**mcr-1 Gene in Latin America: How Is It Disseminated Among Humans, Animals, and the Environment?**

**Silvia Adriana Mayer Lentz**<sup>1,2</sup>, **Tanise Vendruscolo Dalmolin**<sup>3</sup>, **Afonso Luis Barth**<sup>4</sup> and **Andrea Francisco Martins**<sup>1,2,4</sup>

1 Programa de Pós Graduação em Microbiologia Agrícola e Do Ambiente, Universidade Federal Do Rio Grande Do Sul, Porto Alegre, Brazil; 2 Laboratório de Microbiologia Aplicada, Instituto de Ciências Básicas da Saúde, Universidade Federal Do Rio Grande Do Sul, Porto Alegre, Brazil; 3 Faculdade de Saúde, Departamento de Farmácia, Universidade de Brasília (UnB), Brasília, Brazil; 4 Laboratório de Pesquisa em Resistência Bacteriana (LABRESIS), Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

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**INTRODUCTION**

In the last decade, polymyxins have been reintroduced in the therapeutic arsenal to treat severe infections by carbapenem-resistant Enterobacterales. At that time, reports of polymyxin resistance were all due to chromosomal mutations (1). These mechanisms included (i) modifications of the lipopolysaccharides (LPSs) moiety via the addition of cationic groups; (ii) mutations that lead to the loss of the LPS; (iii) porin mutations and overexpression of efflux pump systems; (iv) overproduction of capsular polysaccharide (CPS) in some Gram-negative bacteria (GNB) that hide the polymyxin-binding sites and the release of CPS-trapping polymyxins; and (v) enzymatic inactivation of polymyxins (2). Although some chromosomal resistance mechanisms have been studied since the 1960’s, it was in the late 1990’s, after the reintroduction of polymyxins in the therapeutic arsenal, that this problem became more important (3). In fact, this information is supported by the first report of colistin resistance among *Acinetobacter baumannii* clinical isolates from the Czech Republic in 1999 and *Klebsiella pneumoniae* from Athens in 2004 (4).

However, in 2015, the *mcr-1* gene, associated with IncI2-type plasmid, was identified in *Escherichia coli* resistant to colistin obtained from food animals and humans in China (1). This finding promoted a great concern in the international scientific community since the last therapeutic option to treat serious infections by multidrug-resistant GNB could be exhausted. With the horizontal transfer, the rapid spread of the *mcr-1* gene would be inevitable.

The *mcr-1* gene carried by different plasmid types has already been identified in all five continents from different sources and hosts (1, 5). Surprisingly, Shen and colleagues, in a retrospective study, characterized the early occurrence of the *mcr-1* gene in chicken isolates from 1980’s (6).

So far, a total of 10 different variants (7) of the *mcr* gene have been described mainly among the Enterobacterales, but with the *mcr-1* gene remaining the most prevalent (1). To date, the sequences of 30 *mcr*-1 mutations (*mcr-1.2 to mcr-1.30*) have already been deposited in the GenBank database, differing from *mcr-1* by one or few amino acids. Besides that, 10 *mcr* gene variants (*mcr-1 to mcr-10*) were deposited, with amino acid identity ranging from 31 to 83% (8). These variants were identified at the beginning in Enterobacterales isolates, including *E. coli* (*mcr-1, mcr-2*, and *mcr-3* genes), *Salmonella enterica* (*mcr-4, mcr-5* and *mcr-9* genes), *K. pneumoniae* (*mcr-7* and *mcr-8* genes), and *Enterobacter roggenkampii* (*mcr-10* gene). The exception is due to *mcr-6* gene that was first identified in *Moraxella* spp. After that, some variants were identified in non-fermenter
Gram-negative rods, as *Acinetobacter* spp. (*mcr-1* and *mcr-4*) and *Pseudomonas* spp. (*mcr-1* only) (9, 10).

In general, the isolates carrying *mcr* genes were first isolated from animals such as pigs (*mcr-1*, *mcr-2*, *mcr-3*, *mcr-4*, *mcr-6*, and *mcr-8* genes) and chickens (*mcr-5* and *mcr-7* genes), but *mcr-9* and *mcr-10* genes were identified, for the first time, from human patients (8).

