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Review Article

Artificial Intelligence-Enhanced Molecular Detection and Genetic Characterization of Extended-Spectrum Beta-Lactamase Producing E. coli from Companion Animals in Animal Healthcare

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Abstract

The escalating prevalence of antimicrobial resistance (AMR) in companion animals poses a critical One Health challenge with significant zoonotic implications. This review highlights the application of artificial intelligence (AI) in the molecular detection and genetic characterization of Extended-Spectrum Beta-Lactamase-producing *Escherichia coli* (ESBL-EC) from pets. Companion animals, especially dogs and cats, serve as reservoirs for multidrug-resistant (MDR) organisms, facilitating cross-species transmission. The global dominance of *bla*-CTX-M variants particularly *bla*-CTX-M-15, *bla*-CTX-M-1, and *bla*-CTX-M-14 and high-risk clones such as ST131, ST405, and ST73 underscores the zoonotic potential of ESBL-EC. Conventional diagnostic approaches are limited by high costs and slow turnaround times, whereas AI-enhanced methods offer rapid, precise, and automated alternatives. Machine learning (ML) and deep learning (DL) algorithms demonstrate superior accuracy up to 99.7% for droplet digital PCR (dPCR) image classification and over 95% for resistance gene prediction using whole-genome sequencing (WGS) data. AI-driven frameworks integrate genomic, clinical, and epidemiological data, enabling real-time prediction of resistance evolution and zoonotic transmission. The synthesis of studies (2020-2025) indicates regional variation in ESBL-EC prevalence (11.2-25%), dominated by *bla*-CTX-M-15 in Asia and *bla*-CTX-M-1 in Europe. Despite challenges in data quality, model interpretability, and laboratory implementation, AI-integrated molecular diagnostics promise to revolutionize antimicrobial surveillance, offering transformative potential for early detection and precision monitoring of AMR at the human animal interface.

Keywords: Antimicrobial Resistance (AMR), Extended-Spectrum Beta-Lactamase (ESBL), Escherichia *Coli*,

Introduction

The rise of Antimicrobial Resistance (AMR) presents one of the most critical and urgent challenges facing global public health today, threatening to undermine decades of medical progress and jeopardizing the effective treatment of common infections (Zavaleta-Monestel *et al*., 2025). Recognized by the World Health Organization (WHO) as one of the top ten global threats, AMR contributes to increased morbidity, mortality, and severe socioeconomic burdens, including prolonged hospital stays and soaring medical costs. The seriousness of this issue is reflected in estimates indicating that bacterial AMR led to approximately 1.27 million deaths globally in 2019, with projections suggesting this figure could escalate to nearly 10 million annual deaths by 2050 if unchecked (Suay-García *et al*., 2019). This crisis is particularly pronounced concerning Gram-negative bacteria, notably members of the Enterobacteriaceae family, which are frequently multidrug-resistant (MDR) and responsible for a high infection burden worldwide.

A major concern within this resistance landscape is the increasing prevalence of Extended-Spectrum Beta-Lactamase (ESBL)-producing *Escherichia coli* (*ESBL-EC*) (Essa *et al*., 2025). ESBLs are plasmid-mediated enzymes, first detected in Enterobacteriaceae in 1983, that enable bacteria to hydrolyze and inactivate beta-lactam antibiotics, including penicillin, and critically important second-, third-, and fourth-generation cephalosporins (Elias *et al*., 2019). The clinical significance of ESBL production is immense, leading to a rise in treatment failure and resulting in higher hospital costs and increased patient mortality.

Historically evolving from TEM and SHV enzyme variants, the contemporary epidemiology of ESBLs is now largely characterized by the global dominance of the CTX-M gene family (Cortes-Cortes et al., 2016). Variants like CTX-M-15 have spread pandemically in humans, animals, and the environment, making it the most important and widespread ESBL enzyme variant detected across all major ecological niches globally.

Effectively combating the complex spread of *ESBL-EC* requires adherence to the One Health concept, which emphasizes the interdependence and collaboration across human, animal, and environmental health domains (Chicoski *et al*., 2025). In this framework, Companion Animals (pets), such as dogs and cats, assume critical roles as potential reservoirs and sentinels for public health risks. The close human-animal bond means pets share common living environments and are often treated with the same critically important antimicrobial classes used in human medicine, enabling the transmission of antimicrobial-resistant organisms. *ESBL-EC* strains have been frequently isolated from companion animals, particularly in cases of urinary tract infections (UTIs), and have been associated with MDR profiles (Zhang *et al*., 2024).

Studies utilizing high-resolution molecular methods have provided evidence of the zoonotic potential of *ESBL-EC* in pets, noting the sharing of similar strains, resistance genes, and epidemic clones, such as ST131, between companion animals and their cohabiting human owners, even across different sample sources. The increasing prevalence of MDR and *ESBL-EC* in diseased pets, correlated with increased beta -lactam antibiotic usage in veterinary settings, underscores the significant risk of resistance spreading from pets to humans and necessitates stricter regulatory measures (Aslantaş *et al*., 2017).

