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Antimicrobial Resistance In Extended Spectrum Beta Lactamase Producing Escherichia Coli Triggered By Pesticides

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Abstract

Background: Antimicrobial resistance (AMR), especially those caused by Extended-Spectrum Beta-Lactamase-producing E. coli (ESBL-producing E. coli), are a major global health problem. Knowing that misuse of antibiotics is a key driver in the development of resistance to these microbial agents, the effects of environmental non-antibiotic stressors such as pesticides in agriculture is, however, critically understudied. Objective: Pesticides like Glyphosate, used widely in agriculture for pest control, have been indicated to enhance efflux pump activity, beta-lactamase production and are targets of plasmids that carry antibiotic resistant genes. Thus, such chemicals are increasing AMR in gram-negative bacteria. Materials and Methods: This comparative experimental study analyzed 70 E. coli isolates from three groups: Non-Exposed Control (n = 10), Glyphosate-Exposed (n = 40), Mixed Pesticide-Exposed (n = 20). Isolates were biochemically confirmed. Antibiogram (ABG) was carried out using the Kirby-Bauer method against six agents, including the key ESBL markers Ceftazidime and Cefotaxime, and last-resort antibiotics Imipenem. Results were interpreted according to CLSI guidelines, with the Double-Disk Synergy Test (DDST) being used to phenotypically confirm ESBL production in resistant isolates. Results: susceptibility testing throughout three cohorts illustrates a clear link between chemical stress and resistance. Non-Exposed Control isolates (n = 10) displayed 0% resistance to all of the drugs used in testing. In contrast, the Glyphosate-Exposed group (n = 40) exhibited a surge in Cefotaxime (CTX) resistance of 70.0% (a hallmark ESBL activity), while retaining full Imipenem susceptibility. Resistance was greatest in the Mixed Pesticide-Exposed group (n = 20),

where CTX resistance reached 90.0% (and showed 0% sensitivity) demonstrating DRE-driven chemical stress. This group also developed multi-drug resistance (MDR) characteristics, with elements including Gentamicin (30.0%), importantly Imipenem resistance at 10.0% (n=2). Conclusion: Pesticide exposure serves as an environmental selective agent promoting the formation of clinically relevant ESBL resistant mechanisms. These results do not point to any species barrier but can happen across different organisms. The authors argue that these findings require environmental chemical surveillance to be built-into AMR stewardship policy under the "One Health" framework.

Introduction

Antimicrobial resistance (AMR) represents one of the most pressing global public health challenges of the 21st century, surpassing even cancer as a potential leading cause of mortality by 2050, with projections estimating up to 10 million annual deaths if unchecked. This crisis stems from the transformative impact of antibiotics developed in the mid-20th century, which revolutionized healthcare by enabling life-saving procedures like surgery, organ transplants, and chemotherapy (1). However, widespread resistance to commonly used antibiotics has eroded these gains, turning minor infections into life-threatening conditions and increasing risks of death and disability. At the forefront of this issue is ESBL-producing Escherichia coli, a bacterium that has evolved to resist a broad spectrum of β-lactam antibiotics, including third-generation cephalosporins, through enzymes like TEM, SHV, and the CTX-M family. Originally a commensal organism in human and animal guts, pathogenic strains of E. coli now cause severe infections such as urinary tract infections, septicemia, meningitis, and gastrointestinal ailments, often failing initial treatments and necessitating last-resort drugs like carbapenems, which in turn fuel further resistance (2).

The global spread of ESBL-producing E. coli is exacerbated by environmental factors, particularly the extensive use of pesticides since the mid-20th century to boost agricultural yields and ensure food security. While pesticides including insecticides, herbicides, fungicides, and bactericides have protected crops, their residues persist in soil, rivers, and groundwater, disrupting ecosystems and posing human health risks. Emerging evidence links pesticides to AMR through mechanisms like co-selection, where bacteria develop resistance to pesticides via shared efflux pumps, inadvertently conferring multidrug resistance to antibiotics. This creates a vicious cycle, as resistant bacteria proliferate in agricultural environments, contaminating livestock, crops, and the food chain, and even spreading via migratory wildlife across continents. The economic toll is staggering, with projected losses in global GDP amounting to trillions due to reduced productivity, higher healthcare costs, and diminished agricultural output (3,4).

