Co-occurrence of extended spectrum β lactamase and MCR-1 encoding genes on plasmids

Findings reported by Yi-Yun Liu and colleagues[1] identified the plasmid-borne gene *mcr-1* encoding resistance to colistin with a high prevalence in *Escherichia coli* isolates from animals, foodstuff, and human beings in China. The same gene was then reported in Europe (Denmark) among extended-spectrum β lactamase (ESBL) and AmpC-producing *E coli* isolates from chicken meat and human infections, but at a very low prevalence.[2]

We screened ESBL-positive *E coli* isolates collected in France for colistin resistance. Isolates were collected between 2005 and mid-2014 from faeces of diarrhoeic veal calves at farms, as part of a survey in the context of the French antimicrobial resistance Resapath surveillance network for animal pathogens. We screened these isolates for colistin resistance using disk diffusion and minimum inhibitory concentration determination by broth microdilution. We analysed plasmids bearing the *mcr-1* gene by conjugation, S1-pulsed-field gel electrophoresis, PCR-based replicon typing, and Southern blot. We analysed clonal relationship of all isolates by enterobacterial repetitive intergenic consensus PCR and pulsed-field gel electrophoresis.

Of 517 ESBL-producing *E coli* isolates collected, 106 (21%) were *mcr-1* positive. Notably, the oldest *mcr-1*-positive *E coli* isolate had been collected in 2005. The 106 *mcr-1*-positive *E coli* isolates originated from different individuals located in 94 widely distant farms, and they were clonally unrelated.

Sequencing of the whole *mcr-1* gene in 75 *mcr-1*-positive isolates revealed a 100% identity compared with the original sequence. Co-occurrence of the *mcr-1* and *ESBL* genes was identified in a subset of seven isolates, with *mcr-1* and $bla_{CTX\text{-}M\text{-}1}$ being found on a large and conjugative IncHI2-type plasmid together with genes conferring resistance to sulfonamides and tetracyclines, two antibiotics widely used in veterinary medicine.

These findings demonstrate a colocation of the *mcr-1* gene along with an *ESBL* gene on a single plasmid, and additional studies are needed to clarify the diversity of the plasmid backbones spreading these two genes within our collection. Noticeably, the prevalence of the *mcr-1* gene among ESBL producers in veal calves was much higher than that found in ESBL-positive *E coli* isolates in human beings and chicken meat reported in Denmark.[2] This difference may reflect a major spread of the *mcr-1* gene in European live animals. We showed that the dissemination of *mcr-1*, at least in France, had already occurred more than a decade ago, with one *E coli* isolate collected in 2005 identified as *mcr-1* positive.

Altogether, available data reveal the occurrence of *mcr-1* among different animals and human contexts over time.[1–3] Worryingly, we show that selection pressure with broad-spectrum cephalosporins may select for colistin resistance and vice-versa, further highlighting the likelihood of a pandemic spread of *mcr-1*. Of note, the substantial use of tetracyclines and sulfonamides in animals might also substantially contribute to the dissemination of *mcr-1* plasmids.

In a one-health perspective, and considering the renewed importance of colistin in human medicine, our data and those from others underscore the urgent need to limit the spread of *mcr-1*-positive plasmids by reconsidering the massive use of colistin in veterinary medicine worldwide.

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