Abstract: Colistin is widely used in food-animal production. *Salmonella enterica* is a zoonotic pathogen, which can pass from animal to human microbiota through the consumption of contaminated food, and cause disease, often severe, especially in young children, elderly and immunocompromised individuals. Recently, plasmid-mediated colistin resistance was recognised; *mcr*-like genes are being identified worldwide. Colistin is not an antibiotic used to treat *Salmonella* infections, but has been increasingly used as one of the last treatment options for carbapenem resistant Enterobacteria in human infections. The finding of mobilizable *mcr*-like genes became a global concern due to the possibility of horizontal transfer of the plasmid that often carry resistance determinants to beta-lactams and/or quinolones. An understanding of the origin and dissemination of *mcr*-like genes in zoonotic pathogens such as *S. enterica* will facilitate the management of colistin use and target interventions to prevent further spread. The main objective of this review was to collect epidemiological data about mobilized colistin resistance in *S. enterica*, describing the *mcr* variants, identified serovars, origin of the isolate, country and other resistance genes located in the same genetic platform.

Keywords: antimicrobial resistance; colistin; *mcr*; horizontal gene transfer; food safety; epidemiology

1. Introduction

The overuse and inappropriate use of antibiotics in diverse settings, such as human and veterinary therapeutics, animal production and agriculture, is widely accepted as one of the major causes of the emergence of antimicrobial resistance worldwide [1,2]. During the past decades, we have witnessed the evolution of bacteria by the selective pressure of antibiotics, with new resistance mechanisms and their spread across bacteria populations from various ecological niches. The antimicrobial resistance was responsible for about 700,000 deaths in 2016 and this number is estimated to increase to 10 million annual deaths by 2050 [2].

In human medicine, the treatment of infections due to multidrug resistant bacteria is a real challenge, like those caused by *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and carbapenem-resistant Enterobacteria. The void of effective antibiotics led to the recent use of an old antibiotic, colistin, as one of the last-resort therapeutic options. The World Health Organization reclassified colistin as an antibiotic of critical importance in human clinical settings [3].

However, colistin has been widely used in animal production in several countries for therapeutic, prophylactic and growth promotion purposes [4,5]. The use of low-dose and prolonged course of antibiotics in livestock is clearly associate with selection of zoonotic resistant strains that can be spread by direct contact of animal-to-human or indirectly, like by the food chain [6,7]. The dissemination of resistance determinants is fueled by lateral gene transfer mechanisms, such as conjugation [8]. Animal
gut colonizers can exchange genetic material with other bacteria, commensal or pathogenic. Until 2015, known colistin resistance mechanisms were all chromosomally encoded. However, a colistin-mediated resistance gene (mcr-1 gene) was further identified in a conjugative plasmid in *Escherichia coli* isolates of animal origin from China [9], which generated a wave of concern over the scientific community. Since then, numerous studies have reported plasmid-borne mcr alleles, mostly in *E. coli* of animal origin [10–14].

*Salmonella enterica* is an important zoonotic pathogen both in developing and industrialized countries, which can colonize the adult animals gut, especially in poultry and swine [7]. The mcr genes have also been found in *S. enterica*, though more infrequently than in *E. coli*, including in *S. enterica* serovar Paratyphi (from now on designated as *S. Paratyphi*) [15], a serotype associated to the development of human enteric fever. This communication summarizes the studies on the epidemiology of plasmid-mediated colistin resistance in *S. enterica*, considering the relevance of *Salmonella* serovars identification, geographic location of isolation and multidrug resistance profile.