**EPIDEMIOLOGY OF POLYMXYN RESISTANCE**

The resistance to polymyxins was attributed mainly to chromosomal mutations and is rare in human clinical isolates (0.67–1.6%) (11). Nevertheless, this differs among bacteria species, being higher in *K. pneumoniae* and *A. baumannii* (20–80%) (4) in contrast to lower rates in *E. coli* (0.2–0.6%) (11).

The polymyxin resistance rate associated to plasmid, as *mcr-1*, is also low in humans (~1%) (4). On the other hand, according to a large US surveillance study, the association between *mcr-1* and other antibiotic resistance genes, such as extended-spectrum β-lactamase (ESBL) and carbapenemases, may reach 32% of prevalence in *K. pneumoniae* (11). Regarding the mortality associated with infections caused by colistin-resistant isolates in humans, the rate is variable, and it is higher in critically ill patients (30–37%) including those previously exposed to colistin (4). The mortality rate may reach 100% in patients with nosocomial infections caused by pan–drug-resistant *K. pneumoniae*.

It is important to emphasize that the prevalence of *mcr-1* gene is higher among production animals, mainly in pig and chicken isolates (5). The data show colistin resistance rates of ~70% in *E. coli* isolates from China and ~90% among Enterobacterales in some European countries (8). So, these data corroborate with the scientific evidence that the worldwide spread of the *mcr-1* gene is mainly associated with the large amounts of colistin use in production animals, and its emergence is a particular threat to public health as colistin is considered the last-resort antimicrobial for treatment of severe human infections, and its use in livestock production contributes to emerging resistance globally (1).

**mcr-1 IN LATIN AMERICA**

In Latin America, a systematic review analysis showed that the prevalence of *mcr-1* gene is higher in isolates from animals (8.7%) than in food (5.4%) and humans (2.0%) (12). To the best of our knowledge, the first reports of *mcr-1* gene in Latin America dated from July and October 2012 when this gene was identified in *E. coli* isolates from two inpatients in different hospitals in Argentina (Table 1) (13). Patients presented neurological disease and diabetes, and the *mcr-1*–positive isolates were obtained from blood and urine, respectively. In this study, the authors evaluated the presence of the *mcr-1* gene in 87 colistin-resistant clinical human isolates from 2008 to 2016 (28 *E. coli*, 19 *K. pneumoniae*, 36 of other members of the Enterobacterales, and 4 non-fermenter Gram-negative rods), and nine isolates of *E. coli* were *mcr-1* positive. These isolates were associated with human infections, mainly in males, and the average age of the patients was 68.5 years. All *mcr-1*–positive *E. coli* isolates were genetically unrelated as determined by pulsed-field gel electrophoresis, and the resistance mechanism was horizontally transferable by conjugation (13). Still, in 2012, other studies reported *mcr-1* harboring *E. coli* recovered from Kelp Guls in Argentina (14) and from swine in Brazil (Table 1) (15).

Since 2012, the *mcr-1* gene has already been identified in bacteria from humans, animals, animal food products, and environmental sources in different countries in Latin America, including Brazil (15), Bolivia (16), Colombia (17), Chile (18), Uruguay (19), Paraguay (20), Peru (21), Mexico (22), Venezuela (23), and Ecuador (24). Brazil is the country with the highest number of *mcr-1*–positive bacteria reported in Latin America mainly from bacterial isolates obtained from poultry rectal swabs (15) (Table 1).

It is important to consider that Brazil is the fourth largest pork producer and exporter and the largest chicken meat exporter in the world, which could contribute to the high prevalence of the *mcr-1* gene in this country (25). As in other countries, the colistin was extensively used in Brazil as a growth promoter for many years. In 2016, the government published restrictions on the use of colistin in animal production (1, 26), which came into force in 2018. However, the use of colistin to treat or prevent infections in veterinary medicine including animal productions is still allowed.

*E. coli* is the most common species harboring the *mcr-1* gene in Latin America countries. However, many other Enterobacterales members such as *K. pneumoniae*, *Salmonella* spp., *Citrobacter* spp., and *Enterobacter* spp. were also reported as positive for the *mcr-1* gene (17, 27). In addition to *mcr-1*, other variants of the gene were reported rarely in Latin America, such as *mcr-3*, *mcr-5*, *mcr-7*, and *mcr-9* (28–30).

