**MCR-1 Colistin Resistance in Escherichia coli Wildlife: A Continental Mini-review**

**Ahtesham Ahmad Shad**

Institute of Microbiology, University of Agriculture, Faisalabad, Pakistan

**Abstract**

Antimicrobial resistance is one of the major leading problems and an issue for medical science in this era. Despite of being successful in treating bacterial infections and developing novel antibiotics, we are unfortunately going back to pre-antibiotic era. ESBLs, Carbapenemases and **MCR-1** genes are the predisposing factors together in emerging horizontal resistance. The focus of this mini-review is to give a glance on **MCR-1** gene mechanism of resistance in Escherichia coli and also plasmid profile and phenotypic characteristics of wildlife strains in continents, keeping resistance to colistin.

As the global transmission of resistance has accounted the wildlife as one of the major culprits.

**Keywords:** **ESBLs**, **MCR-1**, ESKAPE, Polymyxin E

**Introduction**

Antimicrobial resistance is one of the notoriously leading issue and universal threat to one health in this era. WHO and US Centers for Disease Control and Prevention are clearly stating about medical science going towards pre-antibiotic era [1]. The specific markers of resistance ESBLs, Carbapenemases and **MCR-1** genes are helping in prevailing resistance among bacterial strains [2]. The discovery of plasmid mediated colistin resistance in the normal and routinely survey of China is devastating finding to one health [1]. Then the rash of reports started globally in alarming the human and as well animals health [3]. Within just three months of first discovery in November 2015, the spread of **MCR-1** gene evidently supported by medical society worldwide [4]. Isolation of **MCR-1** gene from different locations and samples raised up the need to understand mechanisms underlying in spreading it globally, especially samples from Humans, animals and environment i.e. soil, river water [3,4]. As the colistin was the drug of choice or the drug of last-resort antibiotic in controlling the infections caused by multi-drug resistant pathogens in past i.e. ESKAPE [3]. The deteriorating power of this powerful and effective antibiotic posing by **MCR-1** gene is a huge danger [5]. The focus of this mini-review is to highlight the basics of **MCR-1** resistance mechanism in **E. coli** and we aim to describe and provide the reader with a glance on plasmid and phenotypic characteristics in **E. coli** of wildlife origin continents.

**E. coli**

**E. coli** is a straight Gram-negative rod, most abundant facultative anaerobe in colon and feces. It has three antigens that are used to identify the organism in epidemiologic investigations: the O, or cell wall, antigen; the H, or flagellar; and the K, or capsular, antigen [6]. Because there are more than 150 O, 50 H, and 90 K antigens, the various combinations results in more than 1000 antigenic types of **E. coli** [6,7].

**E. coli** is the most common cause of urinary tract infection and sepsis, it is one of the two important causes of neonatal meningitis and the agent frequently associated with “traveler’s diarrhea”, a watery diarrhea (8).

**E. coli** has three major serotype classes (O, H, K), four phylogenotypes (A, B1, B2, D), and two broad pathotypes (Extraintestinal **E. coli** (ExPEC) and Diarrheagenic **E. coli**). The Diarrheagenic **E. coli** has six distinct classes (Enteropathogenic **E. coli** (EPEC), Enterohaemorrhagic **E. coli** (EHEC), Enterotoxigenic **E. coli** (ETEC), Enteroinvasive **E. coli** (EIEC) and Diffusely adherent **E. coli** (DAEC) (9).

**MCR-1** gene discovery

The first report of plasmid mediated colistin resistance designated as **MCR-1** is from China during a routine surveillance project on antimicrobial resistance in commensal **E. coli** from food animals. **MCR-1** gene was isolated from a pig of **E. coli** strain SHP45 [8].

**MCR-1** mechanism of resistance

Previously, all reported polymyxin resistance mechanisms are chromosomally mediated, and involve modulation of two component regulatory systems (eg, pmrAB, phoPQ) [9].

Based on sequence alignment, **MCR-1** should be a phosphoethanolamine transferase, a member of YhjW/YjdB/YijP superfamily, which catalyzes the addition of phosphoethanolamine to lipid A moiety of lipopolysaccharides (LPS) and therefore confers colistin resistance to its host [10,11].

**Spreading ways or routes of **MCR-1** transmission**

The **MCR-1** gene may undergo evolutionary changes in the animal GI tract upon prolonged usage of colistin as growth promoter. The gene...
is then transmitted to human through the food chain or direct human contact with animals, as well as through contamination of the fresh and seawater system, which in turn cause contamination of vegetables and seafood. The persistence of MCR-1 in the human GI tract microflora can cause further contamination of the water systems through disposal of waste water containing human faeces. Fresh water systems outside these transmission routes remain clear of MCR-1 contamination [12].

