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The rise and spread of *mcr* plasmid-mediated polymyxin resistance

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Abstract

Polymyxins are important lipopeptide antibiotics that serve as the last-line defense against multidrug-resistant (MDR) Gram-negative bacterial infections. Worryingly, the clinical utility of polymyxins is currently facing a serious threat with the global dissemination of *mcr*, plasmid-mediated polymyxin resistance. The first plasmid-mediated polymyxin resistance gene, termed as *mcr-1* was identified in China in November 2015. Following its discovery, isolates carrying *mcr*, mainly *mcr-1* and less commonly *mcr-2* to *-7*, have been reported across Asia, Africa, Europe, North America, South America and Oceania. This review covers the epidemiological, microbiological and genomics aspects of this emerging threat to global human health. The *mcr* has been identified in various species of Gram-negative bacteria including *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Salmonella enterica*, *Cronobacter sakazakii*, *Kluyvera ascorbata*, *Shigella sonnei*, *Citrobacter freundii*, *Citrobacter braakii*, *Raoultella ornithinolytica*, *Proteus mirabilis, Aeromonas*, *Moraxella* and *Enterobacter* species from animal, meat, food product, environment and human sources. More alarmingly is the detection of *mcr* in extended-spectrum-β-lactamases- and carbapenemases-producing bacteria. The *mcr* can be carried by different plasmids, demonstrating the high diversity of *mcr* plasmid reservoirs. Our review analyses the current knowledge on the emergence of *mcr*-mediated polymyxin resistance.

Keywords

mcr; polymyxin resistance; Gram-negative bacteria

Introduction

Polymyxins are cyclic lipopeptide antibiotics that were first discovered in the 1940s (Ainsworth et al. 1947; Benedict and Langlykke 1947; Stansly et al. 1947). Polymyxin B

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and colistin (polymyxin E) were introduced into clinical practice for the treatment of Gram-negative bacterial infections in 1959 (Ross et al. 1959). Their clinical usage was subsequently withdrawn due to high incidence of nephro- and neuro-toxicity, and also due to the introduction of 'safer' antimicrobial agents such as the β-lactams which were equally effective at the time (Fekety et al. 1962; Brown et al. 1970; Koch-Weser et al. 1970). However, over the last two decades the emergence of multidrug-resistant (MDR) Gram-negative bacteria that are resistant to all other antibiotics and paucity of novel antibiotics in the discovery pipeline have led to a resurgence of polymyxin usage in the clinic (Li et al. 2006). Albeit, an increasing incidence of polymyxin-resistant bacterial infections has been reported in both the nosocomial and community settings (Srinivas and Rivard. 2017). The primary mechanism of polymyxin resistance in Gram-negative bacteria involves the modification of lipid A of lipopolysaccharide (LPS), which is a major component of the outer membrane and the initial target of polymyxins. Polymyxin resistance due to modifications of lipid A with positively-charged phosphoethanolamine (pEtN) and/or 4-amino-4-deoxy-L-arabinose (L-Ara4N) was first reported by Vaara et al. (1981); such modifications result in reduced negative charge of the outer membrane and hence reduce the electrostatic interaction with polymyxins (Olaitan et al. 2014; Baron et al. 2016). The modification of lipid A by pEtN and L-Ara4N is mediated by *eptA* and *arnBCADTEF*, respectively, which are regulated by two-component systems (TCSs), PhoPQ and PmrAB (Olaitan et al. 2014). The inactivation of *mgrB*, a negative regulator of PhoPQ system in *Klebsiella pneumoniae*, can lead to the upregulation of PhoPQ, resulting in polymyxin resistance (Poirel et al. 2015). Secondary polymyxin resistance mechanisms independent of modification of lipid A include production of capsular polysaccharide, expression of efflux pumps and an increased expression of outer membrane proteins (Olaitan et al. 2014). Notably, all of the aforementioned mechanisms of polymyxin resistance are chromosomally-mediated (Olaitan et al. 2014; Baron et al. 2016). Polymyxin resistance in *K. pneumoniae* and *Acinetobacter baumannii* is more commonly chromosomal-mediated, and occurs at a higher prevalence in current clinical settings, particularly in Greece and Italy (Giamarellou 2016). On the other hand, *mcr* is the main polymyxin resistance determinant in *Escherichia coli* and high prevalence remains in agriculture globally, especially in China. This is coincident with high polymyxin consumption and usage in the aforementioned countries (Giamarellou 2016; Liu YY et al. 2016).

A plasmid-mediated polymyxin resistance gene named *mcr-1* was first reported in November 2015 (Liu YY et al. 2016). The emergence of plasmid-mediated polymyxin resistance is a matter of great concern due to the potential for rapid horizontal transfer. The *mcr-1* encodes for pEtN transferase enzyme (MCR-1) which catalyzes the addition of pEtN to the phosphate groups in lipid A (Liu YY et al. 2016; Liu YY et al. 2017). The modification of lipid A with pEtN is not a novel mechanism of polymyxin resistance, as this has been frequently associated with the chromosomal gene, *eptA* (*pmrC*) (Olaitan et al. 2014; Baron et al. 2016; Huang J et al. 2017). However, the transferability of *mcr* is of considerable concern due to the potential of MDR Gram-negative bacteria to acquire *mcr*-harboring plasmids, negating antimicrobial therapy with the important last-line polymyxins.

To date, several other MCR have been identified, including MCR-2, -3, -4, -5, -6 and -7, which share 81%, 32.5%, 34%, 36.1%, 83% and 35% in the amino acid sequence identity, respectively, with MCR-1 (*cf.* Supplementary information Table S1) (Xavier et al. 2016; AbuOun et al. 2017, Borowiak, Fischer, et al. 2017; Carattoli et al. 2017; Yin et al. 2017; Yang et al. 2018). An additional minor variant was reported for each of MCR-2, -4 and -5, whereas a greater number of minor variants were identified for MCR-1 (11 variants) and MCR-3 (10 variants) (*cf.* Supplementary information Table S2). It should be noted that *mcr-6* (deposited in Genbank in 2018; accession number: MF176240) was described as *mcr-2.2* in the study published in 2017 (AbuOun et al. 2017).

Epidemiology

Time-line of mcr discovery

From the time-line diagram (Figure 1), we can clearly see the vast increase in the detection of *mcr*-positive isolates from various countries dating from 2009 onwards. Retrospective surveillance studies on stored bacterial isolates revealed that the earliest *mcr* (more specifically *mcr-1*) was identified from chicken in the 1980s in China, when colistin was started being used for farming purposes (Shen et al. 2016). It was then followed by the identification of *mcr* from cattle in 2004 (Italy; *mcr-1*) and veal calves which were raised at local farms in 2005 (France; *mcr-1*) (Haenni et al. 2016). The earliest *mcr*-positive bacterial strain from humans was a *Shigella sonnei* isolated from a hospitalized child in 2008 (Vietnam; *mcr-1*) (Thanh et al. 2016). It is also important to note that to date, the earliest occurrence of *mcr* in isolates from wild animals (fish; *Aeromonas allosaccharophila*; *mcr-3.6*) and environmental samples (seawater; *E. coli*; *mcr-1*) was in 2005 and 2010, respectively (Jørgensen et al. 2017; Eichhorn et al. 2018).

Among *mcr-2* to *-7*, the earliest *mcr-3* (more specifically *mcr-3.6*) was discovered in 2005 (Eichhorn et al. 2018); whereas *mcr-2* (2009), *-4* (2013), *-5* (2011), *-6* (2015) and *-7* (2014) were only identified in strains collected over the past decade (Carattoli et al. 2017; Fisher et al. 2017; AbuOun et al. 2018; Borowiak, Eichhorn et al. 2018; Yang et al. 2018). More retrospective studies involving *mcr* genes should be conducted. Generally, it is evident that *mcr* has already existed for at least three decades.

Geographical spread of mcr

Since the first discovery of the *mcr*, a number of epidemiological studies have been carried out worldwide (Skov and Monnet 2016). The *mcr* has been detected in 47 different countries across six continents: Asia (China, Japan, Laos, Vietnam, Malaysia, Singapore, Cambodia, Bahrain, Taiwan, Hong Kong, Thailand, South Korea, Russia, Pakistan, United Arab Emirates, Saudi Arabia and Oman), Europe (Austria, Estonia, UK, The Netherlands, Norway, Spain, Germany, France, Belgium, Denmark, Italy, Poland, Portugal, Russia, Switzerland, Sweden, Lithuania and Hungary), Africa (Algeria, Egypt, Tunisia, Morocco and South Africa), North America (USA and Canada), South America (Colombia, Argentina, Brazil and Ecuador) and Oceania (New Caledonia and Australia) (*cf.* Table 1 and Figure 2). Among these countries, *mcr* was identified from human sources in 44 countries, livestock in 21 countries, meat and food products in 13 countries and other sources (including pet/exotic/wild animals and environment) in 11 countries. The only countries in which *mcr* have been reported from livestock but not humans are Estonia and Tunisia. No trace of *mcr* has been detected in Antarctica. To date, China, where the first *mcr* was detected, has the highest prevalence of *mcr*-positive isolates (*cf.* Figure 2). This could be due to the fact that polymyxins were heavily used and extensive studies on *mcr* have been conducted in China.

To the best of our knowledge, the presence of all *mcr* except *mcr-6* has been detected in samples from China (Yang et al. 2018; Zhang, Chen, Wang, Butaye, et al. 2018; Zhang, Chen, Wang, Yassin, et al. 2018). Thus far, *mcr-2* (Belgium and Spain), *mcr-3* (Brazil, Denmark, France, Germany, Japan, Spain and Thailand), *mcr-4* (Italy and Spain), *mcr-5* (Colombia, Japan, Spain and Germany) and *mcr-6* (The United Kingdom) have been sparsely detected (Borowiak, Fisher et al. 2017; Carattoli et al. 2017; Liu L et al. 2017; Roer et al. 2017; AbuOun et al. 2018; Eichhorn et al. 2018; Fukuda et al. 2018; García et al. 2018; Haenni et al. 2018; Hammerl et al. 2018; Hernández et al. 2017; Kieffer et al. 2018; Litrup et al. 2017; Wang et al. 2018; Wise et al. 2018; Xavier et al. 2016; Yamaguchi et al. 2018; Yang et al. 2018).

The identification of *mcr* in sea gulls and migratory penguins is an alarming event due to the possibility for rapid global dissemination, as these flight animals are capable to migrate intercontinentally (Liakopoulos et al. 2016; Ruzauskas and Vaskeviciute 2016; Sellera et al. 2016). Trading of food products such as livestock, meat and vegetables can potentially be another significant force driving the spread of *mcr* globally (Hasman et al. 2015; Doumith et al. 2016; Grami et al. 2016; Kluytmans-van den bergh et al. 2016; Veldman et al. 2016). In addition, the global trade of exotic animals (Unger et al. 2016) and human travelers may also play a key role in the dissemination of *mcr* worldwide (Arcilla et al. 2016; Doumith et al. 2016). Fortunately, complete elimination of *mcr*-carrying isolates from travelers after their return to home country signifies that a biological cost could be conferred by *mcr* in the absence of polymyxins as the selective pressure, and as such the spread could be mitigated by limiting the use of polymyxins (Arcilla et al. 2016).