Beyond agriculture, pesticides influence AMR in urban settings and clinical contexts, where household use leads to low-level exposure that selects for resistant microbes in wastewater and municipal systems. Advanced techniques like metagenomic sequencing and transcriptomic studies have revealed how pesticides induce stress responses in bacteria, promoting horizontal gene transfer, mutations, and biofilm formation environments where resistance genes persist and spread. This interconnectedness underscores the need for holistic approaches, as AMR transcends borders through global trade in contaminated food products, affecting both rural and urban communities. Addressing pesticide-driven AMR requires coordinated action to mitigate its role in transforming routine pathogens into untreatable threats, safeguarding human health, agriculture, and economic stability (5,6).

Kurenbach et al. (2015) conducted a groundbreaking study examining the impact of common herbicides—glyphosate, dicamba, and 2,4-D—on bacterial antibiotic resistance using laboratory cultures of E. coli and Salmonella enterica exposed to sub-lethal doses. The findings demonstrated that herbicide exposure increased bacterial resistance to multiple antibiotics, including ciprofloxacin and ampicillin, primarily through the induction of the AcrAB-TolC efflux pump system, which expels toxic compounds like antibiotics from cells. This research highlighted how widely used herbicides could inadvertently foster environmental antibiotic resistance, providing the first evidence that non-antibiotic chemicals act as selective agents for multidrug-resistant traits, with implications for soil, water, and agricultural microbiomes (7).

Building on this, Kurtenbach et al. (2017) delved deeper into the molecular mechanisms by investigating the role of efflux systems in herbicide-mediated resistance. When efflux pumps were chemically or genetically inhibited in bacterial cultures, herbicide-induced tolerance to antibiotics significantly decreased, confirming efflux activity as a key adaptive response to environmental stress. This study reinforced the idea that low-level herbicide exposure serves as a stressor enabling bacteria to survive antibiotic challenges, offering strong mechanistic evidence for how pesticides contribute to AMR via shared resistance pathways, and emphasizing the need for further research into environmental influences on microbial communities (8).

Addressing pesticide-driven antimicrobial resistance offers substantial further benefits beyond immediate health and economic gains, including enhanced environmental sustainability and biodiversity preservation. By reducing pesticide reliance through integrated pest management (IPM) and biopesticides, ecosystems can recover from chemical residues, restoring natural microbial balances in soil and water that support diverse flora and fauna. This shift also promotes safer food production, with organic farming practices gaining traction due to consumer demand, leading to healthier diets and reduced exposure to toxins. Moreover, innovations like bioremediation using engineered microorganisms to degrade pesticide residues can create new industries and jobs in green technology, while global policy coordination fosters equitable development, particularly in low- and middle-income countries, mitigating health disparities and ensuring food security for future generations (9).

Conclusion, the escalating threat of antimicrobial resistance, fueled by ESBL-producing E. coli and amplified by pesticide use, demands urgent, multidisciplinary action to preserve modern medicine and global health. Pesticides exacerbate AMR through co-selection, horizontal gene transfer, mutagenesis, and biofilm formation, creating interconnected risks across human, animal, and environmental domains, with devastating projections of millions of deaths and trillions in economic losses. The cited studies by Kurenbach et al. (2015 and 2017) provide critical evidence of herbicides' role in inducing efflux-mediated resistance, underscoring the need for reduced pesticide use, safer alternatives like biopesticides, and international standards. By integrating policy, research, education, and bioremediation, we can curb this crisis, yielding benefits like ecological restoration and equitable health outcomes. Only through global cooperation can we safeguard antibiotics as vital tools for infection treatment, ensuring a sustainable future for agriculture, trade, and public health (10,11).

