Chapter

Antimicrobial Resistance and Virulence of *Escherichia coli* in the Purview of Public Health Monitoring

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Abstract

Antimicrobial resistance (AMR) has emerged as a major threat to human, animal, and environment health in the developed as well as the developing nations. The usage of antibiotics outside of the prescribed parameters in both the healthcare and livestock sectors is directly tied to this resistance event. Additionally, several *Escherichia coli* strains harbor the AMR genes, which can be transferred to humans leading to public health problems. Depending on the type of antibiotics used, *E. coli* has evolved to prowess several resistance mechanisms. Resistance genes that are horizontally transmissible also encode this resistance mechanism. Different resistance genes for each class of antibiotics are encoded by resistant *E. coli*. In conclusion, the current chapter ushers light on the molecular evolution of resistance and the regulatory genes contributing to the development of MDR in *E. coli*. Moreover, we have also discussed about the inappropriate practices of prescribing the antibiotics leading to intensifying the MDR in bacteria envisaging the implementation of rigorous guidelines for proper use of antibiotics in human beings.

Keywords: *E. coli*, antimicrobial resistance, genes, pathogenicity, virulence

1. Introduction

The primary concern that impacts public health in the twenty-first century is the resistance of pathogenic microorganisms to antibiotics [1]. This resistance is posing a more significant threat to public health worldwide [2]. Numerous classes of antibiotics can simultaneously render microorganisms resistant. The usage of antibiotics outside the prescribed parameters is linked to the emergence of antimicrobial resistance (AMR) [3]. The primary reasons fueling the egression of AMR in bacteria are its inappropriate use in agriculture, retail sectors like pharmacies, industries, and inefficacious prevention and control of infections in health care systems [4, 5].

The gastrointestinal tract of humans and animals is a reservoir of *Escherichia coli* which is a facultative anaerobe and usually, a harmless organism [6]. However, a few strains of *E. coli* have been known to cause infections in the gastrointestinal, urinary, and central nervous systems [7, 8]. Continuous exposure to antibiotics has shown to confer AMR in *E. coli* [9, 10]. Extended-spectrum β-lactamases (ESBLs) are plasmid-mediated enzymes that hydrolyze β-lactam antibiotics, including penicillin, cephalosporin, and the monobactam aztreonam, resulting in multidrug-resistant (MDR) organisms. Bacteria exhibiting ESBLs have been linked with unsatisfactory treatment outcomes [11]. MDR *E. coli* produces ESBLs is an example of antibiotic resistance linked to the infections that can be fatal [12]. Such AMR strains of *E. coli* present in animals are significant in developing infections in humans [6, 13–19]. Studies showed that through the consumption of contaminated food and water, AMR strains of *E. coli* can be transmitted from the environment to humans [9]. Therefore, evaluating the widespread of such MDR *E. coli* in various habitats becomes very necessary for setting guidelines in animal and human health care domains [17–19].

To this end, we conducted a systematic review and meta-analysis to investigate the prevalence, molecular evolution and the regulatory genes contributing to AMR in *E. coli*. We have also discussed the factors contributing to the development of AMR and possible ways to tackle and mitigate multidrug resistant in *E. coli*.

2. An overview of *E. coli*

E. coli is a Gram-negative facultative anaerobe which belongs to *Enterobacteriaceae* family of the Gammaproteobacteria class [20]. It is commonly found as normal microflora in human and animal gut [21]. Sequence analysis of the *E. coli* genome was first reported in 1997. Since then, more than 4800 *E. coli* genomes have been sequenced [22, 23]. *E. coli* has been widely used to monitor AMR in livestock and food of animal origin. This is because *E. coli* can be found in the digestive tracts of warm-blooded animals [24]. Furthermore, various strains of *E. coli* are probable sources of the AMR gene, which can be transmitted to humans through various means [21, 25]. *E. coli* carried through feces or treatment of wastewater disposed of in waterways can pollute the environment [26]. The concentration of *E. coli* per gram of feces differs over the host species, usually reaching 10^7–10^9 in humans and 10^4–10^6 in domestic animals [27]. Shiga toxin-producing *E. coli* (STEC), entero-toxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), diffusely adherent *E. coli*, and entero-invasive *E. coli* are among the six intestinal pathotypes of *E. coli*. These bacteria are categorized according to their pathogenicity mechanisms and virulence traits [28, 31]. *E. coli* is a major cause of enteric foodborne illness, bloodstream infections, intra-abdominal infections, and urinary tract infections (UTIs) in animals and humans [30, 31]. UTIs can also be caused by *Proteus* spp., *Staphylococcus saprophyticus*, *Klebsiella* spp., and other *Enterobacteriaceae* in addition to *E. coli*. However, *E. coli* is regarded as the most prevalent source of nosocomial and community-acquired UTI among bacteria that cause UTIs. Additionally, patients' history of UTI raises their risk of infection [22]. Antibiotics such as cotrimoxazole (trimethoprim/sulfamethoxazole), nitrofurantoin, ciprofloxacin, and ampicillin are used as therapeutic methods for treating UTIs [32, 33]. However, research on antibiotic resistance in *E. coli* isolates from the urinary tract have revealed a rise in resistance to several antibiotics, such as ampicillin and cotrimoxazole [32]. Bloodstream infections brought on by *E. coli* can result in morbidity, death, and other health issues [34]. These infections may raise hospital mortality rates and result in antibiotic resistance, which

