Chapter

# Antimicrobial Resistance in *Escherichia coli*

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## Abstract

The ability of microbes to resist or neutralize the action of drugs that have been used against microbes is considered as antimicrobial resistance (AMR). AMR among different strains of *Escherichia coli* is considered as a major threat to public health. Drug-resistant in *E. coli* is found predominantly in the hospital sittings, in the community, and surrounding environment. It has adopted different defensive strategies to minimize the effects of drugs. Extended-spectrum β-lactamase (ESBL), fluoroquinolones, and carbapenemases have been considered as strong resistance strategies being present in most of resistant bacterial strains. Mobile genetic elements (MGEs) have the major contribution in the transfer of resistance genes in between or among bacterial cells. Plasmids are normally present in most of resistant strains, helping in the transfer of genetic material between bacterial cells. Transposons another MGEs, are being considered as one of the major sources of resistance transmission. Collectively, MGEs play an important role in facilitating in exchange, acquisition, and dissemination of resistance genes. Resistance in *E. coli* has been reported worldwide and there is variation in its resistance pattern. *CTX-M* ESBLs, carbapenems, colistin-resistant, and ST-131 *E. coli* resistant clones are considered the most dominant phenotypes. The aforesaid resistant variants are predominantly found in densely populated regions, Sub-Saharan Africa, China, and South Asian countries.

**Keywords:** antibiotics resistance, trends, mobile genetic elements, epidemiology



## 1. Introduction

Antimicrobial resistance is the capability of bacterial pathogens to neutralize the bactericidal effects of antibiotics. Antibiotic resistance arises due to the changes that take place in bacteria in a way that decreases the efficiency of antibiotics, chemicals, or other mediators that are used for infections control [1]. Globally, antimicrobial resistance is the main problem associated with humans' and animals' health. With the emergence of resistance clones, those antibiotics that were previously considered as broad-spectrum lost their efficacy, this increasing trend in resistant clone posture serious problem for the clinicians to deal with such pathogens. As we know that antibiotics are categorized according to the type of bactericidal activity, their mode of action, their chemical nature, and their origin. Further, these drugs can be characterized on the basis of their mode of action like their involvement in bringing complexity in the synthesis of the bacterial cell wall, depolarization of cell membrane, inhibiting microbial key protein synthesis, and altering nucleic acid synthesis. In early era, microbial secondary metabolites were considered the

main treatment option for microbial infection, but later due to increasing resistance issues, synthetic derivatives of these natural products were being searched. There is a different reason that has pushed microbes to adopt drug resistance strategies. The use and misuse of antimicrobial agents have led to the emergence of resistance [2] Similarly the usage of low-standard antibiotics in some parts of the world particularly in underdeveloped countries may be the source of the emergence of drug resistance [3]. *Escherichia coli* strains are resistant because they are part of the natural microbiota of animals, humans and are found in the ecosystem [4]. *E. coli* is the most prevalent facultative bacteria found in humans and animals some strains being responsible for initiating infections. The foremost concern is their probable transmission of resistant *E. coli* strains among humans and animals. It uses different routes for their transmission such as direct contact, through food chains, or contact with animal excretions. *E. coli* strains that are considered as multidrug or extreme drug-resistant responsible for enteropathogenic and uropathogenic clones are a specific concern for world health. World Health Organization (WHO) have shown serious concern over the freely spread of resistant clone in the community and environment as it will pose threat to human health and the economy [5]. Although, it is one of the main reservoirs of resistance genes that might be responsible for treatment failures in both human and animal medicine. An increasing trend of resistant genes has been observed in *E. coli* in the current decade. Due to its large genomic fragments, MGEs are involved in the transfer of resistance genes in the enterobacteriaceae family, particularly among *E. coli* strains. Plasmids are normally present in most of resistant strains, help in the transfer of genetic material among bacterial species. Transposons another MGEs, are being considered as one of the major sources of resistance transmission. In *E. coli* several antimicrobial resistance trends are associated with plasmid-mediated colistin resistance *Mcr-1* gene [6]. But horizontal gene transfer [HGT] are mainly involved in resistance dissemination [7]. It is estimated that almost 700,000 deaths are attributed yearly, and this could increase to 10 million deaths worldwide annually by 2050. Almost 2.8 million people are suffering, and approximately 35,000 peoples die each year in the USA alone due to antimicrobial resistance [8].

## 2. AMR trends

Capability of bacterial species to resist the action of a particular antimicrobial agent is referred to as antimicrobial resistance, and this phenomenon has been remarkably proliferated over the years. The availability and usage of antimicrobial have contributed in the increased incidence of resistant strains [9]. Though antimicrobial resistance is a natural phenomenon and was considered under control in the past but recently it is envisaged a high-level risk for world health [10]. Mainly three reasons responsible for antimicrobial resistance are; (a) increase usage of antibiotics, (b) due to unseriousness of the patients about treatments being suggested, (c) replacement of the existing class of antibiotics with a new one. Bacterial resistance to antimicrobial agents is classified into three types, namely intrinsic resistance, adopted resistance, and acquired resistance see in **Figure 1**.

