Review Article

A review of colistin-resistant *Escherichia coli* isolates in the Middle East: mechanisms, epidemiology, and dissemination from different sources in humans, animals, foodand soil

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ABSTRACT

Escherichia coli is a normal gut inhabitantthat can cause various diseases ,such as intestinal, urinary tract, bladder infections and systemic infections in humans and animals. The alarming increase in profiles for extended-spectrum β-lactamase- and carbapenemase-producing *Escherichia coli* isolates is a serious problem throughout the world. Colistin is known as a lastresort agent for the treatment of Gram-negative bacterial infections. Inappropriate use of colistin and other classes of antibiotics combined with inadequate infection control, especially in developing countries, can lead to serious public health complications. The global increase in colistin resistance has been reported in many parts of the world, ,including the Middle East. Colistin is used to treat infections caused by extensively drug-resistant Gram-negative bacteria. There are few reliable epidemiologic data on colistin-resistant *E. coli* isolates, and information on colistin-resistant *E. coli* from Asia, the largest, most populous, and most diverse continent in the world, is generally limited compared with Europe and the United States. The data in this review article were compiled from related articles associated with isolated colistin-resistant *Escherichia coli* (*E. coli*) isolates from humans, animals, and food-producing animals. In the Middle East, colistin-resistant *E. coli* isolates were reported from Turkey, Egypt, Saudi Arabia, Algeria, Iran, Iraq, Bahrain, Qatar, Oman, Kuwait, Israel, and Lebanon between 2010 and 2023. While colistin resistance is most commonly observed in *E. coli* isolates, data have shown that *mcr* genes are the most common genes associated with colistin resistance in *E. coli* isolatescompared to mutations in *pmrAsB, phoQ*, and *mgrB* genes.

Keywords: Colistin resistance, *Escherichia coli*, Molecular mechanism, Middle East countries

1. Introduction

E. coli is a normal intestinal inhabitantthat can cause various diseases ,such as intestinal, urinary tract, bladder, and systemic infections in humans and animals (1). The prevalence of multidrug-resistant (MDR)and extensively drug-resistant (XDR) germs and the diversity of resistance profiles of E. coli isolates with extended β-lactamase spectrum (ESBL) and carbapenemase-producing germs (CP-*Ec*) have increased worldwide, which is of concern. Therefore, a new replacement drug is needed. Colistin (polymyxin E) is increasingly used as a 'last' treatment option for infections with Gram-negative MDR/XDR bacteria and as '"rescue therapy" when essentially no other options are available (2). Its mode of action is based on the binding of polymyxins to the LPS of the outer membrane of Gram-negative bacteria and the competitive displacement of divalent cations (Ca2+ and Mg2+) from the negativelycharged phosphate groups of lipid A of the LPS (Fig. 1), leading to changes in cell membrane permeability and bacterial cell death . It seems likely that Gram-negative enteric bacteria from livestock and poultry can be transmitted to humans via handling or use of food of animal origin, leading to the spread of colistin resistance (3). Eggs and broilers have always been traded and transported in different countries around the world. This trade leads to the spread of antibiotic resistance by multidrug resistant organisms ($MDRO_s$), resulting in their global spread when an MDRO is offered into the production chain (Fig.2) (4). A progressive increase in colistin resistance may be associated with the extensive use of colistin in animal husbandry and veterinary medicine, which can spread rapidly through horizontal plasmid transfer (1). The lack of innovation in the development of new antibiotics for Gram-negative MDR/XDR pathogens has forced clinicians to reuse colistindespite its renal toxicity. Colistin has been used primarily in veterinary medicine for decades to treat Enterobacterales infections (4). Inappropriate use of colistin and other classes of antibiotics combined with inadequate infection control, especially in developing countries, can lead to serious in public health complications (1, 5). To reduce the burden of resistance, studying the distribution of colistin resistance in Gram-negative bacteria ,such as *E. coli* strains should be the main focus of infection control in most countries. In this review, we determined the prevalence of colistin-resistant *E. coli* isolates in the Middle East based on literature reviews and positive reports, which are occuring at an alarming rate. There are few reliable epidemiological data on colistin-resistant *E. coli* isolates, and information on colistin-resistant *E. coli* from Asia, the largest, most populous, and most diverse continent in the world, is generally limited compared with Europe and the United States of America . The aim of this study was to provide an overview of the epidemiological characteristics of colistin-resistant *E. coli* isolates and to disseminate the pattern of colistin-resistant genes in *E. coli* isolates of different origins from the Middle East.

2. Mechanism of colistin resistance

Colistin is a cationic, amphipathic molecule containing a non- ribosomally synthesized decapeptide and a lipid tail. Colistin binds to the anionic phosphate groups of the lipid A portion of lipopolysaccharides (LPS) through electrostatic interactions in Gram-negative bacteriaand destabilizes the outer membrane. In recent years, numerous studies have pointed to several outbreaks of infections caused by colistin-resistant bacteria. Until 2015, mutations in chromosomal genes were the only known mechanism for acquired colistin resistance. In November 2015, the plasma- borne phosphoethanolamine (pEtN) transferase *mcr-1*, a horizontally transmissible, plasmid-mediated colistin resistance gene, was first spotted (6). MCR-1 is a membrane-bound enzyme consisting of five hydrophobic transmembrane helices and a soluble form in the periplasmic space. MCR-1 adds a PEA group to the 1(4') phosphate of glucosamine units in LPSlipid A of the bacterial outer membrane via a putative ping-pong mechanism (Fig. 1) (7). After the discovery of the *mcr-1* gene, nine other *mcr* gene types (*mcr-2* to *mcr - 10*) carried by plasmids with different replicon types were detected in isolates from different bacterial species (8). Single nucleotide mutations in the *phoP/Q, pmrAB, mgrB, acrB, LpX ACD* genespreviously detected colistin-resistant *Klebsiella spp.* and *E. coli* isolatesare known "hotspots" for mutations, whereby they may reduce bacterial membrane affinity for cationic polymyxin (Fig. 1). Nucleotide positions with an unusually high mutation frequency are referred to as mutation "hotspots"(9). However, all of these genes have evolved resistance to colistin. Gram-negative pathogens are able to induce cationic changes at phosphate groups in the lipid A components of LPS, which induces resistance to the action of polymyxins. On the other hand, relatively little is known about the mechanisms of colistin resistance in *E. coli*, apart from the acquisition of *mcr*genes. PhoPQThe *phoPQ* expression in *E. coli* is controlled not only by *MgrB* but also by the sRNA MicA, which adds to the mechanisms controlling *PhoPQ* activation and may