**GENETIC CONTEXT AND DISSEMINATION OF mcr-1 GENE**

*E. coli* isolates harboring *mcr-1* gene belong to different sequence types (STs) (31, 32) (Table 1), indicating that the dissemination of the *mcr-1* gene is associated with different clonal strains (1). Loaya-­Villa and colleagues investigated the relationship between an *E. coli* carrying *mcr-1* recovered from the gastrointestinal tract of a boy and an *mcr-1*–positive *E. coli* from fecal samples and rectal/cloacal swabs from his domestic animals. *E. coli* strains from domestic animals and from the boy were different; however, all plasmids harboring the *mcr-1* gene shared 90% nucleotide identity and a highly conserved backbone, supporting the idea of horizontal dissemination of the *mcr-1* gene (32).

In Latin America, the *E. coli* belonging to CC10 clonal complex, known as the largest human clonal complex, was the most reported in previous studies, including the ST744 and ST10 (1, 17, 22, 33). *E. coli* CC10 strains are widely disseminated among humans, animals, meat products, and environmental sources (34, 35) and are designated as multidrug-resistant strains carrying frequently ESBL, among others (5, 31).

The *mcr-1* gene is carried by a wide range of conjugative and non-conjugative plasmid types, including IncX3, IncX4, an
| Period of the study | Country | Source of Isolate | Total Isolates (mcr-carried) | Species | Plasmid Type | Sequence Type (ST) | Genetic Context | References |
|---------------------|---------|-------------------|-----------------------------|---------|--------------|-------------------|----------------|------------|
| 2000–2016 Brazil    | Fecal samples–chicken and swine (Production Animals) | 515 (16) | E. coli | IIncP-1 IncFII IncHI1 | E. coli (ST10, ST37, ST101, ST744, ST1263, ST3056, and ST6627) | Absence of ISApI1 |- | (15) |
| 2002–2016 Colombia  | Urine vaginal secretion blood stool tissue right toe leg secretion abdomen abscess (Human) | 513 (12) | E. coli, S. enterica Typhimurium, K. pneumoniae | IncHI IncX4 | ST10, ST156, ST354, ST8492, ST5208 | mcr-1-pap2 (IncP-1) | ISApI1-mcr-1-pap2 (IncP-1) | (17) |
| 2008–2016 Argentina | Urine, blood, abdomen, abscess, bone (Human) | 87 (9) | E. coli | IIncFII IncHI1 | Absence of ISApI1 | - | - | (13) |
| 2012 Argentina      | Fecal samples - Kelp gulls penguin (Wild Animal) | 50 (5) | E. coli | IncI2 | ST101 and ST744 | - | ISApI1-mcr-1 | (14) |
| 2012–2018 Argentina | Urine, blood, other samples (Human) | 192 (192) | E. coli | IIncHI2 IncX4 | ST155 (CC10: ST10, ST1141 and ST1286), ST617, ST10, ST410, ST1011, ST1408 | - | - | (37) |
| 2013 Bolivia        | Potatoes (Food) | 83 (1) | C. braakii | IncI2 | - | - | - | (16) |
| 2013 Argentina      | Fecal samples–Chicken (Production Animals) | 10 (10) | E. coli | IncI2 | ST155 (CC10: ST10, ST1141 and ST1286), ST617, ST10, ST410, ST1011, ST1408 | - | - | (33) |
| 2013–2014 Ecuador   | Feces–chicken (Production Animals) | 176 (6) | E. coli | - | - | - | - | (24) |
| 2013–2016 Brazil    | Meat Poultry (Food) | 60 (2) | Salmonella enterica serovar Schwarzengrund | IncX4 | ST96 | parA and hypothetical protein upstream mcr-1 and pap2 downstream | (44) |
| 2013–2017 Chile     | Urine (Human) | 13 (1) | E. coli | IncI2 | ST4204 (CC10) | mcr-1 was delimited upstream by a gene that encodes a pap2 protein and downstream by a relaxase-encoding gene (nkb) | (18) |
| 2014 Argentina      | Clinical samples - dogs and cats (Pets) | 54 (1) | E. coli | IncI2 | ST770 | mcr-1 was delimited upstream by nkb gene which encodes a relaxase and pap2 downstream | (31) |
| 2014–2017 Brazil    | Pork carcasses (Food) | 490 (8) | S. enterica serovar Typhimurium | IncX4 | ST19, ST4556, ST50 | mcr-1 was delimited upstream by IS26 and hypothetical protein and pap2 downstream | (26) |
| 2015 Venezuela      | Fecal samples (Human and Animal) | 93 (2) | E. coli | IncI2 | ST452 and ST19 | Absence of ISApI1 | (23) |
| 2015 Mexico         | Swine stool samples (Production Animal) | 1 (1) | E. coli | IncP0111 | ST744 | ISApI1 upstream mcr-1 gene | (22) |