The most common example of an intrinsic resistance system is the Acr AB/Tol C EPs in *E. coli*, which has a wide substrate specificity and can export antibiotics, detergents, dyes, and various disinfectants [11]. *E. coli*, Tol C has many efflux systems including the resistance-nodulation-division (RND) pumps as well as the main facilitator superfamily (MFS) systems [12]. RND pumps function as proton antiporters and confer resistance to tetracyclines, chloramphenicol, some β-lactams, vancomycin, and fluoroquinolones being supported by intrinsic resistance [13, 14]. While adopted

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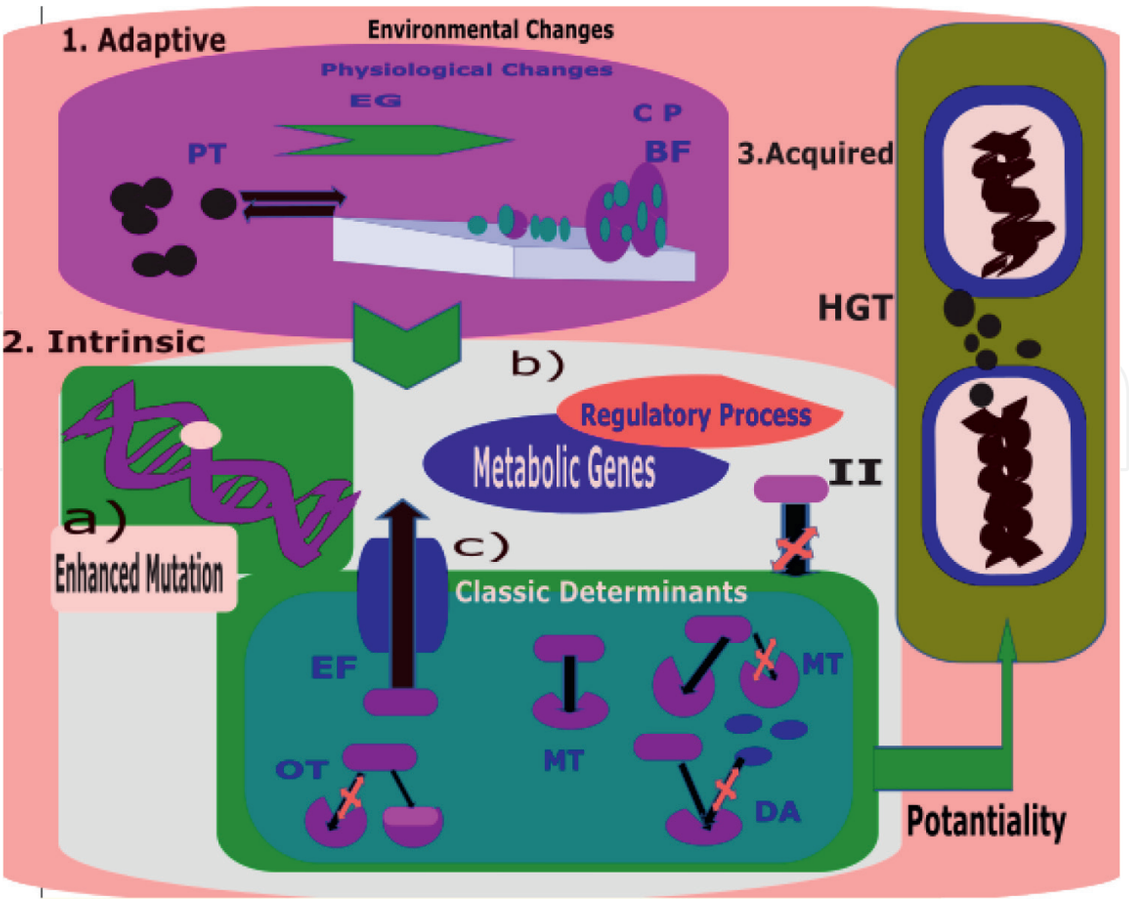