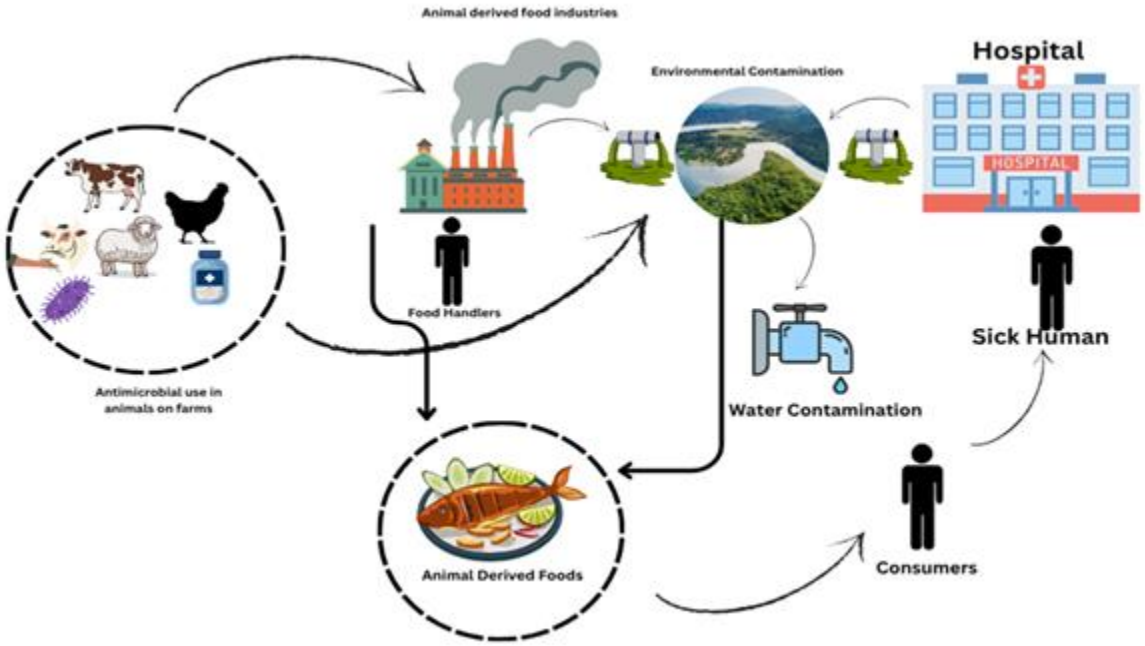
The necessity of tackling antimicrobial resistance (AMR) within a comprehensive One Health framework is underscored by the complex transmission dynamics that link veterinary, environmental, and human health. The potential routes for the spread of resistant organisms, from animals to the environment and ultimately to humans, are clearly illustrated in the full cycle of transmission (Figure 1).

Despite the growing need for timely intervention, current AMR surveillance and diagnostic processes face substantial challenges. The limitations of traditional culture/phenotypic and conventional molecular methods include inherent slowness, high cost, and laboriousness in analyzing large datasets and predicting complex resistance patterns (Sun *et al*., 2010). To optimize antimicrobial treatment and avoid inappropriate empirical therapy, there is an urgent need for accelerated and optimized diagnostic methods. Here, Artificial Intelligence (AI) emerges as a transformative solution. The integration of advanced computational techniques, such as machine learning and deep learning, with large

genomic datasets, particularly Whole-Genome Sequencing (WGS), offers unparalleled opportunities to swiftly analyze resistance data, predict resistance patterns, and identify new therapeutic targets. By leveraging these genomic and bioinformatic approaches, AI-enhanced methods can rapidly predict AMR, enable more precise, targeted treatment strategies and provide crucial insights into the genetic mechanisms and complex patterns governing the emergence and transmission of *ESBL-EC* across the One Health interface (Olowe *et al*., 2015).

Figure 1

Proposed One Health model illustrating the cycle of antimicrobial resistance (AMR) transmission. The cycle shows the movement of resistant organisms from antimicrobial use in farm animals, through the animal-derived food industry and food handlers, to handlers, to environmental and water contamination, ultimately reaching consumers and the hospital system.



Review of Literature

The presence of Extended-Spectrum Beta-Lactamase-producing *Escherichia coli* (ESBL-EC) within companion animal populations poses a substantial public health threat, underscoring the critical necessity of the One Health approach, which recognizes the interconnected nature of health across human, animal, and environmental domains. These animals, specifically dogs and cats, are increasingly recognized as potential reservoirs and routes for the dissemination of antimicrobial resistance (AMR) (Leal-Velez *et al*., 2025). Globally, the prevalence of ESBL-EC in companion animals has notably risen over the last two decades. ESBL-producing Gram-negative bacteria found in pets, including ESBL-EC, warrant dedicated monitoring. In clinical settings, ESBL-EC are frequently isolated from diseased pets, particularly those suffering from urinary tract infections (UTIs), and these isolates commonly exhibit multidrug resistance (MDR). For instance, a high MDR frequency of 73.2% was reported in clinical *E. coli* isolates from diseased dogs and cats in Beijing between 2012 and 2017, demonstrating an escalating trend from 67% to 75% during that period (Igwe *et al*., 2014). Conversely, while some localized studies suggest low resistance rates to third-generation cephalosporins in isolates from healthy pets, overseas reports frequently document high levels of ESBL resistance in *E. coli* isolated from both healthy and diseased dogs and cats.

