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Review of Plasmid-Mediated *mcr-1* Gene in *E. Coli* of Poultry Origin

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Abstract

Antimicrobial resistance (AMR) is one of the significant existing and prevailing problem worldwide. The threat to 'One Health' approach and respected danger of Multi-Drug Resistant (MDR) strains has drawn the attention of medical societies all over the world to ponder upon it for finding possible ways to resolve it. Unfortunately, because of difficulty in understanding complexities of microbial resistance mechanisms and hence slow development of new antibiotics is a milestone. This review aims to brief about plasmid-mediated *mcr-1* gene in *Escherichia coli* (*E. coli*) that makes the bacterium to resist the drug of last-resort i.e. colistin. This polypeptide is a weapon of specific interest to defend against hard to treat bacterial infections especially infections caused by multi-drug resistant pathogens. But, the discovery of *mcr-1* gene and its role in transmitting resistance among same and even different species as well is life-threatening. Moreover, this paper intended to provide an epidemiological view of *mcr-1* gene in *E. coli* from poultry sector. The poultry meat has importance in getting cheap source for protein and its impact of transferring resistance cannot be neglected.

Keywords: AMR; MDR; *E. coli*; *mcr-1*

Abbrevations: AMR: Antimicrobial Resistant; OECD: Organization for Economic Co-operation and Development; CRE: Carbapenem Resistant *Enterobacteriace*; MDR: Multiple Drug Resistance; PUFA: Polyunsaturated Fatty Acids; FDA: Food and Drug Administration; PHA: Public Health Agency; GI: Gastrointestinal Infections

Introduction

Antimicrobial resistant (AMR) bacterial strains have a major threat to public health. According to a recent report the Organization for Economic Co-operation and Development (OECD) describes that infections caused by resistant strains of bacteria could kill about 2.4 million people in Europe, North America and Australia by 2050 unless more is done to tackle the problem and states as "one of the biggest threats to modern medicine". Moreover, 90,000 people in UK will die due to super-bugs. In another previous report about 10 million people will die due to AMR by the year 2050 [1]. The more severe form of anti-microbial resistance seems in future of 21st century can put us in pre-antibiotic era, in which a simple or common infection like minor cuts and injuries could be fatal. The vicious use of antibiotics is the primary cause of developing and spreading resistance [2]. The gradual development and spreading of resistance by multi-drug resistant bacteria especially of Carbapenem Resistant *Enterobacteriace* (CRE) is a major threat and public health problem and nowadays, additionally accompanying colistin resistance becomes severe problem. The colistin is the drug of choice for infections caused by MDR bacteria [3] *E. coli* belongs to the family of *Enterobacteriace*-ae, that was discovered by Theodor Escherich, a German microbiologist in 1884 [4].

The facultative nature, ubiquitous presence and different strains type makes it favorable in most of the harsh environments to sustain its population. The pathogenic as well non-pathogenic *E. coli* both contribute in transferring traits of significance interests to their next generations. *E. coli* are responsible for causing gastrointestinal, respiratory as well as zoonotic diseases by producing harmful toxins and show resistance towards many of the frequently used antibiotics [5]. The growing problem of *Enterobacteriaceae* family can be estimated by the fact that it has caused the death of 3 million people and 200 million cases that makes it as the major human pathogen, and hence the interaction of human with livestock and poultry especially poultry meat can lead its transmission at massive rate that apparently is a hidden fact silently disseminating and propagating it beyond the limits of imagination. The family of drugs beta-lactams are used frequently to resolve the infections caused by *E. coli* [6].

The bacteria possess many of the structures that plays vital role in its survival and growth. One of such entity is plasmids. The double stranded, extra-chromosomal DNA. It helps *E. coli* in transmission of genes of desired traits according to the environment facing by the microbe at a specific time and location. Furthermore, the genes for drug resistance are also passed to their next genera-

tions making them resistant [6]. Plasmids are responsible mainly for the spreading of antibiotic resistance genes in gram negative species. The first report on the importance of Multiple Drug Resistance (MDR) in *Escherichia coli* was reported over 55 year ago in Japan, in the seminal work of Watanabe [7].

The discovery of plasmid-mediated *mcr-1* gene was done in China during a routine surveillance of food producing animals. The occurrence of *mcr-1* gene reports were also accompanied by the medical societies all over the world from human and as well as from environment of different regions across the globe. According to a published report the *mcr-1* gene has been reported from 29 countries in human settings. The reports of *mcr-1* gene from environmental settings were 4 and from animals of food origin and other animals were done by 28 countries. The horizontal gene transfer mechanism favors rapidly dissemination of *mcr-1* gene and hence prone to a leading issue concerning public health. This perspective highlights that an urgent emphasize needed to screen for epidemiology and finding possible solutions to save the drug of last resort i.e. colistin [8].

