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Short Communication

No genetic link between *E. coli* isolates carrying *mcr-1* in bovines and humans in France [☆]Marisa Haenni^{a,*}, Pierre Châtre^a, Racha Beyrouthy^b, Antoine Drapeau^a, Pauline François^a, Jean-Yves Madec^a, Richard Bonnet^{b,c}^a ANSES – Université de Lyon, Unité Antibiorésistance et Virulence Bactériennes, Lyon, France^b Institut National de la Santé et de la Recherche Médicale (UMR 1071), Institut National de la Recherche Agronomique (USC-2018), Université Clermont Auvergne, Clermont-Ferrand, France^c Centre National de Référence de la Résistance aux Antibiotiques, Centre Hospitalier Universitaire, Clermont-Ferrand, France

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ABSTRACT

Background: Colistin is a last-line antibiotic used to treat severe human infections caused by carbapenemase-producing Gram-negative bacteria. In parallel, colistin has massively been used in the veterinary field so that *mcr-1*-positive *E. coli* have spread worldwide in livestock, potentially constituting a reservoir of colistin-resistant isolates that can be further transmitted to humans.

Objectives: In France, the *mcr-1* gene was frequently identified in *E. coli* of bovine origin. This genomic study assessed whether French human *mcr-1*-positive *E. coli* might originate or derive from the bovine reservoir.

Material and methods: Human ($n = 24$) and bovine ($n = 127$) isolates collected between 2011 and 2019 were included and colistin-resistance was confirmed by MICs. The detection of *mcr-1* was performed by PCR. Isolates were short-read whole-genome sequenced and a cgMLST-based phylogeny was constructed. The genetic support of *mcr-1* was identified using short-read sequences or Southern blots.

Results: The *mcr-1* gene was carried by a high diversity of genetic backgrounds, among which ST167 and ST10 were the most widespread. No clonally-related isolates between bovines and humans were observed. In bovines, *mcr-1* was identified on IncHI2 and IncX4 plasmids and increasingly on the chromosome, while it was also found on IncI2 and pO111 plasmids in humans.

Conclusion: Although similar STs (ST744 and ST88) and plasmid types (IncHI2, IncX4) carried *mcr-1*, no hypothesis of a transfer from bovines to humans could be supported by the data. Furthermore, the increasing chromosomal location of *mcr-1* over time may reflect an animal-specific evolutionary pathway deserving further investigation.

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1. Introduction

Colistin has been used since the 1960s to treat food-producing animals, in contrast to a limited usage in human medicine until the 1990s due to severe nephro- and neuro-toxic adverse effects and physicochemical and pharmacological issues. During these years,

an increasing proportion of colistin resistance genes went mostly unnoticed since only chromosomal modifications such as *mgrB* inactivation in *Klebsiella pneumoniae* had been reported. The situation has changed in clinical settings in the last two decades, where colistin has become a therapeutic alternative for infections caused by multidrug-resistant Gram-negative pathogens, particularly those resistant to carbapenems, fluoroquinolones, and aminoglycosides. In 2015, Liu et al. reported the first plasmid-borne gene, called *mcr-1*, which conferred colistin-resistance [1]. This study shed light on the risk that colistin resistance genes could massively spread from animals to humans and led the path to hundreds of other publications, which reported the occurrence of *mcr* genes in En-

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* Corresponding author. Mailing address: Marisa Haenni, ANSES – Université de Lyon, Unité Antibiorésistance et Virulence Bactériennes, 31 Avenue Tony Garnier, 69007 Lyon, France.

E-mail address: marisa.haenni@anses.fr (M. Haenni).

terobacterales worldwide. It is known now that *mcr-1*-positive isolates date back to 1980 and originate from multiple sectors (environment, food, and food-producing animals, humans), making this question an example of One Health problematics [2].

Today, ten *mcr* genes (*mcr-1* to *mcr-10*) and numerous variants have been described, but *mcr-1* remains the most widespread colistin-resistance gene in *Escherichia coli*. The main sequence types (STs) in which *mcr-1* was reported were ST10, ST156, ST101, ST117, and ST6453 [3]. The *mcr-1* gene was mainly located on IncI2 (particularly in Asia), IncHI2, and IncX4 plasmids [4] but also recurrently reported on the chromosome [5,6]. The plasmids' high transfer capacity has facilitated the horizontal dissemination of *mcr-1*, including between isolates from different sectors. Following the discovery of the *mcr-1* gene, and given the extent of its dissemination, international organizations and agencies, as well as more regional authorities, strictly restricted or even banned the use of colistin in animals, leading to a decrease in the last years of the proportion of *mcr-1*-carrying Enterobacterales [7].