lengthens hospital stays [35]. There have been reports of nosocomial bloodstream infections brought on by resistant bacteria, particularly in fragile and high-risk environments like critical care units and pediatric departments [36–38].

3. Molecular evolution of AMR in *E. coli*

AMR has been found to stem from human activities and indiscriminate or irrational uses of antibiotics. Various studies at genomic level pertaining to bacterial commensals and environmental bacteria revealed the presence of significant numbers of resistance determinants already embedded within their genomes not generated from any horizontal transmission and prior to the clinical introduction of antibiotics [39]. The molecular mechanism of emergence of antibiotic resistance and its spread, and persistence in bacterial population may be influenced by the interplay of several factors, such as (*a*) the mutation supply rate, (*b*) the level of resistance conferred by the resistance mechanism, (*c*) the fitness of the antibiotic-resistant mutant bacteria as a function of drug concentration, and (*d*) the strength of selective pressures [40]. Mutation supply rate is said to be determined by population sizes and mutation rates and horizontal gene transfer (HGT). Besides, in human hosts, the extent of genetic heterogeneity in a bacterial population is largely influenced by the mutation supply rate and the host-pathogen interaction [41]. The genetic perspective of AMR remains incomplete and impedes progress towards better patient outcomes and new therapeutics for resistant bacteria [42]. AMR surveillance drive indicated that drug-resistance to all the important antibiotics is in circulation among *E. coli* strains [43], including extended-spectrum β-lactams (ESBL), carbapenems, and more recently, plasmid-mediated colistin resistance (mcr-1), particularly in food animals from Asian countries [44–46]. As inter- and intraspecies HGT and mobile genetic elements are factors for AMR [47], close genomic surveillance of AMR cargo within *E. coli* populations is need of the hour. The mobilization of cargo genes from a donor to a recipient site essentially provides a contribution to HGT [48]. Transposon7 (Tn7)-carrying cargo and as many as 50 Tn7-like transposons identified integrons with antibiotic resistance gene cassettes and heavy metal resistance genes [49].

Mutations are also responsible for the acquisition of amino acid substitutions leading to change of properties of protein structures to provide an altered function and a selective thriving advantage [50]. The newer introduction of more potent antibiotics into clinical settings could potentially trigger the evolution of antibiotic-ring hydrolyzing enzymes rendering powerful drug resistance. These enzymes achieve the ability towards drastically decimating the prowess of antibiotics by acquiring point mutations near or at their active sites that augment catalytic activity of β-lactamases [51]. Since enzymes are endowed with a limited capacity of taking fewer destabilizing mutations before unfolding or loosing activity, newer gain-of-function mutations at active sites often comes at the cost of stability of the enzymes [52, 53]. The alanine to valine (A77V) substitution is such a stabilizing (point) mutation that demonstrates the compensation for a loss in stability associated with substitutions that alter catalytic prowess. This compensation mechanism enables the enzymes to continuum of evolution, resulting in elevated resistance [54].

The unresolved teething problem here is to predict the probability of HGT leading to antibiotic resistance. In this regard, various related factors might play the roles in influencing the probability where particular gene would transfer into a relevant human pathogen have not been very well understood [55]. The global microbiome

might act as a potential source of resistance genes and genes for most classes of antibiotics have been found out in the human gut microbiome [56], and the soil microbiome [57].

Quiet interestingly, it has been hypothesized that within the human microbiota, there has been frequent exchanges between bacteria of antibiotic resistance genes (ARGs), where the intestinal *E. coli* community acts as a melting pot for the HGT [58, 59]. Antibiotic-sensitive bacterial populations developed drug-resistance either through HGTs or mutations and expression of resistance genes from other strains, either distantly or closely related (**Figure 1**). Detection of multiple mutational events can be selected in a step wisely to "train" resistance in a bacterium with successive mutations imparting additive effects [60]. As mentioned before, the human or animal gastrointestinal tract provides an ideal milieu where factors responsible for the upheaval of antibiotic resistance genes and spreading across resident bacterial populations are present [61]. The presence of high cell density is certainly one of the major factors. Additionally, spread of resistant infections is encouraged by selection followed by the innate ability for gene transfer through a variety of different mechanisms [62]. As bacterial cells get exposed to an anti-bacterial drug at sub minimum inhibitory concentrations (MIC), bacteria can thrive to gain resistance under selective pressure [63]. Recent work in this line demonstrated that there may be different resistance mechanisms induced by sub-inhibitory antibiotic exposure compared to lethal selection [64]. In *Salmonella enterica*, sub-inhibitory concentrations of streptomycin selected for high-level resistance through multiple-negligible-effect resistance