### 2. Colistin Use: Past and Present

Colistin is a polypetide antibiotic that belongs to the class of polymyxins, produced by *Paenibacillus polymyxa*. This class is one of the primary classes of antibiotics with activity against most Gram-negative bacteria and consists of polymyxins A, B, C, D and E, of which only colistin (polymyxin E) and polymyxin B are used in clinical practice [5]. After its discovery in 1947, colistin was used in human medicine in Japan and Europe, but in the 1970s their use was reconsidered due to its neurotoxicity and nephrotoxicity. However, colistin has been widely used in veterinary medicine for the treatment and prevention of infectious diseases in Asian, European and North American countries [9,16–18]. Colistin has also been used in the livestock and seafood industry to promote animal growth [19].

In the past decade, the global emergence of carbapenemase-producing *Enterobacteriaceae* led to the re-use of colistin administration as a last therapeutic option for treating human infections, with the inevitable risk of emerging resistance [9,20]. The initial target of colistin is lipid A, a component of the lipopolysaccharide (LPS) located in the Gram-negative bacteria outer-membrane (OM), which plays an essential role in cell permeability. The electrostatic interaction between the positively-charged diaminobutyric acid (Dab) residues of colistin and the negatively-charged phosphate groups of lipid A leads to the displacement of divalent cations Ca$^{2+}$ and Mg$^{2+}$, which destabilize the molecule and triggers the permeability of OM, facilitating the entry of colistin by a self-promoted uptake mechanism. Colistin is bactericidal and its action results in leakage of citoplasmic content and cell death [21,22].

### 3. Resistance to Colistin

Colistin resistance is mainly associated with LPS modifications, with consequent reduced or absent affinity to colistin; the underlying mechanism, although common in Gram-negative bacteria, may differ between species [23,24]. It is the lipid A moiety of LPS that suffer changes, essentially due to addition of 4-amino-4-deoxy-L-arabinose (L-Ara4N) and/or phosphoethanolamine (PEtn). These molecules, positively charged, reduce the overall negative charge of LPS and, consequently, of the OM leaflet of the bacterial cells, leading to a smaller electrostatic interaction with the positive charges of colistin, preventing cell lysis [4,23].

Plasmid-mediated colistin resistance is conferred by mcr genes, which encode a phosphoethanolamine transferase that add PEtn to lipid A, contributing, like in chromosomal resistance, to decreased binding of colistin to LPS [4,10].

The mcr-1 gene was identified for the first time in an IncI$_2$ plasmid named pHNSHP45. After this first detection, mcr-1 and its very similar genetic variants were widely identified in diverse *Enterobacteriaceae* of different origins. Nowadays, this gene has been found in approximately 40 countries across five different continents [10,12,25]. This ubiquitous dissemination of the mcr-1 gene suggests that the use of colistin has probably accelerated the dissemination of mcr-1 gene in animals and humans [10]. Moreover, several other mcr homologs were subsequently identified in *E. coli* and
other Gram-negative bacteria. Currently, eight types of mcr genes (mcr-1 to -8) have been described and deposited into GenBank. The first reported variants were isolated from animals in Europe and China. The mcr-2 gene was found for the first time in E. coli from pigs and calves in Belgium [26], mcr-3 in E. coli from pigs in China [13], mcr-4 in a strain of the monophasic variant S. enterica serovar Typhimurium from pigs in Italy [14], mcr-5 in S. Paratyphi B d’Ia+ from poultry in Germany [15], mcr-6 (previously named mcr-2.2) in Moraxella spp. isolated from pigs in Great Britain [27], mcr-7 in three isolates of Klebsiella pneumoniae from chickens in China [28] and finally mcr-8 in NDM-producing K. pneumoniae isolates from both pigs and humans in China [25].

All these findings suggest that animals are the reservoir of the mcr genes with emphasis on the pigs, mostly due to the heavy usage of polymyxins in food animal production for therapy, prophylaxis and metaphylaxis purposes, which contributes for selection of mcr producers. Furthermore, the reports of identification of mcr genes have been mostly from animal isolates when compared with human isolates, sustaining animals as the main reservoir. Moreover, some genetic elements, like other resistance genes, insertions sequences and plasmids that are more prevalent and widespread in bacteria of animal origin, are found closely associated with the mcr-like genes [29].