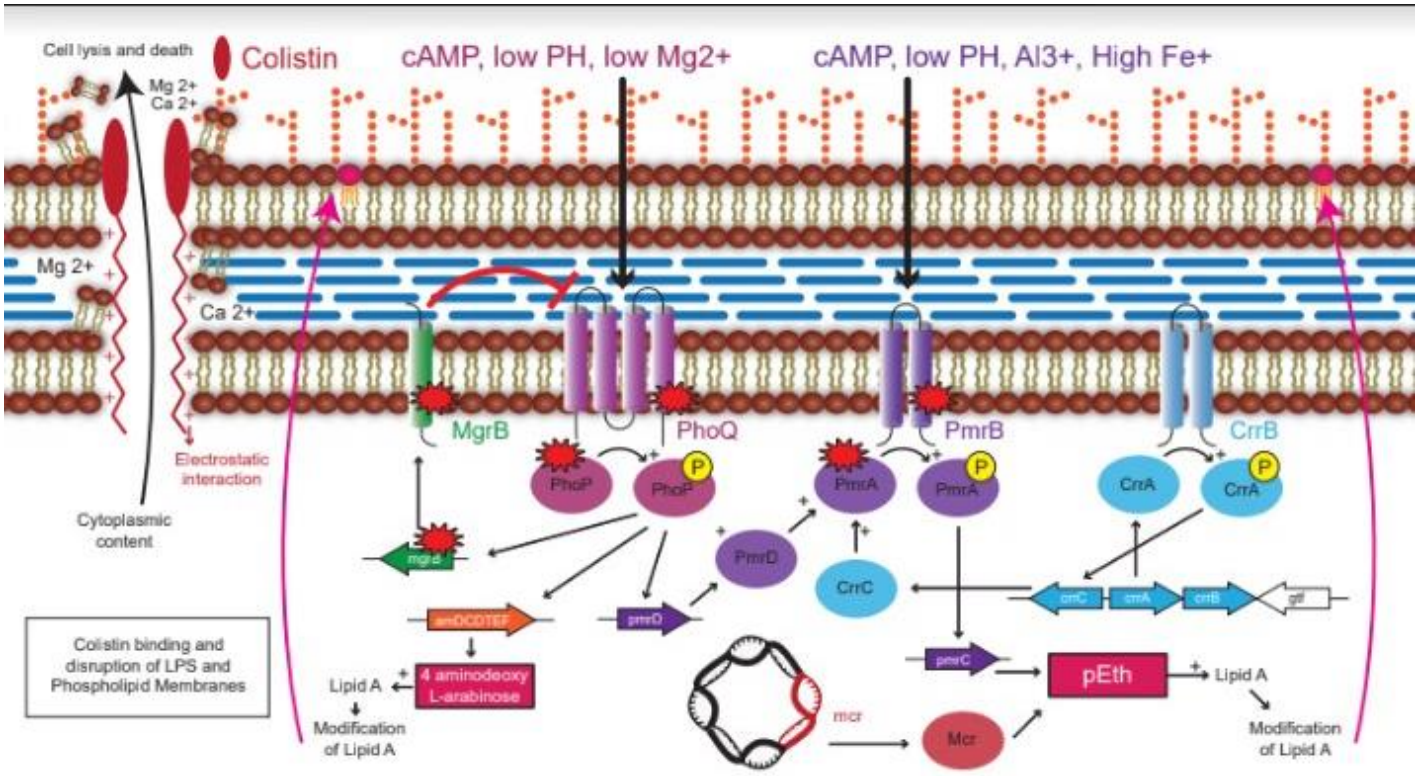

Fig.1. Mechanisms of act and resistance to colistin in Gram-negative bacteria.

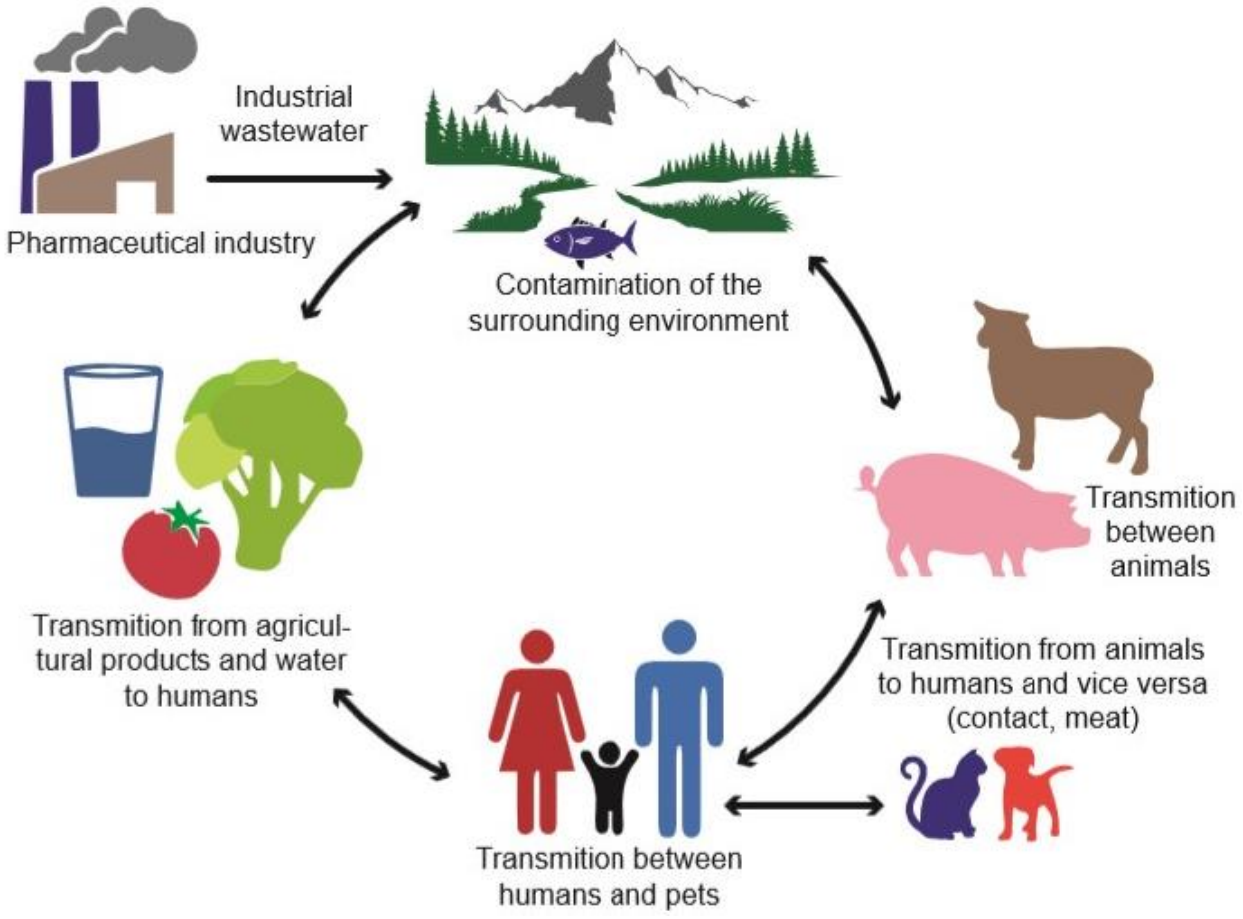

Fig.2. Circulation and dissemination of colistin-resistant Escherichia coli harboring *mcr* genes or either even harboring chromosomal genes, between environment, food, animals, and humans.