**Figure 1.**
*Three types of antimicrobial resistance transmission and virulence factors can be classified into 1. adaptive resistance, 2. intrinsic resistance, and 3. acquired resistance. The adaptive resistance includes, environmentally induced EG (encoded genes) as two phases of bacteria 1) PT represents (planktonic), and BF (biofilms) can induce physiological changes at the cellular level (CP represents cellular process), and cause (a) enhanced mutation levels, (b) modification in metabolic genes and processes of the regulation, (c) classic determinants and a host antibiotic inactivation. Where EF shows efflux, OT (overprotection at the target site), MT (modification at the target site), MT (mutation at the target), DA represents the degradation of antibiotics and II represents impaired influx. This type of resistance increased infections which can potentially be transferred between E. coli strains leading to acquired resistance. Acquired resistance is transmitted through HGT among bacteria.*

resistance contains environmentally induced genetic variations such as biofilm and persisted development, enzymatic driven inactivation of antibiotic see in **Figure 1** [15]. Due to adopted resistance, *E. coli* revealed resistance toward aminoglycoside encoded by *arm-A*, *npm-A*, *rmt-A*, *rmt-B*, *rmt-C*, and *rmt-D* resistant genes [16, 17]. The *rmt* gene provides resistance to gentamicin and amikacin, while *npm-A* provides resistance to gentamicin, neomycin, amikacin, and apramycin. While the most common ESBL gene in *E. coli* isolates of human origin is *blaCTX-M-15* and ST-131 clone and are mainly involved in dissemination AMR [18]. Similarly, the acquired resistance is usually influenced by HGT and may include plasmid-encoded specific EPs and enzymes that alter antibiotics [19, 20]. The increase in carbapenems (CPE) is mainly associated with the extensive dissemination of acquired CPE. CPE encoding genes are usually located in mobile genetic elements (MGEs), implying in the emergence of MDR and XDR strains [21]. Furthermore, colistin believes as a choice of drug for the treatment of resistant pathogens its resistance is facilitated through variations in lipopolysaccharides (LPS). *E. coli* the first pathogen in which plasmid-mediated colistin resistance was observed, through the acquisition of the *MCR-1* gene [6] The *MCR-1* gene could swiftly propagate and can impart resistance to other strains. *MCR-1* protein expression leads to the addition of a phosphor-ethanolamine group to lipid A. This produces a change in the charge of LPS, which in turn reduces the affinity of

| Group of antibiotics | Resistance antibiotics | Enzyme produced | Gene involved | MGEs | Implication in virulence | References |
|---|---|---|---|---|---|---|
| β-Lactams | | β-Lactamases | *Amp C* | Plasmid | Mutation and overexpression of genes | [23] |
| | Penicillin | Penicillinases | | | | |
| | Cephalosporin | Cephalosporinases | *CTX-Ms* | | Plasmid encoded, increased virulence in urinary tract | [24] |
| | | | *OXA* | | Changes in peptidoglycan composition | |
| | Cephamycin | Amp C β-lactamases | *Amp C* | | induced hyperproduction | |
| Fluoroquinolones | Norfloxacin | β-Lactamases ESBL | *Gyr-gene* | Plasmid and Transposons | Interfere with nucleic acid synthesis caused mutation | [25] |
| | Ciprofloxacin | | *Par-C* | | To inhibit topoisomerase IV | |
| Aminoglycosides | Tobramycin | | *Arm-A* | | Higher risk of illness and death | [26] |
| | Gentamicin | | *Rmt-B* | | | |
| | Tetracyclines | | *Tet-A* | | Increased expression of virulence genes | |
| | | | *Tet-B* | | | |
| | | | *Acr-AB* | | | |
| | | | *ANTs* | Plasmid and Genomic Islands | Completely deactivate the enzyme | |
| | | | *AACs* | | | |
| | | | *APHs* | | | |
| Carbapenems | Imipenem-cilastatin | Carbapenemases metallo-β-lactamases | *NDM-1* | Plasmid | Degrade the β-lactam, increase the risk for development of acquired resistance | [27] |
| | | | *OXA-48* | | | |
| Colistin | Polymyxin E | | *Mcr-1* | Plasmid | Cause mutation and reduce the affinity of antibiotics to LPS | [28] |
| Trimethoprim/ sulfamethoxazole | Co-trimoxazole | ESBL | *DHFR* and *DHPS* | Plasmid | Block formation of nucleic acid inhibit dihydropteroate synthetase (DHPS) | [29] |

**Table 1.**
*Antimicrobial resistance, MGEs, and their associated virulence factors.*

colistin for LPS [22]. Resistance to colistin can be due to mutations in chromosomal genes or it may be acquired. Furthermore, quinolones and fluoroquinolones are important antimicrobial agents implied for treating pathogenic microbes associated with humans and animals. Resistance to these antimicrobial agents is generally due to mutations in the drug targets, namely, DNA gyrase and topoisomerase IV genes seen in **Table 1** [30]. All such changes will lead to the transfer of resistance genes from chromosomal DNA into a plasmid, which will have more chances of dissemination in the human population. Additionally, it will be prone more harmful to human health due to variation in their resistance determinant transfer like from chromosome into plasmid, will definitely bring variation in expression pattern and dispersal [28, 31]. Another well-documented example is a transfer of the chromosomal β-lactamase gene *Amp C* to a plasmid and their subsequent global dissemination see in **Table 1** [28].