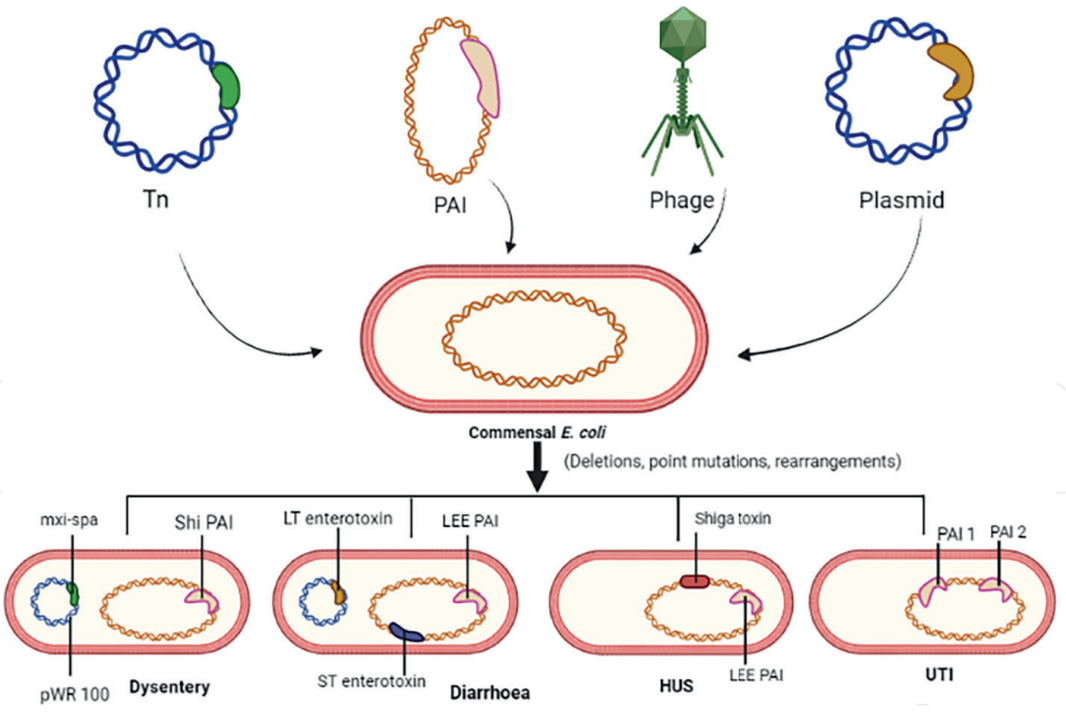

Figure 1.
E. coli virulence factors can be encoded by plasmids (e.g., heat-labile enterotoxin (LT) of ETEC and invasion factors of EIEC), several mobile genetic elements, including transposons (Tn) (e.g., heat stable enterotoxin (ST) of ETEC), pathogenicity islands (PAIs)- e.g., the locus of enterocyte effacement (LEE) of EPEC/EHEC and PAIs I and II of UPEC and bacteriophage (e.g., Shiga toxin of EHEC). Deletions, additions, and other genetic rearrangements may result in evolution of wild type to pathogenic E. coli strains responsible for causing dysentery (EIEC), diarrhea (EPEC, EAEC, EHEC, DAEC), urinary tract infections (UPEC) and hemolytic uremic syndrome (EHEC). UTI, urinary tract infection; HUS, hemolytic uremic syndrome. The figure was created using www.BioRender.com.

mutations, whereas lethal selection led to specific target mutations [65]. However, resistant mutants derived from sub-inhibitory fluoroquinolone exposure may not always induce causative changes in the target quinolone resistance determining region (QRDR) [65]. Experimental demonstrations also suggest that alterations in drug efflux systems are a major mechanism under pressure from sub-lethal ciprofloxacin exposure in case of *E. coli* [66]. Concentration-dependent responses are also mooted as anthropic drivers of resistance. These phenomena go beyond changes in resistance genes since different drug concentrations may alter the community behavior in response to drugs [67]. Reports are rife to indicate that for the manifestations of virulence and AMR, *E. coli* are armed with mobile genetic elements such as plasmids, genomic islands (PAIs and resistance islands [REIs]), or transposons [68]. The ability of mobile genetic elements is acquired at a higher rate [69] rendering *E. coli* ST131 an ideal subject to examine the co-evolution of AMR and virulence [70]. In such *E. coli* ST131 population, chromosomal mutations in quinolone-resistance determining regions (QRDR) of gyrA and parC, conferring high-level fluoroquinolone resistance were reported in the phylogenetic subclades, C1, and C2 [71, 72].