contribute less than deletion or inactivation of *mgrB* to colistin resistance. Colistin resistance in clinical *E. coli* strains has previously been associated only with BasRS resistance mutations in *E. coli*. The two-component system PmrAB (BasRS) plays a key role in mediating the modification of LPS that leads to colistin resistance in Gram-negative bacteria. In *E. coli* strains, activation of BasRS leads to increased expression of several operons, including eptA, which encodes a lipid A-specific phosphoethanolamine transferase (10). These point mutations are associated with colistin use. In contrast, plasmid-mediated resistance is a constant resistance unrelated to colistin use. It is essential, not only for *E. coli* but also for *Pseudomonas aeruginosa* and *Klebsiella pneumonia.* Thus,mutations in *pmrAB* genes lead to an increase in MIC values against colistin, and the presence of *mcr-1* in isolates resulted in a four- to eightfold increase in colistin MIC (11) Details are shown in Fig. 1.

3. A review of the occurrence and spread of colistin-resistant *E. coli* and associated mechanisms in the Middle East

In the current study, we searched the available data on the molecular mechanisms and prevalence of colistin-resistant *Ecoli* isolates in the Middle East. Using the keywords colistin resistance, *Escherichia coli*, molecular mechanism, Middle Eastern countries, relevant scientific articles were searched in PubMed, Google Scholar, andScopus databases, which are popular search engines in medical sciences in English. The searches were conducted between 2010-2023. All studies included in our survey are summarized in Table 1. In this study, we designed the scheme of the plasmid- encoded colistin-resistant gene*mcr1*, and the other companion genesthat may be present together with the *mcr-1* gene (Fig. 3).

3.1. Iran:

Recently, a study was conducted in Iran, and for the first time, *mcr-1* was detedcted in *E. coli* isolates rom livestock and wastewater (12). In a recent study, 37 (10.8%) colistin-resistant *E. coli* isolates were detected (MIC values >2 mg/L) and 36 fingerprint patterns were identified in colistin-resistant *E. coli* using ERIC- PCR (13)(Table 1).

3.2. Egypt:

In a study conducted in broiler poultry farms in Egypt the *mcr*-1 gene was detected in 18 of 28 *E. coli* isolates(14). In 2019-2020 *mcr-1* was detected in chicken farms(15) and also in patients with urinary tract infections(16). Of 38 animal isolates tested, only one *E. coli* isolate was positive for the *mcr-1* gene. It is noteworthy that the presence of the *mcr-1* gene was confirmed for the first time in Egypt (accession no. LC114017), belonging to ST10 (17). in another work, four *mcr-1*-positive colistin-resistant *E. coli* were detected in 200 samples of Karish cheese, belonging to the dominant uropathogenic *E. coli* ST69 lineage. In addition, the plasmid pEGY1-MCR-1 was part of the IncHI2 incompatibility group found in this study. This was consistent with data from the Kingdom of Saudi Arabia and Qatar, suggesting a possible distribution of pEGY1-MCR-1-like plasmids in the Middle East (18). In a study conducted by Zaki *et al*. 50 Enterobacterales species resistant to colistin. *E. coli* isolates (21/50) shown resistance to colistin were investigated with an MIC >2 mg/L. An *E. coli* strain carrying *mcr-1* was associated with colistin MIC >16 mg/L(11). In a recent study, colistin resistance genes (*mcr-1* and *mcr-2*) were detected in *E. coli* isolates from migratory birds, water sources, and humans. Data suggest that colistin resistance genes (*mcr-1,2*) are on the rise in water sources, humans and, animals (19). In addition, the *mcr-1* gene was detected in a bla_{NDM-1}-positive *E. coli* strain of 18 colistin-resistant *E. coli* isolates. Other carbapenemases (KPC, VIM, IMP, SIM, GIM, and SPM) were not detected. None of the 18 colistin-resistant *E. coli* isolates carried the *mcr-2* gene. *mgrB* genes were detected by PCR, and *mgrB* mutations were not found in colistin-resistant *E. coli* strains. The MIC of colistin by broth microdilution was ≥ 4 mg/L for an *mcr1*-positive *E. coli* strain. The *mcr-1* gene was 100% identical to the known *mcr-1* sequence (Genbank: NG_050417.1, Liu *et al*., 2016) (20). Among the 128 colistin-resistant strains, one *mcr1*-positive MDR *E. coli* isolate (MC13) was observed from beef sausage samples. In this study, the *mcr-1* gene was located on an IncI2-type self-congugating plasmid with a size of 64.6 kb (21).

Table 1. Studies' characteristics related to colistin-resistant *E. coli* isolates from humans, animals, and environment in Middle East countries