MATERIAL AND METHODS

This experimental study evaluates antimicrobial resistance in ESBL-producing E. coli by comparing bacterial isolates from pesticide-treated agricultural fields (exposed to glyphosate, chlorpyrifos, and cypermethrin) versus pesticide-free fields, conducted over 4 months at Choudhry Muhammad Akram Teaching Hospital Laboratory. A

sample size of 138 was calculated using a formula assuming 10% prevalence and 5% margin of error, with stratified random sampling from three fields (each with three collection sites) to ensure coverage. Soil (50g from top 10cm) and water (100mL) samples are collected post-treatment or from untreated fields (no pesticide use for ≥5 years), adhering to inclusion/exclusion criteria for purity and viability. E. coli isolation involves serial dilution, plating on MacConkey and EMB agar, and biochemical confirmation (indole, TSI, citrate, urease, motility tests). Antibiotic susceptibility testing uses Mueller-Hinton agar with disks for β-lactams, carbapenems, fluoroquinolones, and aminoglycosides, incubated at 37°C for 18-24 hours, with zones measured via digital caliper and interpreted per CLSI guidelines; triplicate testing ensures reproducibility. Results are analyzed for resistance patterns, mean zone diameters, and susceptibility categories using Excel or SPSS (12,13).

RESULTS:

A total of 70 samples were tested for antibiotic sensitivity testing, out of these 40 (57%) were pesticide exposed, 20(29%) were exposed with mixed pesticides of different kinds, 10 (14%) were not exposed to any kind of pesticides.

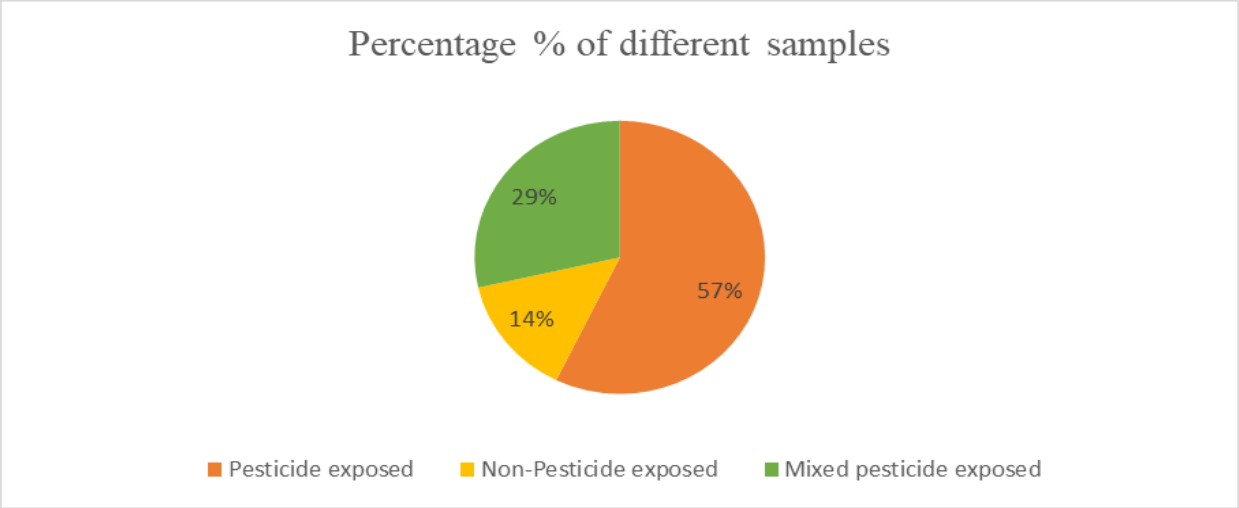

Figure 1: Sample wise distribution

Table 1: Sample wise distribution and percentage of each type of sample

Sample type	No. of samples	Percentage %
Pesticide-exposed	40	57%
Mixed-pesticide exposed	20	29%
Non-pesticide exposed	10	14%

All the samples after isolation from soil checked for sensitivity with 6 antibiotics, each isolate checked for sensitivity with Beta-lactam antibiotics like Cefotaxime and Ceftazidime, and also with other antibiotics like Gentamicin, Imipenem, Amikacin and Ciprofloxacin to check either against them resistance developed or not.