Transmission of mcr

By far, livestock is regarded as the main reservoir for *mcr* due to the heavy usage of polymyxins for prophylaxis, metaphylaxis and therapeutic purposes as well as a growth promoter (Kempf et al. 2016; Liu YY et al. 2016; Nordmann and Poirel 2016). Among livestock, the highest prevalence was observed among poultry, mainly in China and Germany. Approximately one third of the total *mcr*-positive isolates from livestock were from pigs, mainly attributed by China and Japan. The transferability of the *mcr*-carrying plasmid from isolates of animal origin to humans was demonstrated by *in vitro* conjugation and transformation experiments, showing successful transfer of a *mcr-1* plasmid (pHNSHP45) from pig into common human pathogenic Enterobacteriaceae and *Pseudomonas aeruginosa* (Liu YY et al. 2016). Bacteria carrying *mcr* (*mcr-1*) have also been identified from pets and the possibility of these bacteria infecting humans is another avenue towards the interspecies spread (Liakopoulos et al. 2016; Zhang XF et al. 2016). The zoonotic potential of *mcr*-carrying bacteria has been postulated by comparing the genetic determinants of the *mcr*-carrying isolates from animal and human sources (Elnahriry et al. 2016; Poirel, Kieffer, Liassine, et al. 2016; Poirel and Nordmann 2016). Besides, the widespread of *mcr* among livestocks/meat/food products and identification of *mcr* in the human microbiome (*mcr-1*) suggested the potential transmission via the food chain; however, more definite evidence is required to draw this conclusion (Hu Y et al. 2016). The isolation of a *mcr*-positive Enterobacteriaceae (*mcr-1*) from infants who had not started solid diet and had no history of contact with livestock, suggested other possible transmission routes besides food chain and zoonotic transfer (Gu et al. 2016; Zhang R et al. 2016). More worryingly, *mcr* was identified from water sources, including untreated river wastewater, wastewater treatment plants, seawater, lake, pond, canal and well. This could contribute to the rapid spreading of polymyxin resistance to animals and humans (Petrillo et al. 2016; Zurfuh et al. 2016; Fernandes et al. 2017; Hembach et al. 2017; Jørgensen et al. 2017; Marathe et al. 2017; Runcharoen et al. 2017; Sun et al. 2017).

Epidemiology of mcr in humans and potential clinical impact

The *mcr*-positive bacteria have been isolated from people of various ages ranging from new-born to elderly (Prim et al. 2016; Zheng et al. 2016). These include patients, elderly residents at long-term aged care facilities in Italy (Giufrè et al. 2016), European travelers who had visited South America, Africa and Asia countries (Arcilla et al. 2016; Bernasconi et al. 2016; Doumith et al. 2016), as well as pilgrims who had traveled to Mecca during Hajj (Leangapichart et al. 2016). The most worrying situation is the detection of *mcr* in asymptomatic patients (Hu Y et al. 2016; Olaitan et al. 2016; Ruppé et al. 2016), which might further contribute to the silent dissemination. The vast majority of *mcr*-positive isolates were recovered from fecal samples (*cf.* Supplementary information Table S3). The Gram-negative species carrying *mcr* isolated from patients diagnosed with gastrointestinal disorder include *E. coli*, *K. pneumoniae* and *Salmonella enterica* (Doumith et al. 2016; Gu et al. 2016; Ye et al. 2016). The presence of *mcr* in *Shigella sonnei* (*mcr-1*) has been reported only once from a child suffering from dysenteric diarrhea (Thanh et al. 2016). Findings of *mcr*-positive isolates in the human gut microbiome (*mcr-1*) of healthy individual is a matter of great concern as gut flora can act as a mixing vessel which facilitates *mcr* dissemination by horizontal gene transfer (Hu Y et al. 2016; Ruppé et al. 2016). The *mcr*-harboring bacterial species isolated from patient urine samples were mainly *E. coli*, and less frequently *K. pneumoniae*, *Enterobacter cloacae* and *S. enterica* (*cf.* Supplementary information Table S3). Another *mcr*-carrying *Enterobacter* species, *Enterobacter aerogenes* was reported twice from clinical patients in China (Zeng et al. 2016; Wang Y et al. 2017). It is worth noting that the *mcr*-positive bacterial species isolated from bloodstream were mainly *E. coli*, with the exception of a few reports on *mcr*-harboring *S. enterica* and *K. pneumoniae* (*cf.* Supplementary information Table S3). Fortunately, many clinical *mcr*-harboring isolates were still susceptible to a number of other antimicrobial agents such as carbapenem and tigecycline (Quan et al. 2017; Saavedra et al. 2017). It is debatable whether surveillance cultures should be conducted for *mcr* when strains are still susceptible to most of antibiotic classes. Nevertheless, the dissemination of *mcr*-mediated polymyxin resistance should not be dismissed, as plasmids can be easily mobilized to MDR Gram-negatives.

Microbiology

Impact of mcr on polymyxin susceptibility

Transformation and conjugation methods are frequently utilized to study the transferability of the *mcr*-carrying plasmids and the impact of its acquisition on the polymyxin MIC (*cf.* Table 2). Broth microdilution is well accepted as the best method for testing polymyxin susceptibility, while other methods (*e.g.* Etest and disk diffusion) are less reliable but still used in clinical microbiology laboratory worldwide (Poirel, Jayol, et al. 2017; Simar et al. 2017). Generally, an increase in the polymyxin MICs was observed as *mcr*-carrying plasmid was introduced into polymyxin-susceptible strains (*cf.* Table 2). The successful conjugation of most *mcr*-harboring plasmids into the recipient strains led to the formation of transconjugants with comparable polymyxin MICs (4 – 16 mg/L) as the respective *mcr* donor strains (*cf.* Table 2). Further increased in colistin resistance in originally resistant *E. coli* strains (2 mg/L to 8 mg/L; 8 mg/L to 32 mg/L) was observed when *mcr-1* plasmid was introduced into these two strains with an existing chromosomal *pmrB* mutation which is known to confer polymyxin resistance (Jayol et al. 2017). The extent of polymyxin resistance was not affected by the co-existence of multiple *mcr*-harboring plasmids in a single isolate (Li R et al. 2017; Zurfluh et al. 2017). However, a study demonstrated higher colistin MICs (8 mg/L) in *S. enterica* carrying multiple copies of *mcr-5*-harboring plasmid, as compared to the isolates with only one copy of chromosomal *mcr-5* (4 mg/L) (Borowiak, Fischer, et al. 2017). Although we know that *mcr* confers resistance to polymyxins, unexpectedly *mcr* (more specifically *mcr-1*) has also been detected in colistin-susceptible *E. coli* strains (colistin MICs of 0.125 and less than 0.06 mg/L) (Liassine et al. 2016; Quan et al. 2017). The *mcr-1* in a susceptible strain was reactivated following exposure to polymyxin, leading to a polymyxin-resistant phenotype (Thanh et al. 2016). This brings about the possibility for silent dissemination of *mcr* and further reactivation of the gene following polymyxin exposure.

Prevalence of mcr in Gram-negative species

E. coli is the most prevalent species among the *mcr*-positive isolates reported so far, accounting for approximately 91% of the total *mcr*-carrying isolates, followed by *S. enterica* (~7%) and *K. pneumoniae* (~2%). It is noteworthy that the total number of *S. enterica* screened for *mcr* was at least 12-fold greater than *K. pneumoniae*. This is likely due to the fact that *S. enterica* is one of the major food-borne pathogens and *mcr* is very likely to be disseminated via food chain (Zurfluh et al. 2017). The *mcr* has been detected on very rare occasion in *Klebsiella oxytoca*, *Citrobacter freundii*, *Citrobacter braakii*, *Cronobacter sakazakii*, *Kluyvera ascorbata*, *Shigella sonnei*, *Raoultella ornithinolytica*, *Proteus mirabilis, Moraxella, Aeromonas* and *Enterobacter* species with a total prevalence rate of approximately 0.2%. Among the bacterial species which have been tested, *mcr* has not been detected in wild-type isolates of *Klebsiella ozaenae*, *Morganella morganii*, *Providencia rettgeri, Pseudomonas aeruginosa*, *Campylobacter*, *Serratia* and *Acinetobacter* species. Although *mcr* has yet to be found in wildtype *Pseudomonas* and *Acinetobacter* species, it has been demonstrated that, after *mcr-1* was introduced into *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, their lipid A was modified by pEtN; interestingly, greater colistin resistance was observed in *Acinetobacter baumannii* (64- to >128-fold increase in colistin

MICs) as compared to only modest changes in colistin susceptibility in *Pseudomonas aeruginosa* (2- to 4-fold increase in colistin MICs) (Liu YY et al. 2017). Overall, the true prevalence of *mcr* has yet to be fully understood due to the limits of many studies which only screened for the presence of *mcr* in extended-spectrum-β-lactamase (ESBL)-producing isolates and polymyxin-resistant isolates. Such limitations could lead to the underestimation of the true prevalence for *mcr* isolates.

Co-occurrence with β-lactamases and carbapenemases

Carbapenem is often the treatment option for ESBL-associated bacterial infection and unfortunately increasing emergence of carbapenemase-producing bacteria has been reported (Meletis 2016; Thomson 2010). This situation has brought back polymyxins as a last-resort against carbapenemase-producing MDR Gram-negative bacteria (Trecarichi and Tumbarello 2017). Hence, the co-occurrence of *mcr* with carbapenemases may herald the rise of a post-antibiotic era. The *mcr* was found to be frequently associated with β-lactamase-producing Enterobacteriaceae carrying $bla_{\text{CTX-M}}$ and bla_{TEM} of various variants as well as carbapenem-resistant Enterobacteriaceae harboring $bla_{\text{OXA-48}}$, $bla_{\text{OXA-181}}$, $bla_{\text{KPC-2}}$, $bla_{\text{KPC-3}}$, $bla_{\text{NDM-1}}$, $bla_{\text{NDM-4}}$, $bla_{\text{NDM-5}}$ and $bla_{\text{NDM-9}}$ (*cf.* Supplementary information Table S4). Importantly, the discovery of β-lactamase and carbapenemase genes co-localizing with *mcr* on the same conjugative plasmid is the most worrisome, as Gram-negative pathogens can acquire both types of antibiotic resistance genes via horizontal transmission. The co-localization of the β-lactamase and carbapenemase genes ($bla_{\text{TEM-1}}$, $bla_{\text{CTX-M-1}}$, $bla_{\text{CTX-M-55}}$, $bla_{\text{NDM-5}}$) with *mcr* most commonly occurs on the IncHI2 (Grami et al. 2016; Sonnevend et al. 2016; Zurfluh, Klumpp, et al. 2016; Yi et al. 2017) and IncI2 (Sonnevend et al. 2016; Yang YQ et al. 2016; Yi et al. 2017) plasmids, and less commonly on IncFI (Zeng et al. 2016; Zhong et al. 2016), IncK2 (Donà, Bernasconi, Pires, et al. 2017) and IncX3-IncX4 hybrid plasmids (Sun et al. 2016).