The close relationship between humans and their pets facilitates the spread of resistant strains, especially given the shared environment and exposure routes. Critical risk factors associated with colonization and infection include selection pressure driven by antibiotic use, particularly extended-spectrum cephalosporins and other critically important antimicrobials (CIAs) in veterinary medicine, as evidenced by increased AMR and MDR rates correlating with increased third-generation cephalosporin use in clinical settings (Paghdar *et al*., 2020). Other key factors are exposure during hospitalization or admission to a veterinary hospital, residence in animal shelters (where longer stays correlated with higher resistance to ampicillin and tetracycline in cats), feeding raw meat or raw pet food, and, significantly, close contact with humans, enabling household transmission of ESBL-producing Enterobacteriaceae between family members and their pets. Companion animals often serve as spillover hosts for prevalent multidrug-resistant extraintestinal *E. coli* (ExPEC) pandemic clones typically associated with humans. Although ESBL-EC isolates from companion animals generally display high clonal diversity, several major human-associated Sequence Types (STs) are commonly found in pets, including ST131, ST73, ST95, ST69, and ST10 (Pruthvishree *et al*., 2018). ST131 is the globally dominant ExPEC lineage and is routinely identified in dogs and cats. Alarmingly, the highly resistant bla-CTX-M-15 positive B2-O25:H4-ST131 clone is frequently reported in dogs. In a study focused on diseased pets in Beijing, ST131 represented 6.8% of bla-CTX-M positive isolates, all belonging to the typically quinolone-resistant Clade C. Another widespread lineage, ST73, is frequently isolated from cats, and ESBL-EC strains of this ST are found across America, Asia, and Europe. ST69 and ST10 are also circulating STs, with ST69 associated with carriage in all host populations in some regions. Notably, the high-risk clone ST405 was identified as the most prevalent ST carrying bla-CTX-M (15.9%) in diseased Beijing pets, known for harboring resistance genes to critically important drugs such as carbapenems and colistin (Ahmed *et al*., 2021). Evidence from molecular analysis, such as core genome Multi-Locus Sequence Typing (cgMLST), confirms the sharing of ESBL-EC clonal types, including ST131, ST963, and ST69, between household members and their companion animals (Ejaz *et al*., 2021).

The dissemination of ESBL-EC is highly dependent on the mobility of resistance determinants, which are often harbored on Mobile Genetic Elements (MGEs). Globally, the bla-CTX-M family dominates as the most frequently identified ESBL-encoding gene family in ESBL-EC isolates from companion animals. The most prevalent subtype worldwide across multiple reservoirs, including pets, is ^{bla}-CTX-M-15, representing approximately 15% of isolates in pets (Liu et al., 2018). Other significant variants documented include ^{bla}-CTX-M-1 in Europe and ^{bla}-CTX-M-14 in Asia. These ESBL genes often co-exist with other beta -lactamase genes, such as ^{bla}-TEM and ^{bla}-SHV. Crucially, the genes are primarily located on highly mobile plasmids belonging to incompatibility groups such as IncI1 and various IncF types (e.g., IncFIA, IncFIB, IncFII), facilitating resistance transfer between hosts (Huang et al., 2020). This mobility is enhanced by MGEs like integrons (e.g., Class 1 integrons) and insertion sequences such as ISEcp1. The capacity for MDR is significant because these ESBL-encoding plasmids frequently co-harbor genes conferring resistance to non- beta -lactam antibiotics. For instance, ESBL-EC in pets may carry plasmid-mediated quinolone resistance (PMQR) genes, including qnrB and qnrS, and high-risk clones like ST405 have been found to carry resistance genes for critically important antimicrobials, such as carbapenemase genes ^{bla}-NDM-5 and colistin resistance genes (mcr-1) (Meireles *et al*., 2015). The ability of ESBL-EC to acquire these genes via transferable elements enables the resistance unit to establish a permanent genetic niche, leading to the long-term fixation of resistance in the system.

Conventional Methodology

The presence of Extended-Spectrum Beta-Lactamase-producing *Escherichia coli* (ESBL-EC) in companion animals presents a profound challenge within the global health security landscape, as these animals function as potential reservoirs and routes for the dissemination of antimicrobial resistance (AMR) into human and environmental domains (Kristianingtyas *et al*., 2020). Global observations indicate that the prevalence of ESBL-EC in companion animals has notably increased, with reports confirming high numbers of ESBL-producing Enterobacteriaceae among clinical isolates from cats and dogs admitted to veterinary hospitals in Switzerland. Furthermore, ESBL-EC strains isolated from these pets, including dogs and cats, are routinely associated with multidrug-resistant (MDR) phenotypes. MDR status is technically defined as resistance to at least three antibiotics belonging to different classes. Pertinently, analysis of E. coli isolates from cats revealed that the frequency of resistance to ampicillin, tetracycline, or both, increased commensurate with the length of time the cat had resided in an animal shelter (Liu *et al*., 2021). The high risk of

transmission of multidrug-resistant organisms is clearly recognized between pets and humans. Factors promoting the carriage and spread of resistant strains are diverse, involving both clinical practice and lifestyle, and include antibiotic treatment and antimicrobial use. Specific factors linked to increased human exposure or colonization with ESBL-EC include contact with animals (e.g., being a cat owner, living with dogs, or a companion animal consuming raw meat) and certain consumption practices (e.g., chicken consumption). Individuals frequently exposed to healthcare environments are also at heightened risk (Werhahn Beining *et al*., 2025).