4. Regulatory genes in MDR *E. coli*

The emerging MDR of *E. coli* to several antibiotics is a significant problem leading to the development of pan resistant species and is the major bottleneck in the treatment of diseases. Development of resistance in bacterial pathogens is an adaptive trait and is acquired mainly either by HGT of mobile genetic elements carrying resistance or de novo mutations. *E. coli* strains producing ESBL enzymes like Cefotaximase-Munich (CTX-M) β-lactamases are emerging with higher frequency in hospital and healthcare-associated setups leading to community-onset urinary tract and bloodstream infections [73]. In many Gram-negative bacteria, chromosomal loci specifying global regulatory proteins that control MDR have been characterized in bacteria including *E. coli, Klebsiella pneumoniae,* and other *Enterobacteriaceae*, and *Neisseria gonorrhoeae*, *Bacillus subtilis,* and *S. aureus* [74]. In most instances, the regulatory proteins function as activators or repressors of transcription and contain either a single DNA-binding domain or two separate regions responsible for DNA binding and interacting with small-molecule substrates [75]. The potential genes responsible for encoding MDR in *E. coli* are listed in **Table 1**.

ESBLs hydrolyze and cause resistance to oxyimino-cephalosporins (e.g., cefotaxime, ceftazidime, ceftriaxone, cefuroxime and cefepime), monobactams (e.g., aztreonam), aminoglycosides and co-trimoxazole. ESBLs have evolved due to point mutations around the active site of β-lactamase [90]. Reports have described *ampC* genes present on the plasmid can be potentially transferred among *E. coli*, *Klebsiella* spp., and *Salmonella* spp. [76]. The ESBL/*ampC* genes are often surrounded by mobile genetic elements (e.g., transposons, IS elements or class 1 integrons), that mediate transmission, and involved in the expression of the genes IS*Ecp1* and IS*CR1* [77]. Gene encoding for CTX-M β-lactamases, $bla_{\text{CTX-M}}$ is encoded by narrow host-range incompatibility type plasmids (i.e.IncFI, IncFII, IncHI2 and IncI) or the broad host-range incompatibility type plasmids (i.e. IncN, IncP-1-a, IncL/M and IncA/C) and is associated with highly efficient mobile genetic element IS*Ecp1* [78–80]. Insertion sequence IS*Ecp1* belongs to the chromosomes of the environmental bacteria called *Kluyvera spp*. [91]. Plasmids encoding for CTX-M-15 also carry additional antibiotic resistance genes—$bla_{\text{OXA-1}}$, $bla_{\text{TEM-1}}$, *tetA*, *aac(6′)-Ib-cr* and *aac(3)-II*, often

Sr. No	MDR Gene(s)	Localization of Gene	Function of Gene	Reference
1	*ampC*	Plasmid	Mediate resistance to cephalothin, cefazolin, cefoxitin, most penicillin, and beta-lactamase inhibitor-beta-lactam combinations.	[76]
2	*ISEcp1*	Plasmid	Mobilize adjacent DNA sequences by a so-called one-ended transposition mechanism.	[77]
3	*ISCR1*		Promoters in the expression of antibiotic resistance genes.	[77]
4	*blaCTX-M*	Plasmids	Promotes resistance to several antibiotics.	[78–80]
5	*IncFI*	Plasmid	Confers resistance to many antibiotic molecules.	[78–80]
6	*IncFII*	Plasmid	Confers resistance to many antibiotic molecules.	[78–80]
7	*IncHI2*	Plasmid	Responsible for mediating the horizontal transfer of numerous classes of resistance genes.	[78–80]
8	*IncI*	Plasmid	Mediating the horizontal transfer of numerous classes of resistance genes.	[78–80]
9	*IncP-1-a*	Plasmid	Known to spread genes between distinct phylogenetic groups of bacteria.	[78–80]
10	*IncL/M*	Plasmid	Role in the spread of genes encoding drug-resistance factors.	[78–80]
11	*ST-131*	Plasmid	Predominantly responsible for this global FQ-R and ceph-R pandemic causing millions of AMR infections annually.	[81]
12	*MCR-1*	Plasmid	Provides instructions for making a protein called the melanocortin 1 receptor.	[82]
13	*pp-flo*	Conjugative Plasmids	Facilitates their fast and efficient dissemination among bacteria of same or different species and genera.	[83]
14	*floSt*	Conjugative Plasmids	Facilitates their fast and efficient dissemination among bacteria of same or different species and genera.	[83]
15	*flo*	Conjugative Plasmids	Facilitates their fast and efficient dissemination among bacteria of same or different species and genera.	[83]
16	*floR*	Conjugative Plasmids	Facilitates their fast and efficient dissemination among bacteria of same or different species and genera.	[83]
17	*Mef(B)*	Transposable element	macrolide-efflux pump which mediates resistance to macrolides.	[84]
18	*blaOXA-1*	Contained within class 1 integrons	Hydrolyzes broad-spectrum cephalosporins.	[85]
19	*blaTEM-1*	Contained within class 1 integrons	Ampicillin resistance.	[85]