				Gene modifications leading to colistin resistance	AST[a]				
Country	Isolation Year	Number of *Ecoli* isolates (No. (%) of Colistin Resistance)	Sample type (Origin)	*mcr* type (No. (%) of positive *mcr Ecoli*) OR Chromosomal	E[1]	D[2]	K[3]	MLST	Reference
Iran	2020	65(3(4.6%))	rectal stool swab samples from cows and chickens. urban sewage	*mcr-1* (1), *mcr2-6*(0)		*	*	-	(12)
Iran	2017	351(37(10.8%))	Human (b.u.w)[b]	*mcr-1* (6 (1.7%))	*			-	(13)
Egypt	2019-2020	56(23(41%))	Chicken farms	*mcr-1*(56(100%)), *mcr2-5*(0)	*	*	*	-	(15)
Egypt	2019	67(3(4.5%))	patients with urinary tract infections	*mcr-1*(3(4.5%))		*	*	IncHI2:ST4	(16)
Egypt	2014	38 (2.6%)	Animal	*mcr-1* (1(2.6%))				ST10	(17)
Egypt	2015	241[c](1)	Human (ICU) sputum	*mcr-1* (1)		*		ST1011	(50)
Egypt	2016-2017	200(2%)	Raw milk cheese	*mcr-1* (4(2%))				ST69	(51)
Egypt	2016-2018	21 (21(100%))	Human (b.u.w)	*mcr-1* (1(4.7%)), *mcr-2* (0)		*		-	(11)
Egypt	2016	63(5(8%))	Broiler	*mcr-1* (5(8%))	*			-	(52)
Egypt	2017-2018	79(15(18.9%))	1.n: 62 birds faecal(1.1: Resident birds,1.2: Migratory birds) 2. n: 7 Surface water samples 3.n: 10 Human stool	*mcr-1:* 1.1 (3 (9.1%))[d] 1.2 (6 (20.6%)) 2. (2 (28.5%)) 3. (1 (10%)) *mcr2:* 1.2. 1 (3.4%) 2. (1 (14.2%)), 3.(1 (10%)) Both of *mcr* 1,2 genes: (1 (3.4%))				-	(19)
Egypt	2016-2017	200 (18(9%))	Human (Clinical samples)	*mcr-1:* (1(5.5%)), *mgrB*:0	*	*		-	(20)
Egypt	2019	128 colistin-resistant strains	Meat samples	*mcr-1:* (1 *Ecoli*)		*		ST101	(21)
Egypt	2017-2019	140(21(15%))	Respiratory samples from chest ICU	*mcr-1:* 21(15%) *mcr*2-5:0		*			(53)
Turkey	2019	11	Retail raw chicken meat	*mcr-1* (1 *Ecoli*)				IncI2	(22)
Turkey	2017-2018	80 (4(5%))	Chicken meat	*mcr-1:* (4(5%))		*		ST3941, ST1049	(23)
Turkey	2014-2015		Human Bloodstream infection	-		V2		-	(24)
Turkey	2018-2019	49 (5(10.2%))	Cattle and Sheep	*mcr-1*:0, *mcr-2*: (3), *mcr-3*: (5), *mcr-2, mcr-3*: (5), *mcr-4*:0, *mcr-5*:0		*		-	(54)
Oman	2014-2016	1[f]	Bloodstream	*mcr-1*:(1), *mcr-2*:0	*			ST10	(25)
Kuwait	2017-2018	46 (2(4.6%))	(b.u[b]) and Respiratory	-		*		-	(55)
Arabian Peninsula (Bahrein, Saudi Arabia and United Arab Emirates)	2012-2015	4[f]	B.U.W	*mcr-1* :(4)		*		ST648, ST224 ST68, ST131	(26)
Bahrain	2012-2017	50 (2(4%))	Clinical samples	-		*		-	(27)
Bahrain	2015	6 (4(66.6%))	Groin or perirectal surveillance swabs from a middle-aged male	*mcr-1*:(4)	*	*		ST-617	(28)
Israeal	2013-2014	10(1(10%))	Rectal swabs, wound, Sputum	-		*	*	-	(29)
Iraq	1987	430(77(18%))	Milk product	-			*	-	(30)
Algeria	2021	33(8(24%))	Migratory bird	*mcr-1*:(8)			*	ST58, ST224, ST453, ST1286, ST2973, ST5542, ST9815 and, ST101.	(56)

Algeria	2019	6(2)	Fresh vegetables	*mcr-1*: (2)			*	ST216 and ST101	(57)
Algeria	2019	17	Chicken meat	*mcr-1*: (11(64.7%))				IncFV and IncFIIK	(58)
Algeria	2011	1	Urine sample of an 18-year-old polytrauma man	*mcr-1:* (1)		*	*	ST405	(31)
Algeria	2016-2018	8 [f]	Agricultural soils and horse manure and bovine manure	*mcr-1*:(6), *mcr-2*:0, *mcr3*:(2) *mcr4*;0, *mcr5*:0		*		*mcr1*: ST10, ST405, ST345 *mcr3*: ST155	(32)
Algeria	2015 -2017	237(1)	Urine sample from a 69-year-old man	*mcr1*: (1) *mcr2*-8: 0		*		-	(33)
Algeria	2016	246 colistin-resistant strains	Seawater of Algiers coast	*mcr-1*: (2)		*		ST23, ST115	(34)
Algeria	2016	1(1)	Human, fresh stool samples	*mcr-1*: (1)	*			ST405	(35)
Qatar	2020	2 [f]	Human, rectal swabs	*mcr-1*:(2)			*	ST540,ST115	(37)
Qatar	2016-2018	3 [f]	Human, Wound–Drainage,Urine	*mcr-1.1* (1)			*	ST156,ST1193, ST452	(38)
Lebanon	2019	9	Rectal swab of inhabitants of two Syrian refugee camps	*mcr-1*:(5)	*	*	*	ST361, ST1294, ST648, ST2001, ST101, and ST4187	(41)
Lebanon	2020	84	Food workers	*mcr-1.1 (6)*					(40)
Lebanon	2016-2017	5[f]	Rectal swab	*mcr1-5*: 0 Disruption of: *pmrA/B*:1 *pmrA*:2 *pmrB*:1 *phoPQ*:4 *mgrB*:0		*		ST131,ST6174 ST405, ST162 ST1451	(42)
Lebanon	2017	105(23(21.9%))	Swine fecal	*mcr-1:* (23)		*	*	-	(43)
Lebanon	2015	36[f]	Domestic and sewer waters	*mcr-1:* (36)		*	*	-	(44)

Antimicrobial Susceptibility Testing Methods 1. E-test 2. Dilution methods (Agar or broth) 3. Kirby-Bauer

[b] b:blood, u:urine, w:wound, s:stool, t:tracheal

[c] 241Gram-negative clinical bacteria

[d] 1.percent of positive-*mcr-Ecoli* from wild birds faecal 2. percent of positive-*mcr-Ecoli* from surface water sample 3. percent of positive-*mcr-Ecoli* from human stool

