated by irrational antibiotic use, the high mobility of genetic elements such as plasmids and integrons, and environmental conditions that favor the exchange of resistance genes. Transmission pathways involving the food chain, wastewater, human-animal interactions, and wildlife reinforce the environment's role as a reservoir and intersectoral link. ESBL *E. coli* control efforts must be comprehensively implemented through a One Health approach that integrates genomic surveillance, antibiotic control in the medical and veterinary sectors, and improved sanitation and environmental management. This integrated approach is key to suppressing the spread of antimicrobial resistance and protecting human and animal health and the sustainability of ecosystems in the future.

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Conflict of interest

The authors declare that there is no conflict of interest.

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