(Continued)
| Period of the study | Country       | Source of Isolate                | Total Isolates (mcr-carried) | Species                  | Plasmid Type | Sequence Type (ST) | Genetic Context                                                                 | References |
|---------------------|---------------|----------------------------------|------------------------------|--------------------------|--------------|--------------------|----------------------------------------------------------------------------------|------------|
| 2015–2016 Brazil    | Rectal swab and urine (Human) | 140 (2)                          | E. coli                     | IncX4                    | ST206 and ST354 | mcr-1 was delimited upstream by IS26 and hypothetical protein and pap2 downstream | (46)       |
| 2016 Brazil         | Seawater (Environment)         | 11 (3)                           | E. coli                      | IncX4                    | –            | –                  |                                                                                  | (36)       |
| 2016 Ecuador        | Fecal swabs and soil fecal from chicken and two dogs (Domestic Animals) | 42 (3)                           | E. coli                      | IncI2                    | ST3941, ST1630, ST2170 | mcr-1 was delimited upstream by nikB gene and pap2 downstream | (32)       |
| 2016 Brazil         | Rectal swab (Human)            | 3 (3)                            | E. coli and K. pneumoniae    | IncX4                    | E. coli ST744 and K. pneumoniae ST101 | –                  |                                                                                  | (28)       |
| 2016 Bolivia        | Fecal samples (Human)          | 337 (173)                        | E. coli, C. europaeus, E. hormaechei | IncI2 and IncHI1 (E. coli); Citrobacter and Enterobacter (IncI2) | E. coli (ST48, ST744, ST10, ST206, ST2705, ST2936, ST1286, ST7,570, ST69, ST10, ST117, ST711, ST7571, ST3056) | –                  | mcr-1-pap (IncI2) mcr-1.5-pap ISA17 (IncHI1) ISA17-mcr-1-pap ISA17 (IncHI1) | (27)       |
| 2016–2017 Paraguay  | Urine and feces (Human)        | 150 (7)                          | K. pneumoniae, E. coli, and S. Schwarzengrund | –                        | –                  | –                  |                                                                                  | (20)       |
| 2017 Brazil         | Water Sample from a mangrove (Environment) | 1 (1)                            | E. coli                      | IncX4                    | –            | –                  |                                                                                  | (39)       |
| 2017 Uruguay        | Blood, rectal swab, and urine (Human) | 3 (3)                            | E. coli                      | IncI2 e IncX4            | ST10, ST93, and ST5442 | –                  |                                                                                  | (19)       |
| 2017 Peru           | Urine (Human)                  | 10 (7)                           | E. coli                      | –                        | –            | –                  |                                                                                  | (21)       |
| 2019 Brazil         | Fecal sample and Water from Zoo (Wild Animal and Environment) | 27 (5)                           | –                           | –                        | –            | –                  |                                                                                  | (28)       |
| 2020 Brazil         | Blood, urine, and peritoneal fluid (Human) | 100 (2)                          | E. coli and K. pneumoniae    | IncX4                    | ST471/ST410 (E. coli) and ST15 (K. pneumoniae) | –                  |                                                                                  | (29)       |

-= No data.
IncX3–X4 hybrid, IncH1, IncH11, IncH12, IncP, IncI2, IncF, IncFII, an IncI2–IncFIB hybrid, and IncY (5). The mcr-1 gene can also be integrated into the chromosome of some strains (17). However, in Latin America, only four plasmids have been described so far: IncX4 (36), IncP (22), IncI2 (31), and IncH12 (37), of which the IncX4 plasmid is the most frequent in Brazil (38, 39) (Table 1). There is a clear association between the IncX4 plasmids and the insertion sequences associated with the dissemination of the mcr-1 gene (40).