Potential origins of mcr

Thus far, *mcr-1* to *-7* have been reported. MCR-1 and MCR-2 share the highest percentage of amino acid sequence identity (81%), are believed to be originated from *Moraxella* species, common animal pathogens. MCR-1 and MCR-2 share 59 – 64% amino acid similarities with those found in *M. porci, M. osloensis, M. lincolnii* and *M. catarrhalis* (Kieffer et al. 2017). MCR-3 and MCR-7, which share 70% amino acid similarity, might be of *Aeromonas* origin (Yang et al. 2018; Yin et al. 2017). MCR-4, sharing only 34% amino acid sequence identity with MCR-1 might have been originated from *Shewanella frigidimarina* (Carattoli et al. 2017). MCR-5 has distinct amino acid sequences from the all the others (34 – 37% similarities) and its origin is still unknown (Borowiak, Fischer, et al. 2017). The heavy usage of colistin in animals is very likely a major selective factor facilitating the mobilization of these *mcr* genes from natural source to Enterobacteriaceae.

Genetic organization of mcr-harboring plasmids

The detection of *mcr* on different classes of plasmids indicated a high diversity of *mcr* plasmid reservoirs (*cf.* Table 3). Numerous studies have confirmed *mcr* on three major types of plasmids: IncI2, IncHI2 and IncX4. There are also several other types of plasmids carrying *mcr*, including IncHI1, IncF, IncFI, IncFIB, IncFII, IncP, IncP-1, IncK2 and phage-like IncY (*cf.* Supplementary information Table S5). To date, only *mcr-4* and *mcr-5* have been identified on small ColE-type plasmid (Borowiak, Fischer, et al. 2017; Carattoli et al. 2017). Of all the different plasmid reservoirs, the IncHI2-type plasmids are often associated with various antimicrobials resistance (*cf.* Figure 3). As compared to IncI2 and IncHI2-type plasmids, the genetic contexts are more conserved in IncX4-type plasmids except pICBEC7P*mcr* which has an additional IS*1294* resulting in truncated *mobA* (Sellera et al. 2016) (*cf.* Figure 3). Although *mcr* was initially reported as a plasmid-mediated polymyxin resistance gene, *mcr-1* has been identified in the chromosome of *E. coli* strains and *mcr-5* was identified in the chromosome of a *S. enterica* (*cf.* Supplementary information Table S5). The presence of IS*Apl1-mcr-1* region in the chromosome postulates the importance of IS*Apl1* for the chromosomal integration of *mcr-1* and represents another transmissibility factor for the vertical transmission. Remarkably, a triplicated IS*Apl1-mcr-1-*Δ*pap* in a tandem arrangement in the chromosome was described in an *E. coli* isolated from humans, indicating a more diverse genetic context of *mcr* (Yu, Ang, Chong, et al. 2016).

It has been demonstrated that the transposon Tn*6330* element (IS*Apl1-mcr-1-orf*-IS*Apl1*) could be excised from the plasmid, forming a circular intermediate of IS*Apl1-mcr-1-orf*, which might be integrated into other IS*Apl1*-carrying plasmids (Li R et al. 2016). The mobilization of *mcr-1* by IS*Apl1*-mediated transposition was demonstrated *in vitro* (Poirel, Kieffer and Nordmann 2017). Plasmid analysis from various studies revealed that the IS*Apl1* family transposase does not always co-present with *mcr* in the plasmid. IS*Apl1* is usually present in IncHI2-type plasmids (~200 kb), can be either present or absent in IncI2-type plasmids (~60 kb), and completely absent in IncX4-type plasmids (~30 kb) (*cf.* Figure 3). A possible explanation for this observation is that *mcr* may have originated from plasmid and their co-evolution occurred via acquisition of IS*Apl1*, leading to rapid mobilization onto other plasmids (Kuo et al. 2016; Petrillo et al. 2016). Another possibility is that IS*Apl1* transposase is lost after translocation of the IS*Apl1-mcr-1* element into the plasmid with the purpose to strengthen the stability of *mcr per se* in the plasmid (Li A et al. 2016; Snesrud et al. 2016). The *mcr-3* was found to be associated with Tn*As2* (Yin et al. 2017) and Tn*As3* (Liu L et al. 2017), which are the Tn3-family transposon and were found only in *Aeromonas salmonicida*. This fortifies the possible transfer of *mcr-3* from *Aeromonas* species to Enterobacteriaceae. The *mcr-5* gene was found to be located on a Tn3-family transposon which has been identified in *Cupriavidus gilardii* (Borowiak, Fischer, et al. 2017).

The transferability of *mcr*-carrying plasmids between bacteria depends on the conjugative properties of the plasmid backbone. The defective conjugation potential can be due to the disrupted or lacking of *tra* region (encodes for conjugal transfer protein) (Bernasconi et al. 2016; Cui et al. 2017). The *mcr-1* carrying plasmid, p*MCR*_1410 from *Kluyvera ascorbata* was found to possess the ability to transfer between different Gram-negative species, unlike the first *mcr-1*-harboring plasmid identified, pHNSHP45. Comparison of pMCR_1410 and pHNSHP45 revealed that the absence of *traC* in pHNSHP45 could cause its inability for interspecies conjugation, suggested that *traC* gene could possibly be responsible for interspecies transfer of the plasmid (Zhao and Zong 2016). This finding is alarming due to the potential for the spread of *mcr* to a more diverse bacterial species pool, which highlights the need for further investigations into the genes involved in the conjugative transfer of *mcr*.

Future perspective

Since the discovery of *mcr*, the number of *mcr*-harboring isolates has been increasingly reported worldwide at an alarming rate. Notwithstanding, the prevalence of *mcr* remains much higher in livestock as compared to humans, which is in line with its purported agricultural origins. Luckily, the use of colistin has been recently banned for agriculture purposes in China and Brazil (Walsh and Wu 2016; Monte et al. 2017). The increasing usage of polymyxins clinically may increase the potential for wide dissemination of *mcr* in the nosocomial setting. As polymyxins are the last therapeutic option for life-threatening infections caused by Gram-negative 'superbugs', every effort must be made to minimize the emergence of resistance, in particular due to *mcr*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosure statement

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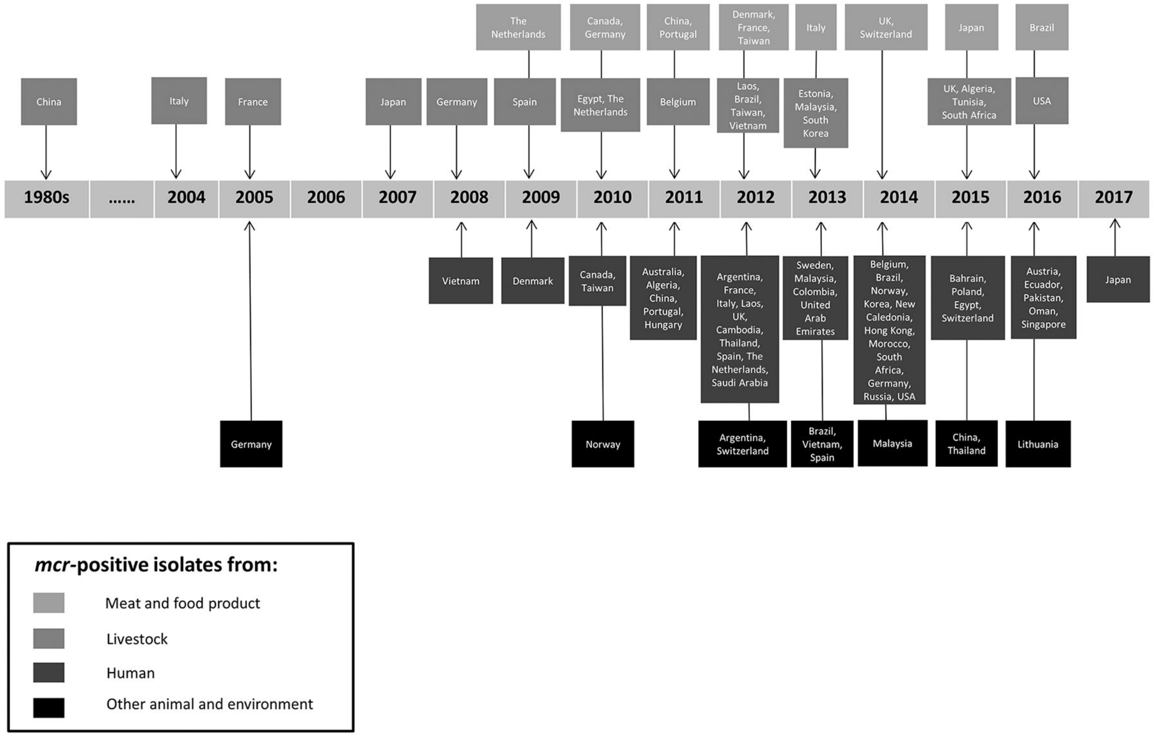

Figure 1.

Time-line of the first identification of *mcr* in each country.

Figure 2.
Geographical distribution of *mcr*-carrying bacteria.

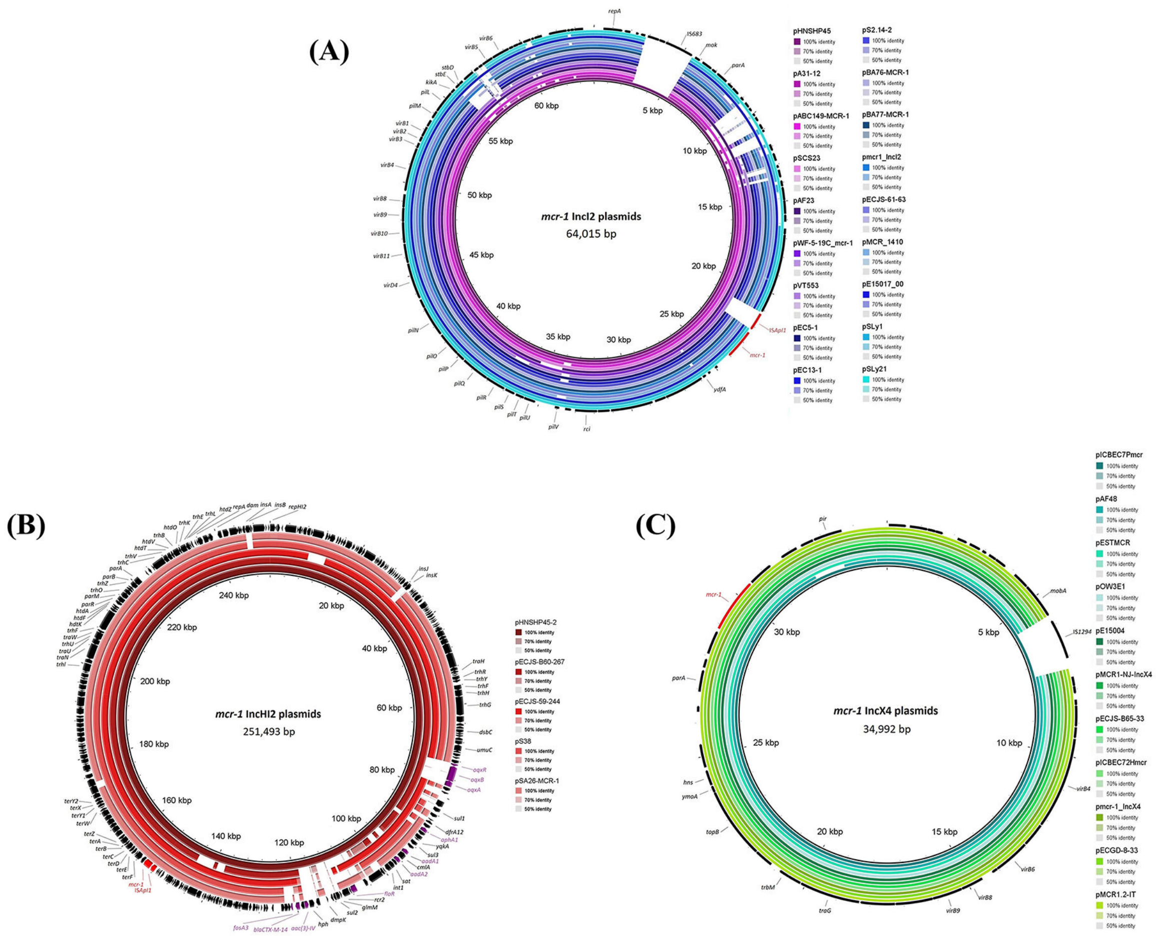

Figure 3.