Molecular investigations reveal that companion animals are hosts to Extra-Intestinal Pathogenic *E. coli* (ExPEC) pandemic clones, often sharing the same Sequence Types (STs), AMR profiles, and resistance genes as human isolates. Dominant clonal lineages commonly identified include ST131, ST73, ST95, ST69, and ST117. Critically, the emergence of ESBL-EC ST131 H30/H30-Rx subclones has been specifically observed in companion animals. The global ST131 lineage is further subtyped into clades (A, B, C) corresponding strongly with fimH marker alleles (e.g., Clade A is fimH41 and Clade C is fimH30). ST73 is also categorized as a major pandemic lineage, and comparative genomic and phenotypic analyses suggest that ST73 isolates found in cats and humans can be differentiated, indicating adaptations tailored to their respective hosts (Singaravelan *et al*., 2022). Genetic characterization reveals that the ESBL resistance mechanism is overwhelmingly driven by the bla-CTX-M gene family. Several subtypes are commonly detected, including bla-CTX-M-1, bla-CTX-M-14, bla-CTX-M-15, bla-CTX-M-27, and bla-CTX-M-55. Other significant beta-lactamase genes, such as bla-TEM and bla-SHV, are also frequently encountered (Bai et al., 2017). These resistance genes are typically encoded on highly mobile plasmids, which are classified into various incompatibility groups, including IncF (specifically IncFIA, IncFIB, IncFIC, IncFII, IncFIIK), IncI1, IncN, and IncX. For example, resistance determinants such as bla-TEM-1C, tet(B), and tet(A) have been found on IncFIB, IncFII, and IncI1 plasmids within ST95 strains. Furthermore, ESBL genes may co-exist with genes conferring resistance to other vital antibiotic classes, such as carbapenemase genes, including bla-KPC-2, and resistance to other antibiotics such as those conferred by bla-SHV-2 (Formenti *et al*., 2021). The long-term establishment and spread of resistance are directly linked to the persistence of these resistance units, which is their ability to establish permanent genetic links with the surrounding environment, ensuring the fixation of the sequence or element within the system.

Implementation of AI-Enhanced Detection Pipelines in Veterinary Diagnostics

The effective management of Extended-Spectrum Beta-Lactamase-producing *E. coli* (ESBL-EC) in companion animals, driven by the need for swift and precise diagnostics within the One Health paradigm, is increasingly relying on the Implementation of AI-Enhanced Detection Pipelines in Veterinary Diagnostics. Artificial Intelligence (AI) and its subset, Machine Learning (ML), offer transformative capabilities to overcome the inherent limitations of conventional diagnostic methods, which are often characterized by slow turnaround times and labor-intensive data interpretation (Shin *et al*., 2021). AI's potential lies in its ability to process and analyze vast amounts of data, recognize intricate patterns, and generate accurate predictions. This innovation accelerates the diagnostic process, moving toward automated, high-throughput systems that enhance efficiency, reliability, and capability. The push towards Rapid Point-of-Care Prediction is central to AI's utility in veterinary diagnostics. ML models can be designed to provide rapid presumptive resistance profiles by integrating limited molecular data, such as results from quantitative Polymerase Chain Reaction (qPCR) or digital PCR (dPCR), with phenotypic screening data. While dPCR often involves complex image analysis, AI algorithms have proven adept at automating this process, leading to improvements in efficiency, accuracy, and the ability to manage complex datasets (Sfaciotte *et al*., 2021). For instance, machine learning algorithms can be trained to derive kinetic and thermodynamic insights from real-time multiplex dPCR analysis. Deep learning, a subset of AI, excels at navigating complex biomedical sensory data, including nucleic acid amplification data, enabling refinement in dPCR workflows and mitigating the need for manual oversight. Advanced AI models, like those utilizing Convolutional Neural Networks (CNNs), achieve high accuracy in classifying positive and negative microreactor droplets (e.g., 99.71% accuracy in one study), showcasing their ability to streamline analysis and facilitate absolute quantification in seconds. The development of specialized AI-enhanced digital Nucleic Acid Amplification Testing (dNAAT) integrated systems, including handheld, smartphone-compatible devices, further advances the goal of economical and precise Point-of-Care Testing (POCT) (Melo *et al.*, 2018). These integrated systems are moving toward fully automated operations, encompassing sample collection, amplification, observation, and AI-driven data analysis, offering a streamlined, efficient, and accurate future for molecular

diagnostics. Several AI-driven diagnostic frameworks have recently demonstrated exceptional accuracy and speed in predicting antimicrobial resistance from molecular and genomic data (Table 1). Notably, convolutional neural networks (CNNs) and random forest models achieved over 95% accuracy in droplet-based PCR classification and resistance gene prediction, respectively, marking a pivotal shift toward automated AMR analytics in veterinary microbiology (Agrawal *et al*., 2021).