Results of Pesticide exposed sample

To assess whether glyphosate exposure triggered ESBL production, the resistance profile of the exposed E. coli isolates(n=40) was tested against some antibiotics. Out

of 70 samples, 40 exposed to pesticide glyphosate, of which Cefotaxime showed sensitivity for 2(5%), intermediate for 10(25%) and resistant for 28(70%) samples, Ceftazidime showed sensitivity for 19(47.5%), intermediate for 8(20%) and showed resistance for 13(32.5%) samples, Amikacin showed sensitivity for 25(62.5%), Intermediate for 13(32.5%) and resistant for 2(5%). Imipenem shows sensitivity for 35(87.5%), intermediate for 5(12.5%) and was not resistant for any sample. Ciprofloxacin showed sensitivity for 27(67.5%), intermediate for 11(27.5%) and resistance for 2(5%) samples. Gentamicin showed sensitivity for 21(52.5%), intermediate for 16(40%) and resistance for 3(7.5%) samples.

Table 2: Susceptibility profile of pesticide-exposed E. coli showing resistance trends against beta-lactam and non-beta-lactam agents.

Antibiotic	Sensitive n (%)	Intermediate n(%)	Resistant n (%)
Cefotaxime	2(5%)	10(25%)	28(70%)
Ceftazidime	19(47.5%)	8(20%)	13(32.5%)
Amikacin	25(62.5%)	13(32.5%)	2(5%)
Imipenem	35(87.5%)	5(12.5%)	0(0.0%)
Ciprofloxacin	27(67.5%)	11(27.5%)	2(5%)
Gentamicin	21(52.5%)	16(40%)	3(7.5%)

The most significant finding was the profound reduction in susceptibility to third-generation cephalosporins, which are the primary substrates for ESBL enzymes. Cefotaxime demonstrated the highest resistance rate, with 70.0% (n=28) of the pesticide-exposed isolates classified as resistant. Similarly, Ceftazidime resistance was observed in 32.5% (n=13) of the population.