Comparison of the genetic context of *mcr-1* harboring (A) IncI2 plasmids with pHNSHP45 as the reference sequence; (B) IncHI2 plasmids with pHNSHP45–2 as the reference sequence; (C) IncX4 plasmids with pICBEC7P*mcr* as the reference sequence, using BRIG (Alikhan et al. 2011). The *mcr-1* and IS*Apl1* transposase are illustrated in red, whereas other antimicrobial resistance genes are illustrated in purple at the outermost circle containing the CDS annotations.

Table 1.

Characterization of *mcr*-harboring bacteria.

Category	Country	Year	Species	Source	No. of isolate	Reference
Human	Algeria	2011	*E. coli*	Urine	1	Berrazeg et al. 2016
			E. coli	Sperm culture	1	Yanat et al. 2016
		2013	*E. coli*	Rectum	7	Leangapichart et al. 2016
			K. pneumoniae	Rectum	1	Leangapichart et al. 2016
		2014	*E. coli*	Rectum	1	Leangapichart et al. 2016
	Argentina	2012	*E. coli*	Blood (n=1 ***mcr-1.5***) Urine (n=1)	2	Rapoport et al. 2016; Tijet et al. 2017
		2013	*E. coli*	Abdominal (n=1 ***mcr-1.5***) Blood (n=1)	2	Rapoport et al. 2016; Tijet et al. 2017
		2015	*E. coli*	Urine (n=2 ***mcr-1.5***) Blood (n=1) Bone (n=1)	4	Rapoport et al. 2016; Tijet et al. 2017
		2016	*E. coli*	Abscess	1	Rapoport et al. 2016
	Australia	2011	*E. coli*	Urine	1	Ellem et al. 2017
		2013	*E. coli*	Urine	1	Ellem et al. 2017
	Austria	2016	*E. coli*	Fecal sample	1	Hartl et al. 2017
	Bahrain	2015	*E. coli*	Wound (n=1) Urine (n=1)	2	Sonnevend et al. 2016
		2015	*E. coli*	Groin and peri-rectal	4	Snesrud et al. 2017
	Belgium	2014 – 2015	*E. coli*	NA	1	Castanheira et al. 2016
		2015	*E. coli*	Pus	1	Huang TD et al. 2017
	Brazil	2014 – 2015	*E. coli*	NA	1	Castanheira et al. 2016
		2015	*E. coli*	Rectum (n=2) Blood (n=1)	3	Conceição-Neto et al. 2017
		2016	*K. pneumoniae*	Urine	1	Aires et al. 2017
		2016	*E. coli*	Wound	1	Fernandes, McCulloch, et al. 2016
	Cambodia	2012	*E. coli*	Fecal sample	1	Stoesser et al. 2016
	Canada	2010	*E. coli*	Blood	2	Walkty et al. 2016
		2011	*E. coli*	Gastrostomy tube site, rectum	1	Mulvey et al. 2016
		2015 – 2016	*E. coli*	Urine	1	Payne et al. 2016

Category	Country	Year	Species	Source	No. of isolate	Reference
	China	2011 and earlier	NA	Fecal sample (Human microbiome)	27	Hu Y et al. 2016; Ruppé et al. 2016
		2011	*E. coli*	Abdominal fluid	1	Wang X et al. 2017
			K. pneumoniae	Wound	1	Wang X et al. 2017
		2012	*E. coli*	Blood (n=8) Urine (n=1) Rectum (n=25)	34	Lima Barbieri et al. 2017; Quan et al. 2017; Wang X et al. 2017; Wang Y et al. 2017
			K. pneumoniae	Blood	3	Wang X et al. 2017
			S. enterica Enteritidis	NA	2	Cui et al. 2017
			S. enterica Typhimurium	NA	1	Cui et al. 2017
		2013	*E. coli*	Blood (n=11) Drainage fluid (n=1) Abdominal fluid (n=4) Sputum (n=1) Urine (n=1)	18	Quan et al. 2017; Wang X et al. 2017; Wang Y et al. 2017
			S. enterica	NA	1	Cui et al. 2017
			S. enterica Typhimurium	NA	5	Cui et al. 2017
		2014	*E. coli*	Urine (n=5) Sputum (n=3) Drainage fluid (n=9) Bile (n=2) Ascites (n=3) Wound (n=1) Blood (n=22) Pus (n=1)	46	Du et al. 2016; Liu YY et al. 2016; He QW et al. 2017; Quan et al. 2017; Wang X et al. 2017; Wang Y et al. 2017
			K. pneumoniae	Urine (n=1) Sputum (n=2) Blood (n=1)	4	Liu YY et al. 2016; Quan et al. 2017
			Enterobacter aerogenes	Vaginal secretion	1	Zeng et al. 2016
			Enterobacter cloacae	Urine	1	Zeng et al. 2016
			S. enterica	Rectum (n=1$^{mcr\text{-}1.6}$) NA (n=3)	4	Cui et al. 2017; Lu et al. 2017
		2014 – 2015	*E. coli*	NA	2	Zhang R et al. 2017
		2015	*E. coli*	Abscess (n=2) Fecal sample (n=63) Blood (n=10) Urine (n=20) Ascites (n=1) Bile (n=8) Catheter (n=2) Drainage fluid (n=7) Pus (n=1) Respiratory tract (n=1) Secretion (n=8) Sputum (n=13) Wound (n=1)	137	Du et al. 2016; Gu et al. 2016; Ye et al. 2016; Yu H et al. 2016; Zhang R et al. 2016; Zhang XF et al. 2016; He QW et al. 2017; Tian et al. 2017; Wang Y et al. 2017
			K. pneumoniae	Fecal sample (n=2) Surgical wound (n=1) Peritoneal fluid (n=1) Sputum (n=1)	5	Du et al. 2016; Gu et al. 2016; Tian et al. 2017;

Category	Country	Year	Species	Source	No. of isolate	Reference
						Wang Y et al. 2017
			S. enterica Typhimurium	NA	16	Cui et al. 2017
		2016	*E. coli*	Fecal sample	34	Zhong et al. 2016; Hu et al. 2017; Zheng et al. 2017
			K. pneumoniae	Sputum	4	Tian et al. 2017
			Citrobacter freundii	Fecal sample	1	Hu et al. 2017
		2017	*E. coli* [***mcr-3.5***]	Abdominal abscess	1	Liu L et al. 2017
		NA	*E. coli*	Blood	2	Zheng et al. 2016
			K. pneumoniae	NA	13	Wang Y et al. 2017
			Enterobacter cloacae	NA	1	Wang Y et al. 2017
			Enterobacter aerogenes	NA	1	Wang Y et al. 2017
	Colombia	2013	*E. coli*	Leg secretion (n=1) Blood (n=1)	2	Saavedra et al. 2017
		2015	*S. enterica* Typhimurium	Fecal sample (n=1) Urine (n=1)	2	Saavedra et al. 2017
		2016	*E. coli*	Urine (n=2) Vaginal secretion (n=1) Abdominal abscess (n=1) Toe tissue (n=1) NA (n=1)	6	Saavedra et al. 2017
			K. pneumoniae	Blood	1	Saavedra et al. 2017
			S. enterica Typhimurium	Fecal sample	1	Saavedra et al. 2017
	Denmark	2009	*S. enterica* Typhimurium ***mcr-3***	NA	1	Litrup et al. 2017
		2010	*S. enterica* O:4,5,12;H:i:- ***mcr-3***	NA	1	Litrup et al. 2017
		2011	*S. enterica* O:4,5,12;H:i:- ***mcr-3***	NA	2	Litrup et al. 2017
		2012	*S. enterica* Typhimurium ***mcr-3***	NA	2	Litrup et al. 2017
			S. enterica O:4,5,12;H:i:- ***mcr-3***	NA	1	Litrup et al. 2017
		2014	*S. enterica* Typhimurium	NA	2	Torpdahl et al. 2017
			E. coli [***mcr-3***]	Blood	1	Roer et al. 2017
		2015	*E. coli*	Blood	1	Hasman et al. 2015
			S. enterica Typhimurium	NA	2	Torpdahl et al. 2017
			S. enterica O:4,5,12;H:i:- ***mcr-3***	NA	1	Litrup et al. 2017

Category	Country	Year	Species	Source	No. of isolate	Reference
		2016	*S. enterica* O:4,5,12;H:i:- ***mcr-3***	NA	1	Litrup et al. 2017
		2017	*S. enterica* O:4,5,12;H:i:- ***mcr-3***	NA	1	Litrup et al. 2017
	Ecuador	2016	*E. coli*	Peritoneal fluid	1	Ortega-Paredes et al. 2016
	Egypt	2015	*E. coli*	Sputum	1	Elnahriry et al. 2016
	France	2012 – 2013	*K. pneumoniae*	Fecal sample	2	Rolain et al. 2016
		2016	*E. coli*	Fecal sample	1	Beyrouthy et al. 2017
	Germany	2014	*E. coli*	Wound	1	Falgenhauer, Waezsada, Yao, et al. 2016
		2014 – 2015	*E. coli*	NA	5	Castanheira et al. 2016
		2016	*E. coli*	Urine	1	Fritzenwanker et al. 2016
	Hungary	2011	*E. coli*	Blood	1	Juhász et al. 2017
	Hong Kong	2014 – 2015	*E. coli*	NA	1	Castanheira et al. 2016
		2015 – 2016	*E. coli*	Blood (n=2) Fecal sample (n=1) Urine (n=1)	4	Wong et al. 2016
		2015 – 2016	*Enterobacter cloacae*	Fecal sample	1	Wong et al. 2016
	Italy	2012 – 2015	*S. enterica*	NA	10	Carnevali et al. 2016
		2013	*E. coli*	Urine	1	Cannatelli et al. 2016
		2014	*E. coli*	Urine, surgical wound	3	Cannatelli et al. 2016
			K. pneumoniae ***mcr-1.2***	Rectum	1	Di Pilato et al. 2016
		2015	*E. coli*	Urine (n=4) Intestinal colonization (n=3)	7	Cannatelli et al. 2016; Giufrè et al. 2016
		2014 – 2015	*E. coli*	NA	4	Castanheira et al. 2016
		2016	*E. coli*	Blood	2	Corbella et al. 2017
			S. enterica Typhimurium ***mcr-4.2***	Fecal sample	2	Carretto et al. 2018
		2017	*E. coli*	Blood	1	Corbella et al. 2017
	Japan	2017	*E. coli*	Fecal sample	1	Tada, Uechi, et al. 2017
	Kingdom of Saudi Arabia	2012	*E. coli*	Blood	1	Sonnevend et al. 2016
	Laos	2012	*E. coli*	Fecal sample	6	Olaitan et al. 2016