**MCR-genes types discovered so far**

Five colistin resistance genes (MCR-1, MCR-2, MCR-3, MCR-4 and MCR-5) have been described, few data are available on the prevalence of MCR-genes other than mcr-1 in human samples [13]. Moreover, so far six different variants of the MCR-1 gene (MCR-1.2 to MCR-1.7), which differ from each other by a single amino acid have been described in Enterobacteriaceae [14].

**Why wildlife is so important to analyze for MCR-1 gene?**

The development of bacterial resistance is a naturally occurring evolutionary mechanism of micro-organisms, but the wide spread use and misuse of antibiotic agents in humans and animals has accelerated this process. MCR-1 is one of the few and clear example of the animal origin of a resistance trait that may later hit the entire human health [2,15].

Since, most emerging human diseases have come from wildlife and natural environment and wildlife is considered to be a “melting pot” and dissemination route of antibacterial resistance [16].

**Role of wildlife in transmission of the MCR-1 gene**

The use of antimicrobials in veterinary medicine creates a selective pressure for the emergence of antimicrobial resistant bacteria, including animal human pathogens that have animal reservoirs and commensal bacteria from animals bacteria selected by this pressure can spread to humans either by direct contact with animals or food products, or indirectly via environmental pathways and/or non-food producing animals (Figure 1) [17].

Wildlife is a major zoonotic origin of transmission of various bacterial genes and hence the diseases among the domestic animals and human ecosystem [18].

<table>
<thead>
<tr>
<th>Continents</th>
<th>Country</th>
<th>Species</th>
<th>ST-type</th>
<th>Plasmid</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - South America</td>
<td>Argentina</td>
<td>Larus dominicanus</td>
<td>1, STF101, 2, STF44</td>
<td>IncI2</td>
<td>2016</td>
</tr>
<tr>
<td>2 - Europe</td>
<td>Lithuania</td>
<td>Larus argentatus</td>
<td>-</td>
<td>SHP45</td>
<td>2016</td>
</tr>
<tr>
<td>3 - Asia</td>
<td>Pakistan</td>
<td>Fulica atra</td>
<td>ST354</td>
<td>IncI2</td>
<td>2016</td>
</tr>
</tbody>
</table>

Table: 1 MCR-1 in wildlife of Subcontinents.

**Global distribution of E. coli harboring MCR-1 gene**

Wild birds and animals are the potential reservoirs and vectors for the global distribution of MCR-1, it has been identified on Enterobacteriaceae isolates from food-producing animals, companion animal, food products, the environment and humans worldwide [2,19].

The gene has been found primarily in E. coli but has also been identified in other members of the Enterobacteriaceae in human, animal, food, and environmental samples on every continent [20]. The MCR-1 gene has been rapidly detected in several European, Asian, South-East Asian, South American, Northern American and African countries. Retrospective studies led to establishing the presence of the MCR-1 gene in China as early as the 1980s and in Europe since 2005 [21]. The global distribution of MCR-1 over at least five continents is well documented, but little is known about its origin, acquisition, emergence, and spread [22].

A plasmid-mediated (horizontally transferable) colistin resistance (MCR-1) gene was recently reported in China and subsequently detected in Asia (Vietnam, Laos, Thailand, Cambodia, Malaysia, Singapore, Taiwan and Japan), Europe (The Netherlands, Germany, Belgium, Switzerland, France, Denmark, United Kingdom, Spain, Italy, Sweden and Portugal), Africa (Algeria, Egypt, South Africa and Tunisia), and America (Canada, Argentina and Brazil) [23].

**Continental plasmid profile and phenotypic characteristics of E. coli harbouring MCR-1 gene of wildlife origin**

A brief summary is given below in Table 1, Continents in which the MCR-1 harboring colistin resistance gene has been reported from E. coli of only wildlife origin so far:

The first report of the dissemination of the MCR-1 gene in Kelp gulls is from ushuaia, Argentina. The fact that gull species migrate, sometimes even between continents, indicates that they may play a role in the global dissemination of these clinically relevant bacteria. The association of the MCR-1 gene with conjugative IncI2 plasmids also among gulls illustrates a successful plasmid–gene combination, resulting in the emergence spread of this gene [24]. The first known occurrence of the MCR-1 gene in E. coli carried by a wild migratory bird—the European herring gull (Larus argentatus) [25]. The first detection of MCR-1 in colistin-resistant extended spectrum β-lactamase-producing E. coli (ESBL-E. coli) isolated from wild transboundary migratory waterfowl species Fulica atra from Pakistan, Asia [26].

**Conclusion**

No doubts, a set of data has been reported so far from wildlife [24-26]. But it is not sufficient to estimate and account for MCR-1 gene distribution in E. coli wildlife globally. There is an urgent need and we emphasize to look for MCR-1 gene, not only in birds but also in animals. Although birds can travel and disseminate more than animals, but we cannot neglect the impact of interaction between domestic and wildlife animals, as indicated from wild animals in Poland [16]. Also, we suggest investigating MCR-1 gene presence in other continents of...
wildlife, so that a more comprehensive picture can be established in accounting MCR-1 gene.

References