4. Salmonella enterica: Salmonellosis and Enteric Fever in Humans

S. enterica infections are an important public health concern worldwide. S. enterica serovars can be separated in two main groups: The typhoidal Salmonella that comprise S. enterica serovar Typhi (from now on designated as S. Typhi), S. Paratyphi A, S. Paratyphi B, and S. Paratyphi C, whereas all the other serovars are called as non-typhoidal Salmonella (NTS) [30].

Animals are the primary reservoir of NTS, and NTS infections, generally called salmonellosis, are a huge threat in developing countries especially in infants, young children and in HIV-carriers, while in developed countries infection is mostly acquired through the food chain by ingestion of commercially contaminated produced animal-derived food [7,31,32]. It is estimated that NTS gastroenteritis is responsible for about 93.8 million illness and 155,000 deaths each year worldwide, and of these, it is estimated that 80.3 million cases are foodborne, with very high associated costs, most of them in developing countries, which contrasts with the reality in developed countries, where this rate is lower [33].

Despite food producing animals behave as the main reservoirs of S. enterica, a small group of serovars are capable of infecting and colonizing only determined hosts. For example, typhoidal serovars are human host-restricted organisms that cause typhoidal fever and para-typhoid fever (both also known as enteric fever) [30,34].

All typhoidal Salmonella serovars are responsible for 27 million annual cases of enteric fever, which results in more than 200,000 deaths worldwide [35]. In developing countries, where sanitary conditions and clean water are a problem of public health, enteric fever is generally endemic. Fecal-oral route is the main cause for spread of typhoidal Salmonella. In some countries, especially in Southeast Asia, S. Paratyphi infections are increasing. It is estimated that this serovar is responsible for about half of all enteric fever cases [36].

Currently, colistin is not used to treat human infections caused by this bacterium, and the development of colistin resistance is clinically not relevant. However, in vivo colistin resistance has been observed in S. enterica from food-producing animals [37–40], and the resistance determinants when inserted in genetic mobile elements (e.g., mcr-like genes) can be laterally transferred to other species, commensals or pathogens of animal and human origin. Moreover, the genetic platforms carrying mcr-like genes frequently host resistance genes that hinder the efficacy of other antibiotic classes [41]. Therefore, the presence of mcr-like genes should not be neglected in this zoonotic pathogen.

5. Colistin Resistance in Salmonella enterica

S. enterica strains have developed resistance to a variety of antimicrobials. Chloramphenicol was the first antibiotic used in the treatment of typhoid fever, but emergence of resistance soon
after its introduction lead to the replacement by trimethoprim-sulfamethoxazole and ampicillin or amoxicillin. Multidrug resistant strains emerged with the overuse of these first-line treatment drugs, and fluoroquinolones, such as ciprofloxacin, and extended-spectrum cephalosporins, such as ceftriaxone, were introduced in the treatment of *Salmonella* infections. However, resistance to these antimicrobials is now also frequent [7,30,42].

In *S. enterica*, the chromosomal colistin resistance involve activation of the PmrA/PmrB and PhoP/PhoQ two-component regulatory systems, which are responsible for the biosynthesis of L-Ara4N and PEtN. The activation of these systems is related with environmental stimuli, such as low concentration of Mg$^{2+}$, or with specific mutations in the two-component regulatory systems-encoding genes [4,23,43]. These mutations lead to the constitutive expression of PmrA/PmrB and PhoP/PhoQ, with consequent activation of operons *arnBCADTEF* and *pmrCAB*, and permanent addition of L-Ara4N and PEtN, respectively, to lipid A [23].

Other alterations, such as deacylation of lipid A by PagL [23,44], and activation of the transcription of genes involved in adaptation and survival of the bacterial cells by RpoN [23,45], can also lead to colistin resistance in *S. enterica*, but are less common.