## 3. Mobile genetic elements of *E. coli* associated with antibiotic resistance genes

Mobile genetic material (MGEs) has an important role in transferring resistance. Mutation has a key role in bringing changes in a particular DNA fragment. Similarly, HGT, transfer of plasmid or transposons have the major contribution in developing resistance to the reagent. Considering if point mutation brings changes in a promotor region, it will have an impact on the expression of genes [32]. Similarly, a point mutation in the gyrase gene has developed to fluoroquinolone-resistant phenotype [30]. Exogenic resistance genes encoded on plasmids, phage, integrons, and transposons can transfer horizontally through conjugation, transformation, or transduction and can encode all the 3-resistance mechanism (intrinsic, adopted, acquired) Details of genes, their mechanisms, and pathways are explained in the following section.

Resistant pathogens are a major source of infectious diseases worldwide. Infections due to MDR bacteria have considerably increased health care costs. Due to resistant pathogens, morbidity and mortality have been reported in different parts of the world. Molecular characterization showed that extensive multi drug-resistant has commonly been accomplished by the acquisition of pre-existing causes followed by amplification in response to selection. The accumulation, retention, and transfer of resistant genes are frequently due to the activities of MGEs of *E. coli*, MGEs are known as non-core genes, and have a significant contribution to the plasticity of bacterial genomes. Transposable elements, integrons (In), Plasmids, gene cassettes, insertion sequences (IS), bacteriophages, and genomic islands (GIs), all are considered as MGEs. Though, from 20 sequenced *E. coli* genomes, almost 2000 genes were detected to be noncore genes [33]. Transposons (Tn) and IS are discrete segments of DNA that can almost randomly transfer themselves within a DNA molecule. Other mobile elements, like integrons (In), use site-specific recombination to transfer resistance genes among distinct sites. Similarly, these types of MGEs are mostly present in different locations in the form of multiple copies in the genome, they can also facilitate homologous recombination (interchange of sequences between same or different segments). Genetic exchange of Intercellular mechanisms contain transduction (facilitated by bacteriophages), conjugation/mobilization (facilitated by plasmids and integrative conjugative elements [ICE]), and transformation (uptake of various superfluous types of MGEs) support the rapid development of various multi-resistant bacteria in the aspect of antibiotics chemotherapy [34]. Within genomic DNA the presence/absence of MGEs can lead to modification in pathotypes of *E. coli*. In fact, strains of *E. coli* have been identified as part of the normal microbiota of the human gastrointestinal tract. In addition,

there are also pathogenic strains, and thereby the *E. coli* strains are characterized either as (i) non-pathogenic, which are commensal (ii) intestinal pathogenic strains (IPEC), or (iii) extraintestinal pathogenic (EXPEC) strains. Integration, excision, and rearrangements of the DNA fragments can be the mechanisms behind the rapid evolution of pathogenic *E. coli* strains [35].

### 3.1 Transposons

Transposons (Tn) can be defined as a DNA sequence that has potential to jump into different locations of the genome hence, they are called jumping genes. Transposons are divided into two-main groups: class I (Retrotransposons) and class II (DNA transposons). Retrotransposons are mostly found in eukaryotic organisms while DNA transposons can be found in both prokaryotes and eukaryotes. Prokaryotic DNA transposons harbor antibiotic resistance genes. It has the potential to move from plasmid to plasmids or from chromosomal DNA into a plasmid, as a result, it became the source of resistant genes dissemination [36, 37]. Transposon's elements have two major characteristics that differentiate them from other genetic elements. on basis of its mobile nature, it can move from one place to another and bring variation in the genetic makeup of the organism. During transpositions process, transposons can transmit resistance genes and can multiply intracellularly. Despite its large number, only few copies get access into an integral part of the genome. Transposons have stability and are maintained by their capability to replicate and maintain their existence [38]. Transposable elements have an important role in genome evolution and organization [39]. *E. coli* transposable elements are divided into three different types: (a) composite transposons, (b) non-composite transposons, (c) insertion sequence elements (ISE). Composite and non-composite transposons have extra genetic material not related to transposition, for example, antibiotic resistance genes. Composite transposons are lined by the IS. IS elements are the simplest type of transposable elements and do not carry extra genetic information apart from those needed for their mobility [40].