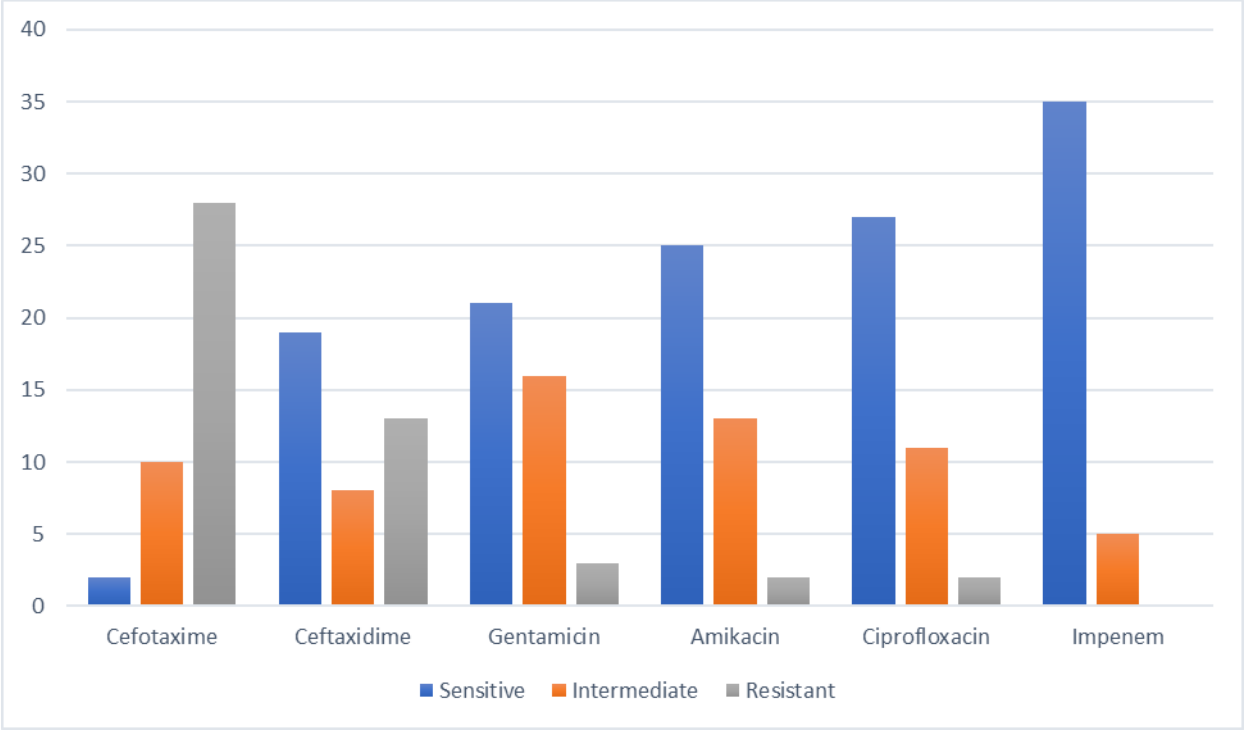

Figure 2: Susceptibility profile of pesticide-exposed E. coli showing resistance trends against beta-lactam and other agents

Furthermore, the data indicates a broader stress response; Gentamicin and Ciprofloxacin showed elevated "Intermediate" counts (40.0% and 27.5% respectively).

Results of mixed-pesticide exposure samples

To determine if exposure to a combination of pesticides exerts a synergistic selective pressure on E. coli, the susceptibility profile of samples treated with a mixed pesticide solution (n=20) was analyzed. Out of 70 samples, 20 were exposed to mixed pesticides, of which Cefotaxime showed sensitivity for 0(0%), intermediate for 2(10%) and resistant for 18(90%) samples, Ceftazidime showed sensitivity for 0(0%), intermediate for 11(55%) and showed resistance for 9(45%) samples, Amikacin showed sensitivity for 10(50%), Intermediate for 7(35%) and resistant for 3(15%). Imipenem shows sensitivity for 13(65%), intermediate for 5(25%) and resistant for 2(10%) samples. Ciprofloxacin showed sensitivity for 12(60%), intermediate for 3(15%) and resistance for 5(25%) samples. Gentamicin showed sensitivity for 12(60%), intermediate for 2(10%) and resistance for 6(30%) samples.

Table 3: Susceptibility profile of Mixed pesticide-exposed E. coli showing resistance trends against beta-lactam and non-beta-lactam agents.

Antibiotic	Sensitive n (%)	Intermediate n(%)	Resistant n (%)
Cefotaxime	0(0%)	2(10%)	18(90%)
Ceftazidime	0(0%)	11(55%)	9(45%)
Amikacin	10(50%)	7(35%)	3(15%)
Imipenem	13(65%)	5(25%)	2(10%)
Ciprofloxacin	12(60%)	3(15%)	5(25%)
Gentamicin	12(60%)	2(10%)	6(30%)

Exposure to the complex chemical mixture resulted in an escalation of Cefotaxime resistance to 90.0% (n=18), with zero isolates retaining sensitivity. Furthermore, Ceftazidime susceptibility was entirely lost, registering 0% sensitivity and 45.0% resistance (n=9). This amplified resistance profile suggests that the combination of pollutants generates synergistic stress, pushing the bacterial population to a far more resilient state than exposure to glyphosate alone.