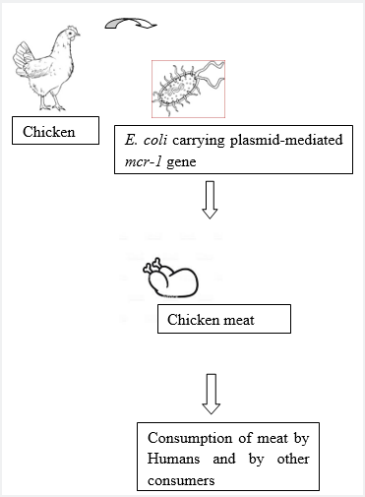

Figure 1: Transmission of *mcr-1* gene through poultry.

There are different sources and reservoirs to transmit to different hosts like direct and indirect contact by inanimate objects, from waste-water and food-producing animals i.e. poultry meat [9]. The simplified transmission through poultry is illustrated in Figure 1. The focus of this review is to highlight plasmid mediated *mcr-1* gene in *E. coli* of poultry origin. The poultry meat is a cheap source of getting rich quantities of protein by consumers all around the world by human population. Moreover, this paper also aims to provide an epidemiological view of plasmid-mediated colistin resistance in poultry sector.

Importance of Poultry Sector

Poultry sector is an important source of a countries own need of fulfilling the nutritional values of community and also exporting helps in the growth of economy. Poultry has a huge impact in humans, as we get eggs and meat for our commercial and other purposes i.e. restaurants, home etc. Interestingly, the poultry meat is an important source of providing essential Polyunsaturated Fatty Acids (PUFA), most importantly omega (n)-3 fatty acids. It plays an important role in brain function and development [10]. The production of poultry meat and eggs has been increased in recent years and it will expect to move on this fashion. It is also predicted that the poultry production will increase in next two decades in developing countries, because of the fact of demand by increasing in urbanization, need of rapid economical growth and nutritional need [11].

Use of Colistin in poultry

Colistin has been used as a feed additive to promote growth and also to resist bacterial infections in poultry. The historical use of colistin in Europe was linked to 1950s, unfortunately little is known about its prior use [7]. The Food and Drug Administration (FDA) and also the Public Health Agency (PHA) of Canada took a step to never license the compounds containing colistin for use of any purpose used orally previously in livestock [12]. Globally, China is the leading producer of colistin and hence also the largest user. The production rate is 17.5 million tones and use 90 % of its production [13].

The use of colistin is indication of most infections caused by family *Enterobacterriacae* in most of the livestock animals and poultry. The Gastrointestinal (GI) Infections are common targets of colistin [13]. In poultry, the most common indications for use of colistin is *collibacillosis*, while GIT infections are treated in other livestock animals. The colistin is also used in low amounts to enhance growth of livestock and other animals [14]. Moreover, against the primary diarrheal diseases caused by *E. coli*, colistin is not the drug of choice, because of poor absorbance from the GI tract [15].

Epidemiological view of Plasmid-mediated *mcr-1* gene in E. coli from Poultry

In Europe the prevalence rate of *mcr-1* has found to be low for chickens but increased in turkeys. The recent European report of AMR shows resistance to colistin in poultry meat found to be 3.9%, while in turkey meat 10.9%. The moderate rate of *mcr-1* gene has been found in flocks of turkeys and meat in Germany also. While high prevalence rate found to be in Portugal [16,17]. In China, colistin resistance in broilers were low, while one study reported high prevalence of about 14% [18]. In Asia, clinical samples of *E. coli* in chickens showed low resistance to colistin, while a report from China showed comparatively high rate of 73.1% [19]. A study reported from Pakistan; *mcr-1* gene was found to be in *collibacillosis* affected poultry in *E. coli* samples [20]. In another recent report from Pakistan, the prevalence rate of *mcr-1* gene was found to be 8% positive in commensal *E. coli* samples from healthy broilers [21]. The 10 positive *E. coli* samples were reported from Brazil out of 343 [22]. Whereas moderate rate of gene also founded in chicken meat [23-27]. Moreover, few reports have been documented from Africa, South Africa and in broilers from Tanzania. The continental studies isolating *mcr-1* gene is illustrated in Table 1.

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Table 1: Continental-wise study done in poultry reporting *mcr-1* gene originated from [3].

Sr. No	Continents	Studies No. done (n=)	Most Represented Countries	References
1	Europe	30	$a).Denmark$ $b).\ Portugal$ $\}n=4$	[3]
			$c).Italy$ $d).Switzerland$ $e).Norway$ $f).\ Netherland$ $\}n=3$	
2	Asia	23	a). China, n=14	
			b). Japan, n=5	
3	South America	4	a). Brazil, n=3	
4	North America	1		
5	Africa	2		

Conclusion

To conclude, poultry industry has a significant impact in a country own purpose of use and also to export for the growth of their economy as well. As poultry birds raising especially of chicken and turkeys for consumption of meat and getting eggs to fulfill nutritional values are common around the world. So, there is an urgent need for screening *mcr-1* gene in poultry worldwide and more importantly in developing countries because of increasing production of poultry as compared to previous two decades. Moreover, we also suggest there should be special addressing and awareness campaigns and actions should be taken together, so that a person should know the meat with respected danger of resistant strains and possible source of infectious routes. This will also help an individual to take part his role in minimizing the rapidly spreading colistin resistance in poultry section.

Conflict of Interest

The authors declare that they have no conflict of Interest.

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