Category	Country	Year	Species	Source	No. of isolate	Reference
		2012	*K. pneumoniae*	Fecal sample	4	Rolain et al. 2016
	Malaysia	2013	*E. coli*	Urine	1	Yu, Ang, Chin, et al. 2016
		2014 – 2015	*E. coli*	NA	1	Castanheira et al. 2016
	Morocco	2014	*E. coli*	Rectum	2	Leangapichart et al. 2016
	New Caledonia	2014	*E. coli*	Ascites (n=1) Gastric fluid (n=1)	2	Robin et al. 2016
	Norway	2014	*E. coli*	NA	1	Solheim et al. 2016
	Oman	2016	*E. coli*	Blood	1	Mohsin et al. 2017
	Pakistan	2016	*E. coli*	Wound	1	Mohsin et al. 2016
	Poland	2015	*E. coli*	Urine	1	Izdebski et al. 2016
	Portugal	2011 – 2012	*S. enterica* 1,4,[5],12:i:-	Blood, fecal sample	4	Campos et al. 2016
		2016	*E. coli*	Urine	1	Tacão et al. 2017
	Russia	2014 – 2015	*E. coli*	NA	1	Castanheira et al. 2016
	Singapore	2016	*E. coli*	Urine	2	Teo et al. 2016
		2016	*K. pneumoniae*	Urine	1	Teo et al. 2016
	South Africa	2014 – 2016	*E. coli*	Blood (n=1) Wound (n=1) Pus (n=1) Urine (n=6)	9	Coetzee et al. 2016; Poirel, Kieffer, Brink, et al. 2016
		2016	*E. coli*	Urine (n=9) Superficial abdominal swab (n=1)	10	Newton-Foot et al. 2017
		2016	*K. pneumoniae*	Sputum (n=2) Urine (n=2)	4	Newton-Foot et al. 2017
		2016	*K. oxytoca*	Superficial abdominal swab	1	Newton-Foot et al. 2017
	South Korea	2014 – 2015	*E. coli*	Blood	1	Kim et al. 2017
	Spain	2012	*E. coli*	Blood	1	Prim et al. 2016
		2013	*E. coli*	Sputum (n=3) Blood (n=4) Urine (n=1)	8	Prim et al. 2016
		2014	*E. coli*	Urine (n=2) Surgical wound (n=1)	3	Prim et al. 2016
		2015	*E. coli*	Urine	3	Prim et al. 2016
		2014 – 2015	*E. coli*	NA	3	Castanheira et al. 2016
		2016	*E. coli*	Peritoneal fluid (n=1) Sputum (n=1)	2	Ortiz de la Tabla et al. 2016; Sánchez-Benito et al. 2017
		2012 – 2015	*E. coli*	Blood (n=5), urine (n=6), sputum (n=3),	15	Prim et al. 2017

Category	Country	Year	Species	Source	No. of isolate	Reference
				surgical wound secretion (n=1)		
	Sweden	2013	*E. coli*	Fecal sample	1	Vading et al. 2016
	Switzerland	2015	*E. coli*	Urine (n=1) Fecal sample (n=3, 1$^{mcr\text{-}1.2}$) Blood (n=2)	7	Bernasconi et al. 2016; Nordmann, Lienhard, et al. 2016; Poirel, Kieffer, Liassine, et al. 2016; Donà, Bernasconi, Kasraian, et al. 2017
		2016	*E. coli*	Urine (n=1) Fecal sample (n=2)	3	Zurfluh et al. 2017
	Taiwan	2010	*E. coli*	Sputum	1	Kuo et al. 2016
		2012	*E. coli*	Urine	2	Kuo et al. 2016
		2014	*E. coli*	Ascites (n=1) Abscess (n=2) Blood (n=3) Urine (n=5)	11	Kuo et al. 2016
			S. enterica Typhimurium	NA	5	Chiou et al. 2017
		2015	*S. enterica* Typhimurium	NA	3	Chiou et al. 2017
			S. enterica Newport	NA	1	Chiou et al. 2017
			S. enterica Albany	NA	1	Chiou et al. 2017
		NA	*E. coli*	Urine	1	Lai et al. 2017
	Thailand	2012	*E. coli*	Fecal sample	2	Olaitan et al. 2016
		2014 – 2015	*E. coli*	Urine	1	Runcharoen et al. 2017
		2016	*E. coli*	Urine	1	Paveenkittiporn et al. 2016
	The Netherlands	2012 – 2013	*E. coli*	Fecal sample	6	Arcilla et al. 2016
		2014	*E. coli*	Fecal sample	1	Nijhuis et al. 2016
		2015	*E. coli*	Fecal sample	2	Nijhuis et al. 2016
		2014 – 2015	*E. coli*	Fecal sample	1	Terveer et al. 2017
	The United States	2014	*E. coli*	Urine	1	Mediavilla et al. 2016
		2015	*E. coli*	Urine	1	Castanheira et al. 2016
		2015	*E. coli*	Blood	1	Macesic et al. 2017
		2016	*E. coli*	Urine	1	McGann et al. 2016
		2016	*E. coli*	Fecal sample	1	Vasquez et al. 2016

Category	Country	Year	Species	Source	No. of isolate	Reference
	The United Kingdom	2012	*S. enterica* Typhimurium	Fecal sample	1	Doumith et al. 2016
		2013	*E. coli*	Fecal sample (n=1) Blood (n=1)	2	Doumith et al. 2016
		2014	*E. coli*	Blood	1	Doumith et al. 2016
		2014	*S. enterica* Typhimurium	Fecal sample	2	Doumith et al. 2016
		2014	*S. enterica* Virchow	Fecal sample	1	Doumith et al. 2016
		2015	*S. enterica* Typhimurium	Fecal sample	5	Doumith et al. 2016
		2015	*S. enterica* Paratyphi	Fecal sample	1	Doumith et al. 2016
	United Arab Emirates	2013	*E. coli*	Blood	1	Sonnevend et al. 2016
	Vietnam	2008	*Shigella sonnei*	Fecal sample	1	Thanh et al. 2016
		2012 – 2013	*E. coli*	Rectum	3	Trung et al. 2017
		2014	*E. coli*	Urine (n=1) Pus (n=1)	2	Tada, Nhung, et al. 2017
Livestock	Algeria	2015	*E. coli*	Chicken	1	Olaitan et al. 2016
	Brazil	2012	*E. coli*	Pig	2	Fernandes, Moura, et al. 2016
		2013	*E. coli*	Chicken	14	Fernandes, Moura, et al. 2016
		2015	*E. coli*	Chicken	10	Lentz et al. 2016
	Belgium	2011 – 2012	*E. coli*	Calf (n=6) Pig (n=7) Calf (n=1$^{\textit{mcr-2}}$) Pig (n=2$^{\textit{mcr-2}}$)	16	Malhotra-Kumar, Xavier, Das, Lammens, Butaye, et al. 2016; Xavier et al. 2016
		2013	*E. coli*	Cattle (n=1) Pig (n=1)	2	El Garch et al. 2016
		2015 – 2016	*E. coli*$^{\textit{mcr-4}}$	Pig	2	Carattoli et al. 2017
	China	1980s	*E. coli*	Chicken	3	Shen et al. 2016
		2004 – 2006	*E. coli*	Chicken	8	Shen et al. 2016
		2007	*S. enterica* Typhimurium	Chicken	1	Li XP et al. 2016
		2008	*S. enterica* Typhimurium	Pig	2	Li XP et al. 2016
		2009	*E. coli*	Chicken	6	Shen et al. 2016
			S. enterica Typhimurium	Pig	1	Li XP et al. 2016
		2010	*E. coli*	Chicken	13	Shen et al. 2016; Yang YQ et al. 2017
			S. enterica Typhimurium	Duck	1	Li XP et al. 2016

Category	Country	Year	Species	Source	No. of isolate	Reference
		2011	*E. coli*	Chicken (n=30) Pig (n=3)	33	Li Z et al. 2016; Shen et al. 2016; Yang YQ et al. 2017
		2012	*E. coli*	Pig (n=33) Chicken (n= 42)	75	Li Z et al. 2016; Liu YY et al. 2016; Shen et al. 2016; Lima Barbieri et al. 2017; Yang YQ et al. 2017
		2013	*E. coli*	Pig (n=69) Chicken (n=39) Chicken (n=1$^{mcr-1.3}$)	109	Li Z et al. 2016; Liu YY et al. 2016; Shen et al. 2016; Lima Barbieri et al. 2017; Wang X et al. 2017; Yang YQ et al. 2017
		2014	*E. coli*	Pig (n=67) Chicken (n=26)	93	Liu YY et al. 2016; Shen et al. 2016; Lima Barbieri et al. 2017; Yang YQ et al. 2017
			Citrobacter freundii	Pig	1	Li XP et al. 2017
			K. pneumoniae $^{mcr-7}$	Chicken	1	Yang et al. 2018
		2010 – 2015	*K. pneumoniae*	Chicken (n=7) Chicken (n=2^{mcr-7})	9	Yang et al. 2018
		2014 – 2015	*E.coli*	Pig	35	Li R et al. 2017
			S. enterica	Chicken	4	Yang YQ et al. 2016
		2015	*E. coli*	Duck (n=2) Chicken (n=66) Cattle (n=1) Pig (n=1^{mcr-3})	70	Liu BT et al. 2016; Yang RS et al. 2016; He T et al. 2017; Yang YQ et al. 2017; Yi et al. 2017; Yin et al. 2017
			Aeromonas veronii $^{mcr-3.3}$	Chicken	1	Ling et al. 2017
			Cronobacter sakazakii	Chicken (n=2)	2	Liu BT et al. 2016
		2015 – 2016	*S. enterica*	Chicken (n=6) Pig (n=6)	12	Ma et al. 2017
		2017	*Aeromonas caviae* $^{mcr-3.10}$	Duck	1	Wang et al. 2018
			E. coli $^{mcr-3.10}$	Duck	1	Wang et al. 2018
			Proteus mirabilis $^{mcr-3.10}$	Duck	1	Wang et al. 2018
	Egypt	2010	*E. coli*	Chicken	4	Lima Barbieri et al. 2017
		2014	*E. coli*	Cattle	1	Khalifa et al. 2016
	Estonia	2013	*E. coli*	Pig	3	Brauer et al. 2016
	France	2005 – 2014	*E. coli*	Calf	106	Haenni et al. 2016