Sr. No	MDR Gene(s)	Localization of Gene	Function of Gene	Reference
20	*tetA*	Contained within class 1 integrons	Resistance to tetracycline by an active tetracycline efflux.	[85]
21	*aac(6′)-Ib-cr*	Contained within class 1 integrons	Conferring resistance to tobramycin, amikacin, and kanamycin.	[85]
22	*aac(3)-II*	Contained within class 1 integrons	Catalyze the covalent acetylation of a wide variety of aminoglycosides.	[85]
23	*cat I*	Chromosome	Inactivate chloramphenicol, thiamphenicol, azidamfenicol, and florfenicol.	[86]
24	*cat A*	Chromosome	provides instructions for making pieces (subunits) of catalase	[86]
25	*cat B*	Chromosome	provides instructions for making pieces (subunits) of catalase.	[86]
26	*etk*	Long arm of chromosome 7 at position 7q31.2	Regulating the polymerization and transport of virulence-determining capsular polysaccharide (CPS).	[87]
27	*AcrAB*	Upstream of *acrAB* operon	Preserve resistance acquisition by plasmid transfer in the presence of antibiotics with other modes of action.	[88]
28	*ISEcp1*	255 bp upstream of *blaCTX-M-15*	Mobilize adjacent DNA sequences by a so-called one-ended transposition mechanism.	[89]

Table 1.
List of genes encoding multiple drug resistance in E. coli.

contained within class 1 integrons [79, 85]. ESBL-producing Enterobacteriaceae are now significantly emerging in the community. The prototype *cat* genes (*cat I*, *cat II*, *cat III*, *cat A*, *cat B*, etc.) encode for chloramphenicol acetyltransferases (CAT) which can inactivate chloramphenicol as well as thiamphenicol, azidamfenicol, and florfenicol [86]. CATs are detected in a wide variety of bacteria including *E. coli*. *cat I* was originally identified as part of transposon Tn9 in *E. coli* and has been detected in several resistance plasmids of Gram-negative bacteria [92]. Various groups of *cat* genes are often located on small multicopy plasmids also carrying streptomycin resistance or macrolide resistance gene [93]. Export of chloramphenicol and florfenicol out of the bacterial cell via specific membrane transporters or multidrug transporters is another mechanism of resistance shown by microorganisms. Genes encoding for such transporters/efflux proteins (E-1 to E-8) are found in several clinically relevant and environmental bacteria [94]. A number of genes [*pp-flo*, *cmlA*-like, *floSt*, *flo*, or *floR*] grouped in E-3 mediate combined resistance to chloramphenicol and florfenicol. These genes show high homology [96–100%] and their protein products also show 88–100% identity. Often these genes coding for CATs and specific transporters are located on conjugative plasmids, gene cassettes and associated with transposon elements. This facilitates their fast and efficient dissemination among bacteria of same or different species and genera.

Sulphonamide resistance genes *sul1* and *sul2* encoding for dihydropteroate synthase enzymes have been known since decades [83]. A third sulphonamide resistance gene, *sul3*, was identified from porcine *E. coli* [95]. *Mef* (B) gene encoding for macrolide-efflux pump which mediates resistance to macrolides was found located in the vicinity of *sul3* in porcine *E. coli* [84]. In previous reports, mef (A), a homolog of mef (B) was found to be present only in Gram positive bacteria being encoded on a transposable element. However, the emergence of new resistance genes is *E. coli* isolates reflects on the positive selection pressure for sulphonamide and macrolide resistance despite its restricted use is many countries.

In *E. coli*, the MarA is the protein that regulates the expression of many chromosomal genes (the Mar regulon), including those specifying an MDR efflux pump and other proteins (e.g., porins) that mediate antibiotic susceptibility [96]. In *E. coli*, over expression of this MarA leads to reduced expression of the OmpF porin [97] as well as increased expression of the multidrug efflux pump AcrAB [88], thereby conferring resistance to a large number of antimicrobial agents. Resistance-nodulation-division (RND) pumps in *E. coli*, TolC plays the roles of proton antiporters and confer resistance to many important antibiotics, tetracyclines, chloramphenicol, some β-lactams, vancomycin, and fluoroquinolones [98, 99].