[f] CR:Colistin-Resistant *E. coli*

V2: VITEK-2

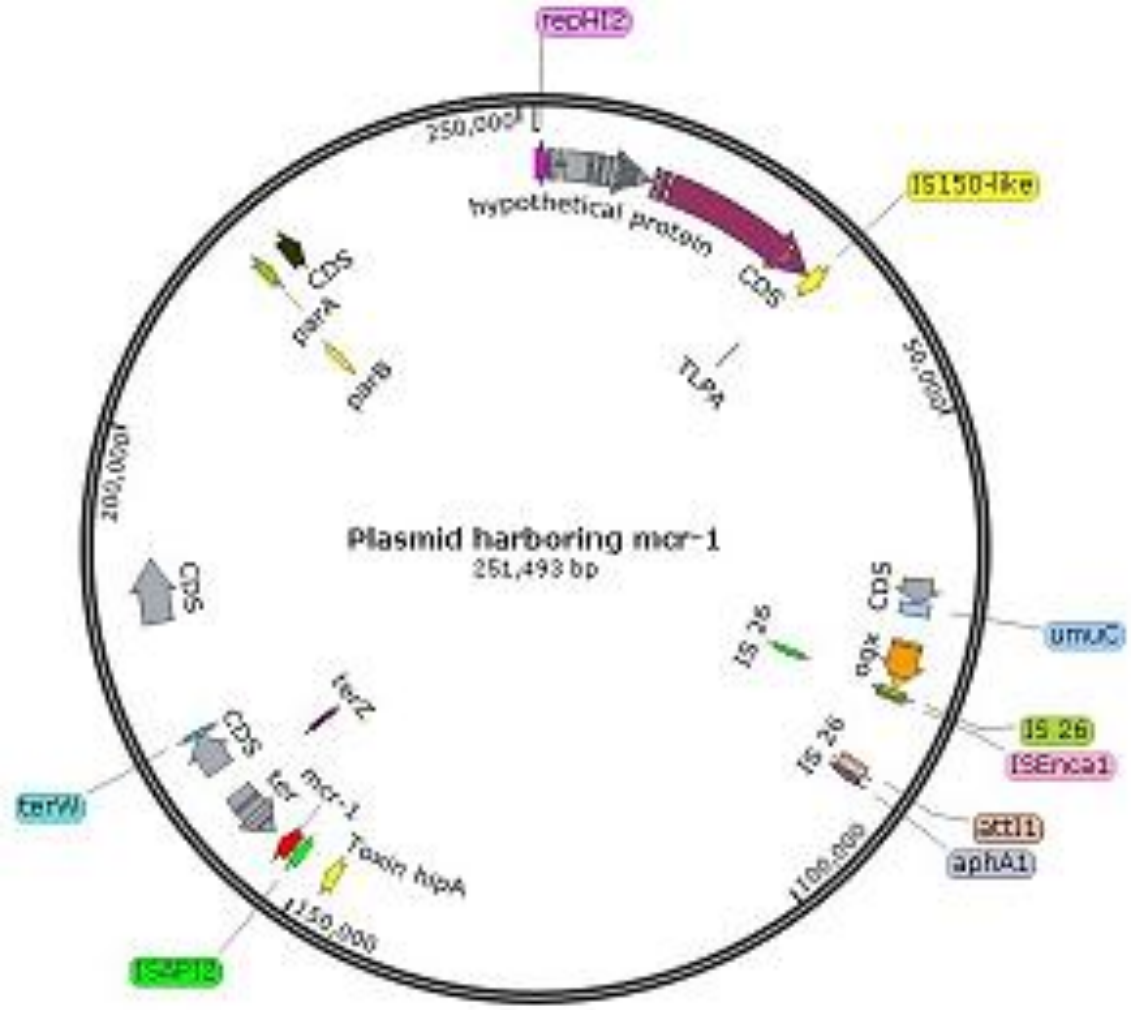

Fig. 3. Schematic representation of plasmid-encoded colistin-resistant gene, *mcr-1*, and the other accompanying genes, like some genetic elements, insertions sequences, and other antibiotic resistance genes, can be transported with the mcr1 gene inside a plasmid.

3.3. Turkey:

In 2019 *mcr-1* was reported in retail raw chicken meat (22). The first report of *E. coli* carrying the *mcr-1* gene, with colistin MICs of >8 mg/L, **was** reported from Turkey by Kurekci *et al* (2018)(23). A three-year study of ICU samples showed that 99%, 100%, and 99% of *E. coli* strains were sensitive to colistin in 2014, 2015, and 2016, respectively (24).

3.4. Oman and Kuwait:

Mohsin *et al*. reportedan *E. coli* isolate (OM97) carrying the *mcr-1* gene with an MICof 4 mg/L. The *mcr-1* gene was located on an IncI2-type congugative plasmid with a size of 63722bp size (25). In another study, four colistin-resistant *E. coli* strains with MICs of ≥2 mg/L had *mcr-1* genes. These *mcr-1* genes were found in the countries of Bahrain (two isolates), Saudi Arabia (one isolate), and the United Arab Emirates (one isolate). A colistin-resistant *E. coli* strain from Saudi Arabia carried the carbapenemase gene bla_{NDM-1},and the. *E. coli* strain from the United Arab Emirates also carried a $bla_{CTX-M-64}$ gene. Three colistin-resistant *E. coli* strains carried *mcr-1* on IncI2=type plasmids. In the fourth strain, *mcr-1* was on a 240 kb IncHI2 plasmid in association with 13 other resistance genes (26).

3.5. Bahrain:

Of 50 *E. coli* strains, only 2 were colistin-resistant. In addition, 5 E. coli of the total E. coli isolates were found to have combined resistance to colistin and (27). In anotherstudy, 4 colistin-resistant *E. coli* strains were detected from 6 serial clinical isolates from a patient after a short hospital stay in Bahrain. WGS showed that the six isolates consisted of two different strains: a first ST-617 *E. coli* strain with *mcr-1* and a second, *mcr-1*-negative ST-32 *E. coli* strain that emerged 2 weeks after the hospitalization. Thirteen antibiotic resistance genes were found in the ST-617 isolates. Manual broth microdilution and colistin E assay confirmed that four isolates carrying *mcr1* had a colistin MIC of 0. 0004 mg/L (28).

3.6. Syria:

Lerner et.al. found in 2015 that an isolateof 10 carbapenemase-producing *E. coli* isolates obtained from wounded Syrian patients admitted to hospitals in northern Israel was non susceptible to colistin(29).

3.7. Iraq:

Evaluation of antibiotic susceptibility of 430 *E. coli* strains isolated from three types of locally processed Iraqi dairy products revealed that 77 of 430 (18%) were resistant to colistin(30).