Category	Country	Year	Species	Source	No. of isolate	Reference
		2004	*E. coli*	Cattle	1	El Garch et al. 2016
		2005	*E. coli*	Cattle	1	El Garch et al. 2016
		2006	*E. coli*	Pig	2	El Garch et al. 2016
		2007	*E. coli*	Cattle (n=2) Pig (n=1)	3	Brennan et al. 2016; El Garch et al. 2016
		2008	*E. coli*	Cattle (n=1) Pig (n=1)	2	El Garch et al. 2016
		2009	*E. coli*	Pig	3	El Garch et al. 2016
		2010	*E. coli*	Cattle (n=4) Pig (n=5)	9	El Garch et al. 2016
		2011	*E. coli*	Cattle (n=1) Pig (n=2)	3	El Garch et al. 2016; Perrin-Guyomard et al. 2016
		2012	*E. coli*	Pig	3	El Garch et al. 2016
		2013	*E. coli*	Chicken (n=3) Pig (n=4)	7	El Garch et al. 2016; Perrin-Guyomard et al. 2016
			S. enterica 1,4,[5],12:i:-	Chicken	1	Webb et al. 2016
		2014	*E. coli*	Chicken (n=4) Turkey (n=14) Pig (n=1)	19	El Garch et al. 2016; Perrin-Guyomard et al. 2016
	Germany	2008	*S. enterica* Paratyphi B	Chicken	1	Borowiak, Hammerl, et al. 2017
		2010 – 2011	*E. coli*	Pig	3	Falgenhauer, Waezsada, Yao, et al. 2016
			S. enterica	Pig	1	El Garch et al. 2016
		2010	*E. coli*	Chicken (n=8) Turkey (n=30) Calf (n=15) Pig (n=1)	54	El Garch et al. 2016; Irrgang et al. 2016
		2011	*E. coli*	Laying hen (n=2) Chicken (n=17) Turkey (n=33) Pig (n=13)	65	Irrgang et al. 2016
		2011 – 2012	*E. coli*	Pig farm (boot swab and fecal sample)	43	Roschanski et al. 2017
		2012	*Aeromonas media* ***mcr-3.7***	Turkey	1	Eichhorn et al. 2018
			E. coli	Turkey (n=63) Calf (n=5)	68	Irrgang et al. 2016
			S. enterica Paratyphi B ***mcr-5***	Poultry	8	Borowiak, Fischer, et al. 2017

Category	Country	Year	Species	Source	No. of isolate	Reference
		2013	*E. coli*	Chicken	52	Irrgang et al. 2016
		2014	*E. coli*	Laying hens(n=1) Chicken (n=22) Turkey (n=37)	60	Irrgang et al. 2016
		2015	*E. coli*	Calf (n=1) Pig (n=11)	12	Irrgang et al. 2016
		2016	*E. coli*	Pig	11	Schirmeier et al. 2017
	Italy	2004	*E. coli*	Cattle	2	El Garch et al. 2016
		2006	*E. coli*	Cattle	1	El Garch et al. 2016
		2007	*E. coli*	Pig	3	El Garch et al. 2016
		2008	*E. coli*	Pig	1	El Garch et al. 2016
		2010 – 2011	*S. enterica*	Pig	2	El Garch et al. 2016
		2011	*E. coli*	Pig	1	El Garch et al. 2016
		2012	*E. coli*	Pig	1	El Garch et al. 2016
		2013	*S. enterica* Typhimurium ***mcr-4***	Pig	1	Carattoli et al. 2017
		2014	*E. coli*	Pig	1	El Garch et al. 2016
		2012 – 2015	*S. enterica*	Poultry (n=2) Pig (n=9)	11	Carnevali et al. 2016
		2015 – 2016	*E. coli*	Pig	37	Curcio et al. 2017
		2016	*E. coli*	Pig	1	Pulss et al. 2017
	Japan	2007 – 2014	*E. coli*	Pig	90	Kusumoto et al. 2016
		2008	*E. coli*	Pig	2	Kawanishi et al. 2016; Suzuki et al. 2016
		2010	*E. coli*	Pig	5	Kawanishi et al. 2016; Suzuki et al. 2016
		2011	*E. coli*	Cattle	1	Kawanishi et al. 2016
		2012	*E. coli*	Pig (n=5) Cattle (n=2) Chicken (n=2)	9	Kawanishi et al. 2016
		2013	*E. coli*	Pig (n=3) Cattle (n=1) Chicken (n=2)	6	Kawanishi et al. 2016
			S. enterica Typhimurium	Pig	1	Suzuki et al. 2016
		2012 – 2013	*E. coli*	Cattle	4	Suzuki et al. 2016

Category	Country	Year	Species	Source	No. of isolate	Reference
		2014	*E. coli*	Pig (n=7) Cattle (n=1) Chicken (n=10)	18	Kawanishi et al. 2016
	Laos	2012	*E. coli*	Pig	3	Olaitan et al. 2016
	Malaysia	2013	*E. coli*	Chicken (n=5) Pig (n=1)	6	Petrillo et al. 2016; Yu, Ang, Chin, et al. 2016
	South Africa	2015	*E. coli*	Chicken	19	Perreten et al. 2016
	South Korea	2013	*E. coli*	Chicken	1	Lim et al. 2016
		2014	*E. coli*	Chicken	6	Lim et al. 2016
		2015	*E. coli*	Chicken (n=3) Pig (n=1)	4	Lim et al. 2016
	Spain	2009	*S. enterica* Typhimurium	Pig	1	Quesada et al. 2016
			M. pluranimalium $^{mcr\text{-}2.2}$	Pig	1	AbuOun et al. 2017
		2010	*S. enterica* Typhimurium	Pig	1	Quesada et al. 2016
			S. enterica Rissen	Pig	1	Quesada et al. 2016
		2011	*E. coli*	Pig	1	Quesada et al. 2016
			S. enterica Typhimurium	Pig	1	Quesada et al. 2016
		2013	*E. coli*	Pig	1	Quesada et al. 2016
		2014	*E. coli*	Turkey	3	Quesada et al. 2016
		2015	*E. coli*	Cattle (n=4, 1$^{mcr\text{-}3.2}$)	5	Hernández et al. 2017
		2015 – 2016	*E. coli* $^{mcr\text{-}4}$	Pig	9	Carattoli et al. 2017
	Taiwan	2012	*S. enterica* Typhimurium	Pig	1	Chiou et al. 2017
		2013	*S. enterica* Typhimurium	Pig (n=3) Chicken (n=2)	5	Chiou et al. 2017
			S. enterica Anatum	Pig	3	Chiou et al. 2017
	The Netherlands	2010 – 2011	*E. coli*	Calf (n=15) Chicken (n=2) Turkey (n=1)	18	Veldman et al. 2016
		2012 – 2013	*E. coli*	Chicken	8	Veldman et al. 2016
	The United Kingdom	2014	*M. porci* $^{mcr\text{-}1.10}$	Pig	1	AbuOun et al. 2017
		2015	*E. coli*	Pig	4	Anjum et al. 2016; Duggett et al. 2016
			S. enterica Typhimurium	Pig	1	Anjum et al. 2016

Category	Country	Year	Species	Source	No. of isolate	Reference
			M. pluranimalium $^{mcr-6}$	Pig	1	AbuOun et al. 2017
	The United States	2016	*E. coli*	Pig	3	Meinersmann, Ladely, Bono, et al. 2016; Meinersmann, Ladely, Plumblee, et al. 2016
	Tunisia	2015	*E. coli*	Chicken	37	Grami et al. 2016
	Vietnam	2012 – 2013	*E. coli*	Chicken	19	Trung et al. 2017
		2013 – 2014	*E. coli*	Chicken (n=20) Pig (n=17)	37	Nguyen et al. 2016
		2014 – 2015	*E. coli*	Pig	9	Malhotra-Kumar, Xavier, Das, Lammens, Hoang, et al. 2016
Meat and food product	Brazil	2016	*E. coli*	Chicken meat	8	Monte et al. 2017
	Canada	2010	*E. coli*	Beef (Unknown origin)	2	Mulvey et al. 2016
	China	2011	*E. coli*	Pork (n=3) Chicken meat(n=10)	13	Liu YY et al. 2016
		2013	*E. coli*	Pork (n=11) Chicken meat(n=4)	15	Liu YY et al. 2016
		2014	*E. coli*	Pork (n=29) Chicken meat (n=21)	50	Liu YY et al. 2016
		2015 – 2016	*E. coli*	Retail food sample	109	Liu X et al. 2017
			S. enterica	Chicken meat (n=5) Pork (n=5)	10	Ma et al. 2017
		2015	*E. coli*	Vegetable	3	Luo et al. 2017
			Raoultella ornithinolytica	Vegetable	2	Luo et al. 2017
		2016	*E. coli*	Vegetable	4	Luo et al. 2017
	Denmark	2012	*E. coli*	Chicken meat(imported from Europe)	3	Hasman et al. 2015
		2013	*E. coli*	Chicken meat (imported from Europe)	1	Hasman et al. 2015
		2014	*E. coli*	Chicken meat(imported from Europe)	1	Hasman et al. 2015
	France	2012	*S. enterica* Paratyphi B	Chicken breast (n=1) Ready-to-cook guinea fowl pie (n=1)	2	Webb et al. 2016
		2013	*S. enterica* Derby	Chipolata sausage	1	Webb et al. 2016
	Italy	2013 – 2015	*S. enterica*	Pork	4	Carnevali et al. 2016
	Japan	2015	*E. coli*	Chicken meat	1	Ohsaki et al. 2017
	Taiwan	2012	*E. coli*	Beef	1	Kuo et al. 2016

Category	Country	Year	Species	Source	No. of isolate	Reference
		2013	*E. coli*	Chicken meat	6	Kuo et al. 2016
		2015	*E. coli*	Chicken meat (n=9) Pork (n=2)	11	Kuo et al. 2016
	The Netherlands	2009	*E. coli*	Chicken meat(Unknown origin)	1	Kluytmans-van den bergh et al. 2016
		2013	*S. enterica* Anatum	Turkey meat (imported)	1	Veldman et al. 2016
		2014	*E. coli*	Chicken meat(imported from Europe)	2	Kluytmans-van den bergh et al. 2016
		2015	*S. enterica* Schwarzengrund	Turkey meat (imported)	1	Veldman et al. 2016
			E. coli	Chicken meat	33	Schrauwen et al. 2017
			K. pneumoniae	Chicken meat	2	Schrauwen et al. 2017
		2010 – 2015	*S. enterica* Java	Chicken meat (local)	11	Veldman et al. 2016
	The United Kingdom	2014	*S. enterica* Paratyphi B	Poultry meat (imported from Europe)	2	Doumith et al. 2016
	Germany	2010	*E. coli*	Turkey meat	17	Irrgang et al. 2016
		2011	*E. coli*	Chicken meat	14	Irrgang et al. 2016
			S. enterica Paratyphi B ***mcr-5***	Chicken meat	1	Borowiak, Fischer, et al. 2017
		2012	*E. coli*	Chicken breast (n=1) Turkey hen Schnitzel (n=1) Turkey meat (n=30) Beef (n=2)	34	Falgenhauer, Waezsada, Gwozdzinski, et al. 2016; Irrgang et al. 2016
			S. enterica Paratyphi B ***mcr-5***	Chicken meat	1	Borowiak, Fischer, et al. 2017
		2013	*E. coli*	Turkey meat (n=1) Chicken meat (n=10)	11	Falgenhauer, Waezsada, Gwozdzinski, et al. 2016; Irrgang et al. 2016
			S. enterica Paratyphi B ***mcr-5***	Chicken meat	1	Borowiak, Fischer, et al. 2017
		2014	*E. coli*	Chicken meat (n=1) Turkey meat (n=10)	11	Irrgang et al. 2016
	Portugal	2011	*S. enterica* Typhimurium	Food product (originated from swine and poultry)	3	Figueiredo et al. 2016; Tse and Yuen 2016
		2012	*S. enterica* Typhimurium	Food product (originated from cattle)	1	Figueiredo et al. 2016
		2014 – 2015	*S. enterica* 1,4,[5],12:i:-	Pork meat/carcass	5	Campos et al. 2016
			S. enterica Rissen	Pork carcass	2	Campos et al. 2016