### 3.2 Plasmids

Plasmids are circular, self-replicating extra-chromosomal DNA elements. Besides the genetic information required for the autonomous multiplications, it has extra genetic information needed for suppression of antibiotic actions. It also encodes genes for virulency, involves in the removal of hazardous material, or is required for regulation of other metabolic functions [41]. Plasmids are commonly used cloning vectors and are categorized into different incompatibility (Inc) groups. Inc. groups are designated on basis of the incapability of two plasmids to co-exist together [42]. Same Inc. group of the Inc. plasmids have the same type of replication region and thus have incompatible replication, it cannot co-exist. Plasmids belonging to the IncX family encode different resistance genes, mostly circulated among *Enterobacteriaceae* [43]. For example, an IncX plasmid, which is responsible for encoding *bla-SHV-12* resistant gene was reported in *E. coli*. The *bla-IMP-2* gene, encoding an imipenem-hydrolyzing β-lactamase, is carried by pRJ-18, an IncFIB plasmid [44]. In Europe, ESBL-encoding plasmids belonging to the Inc. F, A/C, N, H12, 11, and K type have been reported. Another important ESBL genes, *CTX-M-1*, is reported in Inc1 or IncN plasmids. For example, *CTX-M-1* ß-lactamase was derived from an animal source disseminated through Inc-1 ST3 plasmid [45]. Similarly, F plasmid, has been reported in *Enterobacteriaceae* [34]. F-like plasmids are also reported in nonpathogenic as well as in pathogenic *E. coli* strains. The whole genome sequence of *E. coli* ST-131 showed the *CTX-M* resistance gene dissemination

and mainly conjugative F plasmid was involved [46]. *Mcr-1* gene conferring resistance to colistin is also spread with help of F Plasmid. Furthermore, this *Mcr-1* gene was found to be carried by 13 various plasmid incompatibility groups and these are Incl-2, Inc-X4, and Inc-HI2 [47]. Some studies have reported transposons involvement in the dissemination of *Mcr-1*. Other *Mcr* genes comprising *Mcr-2*, *Mcr-3*, *Mcr-4*, *Mcr-5* have been seen in a plasmid [48]. Recently in Denmark, a strain identified as *E. coli* ST-410 has been reported harboring resistance toward fluoroquinolones, 3rd-generation, carbapenems, and cephalosporins. Other variants like Inc-X3 plasmid carrying *blaOXA-181* resistant gene and Inc-FII plasmid carrying *blaNDM-5* resistant gene [49]. Plasmids can transfer between bacteria through the conjugation process, that is transfer of genetic material between recipient and donor cell. Conjugative plasmids can transmit transposons or integrons, and such genetic information can be further disseminated horizontally by the conjugation process [50, 51]. For example, *E. coli* is isolated from pig have a conjugative plasmid with *cfr* gene, which conferred resistance to lincosamides, phenicol, pleuromutilin, oxazolidinones, streptogramin [52]. Another important plasmid, a ColV (pCERC3) from a commensal *E. coli* ST95 strains have been reported and revealed resistance against sulfonamide encoded by *sul-3* associated with a class 1 integrons [53] The pE80 plasmid from a foodborne *E. coli* strain encodes multiple resistance determinants *oqx-AB*, *fos-A3*, *blaCTX-M-55*, and *blaTEM-1* and therefore confers resistance to streptomycin, tetracycline, kanamycin and olaquindox/quinolone [54]. In addition to antibiotic resistance genes, plasmids are involved in the transfer of virulence-associated genes. In Germany, outbreaks of enteroaggregative *E. coli* (EAEC)-enterohemorrhagic *E. coli* (EHEC)-O104:H4 strain was reported harboring have three-different plasmids: p-AA (7.4 kb), p-ESBL (89 kb), and p-G (1.5 kb) [55, 56]. p-AA plasmid harboring information for different virulence factors like fimbriae for adherence, diffusion in surface protein, protease, and the virulence regulator A and R [57]. Moreover, an EHEC O104:H7 strain, being isolated from animal's waste, possessed Inc-B/O/K/Z and IncFIB plasmids. It encodes genes responsible for the expression of main virulence genes, including, entero hemolysin and auto transporter [58]. Another important *E. coli* serotype is the O103 serotype, the 2nd most common serogroup main causative agent of human foodborne disease. It has pO157 plasmid encoding different virulence factors including entero hemolysin and type II secretion protein [59].

### 3.3 Bacteriophages

Bacterial viruses that cause infections in bacterial cells are called as bacteriophages. it has an important role in the dissemination of virulence-associated and antibiotic resistance genes among foodborne pathogens, As we know viruses are found ubiquitously and are present in oceans, sewage, soils, and various microbial communities [60, 61]. Phages have an important role in protecting the bacterial colonization of mucosal surfaces [62]. In the case of lytic phages, there has an important role in bacterial DNA transfer, and the process is called transduction (generalized transduction), while temperate phages can transmit only some particular genes in the bacterial chromosome (specialized transduction). During this some segments of bacterial DNA are co-edited with the prophage DNA for example tetracycline resistance gene from the *E. coli* O157:H7 to the K-12 AB-1157 strain of *E. coli* [60, 63]. Bacteriophages are actively in the acquisition of β-lactamase genes such as *blaCTX-M, blaSHV, blaTEM, qnr A, qnr B*, and *qnr S*. like P1 bacteriophage with *SHV-2* gene has been reported [64]. Additionally, phages are also involved in the dissemination and transformation of staphylo-kinase, superantigens, and phosphor-lipase or DNase virulence factors. Bacteriophage λ, transmit not only