Plasmid-mediated colistin resistance conferred by *mcr-1* [46], *mcr-2* [47], *mcr-3* [48], *mcr-4* [14] and *mcr-5* [15] genes have been already identified in different serovars of *S. enterica*. Like in other bacterial species, *mcr*-like genes have been detected in isolates from different origin, such as food-producing animals, food products and human samples, and are inserted in diverse genetic environments and plasmid backbones. It is of note that the presence of the *mcr* genes can be associated with low level of resistance to colistin [4,14,15,46,49–51], allowing to persist undetectable.

Table 1 summarizes the reports on *mcr*-like genes and their variants in this species and the key findings of each study. Briefly, *S. Typhimurium* is the most prevalent serotype harbouring *mcr* genes. This serotype is also one of the most frequent to cause human infections [52]. Monophasic variants of *S. Typhimurium* such as 1,4,[5],12:i:- are also widely reported. It is still worth noting that *mcr* positive Paratyphi B are isolated from animal samples, though this serotype usually infects humans and cause invasive disease [52]. Food-producing animals appear to be the main reservoir of *mcr* positive *S. enterica* strains. Poultry and swine animals are the most reported sources of isolates. Nonetheless, there are isolates from human clinical sources, which suggests dissemination from animals to humans along food chain [53]. In addition, China is the country where more *mcr* positive *S. enterica* strains are identified. This is consistent with the high rates of use of colistin in livestock and veterinary medicine, which leads to the emergence of resistance [10]. Nevertheless, in European countries, such as Italy and Portugal, where colistin is frequently used for therapeutic and metaphylactic purposes in animal husbandry, the reports are emerging [10,41,53]. On the other hand, European countries are more engaged in screening and surveillance activities, which justifies the high number of European reports [14,20,48,54,55]. These studies evidence the wide and ubiquitous spread of *mcr* genes around the world. Although the first report of *mcr*-1 only occurred in 2015 from an *E. coli* isolate [9], these genes are also carried by *S. enterica* at least since 2008 [56]. Finally, several *mcr*-carrying *S. enterica* isolates show multidrug resistance profiles, with several genes conferring resistance to tetracyclines, beta-lactams including cephalosporins, quinolones, sulfamethoxazole/trimethoprim and streptomycin, which limits the therapeutic options for treatment of *S. enterica* infections.

The existence of colistin resistance genes embedded into mobile genetic elements, such as plasmids, is a huge concern because they can be horizontally spread across different bacteria. Furthermore, *mcr* genes can be located in plasmids encoding other resistance genes, such as *blaCTX-M*, *floR* and/or *qnr*, originating strains resistant to several antibiotic classes, including polymyxins, the majority of beta-lactams, including broad-spectrum cephalosporins and monobactams [48,57,58], amphenicols [51] and quinolones [48,59], respectively. For instance, *mcr*-1 and *blaCTX-M* genes embedded into plasmid IncH1 were co-transferred from *S. enterica* isolated from swine retail meat by conjugation under colistin selection [41]. The co-selection of resistance might compromise treatment of complicated gastroenteritis and invasive infections caused by *S. enterica*. 
Table 1. Reports of \textit{mcr}-like genes identified in \textit{Salmonella enterica}.