The proportion of *mcr-1*-positive *E. coli* in humans is still low in Europe (0.15–3.8%) and decreasing, as proved for example in Italy [8]. Nevertheless, *mcr-1* genes still circulate in animals and a few studies suggested that *mcr-1*-carrying isolates could be shared between companion animals and humans [9], or transmitted from poultry or pig to humans [10,11]. In France, compared to others, the bovine sector is the one where *mcr-1*-positive *E. coli* were abundantly reported [12,13]. Consequently, our study aimed to investigate *mcr-1*-positive *E. coli* from bovines and humans in France in the same timeframe and infer any possible genetic similarities between both using whole-genome sequencing.

2. Materials and methods

2.1. Sampling and determination of the colistin MICs

Between 2011 and 2019, 151 *E. coli* isolates carrying the *mcr-1* gene were collected from bovines ($n = 127$) through the antimicrobial resistance surveillance Resapath network (<https://resapath.anses.fr/>) and from humans ($n = 24$) by the National Reference Centre for antimicrobial resistance (Table S1). All isolates were identified by MALDI-TOF, and the presence of the *mcr-1* gene was confirmed by PCR [1]. MICs were determined by broth microdilution, according to the European Committee for Antimicrobial Susceptibility Testing (EUCAST).

2.2. Whole genome sequencing using short-read illumina

For animal isolates, DNA was extracted using the NucleoSpin Microbial DNA extraction kit (Macherey-Nagel, Hoerd, France) according to the manufacturer's instructions. Library preparation (Nextera XT technology) and sequencing (NovaSeq-6000 instrument) were outsourced (Eurofins, Germany). For human isolates, DNA was extracted with a DNeasy UltraClean Microbial kit (Qiagen). The libraries were prepared with a Nextera XT Kit (Illumina, San Diego, CA, USA) and paired-end sequenced by the Illumina MiSeq (2×301 -base pair (bp)) or NextSeq (2×151 bp) systems. After sequencing, the reads were quality trimmed and *de novo* assembled using Shovill v1.0.4, and the quality of assemblies was assessed using QUAST v5.0.2. The average sequencing depth was systematically $\geq 60 \times$ (between 61x and 306x); the number of assembled contigs ranged between 60 and 319 (median 213), and genome sizes between 4810,527 and 5793,574 nucleotides.

STs were determined using the CGE online tool MLST v2.0.4 (<http://www.genomicepidemiology.org/>), while resistance genes and replicon content were inferred using ABRicate v1.0.1 (<https://github.com/tseemann/abricate>). Virulence factors were identified using the VirFinder 2.0 from the CGE.

2.3. Phylogenetic analysis

The cg-MLST phylogeny was determined through the pyMLST pipeline (<https://github.com/bvalot/pyMLST>) using the scheme available on the www.cgmlst.org/ncs, which comprised 2513 alleles for *E. coli* (for allelic matrix, see Table S2). The cut-off for highly related strains was ≤ 10 allelic differences. The resulting tree was visualized using iTol v6 (<http://itol.embl.de/itol.cgi>), and SVG files were processed using Inkscape v1.0 to guarantee the quality of the figures.

2.4. Characterization of the resistance genes and genetic supports

The plasmid content was determined from the WGS data using PlasmidFinder 2.0.1 (<http://www.genomicepidemiology.org/>). Plasmids carrying the *mcr-1* gene were assembled *in silico* when the *mcr-1* gene was located on the same contig as the replicon marker. When *in silico* data showed no co-occurrence on the same contig, plasmids carrying the *mcr-1* gene were detected using S1-PFGE gels followed by Southern blot using adequate probes as previously described [14]. When plasmid location could not be evidenced, the chromosomal location was looked for by PFGE on *I-Ceu1*-digested DNA, followed by Southern blot hybridization using a 16S rDNA probe and adequate probes.

The genetic environment of the *mcr-1* gene was assessed in all isolates where *mcr-1* was carried on a contig larger than 10°000 bp. All corresponding contigs were annotated using the online Bakta tool (Software 1.9.1, DB 5.0.0).