adhesion genes of bacteria but also transfer the housekeeping genes of bacteria. Cytolethal distending toxins (Cdts) are inhibitory cyclomodulins, which prevent eukaryotic cell proliferation, *E. coli* strains are also associated with its production and it has been established that *Cdt-I* produced by EPEC strains the main source was lambdoid prophage [65]. Additionally, *E. coli* phage (lambdoid prophage) transfers the *Cdt* gene group encoding the *Cdt-A*, *Cdt-B*, and *Cdt-C* subunits of the *Cdt-I* holotoxin. One of the important toxins known as Shiga toxin 2, which is a virulence factor in *E. coli* O157:H7 strain being transferred by temperate phage. Furthermore, some other variants of Shiga toxin comprising of the infective *E. coli* O157 strain another variant Shiga toxin 2-c are also encoded by phages. For example, some phages such as phi-C119 can be used as biological control mediators, as they can lyse and infect their bacterial hosts [66].

### 3.4 Genomic islands (GIs)

Genomic islands (GIs) comprise of more than 10 kb DNA in length, exchanged frequently among bacterial isolates. GIs encode proteins for transfer, restriction/alteration, or other proprieties and recombination, for example, gene groups for metabolic adaptation, virulence, and or bacterial resistance [67]. GIs that are involved in the expression of virulence factors is called pathogenicity islands (PAIs) [68]. It encodes VFs comprising of adhesins, invasions, capsule formation, toxins, uptake system of iron, distinct secretion systems. Their GC contents vary in comparison to the genome. Their integration site is situated on the tRNA genes and repeated sequences, which is comprising at least one MGEs containing plasmids remnants, integrons, insertion sequences, and related gene cassettes. For the integration of foreign DNA, tRNA-encoding genes are considered as the hot spot. By site-specific recombination, some PAIs can be edited from bacterial chromosome [69]. Primarily, PAIs have been described in the uropathogenic *E. coli* genome and later cases were reported in other pathogenic bacteria [70]. Currently, PAIs are spread between plants and animals associated with bacterial pathogens, have a great influence on the rapid evolution of virulent and resistant strains. In *E. coli*, the locus of enterocyte effacement (LEE) is best example of PAIs, and its size is about 35 kb. It has a main role in bacterial adherence to the epithelial cells of the intestine [71]. High-pathogenicity Island (HPI) was found in enteroaggregative, enteropathogenic, entero-invasive, and enterotoxigenic *E. coli* [72].

## 4. Global antibiotics resistance in *E. coli*

As earlier described, *E. coli* is one of the important bacteria, causing infections in the gastrointestinal tract [73]. Worldwide, AMRs in *E. coli* have been reported which show significant geographic variation as well as differences in various populations and environments. The evolving of ESBL and fluoroquinolones resistance and lack of availability of effective treatment in infections in *E. coli* strains spread over the last few years. However, if *E. coli* resistance is not tackle will restrict out treatment strategies, and resistant clones spread in the general population [74].

### 4.1 Emergence of *E. coli* resistance in Europe

In European countries, particularly in *E. coli* AMRs are increasing [75, 76]. AMR is a worldwide threat, with an approximately 25,000 deaths occurring in Europe and 23,000 in the United States each year [77]. Due to MDR strains treatment becomes complicated and there are more chances of its spread. In addition,

particularly *E. coli* is mostly involved in community and hospital-acquired infections [78, 79]. The severity of the disease differs considerably depending upon the *E. coli* strains [80]. Considering the case of Europe, faced two epidemics of the hemolytic uremic syndrome (HUS) and bloody diarrhea between May and July 2011. One major epidemic occurred in Germany (almost 4000 cases of bloody diarrhea, 850 of HUS, and 50 death cases were reported), while few cases were reported in southwest France (15 cases of bloody diarrhea and 9 cases of HUS) [81–83]. Commonly, these outbreaks were caused by a strain of Stx producing *E. coli* [84] which possesses a plasmid encoding ESBL [83]. The ratio of *E.coli* O104-H4-infected patients with complications such as HUS are more prevalent than in earlier epidemics [85]. AMRs *E. coli* strains are observed all around Europe. According to the European center for disease prevention and control (ECDC), the resistance in human sources varies significantly between countries [86]. Though, in each country mostly the prevalence of *E. coli* strains were observed resistant to all antibiotic classes such as 3rd generation cephalosporins, fluoroquinolones, and aminoglycosides. The ratio of isolates resistant to cephalosporins was observed highest in Cyprus (36.2%), Slovakia (31%), and Bulgaria (22.9%) and lowest in Sweden (3.0%) and Norway (3.6%) respectively. While less resistant were found against fluoroquinolones in Sweden (7.9%) and Estonia (9.9%) but fluoroquinolones resistance is more prevalent in Cyprus (47.4%) and Italy (40.5%) and furthermore high prevalence rate of isolates resistant to aminoglycosides were observed in the United States (23.9%), Romania (19.6%), Slovakia (17.9%) and Greece (16.8%), Sweden (3.7%). *E. coli* strains resistant to widespread Penicillin were found in 28 countries. Besides this, 0.04% of *E. coli* strains were observed to be resistant to carbapenems. In Europe, according to a current study resistance due to carbapenemases producing are still circulating [87].