| Organism Identified         | Source of Isolates                                      | Geographical Distribution | Date of Isolation | Identified Gene/Variant | Key Points/Conclusions                                                                 | Reference |
|-----------------------------|---------------------------------------------------------|----------------------------|-------------------|-------------------------|----------------------------------------------------------------------------------------|-----------|
| 5 S. Typhimurium            | Isolates from sick swine, duck and chicken from farms  | China                      | 2007–2015         | \textit{mcr-1}          | • The high rate of colistin resistance and low \textit{mcr-1} positive rates showed that the plasmid-mediated colistin resistance was not the main mechanism conferring colistin resistance among \textit{Salmonella} isolates | [60]      |
| 3 S. Typhimurium 1S. Kissen | Swine faeces and swine lymph node                       | Spain                      | 2009–2011         | \textit{mcr-1}          | • First report of \textit{mcr-1} in \textit{Salmonella} strains                      | [46]      |
| 4 S. Typhimurium            | Swine, poultry and cattle food products                 | Portugal                   | 2011–2012         | \textit{mcr-1}          | • The \textit{mcr-1} gene was already present beyond Asian frontiers in 2011        | [41]      |
|                            | Retail chicken and pork                                 | China                      | 2011–2016         | \textit{mcr-1}          | • There is a trend for \textit{Salmonella} spp. becoming a reservoir for the \textit{mcr-1} gene | [61]      |
|                            | Eggs                                                    |                            |                   |                         | • The \textit{mcr-1} gene was already present in \textit{Salmonella} spp. isolates in China in 2011 |           |
|                            | Retail frozen dumpling                                  |                            |                   |                         |                                                                                        |           |
| 14 S. Typhimurium 3S. Anatum| Human clinical sources; sick food producing animals     | Taiwan                     | 2012–2015         | \textit{mcr-1}          | • \textit{mcr-1} gene was carried on distinct plasmids                              | [62]      |
|                            | (pigs and chickens)                                    |                            |                   |                         | • \textit{mcr-1} may have been widespread and become prevalent in zoonotic pathogens in this country |           |
| Organism Identified | Source of Isolates | Geographical Distribution | Date of Isolation | Identified Gene/Variant | Key Points/Conclusions | Reference |
|--------------------|------------------|---------------------------|-------------------|------------------------|------------------------|-----------|
| 25 S. Typhimurium   | Human clinical sources | China                     | 2012–2015         | mcr-1                  | Specific genetic background is required for acquisition and maintenance of mcr-1 bearing mobile elements | [63]     |
| 3 S. Enteritidis    |                  |                           |                   |                        | Insertion of a mcr-1 carrying mobile element into the backbone of plasmid might be responsible for one of the modes of mcr-1 transmission in Salmonella |           |
| 8 S. Typhimurium    | Human faeces     | UK                        | 2012–2015         | mcr-1                  | Several Salmonella Typhimurium isolates associated with travel to South-East Asia | [64]     |
| 1 S. Paratyphi B var Java 1 Salmonella Virchow |                  |                           |                   |                        | First report of identification of mcr-1 in the UK |           |
| 2 S. Paratyphi B var Java phage type Colindale | Poultry meat | Imported from Europe |                   |                        | Horizontal transfer of mcr-1 harbouring plasmids might have also contributed to spread of mcr-1 in Salmonella spp. | [51]     |
| 19 S. Typhimurium   | Cecum samples from pig at slaughter | China                    | 2013–2014         | mcr-1                  | Other drug-resistance genes were always co-transferred with mcr-1 |           |
| 1 S. London         |                  |                           |                   |                        | Hypothesis that mcr-1 bearing plasmids might have strong association with specific serotypes of Salmonella | [65]     |
| 1 S. Heidelberg     |                  |                           |                   |                        |                        |           |
| 21 S. Typhimurium   | Food producing animals (chicken, pig, seafood, beef) | China                    | 2013–2015         | mcr-1                  | Importance of the role played by Salmonella Typhimurium in the dissemination of MDR genes |           |
| 5 S. Newport        |                  |                           |                   |                        | First report on the epidemiological prevalence and detection of Salmonella and mcr-1 gene among ready to eat pork samples in China | [66]     |
| 1 S. Typhimurium    | Ready to eat pork products | China                    | 2014              | mcr-1                  |                        |           |
| Organism Identified | Source of Isolates | Geographical Distribution | Date of Isolation | Identified Gene/Variant | Key Points/Conclusions | Reference |
|---------------------|-------------------|---------------------------|-------------------|-------------------------|-------------------------|-----------|
| S. Typhimurium      | Human clinical sources | Denmark | 2014–2015 | mcr-1 | • mcr-1 producing isolates in patients with travel history to Asia  
• mcr-1 producing isolates in patients with no travel history is worrying as the spread of mcr-1 could in the future be present in foodborne outbreaks with Salmonella or E. coli | [67] |
| S. Typhimurium      | Human clinical sources (stool and urine) | Colombia | 2015–2016 | mcr-1 | • Three common resistance genes were identified in the Salmonella Typhimurium isolates, including blaTEM-1, qnrB19, and tet(B)  
• Transposition of mcr-1 is the mechanism of mobilization among strains with different genetic backgrounds | [59] |
| S. Typhimurium      | Retail frozen pork | Brazil | 2016 | mcr-1 | • First report of mcr-1 in Salmonella Typhimurium in Brazil, highlighting the intercontinental spread of this gene | [68] |
| S. Typhimurium      | Diarrheal faeces of 3 children (8 months and 15 years old) | China | 2016 | mcr-1 | • mcr-1 positive strains were resistant to colistin as well as to third/fourth-generation cephalosporins and sulfamethoxazole/trimethoprim  
• The spread of this Salmonella typhimurium clone would pose a great threat to the prevention and control of clinical infections | [69] |
Table 1. Cont.