3.8. Algeria:

The first report of *mcr-1* in a colistin-resistant *E. coli* strain (breakpoint for resistance: >2mg/l) in Algeria was published in 2016;this strain was collected in 2011. Also in this strain, $bla_{CTX\text{-}M15}$ and $bla_{TEM\text{-}1}$were detected with *mcr-1* (31). The transfer of fertilizers from animals to soil and irrigation water are important sources of colistin-resistant *E. coli* strains on farmsand can lead to a mixture of multiple antibioticresistance and pose a threat to human health. In this study, *mcr1,3* genes were detected in 8 colistin-resistant *E.coli* isolates (MIC ⩾2 mg/L). All eight *E. coli* isolates were not susceptible to amoxicillin, amoxicillin/clavulanic acid, ticarcillin, nalidixic acid, ciprofloxacin, gentamicin, trimethoprim/sulfamethoxazole, and rifamycin; two were also not susceptible to cefotaxime, cefepime and aztreonam, and these two isolates also carried the $bla_{TEM\text{-}12}$ gene in addition to *mcr-1*. The *mcr-1*-positive *E. coli* isolates were assigned to three STs, including ST10 (n = 3), ST405 (n = 2) and ST345 (n = 1), whilst the two isolates carrying the *mcr-3* gene were dedicated to ST155(32). Another study performed on 237 *E. coli* isolatesshowed that one strain was positive for the *mcr-1* gene (MIC of colistin: 4 mg/L), but the isolates were negative in the RT-PCR assay targeting the *mcr-2* to *mcr-8* genes (33). Some studies have shown that environmental contamination is a worldwide problem. In 2016, two colistin-resistant *E. coli* were isolated from seawater in Algeria carrying the *mcr-1* gene on a nonconjugative plasmid. After sequence typing, they were shown to belong to two different types of ST. The two strains were not sensitive to amoxicillin, ticarcillin, piperacillin, gentamicin, nalidixic acid, tigecycline, tetracycline, trimethoprim-sulfamethoxazole and, colistin. Two isolates had colistin MIC values of 4 mg/L and 8 mg/L (34). The colistin-resistant *mcr-1*-bearing*E. coli* (MIC of 4mg/L) was resistant to most antibiotics tested, including B-lactams (amoxicillin, amoxicillin -clavulanate, ticarcillin, cefepime, ceftriaxone, cefotaxime, and aztreonam), gentamicin, trimethoprim/sulfamethoxazole, sulfadiazine, rifampicin, and fluoroquinolones, but remainssensitive to carbapenems, amikacin, tigecycline, fosfomycin, and piperacillin/tazobactam. PCR and sequencing revealed that this isolate contained the $bla_{CTX\text{-}M\text{-}15}$, $bla_{TEM\text{-}1}$, and *qnrB19* genes along with *mcr-1* (35).

3.9. Qatar:

A colistin-resistant *E. coli* strain with resistance to polymyxin Band several lactams was detected. The colistin resistance gene mcr-1was located on a 241-kb IncHI2 plasmid (GenBank accession number KU743384) (36). Tsui *et al*. reported two multidrug-resistant *E. coli* strains carrying the *mcr-1* gene together with the $bla_{CTX\text{-}M\text{-}15}$ and $bla_{NDM\text{-}1}$ genes. These isolates were obtained from rectal swabs of pediatric patients (37). Three *E. coli* isolates showed resistance to colistin with MICs > 4 µg/mL in both Phoenix and SensiTest results. One *E. coli* isolate (EC-12) harbored *mcr-1.1* on the IncI2 plasmid pEC-12. In this study, acquired resistance to colistin via chromosomal (*phoPQ*, *pmrAB*, and *mgrB*) was found not to be involved in colistin-resistant *E. coli* strains (38).

3.10. Lebanon:

In Lebanon, mcr-1.26 was reported for the first time in an MDR *E. coli* isolated from chicken wings(39). In a study conducted on food workers in Lebanon, *mcr-1* was detected in six samples(40). Another study was conducted on rectal swabs from residents of two Syrian refugee camps in Lebanon. The results of this study showed the clonal spread of *mcr-1* among Syrian

refugees (41). Five colistin-resistant *E. coli* were isolated from rectal swabs of 23 different patients (23clinical strains) treated with colistin-carbapenem combination therapy. The MIC of colistin ranged from 8 to 16 mg/L for the *E. coli* strains, with four E. coli strains achieving a MIC of 16mg/L . None of the strains carried *mcr-1* to *mcr-5*. The associated colistin resistance genes ,including *mgrB, pmrA, pmrB, phoP*, and *phoQ*, were amplified and sequenced because no mcr genes were present. In these *E. coli* strains, colistin resistance was associated with mutations in the *pmrA, pmrB, phoP*, and *phoQ* genes that resulted in amino acid changes (42). Of 105MDR *E. coli* isolates, 23 colistin-resistant *E. coli* strains were found, to be positive for *mcr-1*. 105 ESBLs/ampCs strains include *E. coli*that were not carbapenemase producers in this study. Four of the 23 strains were colistin-resistant in ESBL-producing *E. coli*. Of the four ESBL *mcr-1*-positive resistant isolates, CTX-M was detected in two strains, whereas SHV and TEM were detected in all four strains. All strains had a colistin MIC ≥ 0.002 mg/L. *The* MICs of 23 *E. coli* isolates were 4–16 mg/L, except for one strain with a MIC of 0.256 mg/L(43). In the following study in Lebanon, the colistin MIC for the *mcr-1*-positive isolates ranged from 4 to 64 mg/L. In this study, the *mcr-1* gene was located on plasmids belonging to IncI2 and IncX4, as well as IncF plasmids associated with the spread of antibiotic resistance and virulence genes among Enterobacterales. BlaTEM, $bla_{CTX\text{-}M,}$ and bla_{SHV} were detected in 86%, 80.6%, and 13.8% of isolates, respectively. Genotyping of the *mcr-1*-positive *E. coli* isolates was performed using BOX-PCR fingerprinting analysis and all 36 isolates were classified into 25 different genotypes (44).

3.11. Saudi Arabia:

In a study conducted in Saudi Arabia,137 (51%) *E. coli* strains were detectedamong 415 uropathogenic isolates, of which 57 (41.6%) were classified as ESBL producers. Colistin resistance was detected in 9% of uropathogenic isolates, and a few levels were reported 45in *E. coli* isolates (45). Recently, *mcr-1*was detected in poultry meat in Saudi Arabia (46).

3.12. Jordan:

No significant data on colistin-resistant *E. coli* strains were found in this country .

3.13. United Arab Emirates:

An identified colistin-resistant *E. coli* isolate carried the *mcr-1* gene on conjugative plasmids, which was discussed in the Oman and Kuwait section of this article (26).

3.14. Cyprus:

No significant data were found on colistin-resistant *E. coli* strains in this country .