Category	Country	Year	Species	Source	No. of isolate	Reference
	Switzerland	2014	*E. coli*	Vegetable (imported from Thailand and Vietnam)	2	Zurfuh et al. 2016
				Chicken meat (imported from Germany)	4	Donà, Bernasconi, Pires, et al. 2017
		2015	*E. coli*	Chicken meat (imported from Germany and Italy)	2	Zogg et al. 2016
		2016	*E. coli*	Chicken meat (imported from Germany and Italy) Turkey meat (imported from Germany and Italy)	14	Zurfluh, Buess, et al. 2016; Donà, Bernasconi, Pires, et al. 2017
Other animal	Argentina	2012	*E. coli*	Kelp gulls	5	Liakopoulos et al. 2016
	Brazil	2013	*E. coli*	Magellanic penguins	1	Sellera et al. 2016
	China	2016	*E. coli*	Dog (n=4) Cat (n=2)	6	Zhang XF et al. 2016
	Germany	2005	*Aeromonas allosaccharophila* ***mcr-3.6***	Fish	1	Eichhorn et al. 2018
		2006	*Aeromonas hydrophila* ***mcr-3.8, mcr-3.9***	Fish	1	Eichhorn et al. 2018
		2008	*Aeromonas jandaei* ***mcr-3.8***	Fish	1	Eichhorn et al. 2018
	Lithuania	2016	*E. coli*	European herring gulls	1	Ruzauskas and Vaskeviciute 2016
	Vietnam	2013 – 2014	*E. coli*	Asian grass lizard	2	Unger et al. 2016
Environment	Brazil	2016	*E. coli*	Sea water	3	Fernandes et al. 2017
	China	2015	*Kluyvera ascorbata*	Hospital sewage	1	Zhao and Zong 2016
			K. pneumoniae	Hospital sewage	1	Zhao, Feng, et al. 2016
			E. coli	Well water	2	Sun et al. 2017
		2016	*E. coli*	River and lake water	16	Zhou et al. 2017
			Citrobacter freundii	Lake water	2	Zhou et al. 2017
			K. oxytoca	Lake water	2	Zhou et al. 2017
			Citrobacter braakii	Lake water	2	Zhou et al. 2017
			Enterobacter cloacae	River water	1	Zhou et al. 2017
	Germany	2012	*S. enterica* Paratyphi B ***mcr-5***	NA	2	Borowiak, Fischer, et al. 2017
	Malaysia	2014	*E. coli*	Pond water	1	Petrillo et al. 2016
	Norway	2010	*E. coli*	Sea water	2	Jørgensen et al. 2017

Category	Country	Year	Species	Source	No. of isolate	Reference
	Spain	2013	*E. coli*	Sewage water	29	Ovejero et al. 2017
			K. pneumoniae	Sewage water	1	Ovejero et al. 2017
	Switzerland	2012	*E. coli*	River water	1	Zurfuh et al. 2016
	Thailand	2014 – 2015	*E. coli*	Canal water	2	Runcharoen et al. 2017

NA: not available; Isolates carried *mcr-1* unless stated otherwise in superscript.

Table 2.

Polymyxin B and colistin MICs of *mcr*-carrying strains and their respective transformants and/or transconjugants.

Reference	Bacterial strain	Description	*mcr*	Polymyxin B		Colistin	
				MIC (mg/L)	MIC fold-change	MIC (mg/L)	MIC fold-change
Liu YY et al. 2016	*E. coli* SHP45	Original *mcr-1* positive isolate from pig	+	4		8	
	E. coli C600	Recipient	−	0.5	8	0.5	16
	E. coli C600 transconjugant of *E. coli* SHP45	Transconjugant	+	4		8	
	E. coli E11	Recipient	−	0.5	4	0.5	8
	E. coli E11 + pHNSHP45	Transformant	+	2		4	
	K. pneumoniae MPC11	Recipient	−	0.5	8	0.5	16
	K. pneumoniae MPC11 + pHNSHP45	Transformant	+	4		8	
	K. pneumoniae 1202	Recipient	−	0.5	8	0.5	8
	K. pneumoniae 1202 + pHNSHP45	Transformant	+	4		4	
	P. aeruginosa HE26	Recipient	−	0.5	8	0.5	16
	P. aeruginosa HE26 + pHNSHP45	Transformant	+	4		8	
	E. coli W3110 + pUC18	Recipient (lab strain)	−	0.5	4	0.5	4
	E. coli W3110 + $pUC18_{mcr\text{-}1}$	Transformant	+	2		2	
Gu et al. 2016	*K. pneumoniae* 15451–1	Original *mcr-1* positive isolate from human	+	NA		16	
	E.coli C600	Recipient	−	NA	NA	≤1	>16
	E. coli C600 transconjugant of *K. pneumoniae* 15451–1	Transconjugant	+	NA		16	
	E. coli 15451–2	Original *mcr-1* positive isolate from human	+	NA		16	
	E.coli C600	Recipient	−	NA	NA	≤1	>16
	E. coli C600 transconjugant of *E. coli* 15451–2	Transconjugant	+	NA		16	
Yang YQ et al. 2016	*S. enterica* SC23	Original *mcr-1* positive isolate from chicken	+	8		8	
	E. coli J53	Recipient	−	<0.25	>32	<0.25	>32
	E. coli J53 transconjugant of *S. enterica* SC23	Transconjugant	+	8		8	

Reference	Bacterial strain	Description	*mcr*	Polymyxin B		Colistin	
				MIC (mg/L)	MIC fold-change	MIC (mg/L)	MIC fold-change
Zeng et al. 2016	*Enterobacter aerogenes* GB68	Original *mcr-1* positive isolate from human	+	16		16	
	E.coli C600	Recipient	−	<0.25	>64	<0.25	>64
	E.coli C600 transconjugant of *Enterobacter aerogenes* GB68	Transconjugant	+	16		16	
	Enterobacter cloacae GB38	Original *mcr-1* positive isolate from human	+	>32		>32	
	E.coli C600	Recipient	−	<0.25	>64	<0.25	>64
	E.coli C600 transconjugant of *Enterobacter cloacae* GB38	Transconjugant	+	16		16	
Sonnevend et al. 2016	*E. coli* BA76	Original *mcr-1* positive isolate from human	+	NA		16	
	E. coli J53RAZ	Recipient	−	NA	NA	0.25	16
	E. coli J53RAZ transconjugant of *E. coli* BA76	Transconjugant	+	NA		4	
	E. coli BA77	Original *mcr-1* positive isolate from human	+	NA		16	
	E. coli J53RAZ	Recipient	−	NA	NA	0.25	16
	E. coli J53RAZ transconjugant of *E. coli* BA77	Transconjugant	+	NA		4	
	E. coli SA26	Original *mcr-1* positive isolate from human	+	NA		16	
	E. coli J53RAZ	Recipient	−	NA	NA	0.25	16
	E. coli J53RAZ transconjugant of *E. coli* SA26	Transconjugant	+	NA		4	
	E. coli ABC149	Original *mcr-1* positive isolate from human	+	NA		16	
	E. coli DH5α	Recipient	−	NA	NA	0.25	32
	E. coli DH5α + pABC149	Transformant	+	NA		8	
Berrazeg et al. 2016	*E. coli* SE65	Original *mcr-1* positive isolate from human	+	NA		4	
	E. coli J53	Recipient	−	NA	NA	0.125	32
	E. coli J53 transconjugant of *E. coli* SE65	Transconjugant	+	NA		4	
Li XP et al. 2016	*S. enterica* GDS78, GDS79, GDS82, GDS141	Original *mcr-1* positive isolate from animal	+	NA		16	
	E. coli C600	Recipient	−	NA	NA	0.125	32

Reference	Bacterial strain	Description	*mcr*	Polymyxin B		Colistin	
				MIC (mg/L)	MIC fold-change	MIC (mg/L)	MIC fold-change
	E. coli C600 T(GDS78T, GDS79T, GDS82T, GDS141T)	Transconjugant	+	NA		4	
Zheng et al. 2016	*E. coli* 1002	Original *mcr-1* positive isolate from human	+	4		4	
	E. coli J53	Recipient	−	0.25	8	0.5	8
	E. coli J53 transconjugant of *E. coli* 1002	Transconjugant	+	2		4	
	E. coli 2474	Original *mcr-1* positive isolate from human	+	4		4	
	E. coli J53	Recipient	−	0.25	16	0.5	8
	E. coli J53 transconjugant of *E. coli* 2474	Transconjugant	+	4		4	
Zhong et al. 2016	*E. coli* GB049	Original *mcr-1* positive isolate form human	+	16		8	
	E.coli EC600	Recipient	−	0.5	32	0.25	64
	E.coli EC600 transconjugant of *E. coli* GB049	Transconjugant	+	16		16	
	E. coli GB090	Original *mcr-1* positive isolate form human	+	16		16	
	E.coli EC600	Recipient	−	0.5	32	0.25	64
	E.coli EC600 transconjugant of *E. coli* GB090	Transconjugant	+	16		16	
Liu BT et al. 2016	*E. coli* WF5–19	Original *mcr-1* positive isolate from chicken	+	NA		4	
	E. coli C600	Recipient	−	NA	NA	0.25	16
	E. coli C600 transconjugant of *E. coli* WF5–19	Transconjugant	+	NA		4	
	Cronobacter sakazakii WF5–19C	Original *mcr-1* positive isolate from chicken	+	NA		4	
	E. coli C600	Recipient	−	NA	NA	0.25	16
	E. coli C600 transconjugant of *Cronobacter sakazakii* WF5–19C	Transconjugant	+	NA		4	
	Cronobacter sakazakii WF5–21C	Original *mcr-1* positive isolate from chicken	+	NA		4	
	E. coli C600	Recipient	−	NA	NA	0.25	16
	E. coli C600 transconjugant of *Cronobacter sakazakii* WF5–21C	Transconjugant	+	NA		4	

