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Marisa Haenni, Véronique Métayer, Emilie Gay, Jean-Yves Madec. Increasing Trends in Prevalence among Extended-Spectrum- β -Lactamase-Producing *Escherichia coli* Isolates from French Calves despite Decreasing Exposure to Colistin. *Antimicrobial Agents and Chemotherapy*, 2016, 60 (10), pp.6433-6434. 10.1128/AAC.01147-16 . anses-04018219

HAL Id: anses-04018219

<https://anses.hal.science/anses-04018219v1>

Submitted on 7 Mar 2023

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Increasing Trends in *mcr-1* Prevalence among Extended-Spectrum- β -Lactamase-Producing *Escherichia coli* Isolates from French Calves despite Decreasing Exposure to Colistin

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Since the first description of the plasmid-mediated colistin resistance gene (*mcr-1*), over 30 follow-up reports have proved the worldwide geographical distribution of this gene (1, 2). The overall picture indicates a very low prevalence in animals, human beings, and retail food, with two exceptions, the first in China, where *mcr-1* carriage was observed in 21% and 15% of the animals and raw meat samples, and the second in France, where 21% of the extended-spectrum- β -lactamase (ESBL)-producing *Escherichia coli* isolates from calves were *mcr-1* positive (1, 3).

Accepted manuscript posted online 8 August 2016

Citation Haenni M, Métayer V, Gay E, Madec J-Y. 2016. Increasing trends in *mcr-1* prevalence among extended-spectrum- β -lactamase-producing *Escherichia coli* isolates from French calves despite decreasing exposure to colistin. Antimicrob Agents Chemother 60:6433–6434. doi:10.1128/AAC.01147-16.

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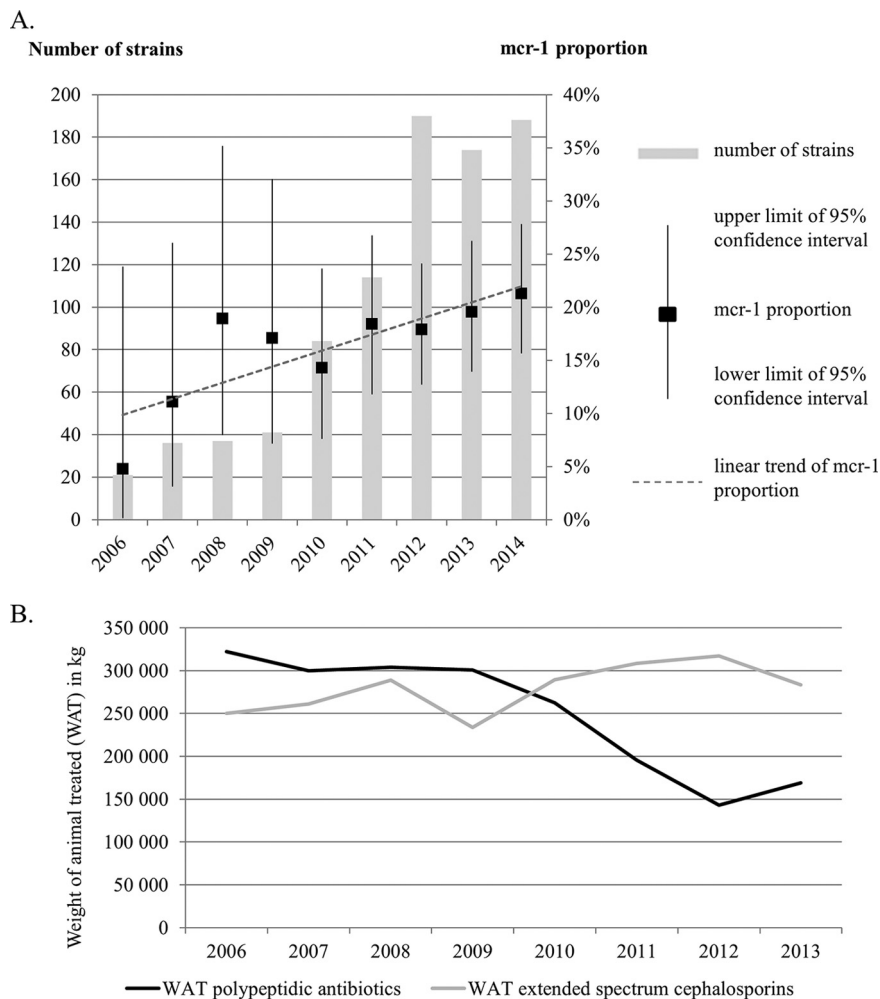


FIG 1 (A) Proportion of *mcr-1*-positive *E. coli* strains among ESBL-producing *E. coli* isolates from French calves and linear trend of the evolution between 2006 and 2014. Upper and lower limits of confidence intervals at 95% of the *mcr-1* proportion are shown. (B) Trends in weights of animals treated (WAT) (bovines) with polypeptidic antibiotics (almost exclusively represented by colistin) or extended-spectrum cephalosporins.