4. Conclusion:

Many studies in the medical field have highlighted the crisis of antibiotic resistance in Enterobacteriaceae as far as resistance to colistin (last in the line of therapy) in pandrogen resistant (PDR) strains is concerned (9). The clinical use of colistin in severe nosocomial infections caused by XDR gram-negative bacteria, particularlycarbapenem-resistant strains, and subsequently colistin-resistant isolates of human origin, are often considered a treatment challenge. The worldwide spread of colistin-resistant gram-negative bacteria of animal origin is almost entirely due to food-producing animals, and is thought to be largely related to the overuse and misuse of antibiotics in veterinary medicine. Colistin resistance of animal origin could also potentially be transmitted to the human microbiome and clinical pathogens (47). Very little has been reported on the prevalence of colistin resistance in general. The percentage of *mcr* genes reported in *E. coli* strains has been presented globally (Fig. 6). (https://card.mcmaster.ca/). In the last 10 years, almost all Middle Eastern countries have conducted studies on *E. coli* strains to determine the rate of colistin resistance. As far as we know, most colistin-resistant *E. coli* strains have been reported from Lebanon, Algeria and Egypt, perhaps because most studies on this topic have been conducted there (Fig. 4). The highest number of *mcr-1*-positive *E. coli* strains was reported from Lebanon, Qatar, the Arabian Peninsula and Bahrain (Fig. 5). It should be considered that inadequate sanitary conditions, overcrowding, and poor infection

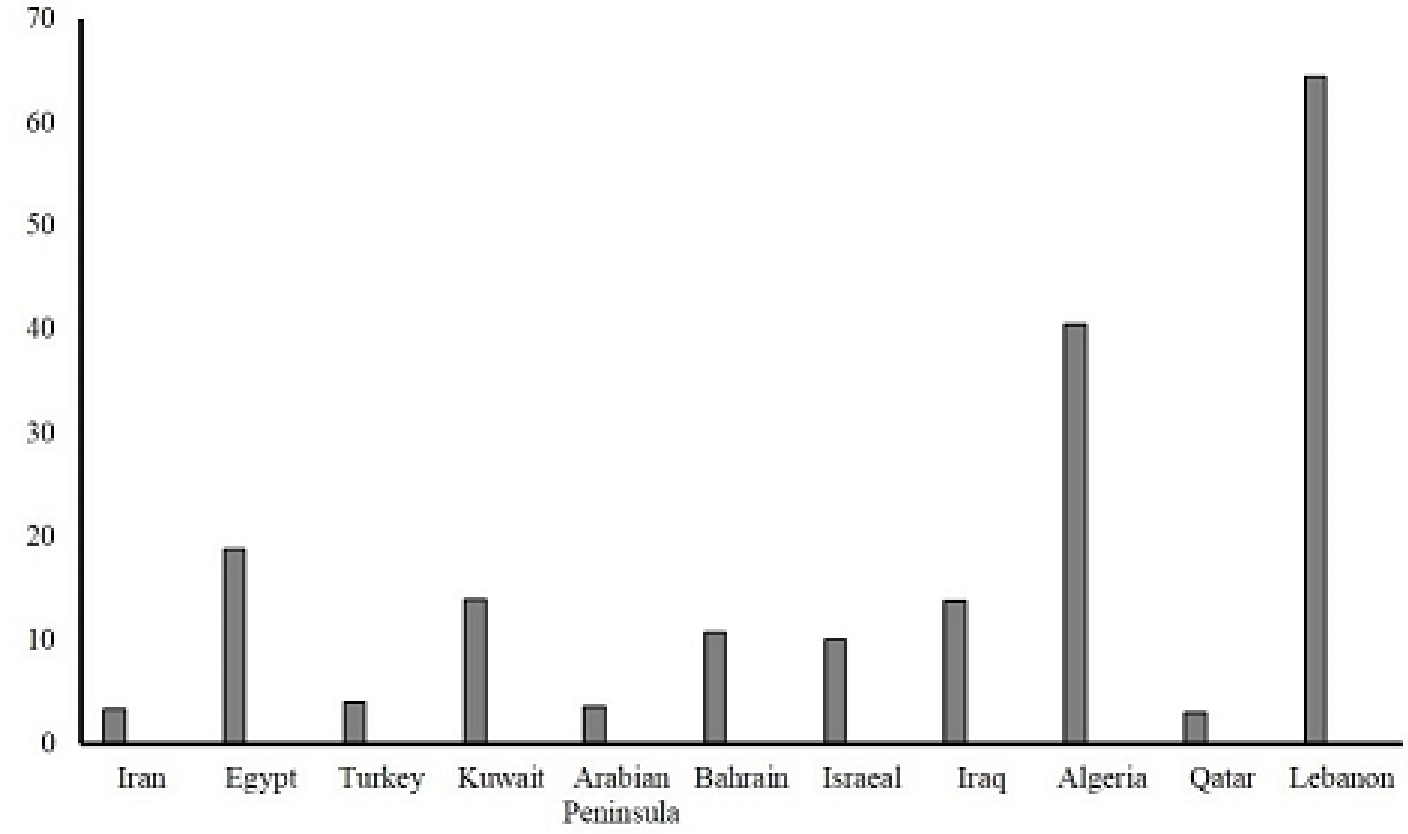

Fig. 4. The percentage of colistin-resistant *E. coli* in middle East countries.