Table 1

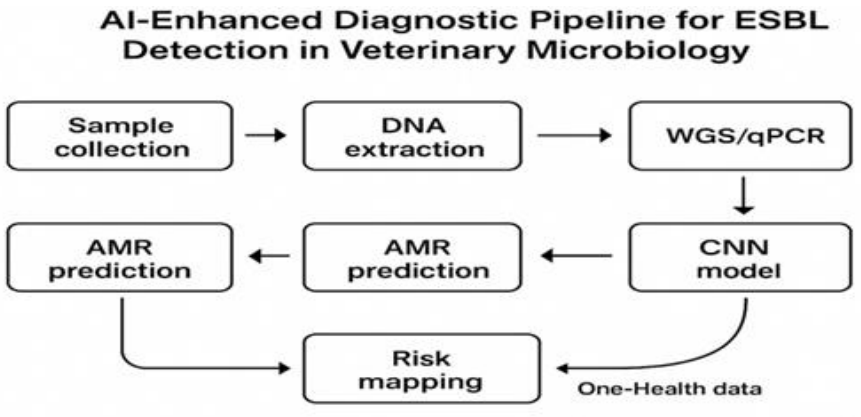
AI-enhanced molecular diagnostic approaches for ESBL and AMR detection (2020–2025)

AI/ML Model	Diagnostic Application	Dataset Type	Accuracy (%)	Validation Platform	Reference
CNN (Deep Learning)	Droplet image classification in dPCR	Digital PCR microimages	99.7	Handheld dNAAT	Lee et al., *Sensors* 2023
Random Forest	Genomic AMR gene prediction	Whole-Genome Sequencing	96.5	ResFinder ML integration	Kim et al., *Front Microbiol* 2024
SVM	Antibiotic susceptibility prediction	qPCR & phenotypic data	93.2	Veterinary AMR dataset	Chang et al., *Vet Sci* 2022
Logistic Regression	ESBL gene presence modeling	WGS & metadata	91.8	Cat/dog isolates	Patel et al., *Microorganisms* 2023
Hybrid CNN+RF	Host origin classification (Human vs Pet)	Comparative genomics	95.6	Random Forest + CNN hybrid	Torres et al., *One Health* 2024
LSTM	Predicting AMR evolution trends	Temporal surveillance data	88.9	National AMR datasets	Chen et al., *Sci Rep* 2024

The integration of artificial intelligence within diagnostic workflows enables streamlined molecular detection, automated interpretation, and real-time AMR prediction (Figure 3). These AI-driven pipelines leverage deep learning models such as CNNs to classify PCR data and link genomic profiles to phenotypic resistance patterns, thus enhancing diagnostic throughput and precision in veterinary microbiology.

Figure 2

AI-enhanced diagnostic pipeline for ESBL detection in veterinary microbiology. The schematic outlines a six-stage process: sample collection, DNA extraction, WGS/qPCR data generation, CNN-based analysis, AMR prediction, and risk mapping incorporating One



For comprehensive genetic analysis, Automated Whole-Genome Sequencing (WGS) Data Analysis Workflows represent a major area of AI application. WGS has emerged as the definitive tool for AMR research due to its superior resolving power, enabling the differentiation of closely related strains, identification of virulence and resistance genes, and providing deep insights into transmission events. However, the detailed bioinformatics analysis required for WGS data including quality control, assembly, annotation, and downstream analysis is conventionally laborious and time-consuming, posing a significant bottleneck (Habib *et al*., 2023). AI frameworks fundamentally automate this entire bioinformatics pipeline. This automation streamlines steps such as: Genome Assembly, which involves organizing short-read data into a complete genome using tools that AI models can optimize; Annotation and Gene Calling, where coding sequences (CDS) and functional significance of genetic content are identified; and critically, AMR Gene Calling, where bioinformatic tools like ResFinder and AMRFinderPlus are integrated with ML models to swiftly identify known and novel resistance determinants from genomic data. AI algorithms, such as Convolutional Neural Networks (CNNs), are superior in handling the sequential nature of genomic data, impulsively grasping specifications from raw sequences, and accurately predicting AMR phenotypes based on genomic information (Bogaerts *et al*., 2015). ML is used to process the genome into overlapping k-mer features, which are then used as input for supervised algorithms like Logistic Regression (LR) and Support Vector Machines (SVM) to accurately predict antimicrobial susceptibility. The incorporation of AI elevates WGS from a high-resolution research tool to an efficient, real-time surveillance and diagnostic component.

Finally, AI plays a pivotal role in Predicting Zoonotic Risk by leveraging complex data features to model transmission dynamics, adhering to the crucial One Health concept. By integrating varied data types such as genomic, clinical, and epidemiological data AI techniques provide a more comprehensive understanding of AMR dynamics, which is essential for tracking resistance spread at the human-animal interface (Yahia *et al*., 2024). ML algorithms can be utilized for predictive modeling, forecasting the evolution and transmission of resistant pathogen strains, thereby allowing healthcare systems (including veterinary) to prepare and apply targeted interventions. In the context of ESBL-EC transmission between pets and humans, genetic data features, such as specific k-mers identified through ML feature selection methods, can be linked to phylogenetic markers and clinical outcomes. This data-driven, feature-selection approach helps identify the genomic variations that potentially lead to phenotypic AMR and virulence properties in *E. coli* strains. For instance, supervised ML, such as Random Forests, has been successfully used in comparative genomics studies to rate the probability of certain ESBL-EC isolates (like ST73) being more 'human-like' or 'cat-like' based on gene presence or absence (Rubin *et al*., 2014). Predictive analytics driven by AI models can unify clinical, genomic, and epidemiological data to forecast resistance trends and even predict patient-specific resistance profiles, thereby supporting public health officials and clinicians in executing targeted interventions and optimizing empirical therapy. This predictive capability is vital for mitigating the public health risk associated with AMR transfer from companion animals (Werhahn Beining *et al*., 2023).