To date, only one study from China has provided dynamic information on the prevalence of the *mcr-1* gene (4). The earliest *mcr-1*-positive *E. coli* isolate from chickens was identified in the 1980s, and a dramatic rise in *mcr-1* prevalence was highlighted over the past 6 years (from 5.2% in 2009 to 30% in 2014) (4). Here, we provide annual figures of the proportion of *mcr-1* among ESBL-producing *E. coli* isolates from French calves from 2006 to 2014. Using the recently published *mcr-1*-specific primers (1), we retrospectively screened our collection of 885 nonduplicate ESBL-producing *E. coli* isolates collected through the long-term French monitoring program Resapath (www.resapath.anses.fr). All isolates were obtained from different individuals and farms and mostly presented differing pulsed-field gel electrophoresis profiles.

As shown in Fig. 1A, the proportion of *mcr-1*-positive *E. coli* strains among ESBL-producing *E. coli* isolates increased from 4.76% in 2006 to 21.28% in 2014. This corresponded to an increase from 1 *mcr-1*-positive strain recovered in 2006 to 37 in 2014. The proportion of *mcr-1*-positive strains increased until 2014, with an estimated rise of 1.28% per year (chi-square test for linear trend, $P = 0.038$). The number of strains tested from 2006 to 2009 was low due to the still limited number of ESBL-producing *E. coli* strains in bovines. Therefore, the confidence intervals of the proportions of *mcr-1*-positive *E. coli* strains among ESBL-producing *E. coli* isolates are wide, but the results of tests for linear trend, which take such variability into account, are statistically significant. Interestingly enough, the 2006–2007 period, which was seemingly a starting point of this rising trend, came shortly after the first reports of ESBL-producing *E. coli* in bovines in France (5). Taking the data together, the increasing *mcr-1* prevalence among ESBL-producing *E. coli* strains clearly differs from the low *mcr-1* prevalences in non-ESBL-producing *E. coli* strains, which stand at around 1.0% in healthy calves (M. Haenni, unpublished data), 0.5% in pigs, 1.8% in broilers, and 5.9% in turkeys (6). This suggests that the use of extended-spectrum cephalosporins may have simultaneously favored the spread of *mcr-1*. This hypothesis is also supported by previous data demonstrating the colocalization in *E. coli* of *mcr-1* and *bla*_{ESBL} genes on a unique IncHI2/ST4 plasmid in French calves (3, 7).

In terms of usage, it was not possible to retrospectively trace the individual treatments, either with colistin or cephalosporins, of the *mcr-1*-positive calves, and this is a limitation of the study. However, as reported in the 2013 sales survey of veterinary medicinal products containing antimicrobials in France (<https://www.anses.fr/en/content/monitoring-sales-veterinary-antimicrobials>), the global exposure of bovines to polypeptidic antibiotics (almost exclusively represented by calves orally treated with colistin) decreased by 52.4% between 2005 and 2013 (Fig. 1B). In contrast, during the same period, the global exposure of bovines to extended-spectrum cephalosporins was constantly high (Fig. 1B) (<https://www.anses.fr/en/content/monitoring-sales-veterinary-antimicrobials>), with the main ESBL reservoir in bovines being found also in calves, as previously reported (8).

Shen et al. attributed the rise in *mcr-1* prevalence in China to a parallel increased use of colistin in food animals (4). In line with recent data on *mcr-1* in Brazilian poultry not exposed to polymyxins (9), our data strongly indicate driving forces for the spread of

mcr-1 other than the use of colistin only, notably operating through the use of extended-spectrum cephalosporins. This reinforces the idea of the need for global intervention programs on the prudent use of all antibiotics in the Agri-Food sector worldwide, beyond the very recent advice of the European Medicine Agency focused on colistin use in food animals (10).

ACKNOWLEDGMENTS

We deeply acknowledge all peripheral laboratories of the Resapath network.

We declare that we have no conflicts of interest.

This study was supported by the Agency for Food, Environmental and Occupational Health and Safety (ANSES) and by a grant of the ANIWHIA ERA-NET project (France).

FUNDING INFORMATION

This work, including the efforts of Marisa Haenni, Véronique Métayer, Emilie Gay, and Jean-Yves Madec, was funded by the Agency for Food, Environmental and Occupational Health and Safety (ANSES). This work, including the efforts of Marisa Haenni, Véronique Métayer, and Jean-Yves Madec, was funded by the ANIWHIA ERA-NET project (France).

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