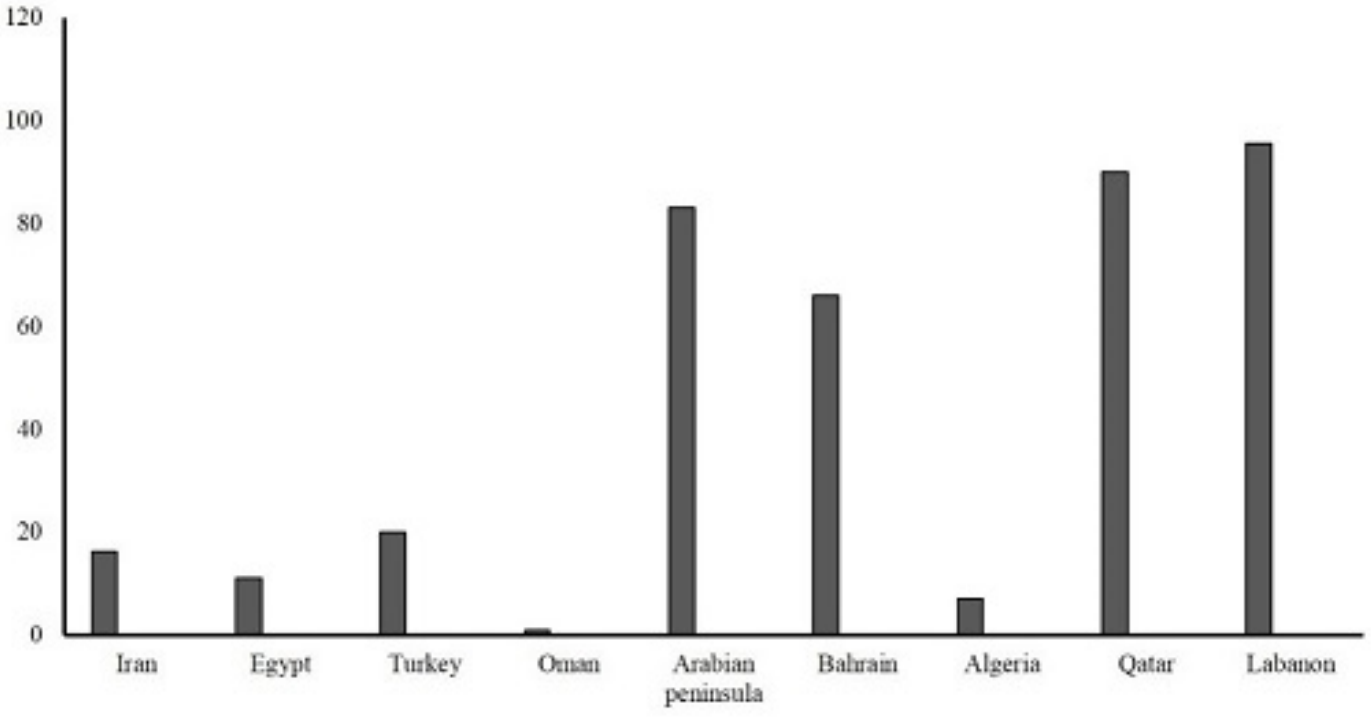

Fig.5. The numbers of *mcr-1*-positive in colistin-resistant *E. coli* in middle East countries.

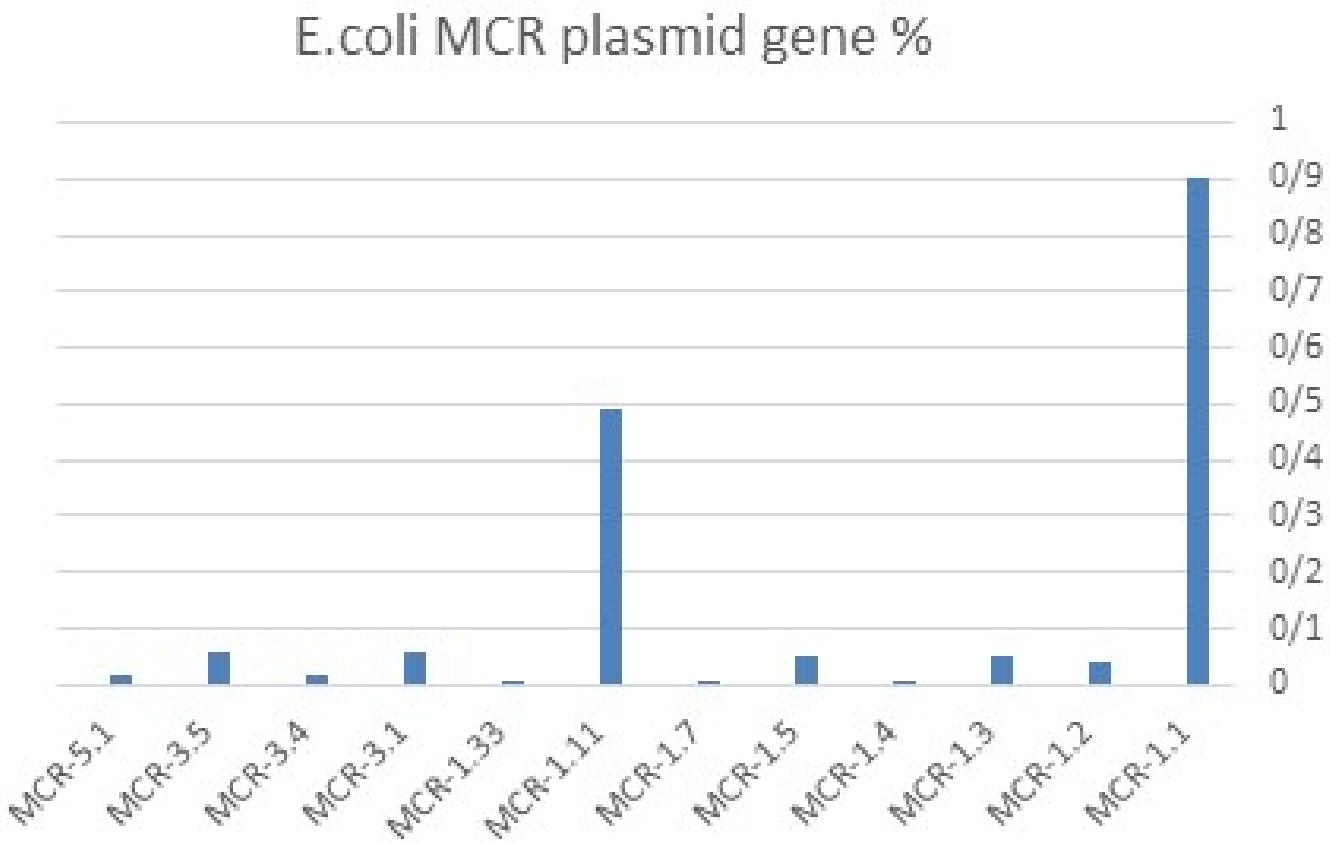

Fig.6. Percentage of *mcr* genes reported in *E. coli*

control practices in animals, as well as over-prescription of antibiotics in health care systems, may contribute to the huge massive of MDR strains(5). It appears that the presence of the *mcr-1* gene is currently the most common strategy for colistin resistance in *E. coli* strains among the known mechanisms. The *mcr-1* gene has been detected in various environmental sources, humans, food animals, and even immigrant birds in these countries. No clear evidence of chromosomal point mutations for colistin resistance analysis was found in *E. coli* isolates in the Middle East, except in one study. We also did not find a large number of documents on the existence of *mcr-2-9* genes in this region. Althoughit appears thatthe rate of colistin resistance due to chromosomal genes was negligible in *E. coli* strains, further studies are needed to determine the true prevalence of chromosomal colistin resistance genes among *E. coli* isolates.

In this study, most colistin-resistant *E. coli* isolates were found to have plasmid -mediated colistin resistance, *mcr genes* (especially *mcr-1*), compared with mutations in the *pmrAB, phoPQ,* and *mgrB* genes, in contrast to *Klebsiella spp*. There are new strategies to control MDR/XDR/PDR bacteria, including phage therapy, nanoparticles, aptamer, and combination therapy(48). According to some studies, the appropriate use of disinfectants (sodium hypochlorite 5%, chloroxylenol (Dettol) 4.8%, Sayasept-HP 2%, chlorhexidine 2%, and ethanol 70%) at the right concentrations for the different bacterial species should also be considered to avoid the induction of resistance mechanisms in bacteria(49).

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Authors' Contribution

Farhad nikkhahi, Sara Rahimi, and Mehdi Bakht wrote the main manuscript text and Sara Rahimi, Zahra and Mehdi Bakht prepared figures and tables. All authors reviewed the manuscript

Ethics

Not applicable

Conflict of Interest

The authors have no conflicts of interest to declare

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