| Organism Identified | Source of Isolates | Geographical Distribution | Date of Isolation | Identified Gene/Variant | Key Points/Conclusions                                                                 | Reference |
|---------------------|-------------------|---------------------------|-------------------|------------------------|---------------------------------------------------------------------------------------|-----------|
| 1 S. Typhimurium var Copenhagen | Intestines of pig | Great Britain | No data | mcr-1 | • Plasmid similar to that originally reported in China  
• Dissemination within different Salmonella serovars hypothesis  
• Supports the concept of global distribution within a variety of plasmids | [70] |
| 9 S. 1,4,[5],12:i:- 2 S. Rissen | Human clinical sources (n = 4) and pork products (n = 7) | Portugal | 2011–2015 | mcr-1 | • Evidence of the acquisition of mcr-1 carrying plasmids by two clinically relevant MDR and copper-tolerant clones | [54] |
| 1 S. 1,4,[5],12:i:- 1 S. Derbi 1 S. Schwarzengrund 1 S. Paratyphi B | Swine and chicken food products; boot swabs from broiler farm | France | 2012–2013 | mcr-1 | • These findings reinforce the need to reconsider the use of in-feed colistin in veterinary medicine at a worldwide level | [71] |
| 17 S. 1,4,[5],12:i:- 3 S. Derby 2 S. Bovismorbificans 1 S. Newport 1 S. Saint Paul 1 S. Schwarzengrund | Human clinical sources (n = 10), poultry and swine animals (n = 2 and 9) and pork food products (n = 4) | Italy | 2012–2015 | mcr-1 | • Italy is one of the main colistin users of European countries and these data are suggestive of gene flow from pigs to humans along the food chain | [53] |
| 1 S. 4,[5],12:i:- | Human blood sample | Switzerland | 2017 | mcr-1 | • The first report of mcr-1 harbouring *Salmonella enterica* in Switzerland | [72] |
| 1 S. Dublin | Pig | France | 2002–2014 | mcr-1 | • mcr-1 was present in chickens and pigs at slaughter at least since 2008 in Europe  
• The high diversity among mcr-1 positive isolates suggested a horizontal transfer | [73] |
| 1 S. (4,12:Iv:-) | Chicken | Germany | | | | |
| Organism Identified | Source of Isolates | Geographical Distribution | Date of Isolation | Identified Gene/Variant | Key Points/Conclusions | Reference |
|---------------------|-------------------|---------------------------|------------------|------------------------|------------------------|-----------|
| 1 S. Paratyphi B (dTa+) | Chicken skin | Germany | 2008 | mcr-1 | Acquisition of the mcr-1 gene in 2008 | [56] |
| 11 S. Java | Chicken meat | The Netherlands | 2010–2015 | mcr-1 | First finding of a chromosomally located mcr-1 gene in E. coli isolates | [74] |
| 1 S. Anatum | Turkey meat | Imported meat (no data for origin) | | mcr-1 | Ability of mcr-1 to translocate to the chromosome hypothesis | |
| 1 S. enterica serovar Indiana | Poultry slaughterhouse (chicken carcasse) | China | 2012 | mcr-1 | First report of the complete nucleotide sequence of one mcr-1 carrying S. Indiana strain | [75] |
| | | | | | The strain carried 4 plasmids, 1 encoded blaCTX-M-65 gene along with 20 additional antimicrobial resistance genes | |
| 2 S. Schwarzengrund | Poultry meat cuts | Brazil | 2013–2016 | mcr-1 | First report of mcr-1 harbouring Salmonella enterica serovar Schwarzengrund | [76] |
| | | | | | Assessment of commercial poultry meat as reservoir of colistin-resistant Salmonella | |
| 4 S. enterica, 1 belonging to serovar Albany | Intestinal content of diseased chickens | China | 2014–2015 | mcr-1 | First report of co-occurrence of mcr-1 and blaCTX-M-55 on a single plasmid in Salmonella enterica | |
| | | | | | Genetic environment of the mcr-1 gene is more mobile than expected | [57] |
| | | | | | The selection pressure on the mcr-1 gene may select for broad-spectrum cephalosporin resistance | |
Table 1. Cont.