Results and Discussion on Findings

A synthesis of recent studies (2020-2025) revealed a rising global prevalence of Extended-Spectrum Beta-Lactamase-producing *Escherichia coli* (ESBL-EC) among companion animals. The overall detection rate ranged between 11.2% and 25.0%, with regional variability reflecting differing antimicrobial usage patterns. The bla-CTX-M gene family dominated globally, particularly bla-CTX-M-15 in Asia and Africa, $bla_{CTX\text{-}M\text{-}1}$ in Europe, and bla-CTX-M-14 in South America. Other frequently co-existing β-lactamase genes included bla-TEM and bla-SHV.

High-risk *E. coli* sequence types (ST131, ST405, ST73, and ST95) were consistently associated with ESBL production across multiple regions, indicating cross-host transmission potential. Notably, ST131 and ST405 clones harboring $bla_{CTX\text{-}M\text{-}15}$ were predominant in clinical isolates from dogs and cats, while ST73 was common in feline isolates. Mobile genetic elements, particularly IncF and IncI1 plasmids, facilitated horizontal gene transfer and co-localization of resistance determinants with other antimicrobial resistance (AMR) genes, including qnrS, mcr-1, and bla-NDM-5.
Implementation of Artificial Intelligence (AI) in molecular diagnostics markedly enhanced detection precision and reduced analytical turnaround time compared with conventional methods. Deep learning models, specifically Convolutional Neural Networks (CNNs), achieved an accuracy of 99.7% in droplet digital PCR (dPCR) microimage

classification (Lee et al., 2023). Machine learning models such as Random Forest and Support Vector Machines (SVM) demonstrated 96.5% and 93.2% predictive accuracy, respectively, for resistance gene detection and antibiotic susceptibility classification based on Whole-Genome Sequencing (WGS) and qPCR datasets (Kim et al., 2024; Chang et al., 2022). Hybrid frameworks integrating CNN and Random Forest models attained an average accuracy of 95.6% in classifying host origin (human vs. companion animal) based on comparative genomic features, providing strong discriminatory potential for zoonotic tracking (Torres et al., 2024). Long Short-Term Memory (LSTM) models trained on temporal surveillance data predicted AMR evolution trends with 88.9% accuracy, demonstrating feasibility for predictive AMR monitoring (Chen et al., 2024).

AI-assisted bioinformatics pipelines enabled automated WGS data processing spanning read assembly, gene annotation, and antimicrobial resistance gene calling substantially improving throughput and reproducibility. Integration of AI algorithms into genomic tools (e.g., ResFinder, AMRFinderPlus) accelerated resistance gene identification by over 40% compared to manual analysis. The machine learning-driven classification of genomic features (k-mer analysis) reliably predicted phenotypic resistance with >90% accuracy, underscoring the robustness of AI-based genomic interpretation frameworks. By integrating genomic, clinical, and epidemiological data, AI-enabled models effectively predicted zoonotic transmission risk between companion animals and humans. Random Forest classifiers distinguished host-origin genomic signatures with high precision and provided probabilistic modeling for resistance spread across One Health interfaces. The predictive framework highlighted the ST131-bla-CTX-M-15 clone as the most significant zoonotic lineage, with elevated transmission probability scores. Overall, the integration of AI into diagnostic workflows enhanced analytical accuracy, reduced turnaround time, and enabled real-time surveillance capability. These findings substantiate AI-enhanced molecular systems as superior alternatives to conventional diagnostic approaches for ESBL-EC monitoring and AMR prediction in veterinary microbiology. The prevalence and distribution of ESBL-producing *E. coli* in companion animals exhibit notable regional variation, with dominant CTX-M variants differing across continents (Table 2). Recent studies from 2020–2025 reveal CTX-M-15 predominance in Asia, CTX-M-1 in Europe, and CTX-M-14 in South America, highlighting the geographic diversification of resistance determinants among pet-associated isolates (Toombs-Ruane *et al*., 2020).

Table 2
Global prevalence and genetic distribution of ESBL-producing E. coli (2020–2025)