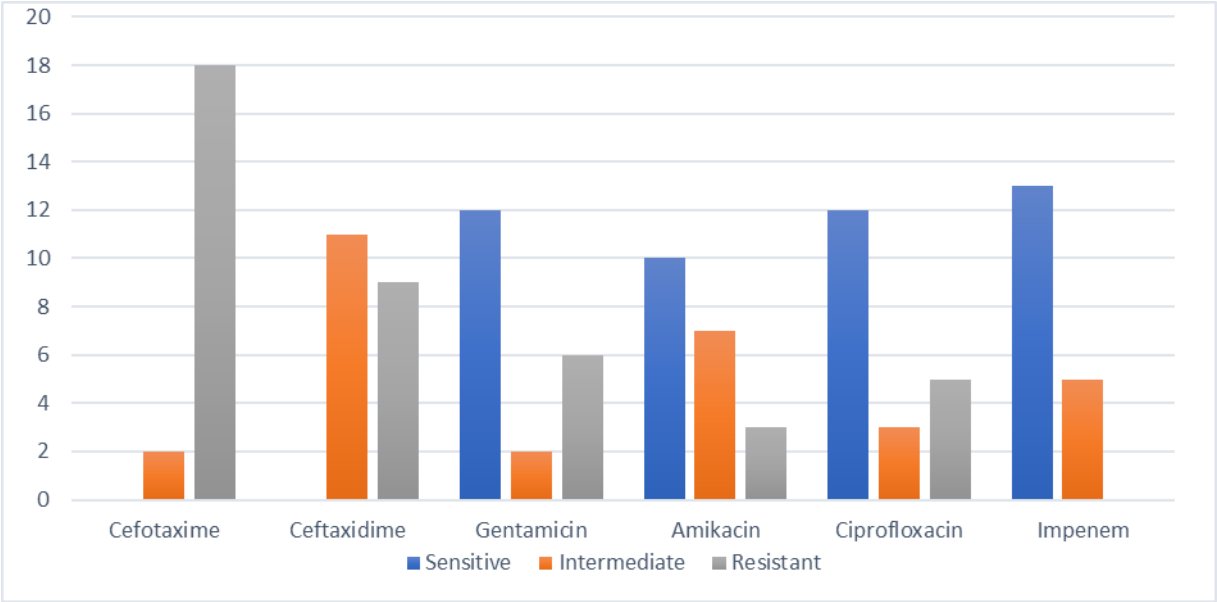

Figure 3: Susceptibility profile of Mixed pesticide-exposed E. coli showing resistance trends against beta-lactam and other agents

Cefotaxime, the primary marker for CTX-M type ESBLs, exhibited a resistance rate of 90.0% (n=18), with no isolates remaining sensitive. Similarly, Ceftazidime showed 0% sensitivity, with the population split between intermediate (55.0%) and resistant (45.0%) phenotypes.

Susceptibility of Non-Exposed Control Isolates

Antibiotic susceptibility testing was performed on 10 E. coli isolates that were isolated from soil in standard conditions without exposure to any pesticides (n=10). These isolates serve as the baseline control for comparison against the exposed groups. Out of 10 samples grown in natural conditions without pesticide exposure, Cefotaxime showed sensitivity for 7(70%), intermediate for 3(30%) and resistant for 0(0%) samples, Ceftazidime showed sensitivity for 9(90%), intermediate for 1(10%) and showed resistance for 0(0%) samples, Amikacin showed sensitivity for 8(80%), Intermediate for 2(20%) and resistant for 0(0%). Imipenem shows sensitivity for 9(90%), intermediate for 1(10%) and was not resistant for any sample. Ciprofloxacin showed sensitivity for 9(90%), intermediate for 1(10%) and resistance for 0(0%) samples. Gentamicin showed sensitivity for 7(70%), intermediate for 3(30%) and resistance for 0(0%) samples.

Table 4: Susceptibility profile of non-pesticide exposed E. coli showing resistance trends against beta-lactam and non-beta-lactam agents.