The most common ESBL gene in *E. coli* isolates of human origin is *blaCTX-M-15* and ST-131 clone and are implicated in AMR dissemination [81]. 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 [100]. Extraintestinal pathogenic *E. coli* (ExPEC) bacteria are the group of pathogenic strains that have the uncanny ability to cause severe ailments, such as urinary tract infections (UTIs) and bacteremia [101]. The emergence of MDR in *E. coli* has already become a global concern, with particular emphasis on *E. coli* sequence type (ST) 131 reported in UTIs. *CTX-M* Drug resistance phenomenon is mediated by extended-spectrum β-lactamases (ESBLs), mainly of the CTX-M family, particularly CTX-M-15 and 14, and less frequently of the SHV and OXA families [102]. CTX-M-15 first detected in *E. coli* isolates from India has become one of the most widely spread CTX-M β-lactamase worldwide. Association of $bla_{\text{CTX-M-15}}$ with the insertion element IS*Ecp1* plays an important role in its expression and mobilization [89]. From UTI patients, *E. coli* and *K. pneumoniae* with CTX-M type ESBLs were isolated. These enzymes are carried by *E. coli* with multidrug resistance phenotype [103]. MDR expressed by CTX-M-producing isolates from the community is often associated with the presence of multiple ESBLs genes, as well as aminoglycoside and quinolone resistance genes, thereby limiting the choice of effective antimicrobial drugs [104]. As mentioned earlier, that evolution in antibiotic resistance enzymes could rely on the acquisition of stabilizing mutations. A77V substitution is one such mutation that was detected in CTX-M extended-spectrum β-lactamases (ESBLs) from a good number of clinical isolates, pointing towards the significance of the β-lactamase evolution in antibiotic resistance in gram-negative bacteria [105].

Resistance to polypeptide antimicrobials like Colistin (CST) have also been reported in *E. coli* isolated from diseased pigs [106]. Most of such isolates also show resistance to sulfonamides, trimethoprim, tetracycline, ampicillin, or chloramphenicol. Acquired resistance to CST is known to be because of lipopolysaccharide (LPS) modifications—the addition of 2-aminoethanol, 4-amino-4-deoxy-L-arabinose (L-Ara4N) or phosphoethanolamine (PetN), or other strategies such as efflux pump and capsule formation. Mutations in chromosomal genes *mgrB*, *mgrR*, *etk* play a

role in resistance to CST in *E. coli* [87]. Resistance to colistin could also be due to mutations in chromosomal genes or it may be acquired. *Colistin-resistance in E. coli* is plasmid-mediated colistin resistance via the acquisition of the *MCR-1* gene that can propagate efficiently and imparts resistance to other bacteria [107]. *MCR-1* protein enables the addition of a phosphor-ethanolamine group to lipid A. This modification imparts a charge alteration on LPS, which in turn reduces the binding affinity of colistin towards LPS [82].

5. AMR in *E. coli*: contributory factors and its mitigation

MDR *E. coli* spreads over time and stop responding to the drugs which makes it difficult to control the infections caused by them. This increases the risk of spreading diseases, developing major illnesses, and their transmission from one person to other. Hence, uttermost attention is required to mitigate MDR as it plays a significant role in the accomplishment of the sustainable development goals (SDGs). There are numerous factors (**Figure 2**) which contribute to AMR in *E. coli* listed below.

5.1 Overuse, misuse, and inappropriate prescribing of antibiotic or antimicrobials (AM)

It has been established that the main factors contributing to medication fatalities include taking antibiotics or AM specifically when not needed or ingesting it more than approved doses and concentrations. For example, any antibiotic used to treat a bacterial infection will kill susceptible bacteria; if appropriately targeted, the pathogenic microorganism will also be eradicated; nevertheless, the antibiotic will also