Reference	Bacterial strain	Description	*mcr*	Polymyxin B		Colistin	
				MIC (mg/L)	MIC fold-change	MIC (mg/L)	MIC fold-change
Ortiz de la Tabla et al. 2016	*E. coli* (unnamed)	Original *mcr-1* positive isolate from human	+	NA		4	
	E. coli Hb101	Recipient	−	NA	NA	0.5	8
	E. coli Hb101 transconjugant of *E. coli* (unnamed)	Transconjugant	+	NA		4	
Lu et al. 2017	*S. enterica* Typhimurium YL14P053	Original *mcr-1.6* positive isolate from human	+	NA		4	
	S. enterica Typhi CT18	Recipient	−	NA	NA	0.125	32
	S. enterica Typhi CT18 transconjugant of *S. enterica* Typhimurium YL14P053	Transconjugant	+	NA		4	
	E. coli J53 Azi[R]	Recipient	−	NA	NA	0.125	32
	E. coli J53 Azi[R] transconjugant of *S. enterica* Typhimurium YL14P053	Transconjugant	+	NA		4	
	K. pneumoniae BJ1988	Recipient	−	NA	NA	0.125	32
	K. pneumoniae BJ1988 transconjugant of *S. enterica* Typhimurium YL14P053	Transconjugant	+	NA		4	
Conceição-Neto et al. 2017	*E. coli* CCBH20178	Original *mcr-1* positive isolate from human	+	NA		8	
	E. coli J53	Recipient	−	NA	NA	<0.125	>32
	E. coli J53 transconjugant of *E. coli* CCBH20178	Transconjugant	+	NA		4	
	E. coli CCBH20607	Original *mcr-1* positive isolate from human	+	NA		8	
	E. coli J53	Recipient	−	NA	NA	<0.125	>32
	E. coli J53 transconjugant of *E. coli* CCBH20607	Transconjugant	+	NA		4	
	E. coli CCBH20180	Original *mcr-1* positive isolate from human	+	NA		4	
	E. coli J53	Recipient	−	NA	NA	<0.125	>64
	E. coli J53 transconjugant of *E. coli* CCBH20180	Transconjugant	+	NA		8	
Aires et al. 2017	*K. pneumoniae* CCBH24080	Original *mcr-1* positive isolate from human	+	NA		16	
	E. coli J53	Recipient	−	NA	NA	<0.125	>64
	E. coli J53 transconjugant of *K. pneumoniae* CCBH24080	Transconjugant	+	NA		8	

Reference	Bacterial strain	Description	*mcr*	Polymyxin B		Colistin	
				MIC (mg/L)	MIC fold-change	MIC (mg/L)	MIC fold-change
Kim et al. 2017	*E. coli* 28	Original *mcr-1* positive isolate from human	+	NA		8	
	E. coli J53	Recipient	−	NA	NA	0.5	16
	E. coli J53 transconjugant of *E. coli* 28	Transconjugant	+	NA		8	
Yin et al. 2017	*E. coli* WJ1	Original *mcr-3* positive isolate from porcine	+	NA		8	
	E. coli C600	Recipient	−	NA	NA	0.5	8
	E. coli C600 transconjugant of *E. coli* WJ1	Transconjugant	+	NA		4	
Liu L et al. 2017	*E. coli* WCHECLL123	Original *mcr-3.5* and *mcr-1* positive isolate from human	+	NA		8	
	E. coli J53	Recipient	−	NA	NA	1	4
	E. coli J53 transconjugant of *E. coli* WCHECLL123 (*mcr-1*)	Transconjugant	+	NA		4	
	E. coli J53 transconjugant of *E. coli* WCHECLL123 (*mcr-3.5*)	Transconjugant	+	NA	NA	4	4
Carattoli et al. 2017	*S. enterica* Typhimurium R3445	Original *mcr-4* positive isolate from pig	+	NA		8	
	E. coli DH5α	Recipient	−	NA	NA	0.25	8
	E. coli DH5α + p*MCR*_R3445	Transformant	+	NA		2	
	E. coli R4287	Original *mcr-4* positive isolate from pig	+	NA		8	
	E. coli CSH26 Rif^R	Recipient	−	NA	NA	0.25	16
	E. coli CSH26 Rif^R transconjugant of *E. coli* R4287	Transconjugant	+	NA		4	

NA: not available; Original *mcr*-positive isolates are highlighted in grey.

Table 3.

Characterization of *mcr*-harboring plasmids with complete sequences in Genbank.

Year	Country	Source	Species	Plasmid	Type	Length (bp)	IS*ApI1*	Accession number
2011 – 2012	Belgium	Pig	*E. coli*	pKP37-BE	IncX4	35,104	−	LT598652
2012	Switzerland	River water	*E. coli*	pOW3E1	IncX4	34,640	−	KX129783
2013	Estonia	Pig	*E. coli*	pEST*MCR*	IncX4	33,311	−	KU743383
2013	Brazil	Magellanic penguin	*E. coli*	pICBEC7P*mcr*	IncX4	34,992	−	CP017246
2014	China	Pig	*E. coli*	pECGD-8–33	IncX4	33,307	−	KX254343
2014	Italy	Human	*K. pneumoniae*	p*MCR*1.2-IT [*mcr-1.2*]	IncX4	33,303	−	KX236309
2014	The United States	Human	*E. coli*	p*MCR*1-NJ-IncX4	IncX4	33,395	−	KX447768
2015	China	Human	*K. pneumoniae*	p*mcr*1_IncX4	IncX4	33,287	−	KU761327
2015	China	Human	*E. coli*	pE15004	IncX4	33,309	−	KX772777
2015	China	Pig	*E. coli*	pECJS-B65–33	IncX4	33,298	−	KX084392
2015	China	Sewage	*E. coli*	p*MCR*_WCHEC1618 [*mcr-1.4*]	IncX4	33,309	−	KY463454
2015	Portugal	Pig	*E. coli*	pLV23529-MCR-1.9 [*mcr-1.9*]	IncX4	33,303	−	KY964067
2015	South Africa	Human	*E. coli*	pAF48	IncX4	31,808	−	KX032520
2016	Brazil	Human	*E. coli*	pICBEC72H*mcr*	IncX4	33,304	−	CP015977
2011	Australia	Human	*E. coli*	pJIE2288–1	IncI2	60,733	−	KY795977
2013	Australia	Human	*E. coli*	pJIE3685–1	IncI2	60,960	−	KP795978
2013	Malaysia	Chicken	*E. coli*	pEC5–1	IncI2	61,735	−	CP016185
2013	Malaysia	Pond water	*E. coli*	pEC13–1	IncI2	60,218	−	CP016186
2013	Malaysia	Chicken	*E. coli*	pS2.14–2	IncI2	60,950	−	CP016187
2013	China	Chicken	*E. coli*	pHeN867 [*mcr-1.3*]	IncI2	60,757	−	KU934208
2014	China	Chicken	*K. pneumoniae*	pSC20141012 [*mcr-7*]	IncI2	65,631	−	MG267386
2015	Bahrain	Human	*E. coli*	pBA76-*MCR*-1	IncI2	64,942	−	KX013540
2015	Bahrain	Human	*E. coli*	pBA77-*MCR*-1	IncI2	62,661	−	KX013539
2015	China	Human	*E. coli*	p*mcr*1_IncI2	IncI2	64,964	−	KU761326
2015	China	Pig	*E. coli*	pECJS-61–63	IncI2	63,656	−	KX084393
2015	China	Hospital sewage	*Kluyvera ascorbata*	p*MCR*_1410	IncI2	57,059	−	KU922754

Year	Country	Source	Species	Plasmid	Type	Length (bp)	IS*ApI1*	Accession number
2015	China	Human	*E. coli*	pE15017_00	IncI2	65,375	−	KX772778
2016	The United States	Pig	*E. coli*	pSLy1	IncI2	65,888	−	CP015913
2016	The United States	Pig	*E. coli*	pSLy21	IncI2	63,329	−	CP016405
2013 – 2015	Argentina	Human	*E. coli*	p*MCR*-M15049 $^{mcr\text{-}1.5}$	IncI2	61,198	+	KY471308
2013 – 2015	Argentina	Human	*E. coli*	p*MCR*-M17059 $^{mcr\text{-}1.5}$	IncI2	61,531	+	KY471310
2013 – 2015	Argentina	Human	*E. coli*	p*MCR*-M19241 $^{mcr\text{-}1.5}$	IncI2	61,584	+	KP471311
2012	China	Chicken	*E. coli*	pA31–12	IncI2	67,134	+	KX034083
2013	China	Pig	*E. coli*	pHNSHP45	IncI2	64,015	+	KP347127
2013	United Arab Emirates	Human	*E. coli*	pABC149-*MCR*-1	IncI2	61,228	+	KX013538
2014	China	Chicken	*S. enterica*	pSCS23	IncI2	65,419	+	KU934209
2014	South Africa	Human	*E. coli*	pAf23	IncI2	61,177	+	KX032519
2015	China	Chicken	*Cronobacter sakazakii*	pWF-5–19C_*mcr*-1	IncI2	65,203	+	KX505142
2015	China	Sewage	*E. coli*	p*MCR*_WCHEC1604-IncI2 $^{mcr\text{-}1.7}$	IncI2	62,098	+	KY829117
2015	South Africa	Chicken	*E. coli*	pVT553	IncI2	62,219	+	KU870627
2011 – 2012	Belgium	Cattle	*E. coli*	pKH457–3-BE	IncP	79,798	−	KU353730
2014	China	Human	*S. enterica* Typhimurium	p*MCR*16_P053 $^{mcr\text{-}1.6}$	IncP	47,824	−	KY352406
2015	China	Hospital sewage	*K. pneumoniae*	p*MCR*_1511	IncP	57,278	+	KX377410
2017	China	Human	*E. coli*	p*MCR*3_LL123 $^{mcr\text{-}3.5}$	IncP	52,208	−	MF489760
2011 – 2012	Belgium	Pig	*E. coli*	pKP81-BE	IncFII	91,041	+	KU994859
2016	The United States	Human	*E. coli*	pMR0516*mcr*	IncF	225,069	+	KX276657
2014	Switzerland	Vegetables (imported from Thailand)	*E. coli*	pH226B	IncHI1	209,401	−	KX129784
2013	Malaysia	Chicken	*E. coli*	pEC2_1–4	IncHI1	230,278	+	CP016183
2013	Malaysia	Pig	*E. coli*	pEC2–4	IncHI1	235,403	+	CP016184
2008	Germany	Chicken	*S. enterica* Paratyphi B	pSE08-00436-1	IncHI2	264,914	+	CP020493
2012	Saudi Arabia	Human	*E. coli*	pSA26-*MCR*-1	IncHI2	240,367	+	KU743384
2013	China	Pig	*E. coli*	pHNSHP45–2	IncHI2	251,493	+	KU341381
2015	China	Pig	*E. coli*	pECJS-59–244	IncHI2	243,572	+	KX084394
2015	China	Pig	*E. coli*	pECJS-B60–267	IncHI2	267,486	+	KX254341

Year	Country	Source	Species	Plasmid	Type	Length (bp)	IS*ApI1*	Accession number
2015	Switzerland	Chicken meat (imported from Italy)	*E. coli*	pS38	IncHI2	247,885	+	KX129782
2015	China	Pig	*E. coli*	pWJ1 ***mcr-3***	IncHI2	261,119	−	KY924928
2015	China	Pig	*E. coli*	pHYEC7-*mcr1*	IncY	97,559	+	KX518745
2016	China	Pig	*E. coli*	p*MCR*-1-P3	IncY	97,386	+	KX880944
2012	Germany	Poultry	*S. enterica* Paratyphi B	pSE12–02541 ***mcr-5***	ColE	17,156	−	KY807920
2013	Germany	Chicken meat	*S. enterica* Paratyphi B	pSE13-SA01718 ***mcr-5***	ColE	12,201	−	KY807921
2013	Italy	Pig	*S. enterica* Typhimurium	p*MCR*_R3445 ***mcr-4***	ColE10	8,749	−	MF543359

Plasmids carried *mcr-1* unless stated otherwise in superscript.