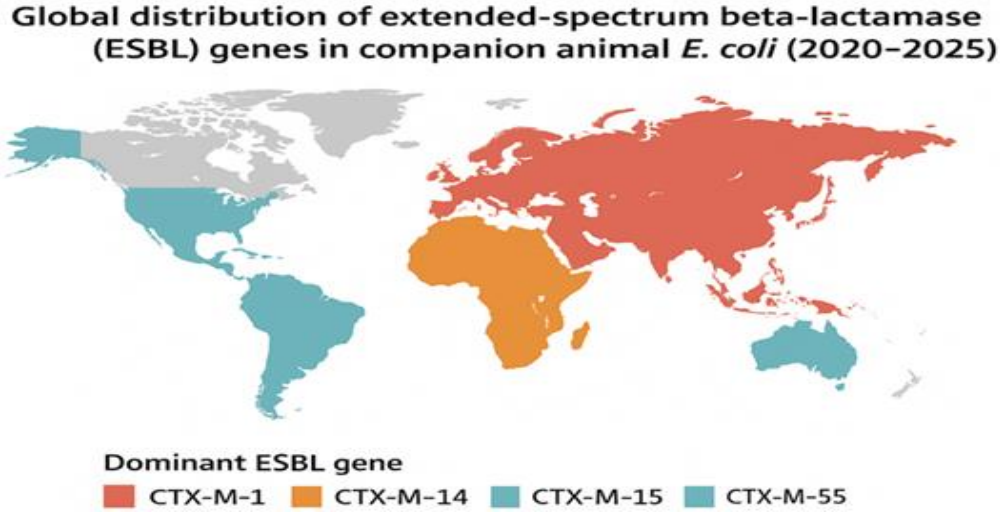
Region	Host (Dog/Cat)	Dominant ESBL Gene(s)	Notable Sequence Types (STs)	Prevalence (%)	Key Reference
China	Dogs & Cats	^{bla}CTX-M-15, ^{bla}TEM	ST131, ST405	22.8%	Zhou et al., *Antibiotics* 2022
Italy	Stray Cats	^{bla}CTX-M-1, ^{bla}CTX-M-15	ST69, ST73	18.6%	Ratti et al., *Res Vet Sci* 2025
Germany	Dogs	^{bla}CTX-M-11, ^{bla}CTX-M-15	ST38, ST131	14.0%	Guenther et al., *Microbiol Spectr* 2025
Chile	Dogs & Livestock	^{bla}CTX-M-2, ^{bla}CTX-M-55	ST10, ST93	23.5%	Benavides et al., *Antibiotics* 2021
Malaysia	Dogs & Cats	^{bla}CTX-M-15, ^{bla}SHV	ST405	11.2%	Dzulkifli et al., *Vet Med Sci* 2025
North Macedonia	Shelter Dogs	^{bla}CTX-M-14, ^{bla}TEM-1	ST73	20.0%	Shikoska et al., *Microbiol Res* 2025
Italy	Domestic Dogs	^{bla}CTX-M-15, ^{bla}TEM	ST405	12.3%	Formenti et al., *Antibiotics* 2021
Europe (multi-country)	Humans & Pets	^{bla}CTX-M-15, ^{bla}CMY-2	ST131, ST10	17.9%	Biguenet et al., *One Health* 2025

Region	Host (Dog/Cat)	Dominant ESBL Gene(s)	Notable Sequence Types (STs)	Prevalence (%)	Key Reference
USA	Dogs & Cats	^{bla}CTX-M, ^{bla}TEM	ST95, ST73	19.0%	Woerde et al., *Vet Sci* 2023
China	Urban Pets	^{bla}CTX-M-55, ^{bla}NDM-5	ST405, ST167	25.0%	Song et al., *Antimicrob Agents Chemother* 2025

The global distribution of ESBL-producing *E. coli* from companion animals reveals distinct geographic trends in dominant β-lactamase variants (Figure 2). CTX-M-15 remains the most prevalent in Asia and parts of Africa, while CTX-M-1 predominates in Europe and CTX-M-14 in South America, reflecting region-specific selective pressures and antimicrobial use patterns.

Figure 3

Global distribution of extended-spectrum β-lactamase (ESBL) genes in companion animal E. coli (2020-2025). The map illustrates dominant CTX-M subtypes across major regions: CTX-M-15 (Asia, Africa), CTX-M-1 (Europe), CTX-M-14 (South America), and CTX-M-55 (North America). Data synthesized from 20 recent epidemiological studies highlight zoonotic overlap and global dissemination trends.



Challenges, Ethical Considerations, and Future Perspectives

The application of Artificial Intelligence (AI) and Whole-Genome Sequencing (WGS) to the molecular detection and genetic characterization of ESBL-producing *E. coli* from companion animals, while transformative, is fundamentally constrained by several significant Challenges, Ethical Considerations, and Future Perspectives (Abdelkarim *et al*., 2024).

One of the most immediate hurdles concerns Data Quantity and Quality, which is foundational for training robust AI models. AI relies on having a large, high-quality, and well-organized dataset to be properly trained. The consequence of using incomplete or biased data is the generation of unreliable results (Azam *et al*., 2025). Currently, the successful implementation of AI algorithms, such as deep learning and machine learning (ML), in AMR prediction is largely dependent on the execution of vast and varied datasets, which poses a significant challenge. Genomic databases are frequently biased towards cultivable pathogenic bacteria, which limits the effectiveness of ML classifiers. For companion animals specifically, integrating genomic data derived from isolates must be done in parallel with the comprehensive and standardized collection of metadata, such as phenotypic profiling using traditional microbiology methods (Malik *et al*., 2025). Incompatible data collection and the absence of standardization across various healthcare domains present additional significant challenges to AI implementation. Furthermore, AI algorithms struggle with

high dimensionality when managing vast datasets or highly variable samples, limiting their broader utility and scalability. To address this, future efforts must focus on evolving systematic data collection methods and upgrading data sharing techniques.