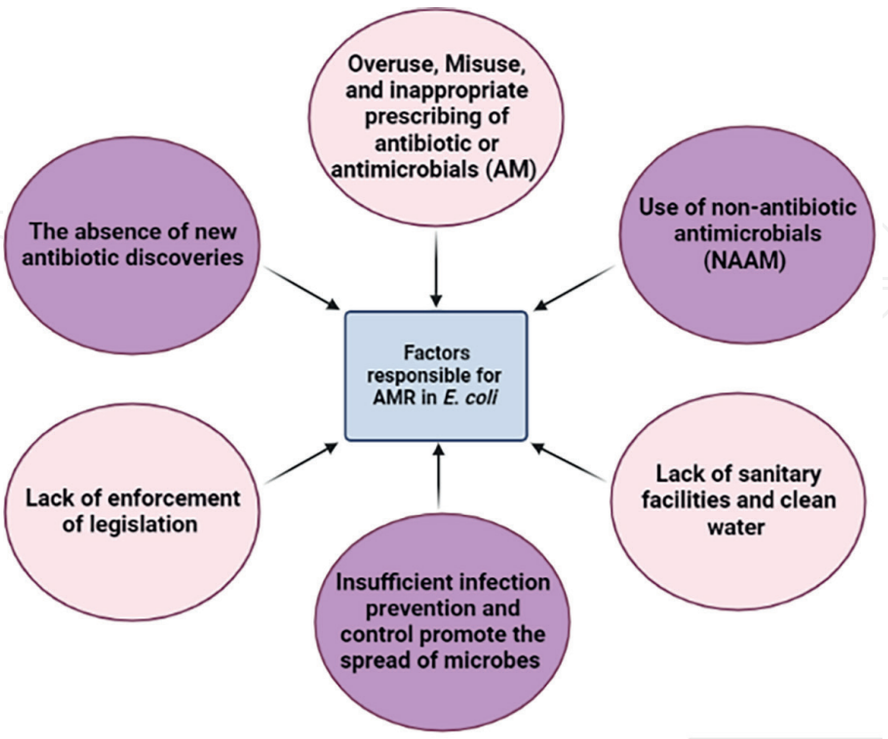

Figure 2.
Different factors responsible for developing the antimicrobial resistance in E coli.

kill any sensitive microbiota in the patient along with the infecting bacteria [108]. If the anatomical region has robust bacteria, whether they come from the healthy microbiota or the pathogenic germs that are being treated, they will proliferate and finally take control. As a result, bacteria are evolving quickly in response to selective antibiotic pressure, which is a significant feature in the growth of multidrug-resistant strains [108]. According to Balbina et al. [109], kanamycin, gentamicin, ciprofloxacin, fluoroquinolones, rifampicin, sulfisoxazole, cefoxitin, ampicillin, and fosfomycin are the most frequently prescribed antibiotics for treating *E. coli* related infections. However, ciprofloxacin is one of the drugs that are most likely to be prescribed incorrectly [109, 110]. Globally, the percentage of human antibiotic use was 65 percent between 2000 and 2015, however, if current trends are not changed, it is predicted that animal antibiotic use will increase by 11.5 percent by 2030, which will contribute to the emergence of additional MDR *E. coli* strains [111]. In the year 2021, Browne and his coworkers [112] reported that the global consumption rate of antibiotics was 14.3 well-defined daily doses (DDD) per thousand people per day in 2018 (40.2 [372–437] billion DDD), up 46% from 9.8 (92–105) DDD per 1000 per day in 2000 [112]. *E. coli* and other strains of the *Enterobacteriaceae* family are becoming gradually resistant to antibiotics due to an intensification in the appearance of membrane proteins that impel the drugs out of the cell, especially in topoisomerases, alterations in the target enzymes, and the presence of mobile genetic elements (plasmids, transposons, and integrons) that support in the lateral transmission of resistance genes in prokaryotes [113–115].

5.2 Use of non-antibiotic antimicrobials (NAAM)

Compared to antibiotics, a lot more non-antibiotic antimicrobial (NAAM) compounds are utilized as biocidal agents. As a result, the environment has significant residual levels of NAAM compounds in the soil, water, and air. One typical biocidal agent, triclosan (TCS), is utilized in more than 2000 different items, including hand washing liquids and toothpaste [116]. According to reports, triclosan causes *E. coli* to develop heritable multi-drug resistance [116]. 1.1×10^5 to 4.2×10^5 kg of TCS is released annually by wastewater treatment plants (WWTPs) in the US alone [117].

5.3 Lack of sanitary facilities and clean water

Water is a vital resource for all living things. All species, including humans, have microbes living inside and on them. According to Collignon et al. [118], environmental variable quantity such as advanced deficient technologies in waste management, availability of non-potable drinking water, overcrowded housing, and poor cleanliness may stimulate the growth and expansion of resistant bacteria globally. The unique capability of *E. coli* in colonization of the animal gut has given additional evolutionary benefit in acquiring resistance attributes from other bacteria in its environment [118]. Antibiotics are frequently used in livestock or food animals to combat and prevent diseases as well as to promote growth, which causes AMR to develop and raises the possibility of antibiotic-resistant bacterial colonization [118]. These bacteria may be spread while handling the animals, slaughtering them, or processing the meat. Additionally, fruits and vegetables can be infected with fecal material directly from the animals or through irrigation water that has been contaminated with animal or human waste [116, 118]. More than 1000 unique antibiotic-resistant genes have been identified in the human gut microbiota, and the transfer of these features between gut

commensals is prevalent, according to one study done by Hu et al. [119]. In underdeveloped regions of the world, antibiotic-resistant strains of *E. coli* are detected at the time of birth, at the highest rates in human feces. Studies in China [114] have stated that ESBL genes in *E. coli* are transmitted by conjugation that enters in food chain directly or indirectly which facilitates explaining why ESBL-producing *E. coli* are so prevalent in feces around the world.