2.5. Statistics

The normality of the MIC distributions depending on the genetic support of the *mcr-1* gene was analyzed using a Shapiro Wilk normality test (significant if p -value < 0.05). Pairwise comparisons were performed using the Wilcoxon rank sum test with false discovery rate (FDR) correction (significant if p -value < 0.05).

2.6. Accession number

The project was deposited in the NCBI database under the Bio-Project accession numbers PRJNA1166088 (for bovine isolates) and PRJNA1172986 (for human isolates).

3. Results

3.1. Colistin-resistance and additional resistance phenotypes

The 127 bovine isolates, mostly from diarrheic calves ($n = 103$), originated from all over France and were collected in 2011–2018, with a peak in 2015–2017 ($n = 93$) (Table S1, Fig. 1), while the 24 human isolates were collected in 2015–2019 predominately from digestive ($n = 10$) and urinary ($n = 9$) samples from all over France (notably from the Auvergne-Rhône-Alpes, Hauts-de-France and Île-de-France regions). One bovine ST101 isolate carried the *stx1* gene, and one human ST6448 isolate displayed the *cdt-III/cnf2* genes.

All isolates displayed the *mcr-1.1* gene, except one human isolate displaying the *mcr-1.2* gene, and four bovine isolates additionally carried the *mcr-3.2* gene (together with the *bla_{CTX-M-55}* gene). MICs to colistin ranged between 2 and 32 mg/L.

Carbapenemase genes (three *bla_{OXA-48}* and one *bla_{NDM-1}*) were identified only in four human isolates. In contrast, ESBL-encoding genes were present in 15 human strains (62.5 %, with notably *bla_{CTX-M-15}* ($n = 4$), *bla_{CTX-M-1}* ($n = 2$) and *bla_{SHV-12}* ($n = 3$)) and 53 bovine isolates (41.7 %, mostly identified as *bla_{CTX-M-1}* ($n = 24$) and *bla_{CTX-M-14}* ($n = 18$)) (Fig. 1). All isolates were multidrug-resistant, except the human *mcr-1.2*-carrying isolate that presented