### 4.2 Emergence of *E. coli* resistance in America

In America, increased resistance of fluoroquinolones and cephalosporin in *E. coli* has been reported [88]. In most patients, *E. coli* ST-131 strains have been reported [89]. ST-131 *E. coli* clone is thought mainly involve in AMRs spreading. The most common clinical manifestation associated with *E. coli* is intraabdominal infection (IAIs). Overall, 26% of *E. coli* infections associated IAI in the Latin American region produced ESBLs compared to with all over the world [90]. Region-wise prevalence of ESBL producing *E. coli* within America varies as in Latin America it was higher in 2008 than earlier according to data being shared by the Study for Monitoring AMR trends (SMART). Many surveillance studies have presented that ESBL-producing bacteria are common in Latin America. According to Tigecycline Evaluation and Surveillance Trial (TEST) in Latin America, during the years 2004–2006, where total of 13.5% of *E. coli* isolates with ESBL phenotypes were identified [18]. According to the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) surveillance study performed in 1997 and 2003, South America had a higher ratio of ESBL producing *E. coli* than North America [91]. Similarly in Colombia in 2002 higher cases of ESBLs producers'strains were documented. Based on available data [21–22%], the percentage of *E. coli* isolates in Latin American was higher as compared to other developed countries of the world [88].

### 4.3 Emergence of *E. coli* resistance e in Africa

Proper prescription of drugs is not strictly followed in the developing world. A similar case is Africa countries where no such policy is implemented. There are several challenges to implement sustainable and effective AMRs monitoring

programs in the sub-Saharan Africa to encounter the rapid dissemination of AMRs [92]. Around 50–60% of *E. coli* infections reported in patients have a resistance nature to most of the available antibiotics i-e amoxicillin, ciprofloxacin, cefixime [93]. A current study reported the 48% prevalence of AMR *E. coli* in hospitalized patients in Brazzaville, Republic of Congo [94]. Similarly in another study where 65% to ceftazidime, 57% to amoxicillin, 51% to piperacillin, and 11% to ofloxacin resistant respectively in *E. coli* were documented [95]. First reported case of EHEC *E. coli* O157-H7 first case was reported in 1982 in the USA while in South Africa and parts of the world in 1990 cases were reported. Was found in 1982 in the United State while, in 1990 in throughout the world [96, 97]. Besides this, many infrequent cases of EHEC have been reported in different parts of South Africa. A total of 40,912 patients under the age of 5 years was hospitalized in 1992 due to the onset of diarrhea [98]. In South Africa, the most common strains detected are EPEC with detection rates ranging from 14.8% to 41.7%. Several pathotypes of *E. coli* are significant causes of diarrhea in children particularly in sub-Saharan Africa [94]. Most of the AMR genes are encoded in *E. coli* on MGEs that are transmissible among bacteria permitting the rapid spread and maintenance of resistance genes among species [99].

### 4.4 Emergence of *E. coli* resistance in Asia

*E. coli* is the most common bacterial pathogen associated with UTIs and IAIs, leading to bacteremia in severe cases, Infections caused by AMRs *E. coli* are becoming a serious threat over the last few years [100]. Strain ST-131 is reported worldwide and its infections rate is soaring. In addition, ST-131 strains have been associated with the increased rate of AMRs with *CTX-M* type ESBLs variant [101]. In Asian countries, *CTX-M* and ST-131producing *E. coli* have evolved as a foremost cause of hospital and community-acquired infections [102]. According to an earlier surveillance study, the occurrence of ESBL producing *E. coli* in Asian countries ranged from 2.3% to 40% [103]. *CTX-M* ESBLs are considered the most dominant phenotype. *CTX-M* producing *E. coli* pose a serious threat for densely populated cities and regions [41, 42]. Additionally *KPC* and *NDM* beta-lactamase-producing *E. coli* have been found to be on the rise in certain parts of Asian countries [104]. In some of the most Asian countries particularly [China, Malaysia, Macau, and Thailand], the prevalence rate in newborn sepsis due to AMR *E. coli* was found about 26.1% [105].

