Editorial

Impact of *mcr-1* harbouring bacteria in clinical settings and the public health sector: how can we act against this novel threat?

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Recently, Quan *et al.* [2017] published a comprehensive multicentre longitudinal study in which they demonstrate that the *mcr-1* colistin resistance gene is only sporadically detectable in *Escherichia coli* and *Klebsiella pneumoniae* from patients with bloodstream infections in China, but untraceable in clinical isolates of the medical important bacteria *Pseudomonas aeruginosa* and *Acinetobacter* spp. In the study, the authors could not attribute undesirable effects of the *mcr-1* occurrence to any of the clinical outcomes of the infected patients. However, taking into account the low *mcr-1* prevalence in the analysed target bacteria, the threat of the novel resistance gene to clinical and public health is not conclusively assessable and needs further investigations (1).

In the last decade, a disturbing increase of multidrug-resistant Gram-negative bacteria has been notified in clinical settings, worldwide (2,3). Polymyxin compounds (e.g., colistin) have for a long time only been used in exceptional cases in medicine because of the potential of severe side effects. Now, they see a revival as last-resort antibiotics in the human medicine to treat severe infections caused by multidrug-resistant, especially carbapenemase-producing Gram-negative bacteria (4). Until 2015, resistance against polymyxin among Gram-negative bacteria was thought to be associated only with chromosomal mutations e.g., in the two-component regulatory systems (PmrAB or PhoPQ), the negative-feedback regulator MgrB or genetic determinants mediating the composition of the lipopolysaccharide (2,5). Thus, dissemination of the chromosomal-associated colistin resistance in bacterial populations was considered limited to the vertical gene transfer. However, some years ago surveillance studies on antimicrobial resistance of Gram-negative bacteria performed by different research groups indicated an annual increase of the proportion of colistin-resistant isolates in different enterobacteria from various sources (i.e., food, livestock) indicating the emergence of a novel colistin resistance mechanism.

In this context, the observations of Liu *et al.* [2016] within a routine surveillance project on antimicrobial resistance in commensal *E. coli* from livestock in China revealed the impact of colistin resistance determinants in a different light (6). The authors described a novel genetic determinant, called *mcr-1* (mobilisable colistin resistance-1), causing increased antimicrobial resistances against polymyxins. The gene product of *mcr-1* exhibits significant homologies to proteins of the phosphoethanolamine transferase enzyme family which catalyses the addition of phosphoethanolamine to lipid A during expression in the bacteria. As *mcr-1* is located on an extrachromosomal element, the authors investigated its transferability via horizontal gene transfer and disclosed that the *mcr-1* harbouring plasmid could be efficiently transferred to *E. coli* with frequencies of 10^{-1} to 10^{-3} per recipient cell *in vivo*. Determination of the *mcr-1* prevalence in isolates recovered between 2011 and 2014 from food products, animals and inpatients in China, indicated high prevalence levels ranging between 15% and 21% in raw meat and livestock, respectively. In contrast to food products and

livestock, the frequency of *mcr-1* harbouring bacteria in inpatients was quite low (<1%) suggesting that the transfer frequency from food and food-producing animals to humans was low (6). However, the observations of Liu *et al.* [2016] on the mobile colistin resistance determinant motivated comprehensive surveillance studies on the *mcr-1* prevalence in food, livestock and inpatients worldwide, especially in countries with a high burden of ESBL (Extended Spectrum Beta-Lactamase) and/or carbapenemase-producing bacteria (6). Screening data on *mcr-1* from various countries indicate that this novel resistance determinant is globally distributed (7,8). Thus, coordinated global action is immediately required to support the fight against pan-drug-resistant Gram-negative bacteria, worldwide (2,3).

One year after the discovery of *mcr-1*, another colistin resistance determinant was identified in porcine and bovine *E. coli* in Belgium and was named *mcr-2*. The expressed enzyme also has a functional relationship to phosphoethanolamine transferase enzymes but exhibits only a limited amino acid homology (76.7%) to MCR-1 (9). According to the phylogenetic relationship of the protein Xavier *et al.* [2016] suggested that MCR-2 might have originated from *Moraxella catarrhalis*. Similar to *mcr-1*, *mcr-2* is also located on a plasmid of the incompatibility group IncX4 (9). Interestingly, the prevalence of *mcr-2* in porcine colistin-resistant *E. coli* in Belgium was higher than that of *mcr-1*. Moreover, the transfer frequency of the identified *mcr-2* plasmid is 1,200-fold higher than that of the *mcr-1*-harbouring IncFII plasmid pKP81-BE (9). This is alarming as it indicates that spread of this gene may occur rapidly. To date, only few *mcr-2*-carrying bacteria were described from different matrices (9,10). However, *mcr-2* screening should be integrated in ongoing molecular epidemiological surveillance of colistin-resistant Gram-negative pathogens to closely monitor its' potential to spread in the bacterial populations. Furthermore, as there is only scarce information on the biology and evolution of *mcr-1/mcr-2*-plasmids available, detailed investigations on the genetic background, the stability and the transferability will be needed.