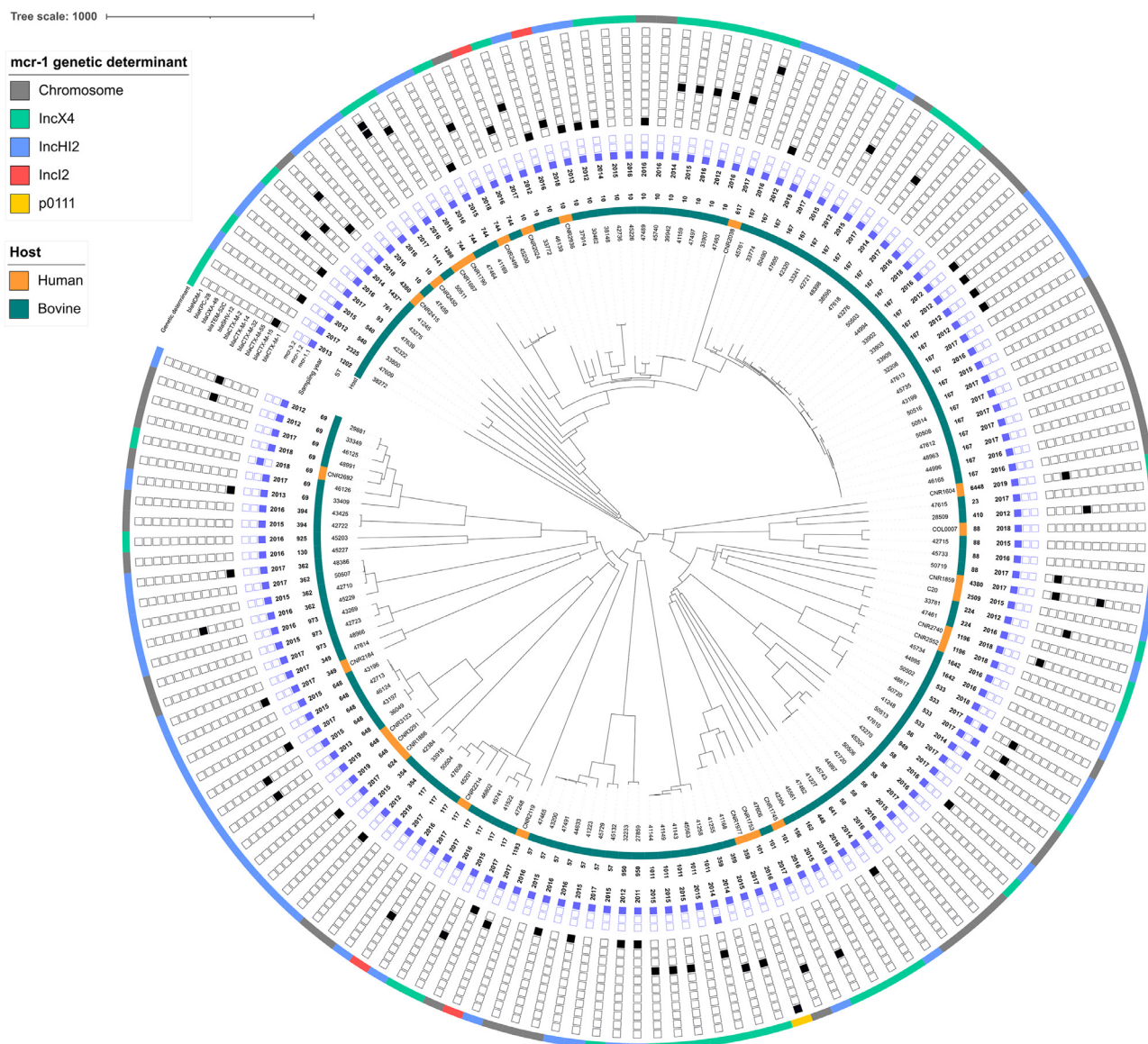


Fig. 1. cg-MLST-based phylogeny of all *mcr-1*-positive *E. coli* isolates collected from humans and bovines. The presence of the *mcr*, *bla*_{ESBL}, and carbapenemase genes are indicated by filled rectangles.

no additional resistance gene. Diverse resistance genes to non-beta-lactam antibiotics were identified (Table S1), including multiple genes conferring resistance to aminoglycosides (147/151 isolates), sulfonamides ($n = 145$, with the frequent *sul1/sul2* association), tetracyclines ($n = 143$, mostly *tet(A)*), or trimethoprim ($n = 130$, mostly *dfrA1*). Mutations conferring fluoroquinolone resistance were also identified in 92 isolates.

3.2. Genetic diversity among *E. coli* isolates

A high genetic diversity was observed, with the identification of 46 STs (Table 1). The ST167 ($n = 27/151$, 17.9%) and ST10 ($n = 18/151$, 11.9%) that belong to the same ST clonal complex 10 were the most frequently identified STs. 23 STs ($n = 23/46$, 50%) were singletons.

Nine STs were shared between human and bovine isolates, but only three (ST10, ST648, and ST744) were found in more than one occurrence in both hosts. Human and bovine isolates belonging to ST744 (encompassing two human and three animal isolates) and ST88 (one human and three animal isolates) were the most closely

related isolates from human and animal sectors with 55 to 75 allelic differences but cannot be considered as clonally related (Table S2). In contrast, bovine isolates of ST10, ST57, ST58, ST69, ST369, ST394, ST553, ST648 and ST1011 differed by less than 10 alleles and, in ST648, two human isolates also differed by only 3 alleles. In all cases in which metadata was available, the isolates came from different districts or were sampled in different years, suggesting an absence of cross-transmissions.

3.3. Genetic determinant carrying the *mcr-1* gene

In animals, the *mcr-1.1* gene was located either on the chromosome ($n = 40$) or on the IncHI2 ($n = 51$) and IncX4 ($n = 36$) plasmids. In humans, the genetic determinants were more diverse, with *mcr-1* carried on the chromosome ($n = 2$) as well as on the following plasmids: IncX4 ($n = 9$, including the *mcr-1.2* gene), IncHI2 ($n = 8$), IncI2 ($n = 4$), and p0111 ($n = 1$). Over the years, the proportion of genes on the chromosome increased, while the proportion of *mcr-1* carried on the IncHI2 and IncX4 plasmids decreased (Fig. 2). Among the 15 STs identified in at least three

Table 1
Distribution of STs between isolates of human or animal origin.