Antibiotic	Sensitive n (%)	Intermediate n(%)	Resistant n (%)
Cefotaxime	7(70%)	3(30%)	0(0%)
Ceftazidime	9(90%)	1(10%)	0(0%)
Amikacin	8(80%)	2(20%)	0(0%)
Imipenem	9(90%)	1(10%)	0(0%)
Ciprofloxacin	9(90%)	1(10%)	0(0%)
Gentamicin	7(70%)	3(30%)	0(0%)

Sensitivity levels were uniformly high. Imipenem, Ciprofloxacin, and Ceftazidime all showed excellent sensitivity at 90.0% (n=9). The remaining drugs (Amikacin, Cefotaxime, and Gentamicin) showed sensitivity rates of 70.0% to 80.0%, with the remaining isolates classified as having intermediate susceptibility.

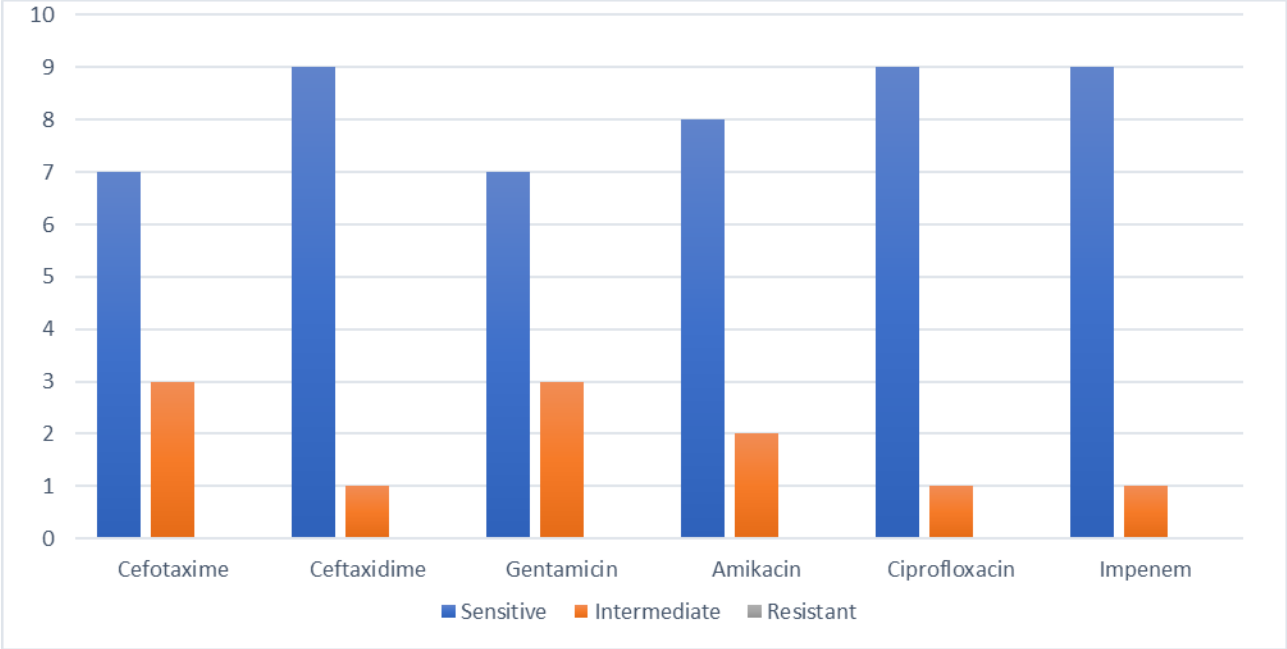

Figure 5: Susceptibility profile of non-pesticide exposed E. coli showing resistance trends against beta-lactam and non-beta-lactam agents.