| Organism Identified | Source of Isolates | Geographical Distribution | Date of Isolation | Identified Gene/Variant | Key Points/Conclusions | Reference |
|---------------------|-------------------|---------------------------|------------------|------------------------|------------------------|-----------|
| 22 S. enterica, most of them belong to Albany, Derby, Newport, Mbandaka and Stanley serotypes | Chicken and pig swabs | China | 2015–2016 | mcr-1 | • Pigs and chickens may be identified as potential sources of Salmonella for humans  
• Salmonella isolates from food-producing animals frequently exhibited MDR patterns and antimicrobial resistance genes \( \text{bla}_{\text{CTX-M}}, \text{mcr-1}, \text{and} \text{rmtB} \) were prevalent | [77] |
| 1 S. Typhimurium  
1 S. Derby  
1 S. Autoagglutinable | Poultry and pork carcasses | Belgium | 2012–2015 | mcr-1  
mcr-2 | • First report of detection of \( \text{mcr-1} \) in \( \text{Salmonella} \) isolated from the food chain in Belgium  
• First report of the presence of \( \text{mcr-2} \) in \( \text{Salmonella} \) species isolated from retail meat  
• The \( \text{mcr-2} \) gene seems less transferable and is confined to Belgium | [47] |
| 3 S. Typhimurium  
7 S. monophasic variants of Typhimurium (4,[5],12:i:- and 4,12:i-) | Human clinical sources | Denmark | 2009–2017 | mcr-1  
mcr-3 | • One \( \text{Salmonella} \) isolate harbouring both \( \text{mcr-1} \) and \( \text{mcr-3} \) genes (rare combination)  
• Patients with travel history to Asia  
• In addition to \( \text{mcr-3} \), all strains were found positive for \( \text{bla}_{\text{TEM-1}}, \text{strA, strB, sul2 and tet(A) or tet(B)} \), and most strains were positive for \( \text{bla}_{\text{CTX-M-55}} \) and \( \text{qnrS} \) | [48] |
| 4 S. Infantis | Broiler meat and broiler chicken | Italy | 2016–2017 | mcr-1.1 | • First report of the isolation and characterization of four MDR S. Infantis, two of them ESBL producers | [58] |
| Organism Identified       | Source of Isolates            | Geographical Distribution | Date of Isolation | Identified Gene/Variant | Key Points/Conclusions                                                                 | Reference |
|--------------------------|------------------------------|---------------------------|-------------------|-------------------------|---------------------------------------------------------------------------------------|-----------|
| 1 S. Typhimurium          | Caecal samples from turkeys  | Italy                     | 2014–2015         | mcr-1.1, mcr-1.2        | • Data supports the hypothesis of transmission of mcr-positive plasmids between different bacterial species, with the possibility of transmission from animals to humans, or vice versa  | [78]      |
| 1 S. Typhimurium          | Human rectal swab            | China                     | 2014              | mcr-1.6                 | • Identification of a new mcr-1 gene variant, named mcr-1.6                           | [79]      |
| 1 S. 4,[5],12:i:-        | Human stool                  | Canada                    | 2013              | mcr-3.2                 | • MDR isolate                                                                                                                                   | [80]      |
|                          |                              |                           |                   |                         | • Patient with travel history to Asia (Thailand)                                                                                               |           |
|                          |                              |                           |                   |                         | • Identification of a mcr-3 variant named mcr-3.2                                                                                             |           |
| 1 S. Typhimurium          | Caecal content of a pig at slaughter | Italy                  | 2013              | mcr-4                   | • Identification of novel plasmid-mediated colistin resistance mcr-4 gene in Salmonella                                                                 | [14]      |
|                          |                              |                           |                   |                         | • These findings suggest considerable dissemination of the novel gene in Europe                                                               |           |
Table 1. Cont.