STs	Humans	Animals	Total
10	3	15	18
23	0	1	1
48	1	0	1
56	0	1	1
57	0	7	7
58	0	6	6
69	1	6	7
88	1	3	4
93	0	1	1
101	2	1	3
117	1	7	8
130	0	1	1
156	0	1	1
162	0	1	1
167	0	27	27
224	0	2	2
349	1	1	2
354	0	2	2
359	1	2	3
362	0	4	4
394	0	2	2
410	0	1	1
448	0	1	1
533	0	4	4
540	0	2	2
617	1	0	1
624	1	0	1
641	0	1	1
648	2	5	7
744	2	3	5
761	0	1	1
925	0	1	1
949	0	1	1
950	0	2	2
973	0	3	3
1011	0	5	5
1141	0	1	1
1193	1	0	1
1196	2	0	2
1202	0	1	1
1288	1	0	1
1437*	0	1	1
1642	0	2	2
2325	0	1	1
2509	1	0	1
4380	1	0	1
6844	1	0	1
Total	24	127	151

Grey boxes indicate STs that are specific to one host.

Blue boxes indicate shared STs between humans and animals.

*: unassigned ST (ST1437 is the nearest match, with *icd1462* in ST1437*, instead of *icd8* in ST1437).

isolates, 12 presented the *mcr-1* gene on different genetic determinants. At the same time, only three were strictly associated with one element, i.e., ST1011 ($n = 4$) associated with IncX4 and ST648 ($n = 7$) and ST362 ($n = 4$) associated with IncHI2.

The genetic environment of the *mcr-1* gene diverged depending on the genetic determinant on which it was carried. When carried on IncX4 plasmids, the *mcr-1* gene was mainly ($n = 12$) found in the DUF2806-*mcr-1*-*pap2*-DUF2776 environment, while it was usually ($n = 6$) surrounded by the upstream IS*Apl1* and the downstream *pap2* gene when located on IncHI2 plasmids. The genetic environments found on the IncI2 and p0111 plasmids were *mbeA-mcr-1-pap2-ydaA* and IS*Apl1-mcr-1-pap2-IS5* family. Finally, when inserted in the chromosome, the genetic environment was diverse

but characterized by the absence of the IS*Apl1* element and the presence of the *pap2* gene.

4. Discussion

This study on *mcr-1*-producing *E. coli* collected from 127 bovines and 24 humans is the largest reported on *mcr*-mediated colistin resistance in France. Moreover, from a One Health perspective, this study is particularly relevant since it spanned over the whole period (2011–2019) where *mcr-1* genes were particularly abundant in livestock. Since then, measures have been taken at diverse national and international levels to restrict the use of colistin in animals [15], initiating a decrease in colistin resistance

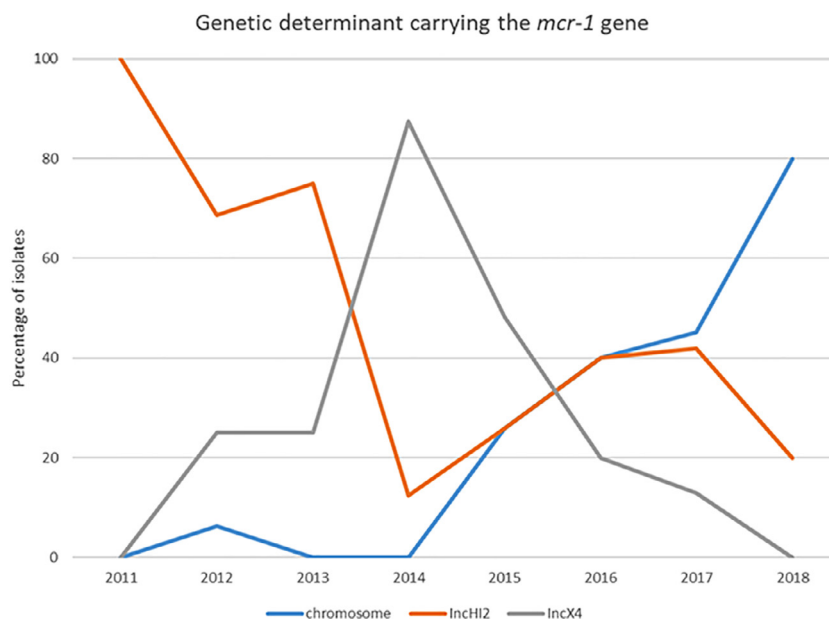


Fig. 2. Proportion over the years of isolates in which the *mcr-1* gene was carried on IncHI2 or IncX4 plasmids or on the chromosome.