DISCUSSION

This study demonstrates a clear link between pesticide exposure and the emergence of antimicrobial resistance (AMR) in Escherichia coli, highlighting how agricultural chemicals influence bacterial adaptation and antibiotic susceptibility (14). Amid growing recognition of AMR as a global health threat, these findings underscore environmental factors' role in resistance spread, showing that pesticides can induce ESBL-producing strains and multidrug resistance (MDR) even without antibiotics. Isolates from pesticide-exposed fields exhibited altered susceptibility patterns, evolving resistance through selective pressure alone (15,16).

In the untreated control group, representing natural environmental conditions, E. coli isolates showed complete sensitivity to all tested antibiotics, including cefotaxime, ceftazidime, ciprofloxacin, gentamicin, imipenem, and amikacin, with high sensitivity rates (e.g., 90% to imipenem, ciprofloxacin, and ceftazidime). No resistance was observed, aligning with studies like Van Bruggen et al. (2019) and Kahlmeter et al. (2003), which found low resistance in uncontaminated soils. This confirms that resistance in exposed groups stems solely from pesticide effects, not pre-existing traits (17,18).

Exposure to glyphosate alone induced significant changes, particularly in β-lactam resistance. Cefotaxime resistance rose from 54% to 70%, indicating ESBL enzyme activity, while ceftazidime resistance reached 32.5% (19). However, imipenem remained fully effective, suggesting glyphosate promotes ESBL-type resistance without affecting carbapenems. This aligns with Kurenbach et al. (2015), who noted glyphosate exposure increased MICs for multiple antibiotics via upregulated efflux pumps, and Kabarrynedium et al., who observed rising ESBL genes in glyphosate-treated soils. Thus, glyphosate can drive resistance in antibiotic-naive populations, even against fluoroquinolones and aminoglycosides (20,21).

The mixed-pesticide group yielded the most alarming results, with synergistic effects from combined chemicals. Cefotaxime resistance hit 90%, with no sensitive isolates, confirming robust ESBL activity (22). Ceftazidime resistance increased, and imipenem resistance surged to 10%, marking carbapenem resistance in an environmental context—a first for this study. MDR traits emerged, including

resistance to gentamicin and ciprofloxacin. These findings echo Motta et al. (2018) and Zhang et al. (2019), who reported that chemical mixtures disrupt microbial communities, favoring resistant strains and amplifying multidrug genes through cumulative stress (23,24).

Co-selection was evident, where pesticide and antibiotic resistance co-evolve via shared mechanisms like efflux pumps or mobile genetic elements (25). Wicke et al. (2019) and Hamieh et al. (2025) support this, noting pesticides enhance plasmid transfer and cross-resistance. The expanded resistance spectrum in mixed exposures reflects synergistic pressures, transforming susceptible bacteria into MDR pathogens (26,27).

Public health implications are profound: Pesticide-intensive agriculture generates resistant E. coli that can enter human systems via water, soil, crops, or contact, as seen in Anjum et al. (2012). Carbapenem resistance complicates treatment, signaling a global AMR crisis exacerbated by environmental chemicals. This study emphasizes the need for stricter controls, integrated pest management, and monitoring to balance agriculture with ecosystem health (28,29).

In conclusion, pesticides drive bacterial adaptation from baseline sensitivity to ESBL and MDR, supporting fears of diminished antibiotic efficacy. Further research on resistance patterns and pesticide regulation is essential to mitigate this interdisciplinary threat across agriculture, microbiology, and public health (30).

CONCLUSION:

Pesticide exposure is a primary driver of antimicrobial resistance in Escherichia coli, causing bacteria to develop resistance traits like ESBL activity and multidrug resistance even without direct antibiotic contact. In the absence of chemical stressors, bacterial populations maintain high susceptibility to antibiotics, as seen in untreated control groups. Individual or combined pesticide exposure significantly alters bacterial physiology, accelerating resistance to multiple antibiotics in agricultural settings. Mixed pesticide environments exert a stronger impact than single pesticides, highlighting synergistic effects from agrochemical interactions. These findings underscore pesticides' role as environmental agents that indirectly threaten human health by disrupting microbial populations, reinforcing AMR's multi-causal nature tied to agriculture and ecology.

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