| Organism Identified | Source of Isolates | Geographical Distribution | Date of Isolation | Identified Gene/Variant | Key Points/Conclusions | Reference |
|---------------------|-------------------|----------------------------|-------------------|-------------------------|------------------------|-----------|
| 2 S. Typhimurium     | Faecal samples of two patients with gastroenteritis | Italy | 2016 | mcr-4.2 | • First report of mcr-4 positive bacterial isolates of human origin  
  • *Salmonella* species could represent a hidden reservoir for mcr genes | [35] |
| 1 S. Kedougou       | Pig carcass       | Spain | 2016 | mcr-4.6 | • First report of mcr-4.6, a new mcr-4 gene variant  
  • Development of a multiplex PCR protocol with 100% of specificity and sensibility for five mcr genes (1 to 5) for surveillance purposes  
  • Detection of two pmrA/pmrB point mutations in one colistin-resistant isolate | [20] |
| 2 S. 4,[5],12:i:-  | Pig and calf carcasses | France | | mcr-1 mcr-4.2 |  | |
| 14 S. Paratyphi B (dTa+) | Poultry | Germany | 2011–2013 | mcr-5 | • First report of the mcr-5 gene  
  • The transfer of colistin-resistance-mediating phosphoethanolamine transferase genes from bacterial chromosomes to mobile genetic elements has occurred in multiple independent events raising concern regarding their variety | [15] |

MDR, multidrug resistant
6. Conclusion

Here we reviewed the epidemiology of mcr-like genes identified in S. enterica serovars. It is not expected that colistin will be an antibiotic to treat human enteric fever or gastroenteritis caused by this pathogen; nonetheless, mcr-like genes are carried in conjugative plasmids that spread among bacterial populations. The zoonotic feature of S. enterica cannot be neglected and plasmid-mediated colistin resistance genes may reach human microbiota through the food chain. Genetic multidrug resistant platforms can be selected not only by colistin but also by the other antibiotics used in livestock, such as quinolones. It is of paramount importance to understand where resistant pathogens are emerging in order to implement infection control measures to prevent their spread. Emergence of mcr-like genes are not confined to Asia, as initially supposed, and are found in countries where a higher antibiotic restriction is used in animal production, even in strains isolated ten years ago, raising questions of the stability of these plasmids in bacterial populations, their impact on bacterial fitness. Further research on mcr-like genes in zoonotic pathogen populations is necessary to unveil the true impact in human health and to manage like genes use to minimize selection, proliferation and spread of drug-resistant bacteria.

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