#### *4.4.1 China*

China was the 2nd largest consumer of antibiotics in 2010 around the world. According to the available data, the prescription of antibiotics for outpatient and inpatient was 52.9% and 77.5% respectively and only 39.4% and 24.6% were considered appropriate respectively. Among BRICS countries only in China usage of antibiotics has been escalated [57%] as compared to other nations [106]. According to European Antibiotic Resistance Monitoring Network (EARS-Net), in *E. coli* resistance to third-generation cephalosporins has surged from 1.7% to 8% in the period between 2002 and 2009 [107]. Similarly in other findings were conducted on bloodstreams infections where *E. coli* is the most common bacteria. Moreover, *CTX-M-14* was reported as the most persistent ESBL while ST-131 was the most prevalent sequence type [108]. China has the world's fast proliferation of antibiotics resistance, the ratio of *E. coli* resistant to 3rd generation cephalosporins was reported 54.2% in China in 2017 which was higher than Europe (54.2%) [109, 110] According to one study, antimicrobial resistance is potentially responsible for 214,000 of 690,000 annual

neonatal deaths (31%) caused by sepsis. Carbapenems are β-lactam antibiotics that are used to cure severe infections caused by MDRs bacteria particularly *E. coli* [111].

*4.4.2 Bangladesh*

In 2004 a study conducted in Bangladesh, observed a high frequency of almost 43.2% of ESBL producing *E. coli* in an urban hospital in Dhaka [112]. In addition, the prevalence rate of *CTX-M* among ESBL was high (76%). In another study conducted on ESBL, 11% positive ESBL cases were reported, and all these belonged to *CTX-M-1* group [112]. Similarly, *NDM* producing *E. coli* has been reported in diarrhea patients [113]. The environment being contaminated human feces which might be the source to affect the bird's fecal flora [114]. The *E. coli* isolates that were detected in water samples were found resistant to almost one antibiotic of the tested antibiotics, Similarly, there are other reports where *E. coli* isolates were found resistant to cefuroxime, nalidixic acid, ciprofloxacin, and tetracycline see in **Table 1** [115].

*4.4.3 India*

India is one of the world most populated country with weak health care systems are exposed to resistant pathogens. In comparison to Pakistan, China, and Iran it has a similar prevalence rate of resistance, In India, the prevalence of ESBLs producing *E. coli* has been observed in a range between 45 and 79% [116]. *CTX-M-15* produces *E. coli* colonization was most common especially among children [55%] who were admitted in intensive care unit (ICU) [117]. Another report from South India where *CTX-M* positive cases were reported in more than 60% of *E. coli* isolates [118]. In all reported the most frequent isolated group was *CTX-M-1* group *E. coli*. In India, the frequency of ESBL producing *E. coli* was 23% among UTIs patients, with *CTX-M-15* and ST-131 *E. coli* strain was the highest [119].

*4.4.4 Pakistan*

Pakistan is the 6th largest most populous country in the world. Resistance has increased in *E. coli* around the world and sensitivity patterns significantly vary across geographic settings and within the populations [120]. Early in 2000, *CTX-M* producing *E. coli* has been found the most widespread uropathogenic in Pakistan [121]. ESBL and Amp C were observed in 35 and 64% of the *E. coli* isolates [122]. Furthermore, pandemic *CTX-M* producing *E. coli* ST-131 were also reported. *NDM*-producing *E. coli* was predominantly found in hospitalized patients with resistance to ceftriaxone. From 2013 to 2017, a comprehensive report was released on the susceptibility pattern of *E. coli* isolates in hospitalized and non-hospitalized patients. Where *E. coli* isolates of hospitalized patients were more resistant to all antibiotics [123]. The variation in the ratio of resistance between hospitalized and non-hospitalized patients forces us for prior antibiotic susceptibility screening [124]. In Enterobacteriaceae *E. coli* has a high resistance to β-lactam antibiotic*s* of having ESBL phenotype [125]. ESBL positive cases have been reported in different parts of the country [126].

## 5. Conclusions

Antimicrobial-resistant in *E. coli* has become a serious and complex problem worldwide in clinical treatment as well as in veterinary medicine. *E. coli* is intrinsically vulnerable to all clinically important antimicrobial agents, but it has great potential to accumulate resistance genes, through acquired resistance (HGT).

Acquired resistance plays an essential role in the acquisition of new properties, such as antimicrobial resistance, emphasizing the remarkable adaptive potential of *E. coli*. In addition, among all the MGEs, Transposons and plasmid have a significant role in the spread of antimicrobial resistance with high potential in resistance gene transmission. In *E. coli* plasmid and transposons mediated genes are involved in the spread of quinolone and *Mcr* resistance genes. The epidemiological study of AMR in *E. coli* revealed that *CTX-M* beta-lactamase and ST-131 clone have emerged as the main cause of hospital and community-acquired infections across the globe noteworthy in developing countries. This is being linked with lack of proper prescription of antibiotics and no such strict policy is in place. There are several challenges to implement sustainable and effective AMRs monitoring programs in Africa as well as in Asian countries to encounter the rapid dissemination of AMR. There is a dire need to support and develop antimicrobial policy, standard therapy guidelines for control of AMR in hospitals as well as in the community. To promote and regulate the balanced use of medicines and ensure proper patient care at all stages, antibiotics without doctor's prescription should be discouraged and ensure continuous access to essential medicines of guaranteed quality at the hospital and community.

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