(<https://shiny-public.anses.fr/ENresapath2/>) [7]. However, the exact impact of such restrictions would need further investigations since, as shown here, *mcr-1*-positive *E. coli* are generally multidrug-resistant so that co-selection of colistin resistance through the use of non-colistin antibiotics most probably still occurs, as well as a mild persistence via the improved intestinal fitness provided by *mcr-1* [16].

Many STs were identified, among which three shared by both humans and animals (ST10, ST101, and ST117) were reported among the major clones carrying *mcr-1* at a global scale [3]. In our study, ST167 was the most widespread *mcr-1*-carrying clone in bovines, found over different years and across different districts, and associated or not with ESBL-encoding genes. In France, ST167 is not among the main clone identified in *mcr-1*-negative *E. coli* from bovines (personal communication, M. Haenni), which makes its overrepresentation among *mcr-1*-positive *E. coli* puzzling. Nevertheless, this ST was identified as globally dominant, also among the increasing clones carrying the *bla*_{NDM-5} gene [17] so that potential transmission between animals and humans has been suggested [18]. In this study, despite its frequent occurrence in bovines, ST167 was not identified in human isolates.

We identified nine shared STs between humans and bovines, including ST167. In only two cases (ST744 and ST88), the number of alleles differing between genomes was around 50. This indicates some similarities between these isolates but does not support any clonal link, especially since the analysis was performed on the core genomes and not using a SNP-phylogeny.

The genetic determinants of *mcr-1*-positive *E. coli* in bovines were IncHI2, the chromosome, and IncX4 in their order of importance. While IncHI2 and IncX4 plasmids have consistently been reported as preferential vectors of the *mcr-1* gene, chromosomal insertions seem more recent but on an increasing trend constituting a notifiable outcome of this study. Overall, the strains harboring the *mcr-1* gene on IncHI2 plasmids were associated with higher MIC values than those harboring the *mcr-1* gene on IncX4 plasmids or on the chromosome (median: 6 versus 4 and 4 µg/ml; mean: 6,3 versus 6,1 and 5,8 µg/ml), but differences were not significant. It was also shown that the presence of *mcr-1* impairs bacterial regrowth after a period of starvation [19]; whether the chromosomal

location of the gene might potentially help regulating the MCR-1 expression and prevent its toxicity is a hypothesis that remains to be tested. In France, chromosomally-carried *mcr-1* genes were already reported in 32.2 % of goat isolates, and the systematic presence of the IS*ApI1* element (either upstream or surrounding the *mcr-1/pap2* genes) ensured its transferability between different genetic backgrounds [6]. Here, no IS*ApI1* element was found around the chromosomally-encoded *mcr-1* genes, potentially favouring its stabilization in non-selective conditions, as has been hypothesized for IncX4 plasmids in which IS*ApI1* is usually absent [20]. Such a chromosomal insertion was also observed in two human isolates in this study, and *mcr-1* was also found on IncI2 ($n = 4$) and pO111 ($n = 1$) plasmids, which have never been reported in bovines in France.

In conclusion, the data provided here highlight that *mcr-1*-positive *E. coli* isolates sharing similarities (same ST, same genetic determinants) are circulating in both bovines and humans in France. Still, they do not support the hypothesis of *mcr-1* transmission events from one host to the other. In all, considering the present genomic data on the most extensive possible collection of *mcr*-positive isolates in France, the low and decreasing prevalence of *mcr* genes in both sectors and the strong restriction use of colistin in farm animals, a shallow risk of supplying humans with *mcr-1*-positive *E. coli* isolates from animals in our country can be most likely anticipated. Nonetheless, new dynamics of the *mcr-1* gene, possibly located on still unidentified and highly transferable plasmid backbones, cannot be ruled out. Also, the co-transfer of *mcr* genes with other resistance genes through selective forces other than colistin use remains plausible. Finally, this study has investigated the relationship between the main current animal reservoir of *mcr* genes in France (bovines) and humans. Still, evolutions in the *mcr* epidemiology in other sectors, such as poultry or the environment, should also be investigated.

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Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval

No ethical approval was needed since samples were sent to veterinary for diagnostic purposes.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jgar.2024.12.021](https://doi.org/10.1016/j.jgar.2024.12.021).

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