The current study of Quan *et al.* [2017] demonstrates that around 1% (20 of 1,495) of *E. coli* and below 1% (1 of 571) of *K. pneumoniae* isolates from patients with bloodstream infections in China harboured the *mcr-1* gene (1). However, molecular data on the prevalence of the *mcr-2* determinant are lacking. The results are based on isolates provided by 28 tertiary hospitals from 22 provinces and municipalities in seven geographic regions of China, representing more than 2/3 of the Chinese territory (1). The *mcr-1* prevalence reported by Quan *et al.* [2017] in the most important Gram-negative bacterial species associated with blood stream infections (*E. coli* and *K. pneumoniae* isolates) was similar to the prevalences reported from other countries (1) (6-8,11,12). Up to now, the *mcr-1* gene is rare among clinical isolates indicating that the exposure to *mcr-1* harbouring bacteria via consumption of contaminated food or the contact with infected livestock into the food chain might still have limited impact on human colonisation. However, the presence of a mobilisable colistin resistance gene increases the risk for a broad dissemination of the determinant via horizontal gene transfer. The impact of colistin-resistance associated chromosomal mutations (*pmrB*, *mgrB*, *pmrA/B*, *phoP/Q*, *and mgrB*) in *mcr-1* harbouring and colistin-resistant isolates of Quan *et al.* [2017] is questionable and has still to be determined (1). Based on the Minimal Inhibitory Concentration (MIC)-data of investigated *K. pneumoniae* isolates, the authors assume that chromosomal mutations might have a synergistic effect on the prevailing colistin resistance phenotype. Phenotypic and genotypic characterisation of the *mcr-1*-positive isolates indicate that they have a highly diverse genetic background (i.e., bio-, phylo- or serotypes) (1,6-8,11,12). Quan and colleagues [2017] identified 17 distinct sequence types (STs) and 20 PFGE-patterns among the 20 *mcr-1*-positive isolates (1). Thus, they suggested that all of these *mcr-1*-positive isolates were from sporadic cases (1). Several other authors of *mcr-1* prevalence studies observed a similar genetic diversity suggesting that the transferability of the different *mcr-1* plasmid variants may not be restricted to specific bacterial genera and species as well as bio-, phylo- or serotypes. Recent research identified various *mcr-1*-harbouring plasmid types of the incompatibility groups IncI2, IncX4, IncHI1, IncHI2, IncF, IncFI, IncFII, and IncP (13). However, detailed information on the acquisition of the *mcr-1* gene to plasmid genomes of various incompatibility groups is missing.

In the study of Quan *et al.* [2017] two plasmid variants of 33 kb (pESTMCR-like) and 61 kb (pHNSHP45-like) belonging to the incompatibility group IncX4 and IncI2, respectively, harbour the *mcr-1* resistance gene (1). These observed variants are in good agreement with the predominant plasmids carrying *mcr-1* as observed by other international research groups. Detailed analyses on the genetic diversity of IncX4 plasmids revealed that this plasmid type comprises a similar genetic background with variable regions. As IncX4 plasmids are narrow

host range-plasmids, replicating only in a few, different bacterial species, the high level of spread and the transfer of the *mcr-1* resistance region to other plasmid types, has still to be evaluated. As determined by Sun *et al.* [2017], many IncX4 plasmids of *E. coli* carry *mcr-1* on the variable region I that constitutes a target for the insertion sequence ISApl1 (13,14). The latter was presumably involved in the transposition of the *mcr-1* resistance (13). The high mobility of the *mcr-1* resistance factor is noteworthy, as many *mcr-1* plasmid types can occur in ESBL- and/or carbapenemase-producing Enterobacteriaceae, posing a threat to public health (15). The IncX4 plasmid is prevalent and widespread in various species of the Enterobacteriaceae originating from humans, animals, and animal products of many countries (i.e., China, Denmark, United Kingdom) (13).

Quan *et al.* [2017] showed that most *mcr-1* harbouring bacteria are susceptible to various other antimicrobials including tigecycline, and the piperacillin/tazobactam combination (1). In all but one isolate the detected resistance determinants against various antibiotics were not located one the *mcr-1* plasmid. However, Quan *et al.* [2017] also showed that the *mcr-1* plasmid is able to coexist with other plasmids containing various resistance factors (e.g., NDM-5) (1,13). The acquisition of the resistance determinant may therefore lead to a drastic increase of multidrug resistant bacteria and thus, to a further limitation in treatment options in clinical settings.