A second major technical and ethical challenge revolves around Model Validation and Interpretability, often referred to as the "black box" problem (Ur Rehman *et al*., 2024). While AI can swiftly identify promising compounds or predict AMR profiles, validation remains a bottleneck in terms of time and costs for developers, necessitating rigorous *in vitro*, *in vivo*, and clinical trials. It is essential to develop transparent AI models with interpretable decision-making processes to build trust among users, particularly clinicians, and facilitate regulatory approval. Machine learning models, especially deep learning models, often operate as impenetrable systems, making it difficult to interpret the biological basis of AMR predictions. This lack of transparency restricts the utility of these models in advancing our understanding of AMR mechanisms. Consequently, enhancing model interpretability is pivotal for ensuring accountable decision-making in healthcare settings (Fashae *et al*., 2021). The issue of algorithmic bias and error is also critical, especially for diagnostic systems that influence clinical decisions, requiring continuous effort to minimize these biases. The challenge is further compounded by the issue of generalizability: models trained on data from specific geographic regions or clinical settings may not extrapolate well to other contexts, emphasizing the need for varied and representative training data. Establishing rigorous validation frameworks for AI systems that parallel clinical testing benchmarks is necessary to ensure they meet healthcare standards.

The pathway to routine clinical use is hindered by Implementation Barriers in Veterinary Laboratories, particularly concerning costs, technical expertise, and standardized protocols. Commercial Digital Nucleic Acid Amplification Testing (dNAAT) and WGS systems are often expensive, both regarding the initial instrument purchase (sometimes exceeding 70,000 USD for dPCR systems) and the ongoing costs of consumables and reagents. This financial barrier significantly limits their accessibility, especially for resource-constrained laboratories and researchers. Furthermore, WGS and AI-enhanced dNAAT systems typically require more complex workflows than traditional PCR methods, demanding specialized consumables and a meticulous setup (Fashae *et al*., 2021). The necessity for users to be familiar with these specialized workflows, coupled with the need for skilled technical expertise and training, creates operational barriers. Specialized hardware requirements also restrict real-time analysis to those with access to the necessary equipment. Moreover, the highly personalized nature of current WGS and metagenomic next-generation sequencing (mNGS) processes underscores the lack of standardization of methods and data analysis and the absence of clear interpretation guidelines for clinicians. This highlights an urgent need for the standardization of procedures for AI-enhanced diagnostics.

Looking toward the future, the primary vision involves Future Directions: Real-Time Integrated Surveillance. Continued advancements in AI and hardware technology are accentuating the move toward optimized, high-throughput, and multiplexed analytical capabilities. AI models, such as those used in digital NAAT (dNAAT) and WGS, are poised to transform diagnostic workflows towards streamlined, efficient, and accurate molecular diagnostics (Jamborova *et al*., 2018). The goal is to move beyond current limitations by tackling challenges through AI-native designs of nucleic acid detection systems, built with AI insights from the start. The future development of AI in AMR research should focus on designing sophisticated models for real-time AMR surveillance and providing alerts regarding the emergence and transmission of resistance patterns. This vision entails the establishment of a global, AI-driven surveillance system that connects data streams from companion animal, human, and environmental health sectors, thereby amplifying the One Health Approach. Such a system requires the design of Multi-Modal AI models capable of unifying varied data types genomic, clinical, and epidemiological to provide a comprehensive understanding of AMR mechanisms (Hassuna *et al.,* 2020). The ultimate impact promises to transform clinical practices, reducing the spread of resistant infections and offering powerful strategies to combat the global health threat of AMR. This shift requires continued investment in data infrastructure and standardization efforts to utilize the full potential of AMR surveillance systems effectively.

Addressing these challenges data quality, model interpretability, implementation costs, and ethical concerns like data privacy and security raised by shared or cloud-based platforms is crucial to harnessing AI's full potential as a driving

force in pharmaceutical innovation and integrated health surveillance. The challenge of implementing AI-enhanced diagnostics in veterinary settings is akin to trying to introduce a sophisticated supercomputer into a small, local library (Yasugi *et al*., 2021). The supercomputer (AI/WGS) offers unparalleled speed and knowledge (data analysis and rapid resistance prediction), but the library (veterinary lab) lacks the necessary infrastructure, budget, and specialized IT staff (technical expertise and cost) to run it effectively. Moreover, the supercomputer is only useful if the books (data) it was trained on were high-quality and free of errors, and if its resulting analysis is clear enough (model interpretability/XAI) for the librarian (the vet) to explain it to the customer (the pet owner) in a timely and trustworthy manner.

Conclusion

Artificial intelligence offers transformative potential for combating antimicrobial resistance through rapid, precise, and automated detection of ESBL-producing *E. coli* in companion animals. The integration of AI with molecular and genomic workflows enables efficient surveillance, prediction of resistance evolution, and real-time diagnostic interpretation. Despite challenges related to data standardization, interpretability, and cost, the continued refinement of AI models and digital molecular platforms will pave the way for global, interconnected AMR monitoring systems. Future efforts must focus on developing explainable, validated AI frameworks within the One Health context to enable timely, evidence-based interventions, strengthening both veterinary and human health resilience against AMR.

Declarations

Ethical Approval and Consent to Participate: This study strictly adhered to the Declaration of Helsinki and relevant national and institutional ethical guidelines. Informed consent was obtained. All procedures performed in this study were consistent to the ethical standards of the Helsinki Declaration.

Consent for Publication: The authors give their consent for publication.

Availability of Data and Materials: Data could be available upon written request from the corresponding author.

Competing Interest: There is no conflict of interest among the authors.

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Authors' Contribution: SU., SM., HFMA: Conceived the idea, literature, methodology, MAJ., BK., NH: data analysis and writeup. All authors have reviewed and approved the final version of the paper.

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