5.4 Insufficient infection prevention and control promote the spread of microbes

Since many sick individuals congregate in hospitals and healthcare centers and antibiotic consumption is prevalent, resistant strains of bacteria are selected for and disseminated throughout these settings, making them important hotspots for most bugs [120]. Additionally, inadequate hygiene habits may make it easier for resistant microbes to transmit from patients or visitors to doctors, nurses, and other healthcare professionals through their hands or clothing [121]. Other risk factors include inadequate sanitation, inappropriate cleaning of the facilities, and dirty equipment. Few isolation rooms and crowded wards further encourage spread [120, 121]. Poor approaches towards reasonably priced medicines, vaccines, and diagnostics are the most defined factors for showing the resistance to antimicrobial treatment case of *E. coli*, which is understudied in many underdeveloped nations [122]. Patients face substantial health risks when doctors attempt to treat infections about which they are ignorant. Medical facilities should set up systems to guarantee the identification and management of a range of bacterial diseases without prescribing incorrect medications [122]. Over time, incorrect medicine prescriptions have led to several patients' deaths and even more severe health issues [120–122] With the right diagnosis and care, patients can reduce their risk of developing medication resistance-related issues. In addition, the ongoing development of strategies for the cultivation of bacteria using a variety of culture media and conditions a process known as culturomics is crucial for the identification of antibiotic resistance genes (ARGs) and the comprehension of the cellular mechanisms underlying the association between ARGs and resistance phenotypes in various bacteria [123]. One of the major issues with building a consolidated database is establishing a clear strategy and making it into a regular practice of environmental-quality monitoring [124].

5.5 Lack of enforcement of legislation

By 2050, it is predicted that antibiotic resistance will have killed more people than cancer today. According to Naghavi's analysis in the published report in the year 2022, there would be 12.7 million deaths caused by bacterial AMR in 2022, out of an expected 495 million deaths linked to bacterial AMR in 2019 [125]. Death by third-generation cephalosporin-resistant *E. coli* was found to be the most prevalent [125]. Therefore, the lawmakers must keep an eye on how often antibiotics or other biocidal chemicals are used. The sum of all the efforts, including legislation, studies of community attitudes and knowledge regarding antibiotics, educational initiatives, and follow-up policies, will undoubtedly contribute not only to reducing antibiotic misuse in the short term but also to fostering appropriate knowledge among society members regarding the advantages of using antibiotics properly. These actions will be crucial to lowering patient demand for antibiotics and preventing detrimental effects on public health and the economy. Although the creation of stringent legislation like "Schedule H1" is crucial, it might only be one component of the solution. Delaying these reforms

emphasizes the risky game we are playing with the health of people and animals, which might have terrible repercussions**.**

5.6 The absence of new antibiotic discoveries

It can be crucial in treating a variety of bacterial illnesses. Some bacterial strains are still evolving and developing medication resistance. Although few new antibiotics are being introduced to the market, they could be useful in attempting to close the gap.

6. Conclusions and future horizons

A persistent global concern in the field of medicine is microbial resistance to antibiotics. One among numerous bacteria is *E. coli*, which is frequently found in humans and animals. Finding novel antibiotic substitutes that are more potent in treating pathogenic infections, particularly the ones caused due to *E. coli* is required since there are less options for antibiotics that are sensitive to this bacterium. *E. coli* and other Gram-negative bacteria have evolved to develop different mechanism to encounter any antimicrobials. Moreover, different studies have showed higher prevalence of ESBL antibiotic resistance and MDR *E. coli* strains in animals than in humans. Besides, the stability and spread of colistin resistance in multiple reservoirs are an emerging public health threat worldwide. Dissemination of antibiotic resistance genes via transmissible plasmids, integrons and transposons to several environmental reservoirs like wastewater treatment plants (WWTPs), agriculture fields, animal manure, and hospital-associated setups is an emerging threat to environmental and public health safety. Our meta-analysis suggests that comprehensive surveilling of hospital-associated diseases, careful monitoring of hospital waste management procedures, supervising antibiotic use in animals, tracking and evaluating antibiotics susceptibility trends, and the development of trustworthy antibiotic strategies may facilitate more corrective actions for the inhibition and control of *E. coli* infections in various parts of the world and practical guidelines can be put in place for proper prescription of antibiotics in humans to ensure better public health monitoring.

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Conflict of interest

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