Quan and colleagues [2017] also analysed the clinical outcome of patients harbouring *mcr-1*-positive isolates but could not observe an effect of the colistin resistance on treatment outcomes. However, it has to be noted that they only observed very few cases, which limits the likelihood of detecting significant effects (1).

As colistin compounds are not reported to be used in Chinese hospitals to treat infections an urgent need to identify the origin of *mcr-1*-harbouring enterobacteria was claimed. The authors suggested that the respective bacteria might be introduced from agricultural settings where in China in and in other countries, large amounts of polymyxins are used (1,6,16). However, reliable data on the role of selective pressure for *mcr-1* harbouring isolates are scarce and do not allow for valid assessments. Nevertheless, for Europe a more restricted use of colistin use in agriculture was already recommended by EMA (16). But as colistin usage has a long tradition in agriculture, more information on the global *mcr-1* prevalence in strains recovered before 2005 is needed.

Many interesting papers on the biology and genetic of *mcr-1* harbouring bacteria or plasmids as well as case reports and prevalence studies have been published recently (data not shown). Nevertheless, many basic genetic issues on the *mcr-1*/*mcr-2* transfer, the origin of the respective resistance gene(s), routes of transmission, and reliable data on the clinical outcome remain unresolved. We only just begin to understand the health risks related to this novel resistance gene.

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References

1. Quan J, Li X, Chen Y, et al. Prevalence of mcr-1 in Escherichia coli and Klebsiella pneumoniae recovered from bloodstream infections in China: a multicentre longitudinal study. Lancet Infect Dis 2017;17:400-10.
2. Tacconelli E, Cataldo MA, Dancer SJ, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant

Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect 2014;20 Suppl 1:1-55.
3. Zowawi HM, Harris PN, Roberts MJ, et al. The emerging threat of multidrug-resistant Gram-negative bacteria in urology. Nat Rev Urol 2015;12:570-84.
4. Kelesidis T, Falagas ME. The safety of polymyxin antibiotics. Expert Opin Drug Saf 2015;14:1687-701.
5. Gunn JS. The Salmonella PmrAB regulon: lipopolysaccharide modifications, antimicrobial peptide resistance and more. Trends Microbiol 2008;16:284-90.
6. Liu YY, Wang Y, Walsh TR, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: A microbiological and molecular biological study. Lancet Infect Dis 2016;16:161-8.
7. Ruppé E, Le Chatelier E, Pons N, et al. Dissemination of the mcr-1 colistin resistance gene. Lancet Infect Dis 2016;16:290-1.
8. von Wintersdorff CJ, Wolffs PF, van Niekerk JM, et al. Detection of the plasmid-mediated colistin-resistance gene mcr-1 in faecal metagenomes of Dutch travellers. J Antimicrob Chemother 2016;71:3416-9.
9. Xavier BB, Lammens C, Ruhal R, et al. Identification of a novel plasmid-mediated colistin-resistance gene, mcr-2, in Escherichia coli, Belgium, June 2016. Euro Surveill 2016;21.
10. Liassine N, Assouvie L, Descombes MC, et al. Very low prevalence of MCR-1/MCR-2 plasmid-mediated colistin resistance in urinary tract Enterobacteriaceae in Switzerland. Int J Infect Dis 2016;51:4-5.
11. Irrgang A, Roschanski N, Tenhagen BA, et al. Prevalence of mcr-1 in E. coli from livestock and food in Germany, 2010-2015. PLoS One 2016;11:e0159863.
12. Kawanishi M, Abo H, Ozawa M, et al. Prevalence of colistin resistance gene mcr-1 and absence of mcr-2 in Escherichia coli isolated from healthy food-producing animals in Japan. Antimicrob Agents Chemother 2016;61.
13. Sun J, Fang LX, Wu Z, et al. Genetic analysis of the IncX4 plasmids: Implications for a unique pattern in the mcr-1 acquisition. Sci Rep 2017;7:424.
14. Snesrud E, He S, Chandler M, et al. A model for transposition of the colistin resistance gene mcr-1 by ISApl1. Antimicrob Agents Chemother 2016;60:6973-6.
15. Falgenhauer L, Waezsada SE, Yao Y, et al. Colistin resistance gene mcr-1 in extended-spectrum beta-lactamase-producing and carbapenemase-producing Gram-negative bacteria in Germany. Lancet Infect Dis 2016;16:282-3.
16. EMA/CVMP/CHMP/231573/2016 CfMPfVuC, Committee for Medicinal Products for Human Use (CHMP). Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health. Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health. 27 July 2016. Available online: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211080.pdf

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