Plasmid analysis has revealed that the insertion sequence ISApl1 (which belongs to the IS30 family transposase), in a composite transposon (ISApl1-mcr-1-ISApl1), is usually present in IncH12-type plasmids (size of 200 kb), being either present or absent in IncI2-type plasmids (60 kb), and completely absent in IncX4-type plasmids (30 kb) (Table 1).

The role of ISApl1 in the mobilization of the mcr-1 gene was demonstrated in vitro by transposition. It was suggested that the recombination events associated with mobilization of the mcr-1 gene were initially mediated by two copies of ISApl1 from an unknown progenitor to a plasmid and subsequently transferred to Enterobacteriales (41).

Besides that, according to Snesrud et al., the presence of a single or two copies of ISApl1 indicates a recent acquisition of the mcr-1 gene, whereas the absence of this insertion sequence could be correlated with the adaptation of the mcr-1 gene to a new host (41).

The regulation mechanism of mcr-1 gene expression is complex and remains unknown. In general, the gene expression is controlled by its promoter and the corresponding activators and/or inhibitors. Zhang et al. suspect that genes encoding activators and/or inhibitors in the host chromosome may affect the expression of the mcr-1 gene found on plasmids IncX4 and other plasmids. They may vary expressively in unlike genetic backgrounds of the different strains and/or mcr-1–harboring plasmids, despite that their promoters are remarkably similar (42).

Although the mobility and dissemination of the mcr-1 gene are associated with ISApl1 and the pap2 gene in most plasmid types (43), the genetic context of the IncX4 plasmid type, in Latin America, is different. This context is characterized by lacking the ISApl1, but it preserves the pap2 sequence and a hypothetical protein (hp) around the mcr-1 gene (26, 44). What would be the explanation for that?

Snesrud et al. analyzed the genetic environment of the mcr-1 gene associated or not with ISApl1 and concluded that the target site duplications generated by ISApl1 transposition are present even in lack of the ISApl1. This result suggests that the mechanism to mobilize the mcr-1 gene is the same as that observed in other plasmids, and after that, the loss of the insertion sequence by recombination events in IncX4 occurs (45).

Furthermore, the IS26 mobile element upstream to the mcr-1 gene has been also associated with IncX4 plasmid types in Brazil, but there are no other reports in Latin America (26, 46) (Table 1). This Insertion Sequence (IS) plays an important role in the dissemination and evolution of the antimicrobial resistance genes on plasmids, including colistin resistance genes (1).

DISCUSSION

In veterinary medicine, colistin is mainly administrated in pigs and poultry production, for prophylaxis or treatment. The spread of colistin resistance may lead to treatment failure, as well as increase the pathogen transmission reach with quality and economic loss in production animals.

Strong scientific evidence indicates that the mcr-1 gene might have originated from animals because (i) colistin has been used extensively for decades in veterinary practices; (ii) mcr-1 gene was largely identified in several animals and animal food products; (iii) the identification of the mcr-1 gene in E. coli isolate recovered before 1980 in China suggests that the emergence of this gene may be linked to the use of colistin as a growth promoter in the poultry industry; and (iv) genetic features of mcr-1 gene associated with ISApl1 were first identified in Actinobacillus pleuropneumoniae, a common animal pathogen (43), which could be involved in recombination events leading to the mobilization of the mcr-1 cassette.

Finally, a recent study has demonstrated that when colistin is banned from use in animal feed, there was a significant decrease of the mcr-1 gene prevalence in most sources, including pig farms, food, and environment samples (47). Given that the production animals can be a reservoir for mcr-1 gene and its dissemination can occur by food and environment, all countries should apply surveillance, monitoring, and restrictive measures to polymyxins use. In Latin America, Brazil, and Argentina (1) have already banned the use of colistin as a growth promoter, but the impact of this measure has not been evaluated yet.

The problem of antimicrobial resistance is related to the use and abuse of antibiotics in humans, animals, and the environment. Besides that, the mcr-1 gene is disseminated mainly by E. coli clones, with a high capacity to survive in different ecological niches, some of them with pandemic and epidemic potential. So, it seems clear that the One Health approach should be adopted to integrate veterinary and human medicine to address antimicrobial resistance.

AUTHOR CONTRIBUTIONS

SAML, TVD, and AFM: conception of the opinion, collected data, and wrote the paper. ALB and AFM: reviewed and edited. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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