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Colistin use and colistin resistance in bacteria from animals

Isabelle Kempf *, Eric Jouy, Claire Chauvin

Ploufragan-Plouzané Laboratory, ANSES (French Agency for Food, Environmental and Occupational Health & Safety), Université Bretagne Loire, Ploufragan, France

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ABSTRACT

Colistin has been used in veterinary medicine for decades, mainly for the prevention and treatment of Enterobacteriaceae infections. However, data regarding colistin resistance in bacteria from animals and food of animal origin are relatively scarce, partly because there are methodological difficulties hampering the analysis of susceptibility to colistin. Most data regarding clinical isolates are related to enteropathogenic *Escherichia coli* and *Salmonella*. The resistance percentages are sometimes high for pathogenic strains, and the *mcr-1* gene has been detected in pathogenic *E. coli* isolates from pigs, cattle and poultry in different countries. The prevalence of colistin resistance in *Salmonella* from healthy animals is usually low but depends on the proportion of intrinsically colistin-resistant serotypes. For indicator *E. coli*, the resistance levels are often very low, although higher levels have been observed in Asia. The *mcr-1* gene has been detected in indicator *E. coli* from pigs, cattle, poultry and their products. Thus, there is an urgent need to re-assess the use of colistin in livestock throughout the world to ensure a global strategy for preserving this last-resort antimicrobial.

1. Introduction

Colistin, also known as polymyxin E, belongs to the polymyxin class of antibiotics, which also includes polymyxin B. Colistin is a cyclic decapeptide bound to a fatty acid chain and is active against many Gram-negative bacteria. Colistin has been used for decades in veterinary medicine. More recently, interest in colistin for human medicine has been renewed because it is now a last-resort drug to treat infections in patients with cystic fibrosis or infections caused by multidrug-resistant bacteria. The plasmid-mediated *mcr-1* colistin resistance gene constitutes a new threat due to the transferability of colistin resistance between bacterial strains and species. This is the context of this brief review of colistin use and resistance prevalence in animals from different countries. Relevant scientific articles were sought using the keywords colistin, resistance, resistant, *mcr-1*, animals, pig, swine, poultry, chicken, broiler, calf or cattle in PubMed and Scopus databases and via the main Web search engines in both French and English so that theses and national reports regarding antimicrobial usage and resistance monitoring could also be checked and consulted (http://www.crl-ar.eu/206-monitoring_reports.htm). Searches were performed from January to mid-April 2016. Usage references were published from 2000, although all but one resistance references were published after 2010. References were downloaded to EndNote.

2. Colistin usage

Colistin (ATCvet codes QJ01XB and QJ51XB) has been used in veterinary medicine for decades and is still administered on all continents (Fig. 1). Used as a growth promotant in certain countries such as China [1], India [2], Japan [3] and Vietnam [4], colistin can be administered alone or in combination orally, topically (as eye or ear drops), by injection or via the intramammary route. It can also be used to treat all terrestrial and aquatic animal species.

The main indications for colistin are the prevention and treatment of Enterobacteriaceae infections. In pig production, usage is therefore mainly related to the treatment of digestive disorders [39], as observed in all species within Europe, where polymyxins have represented 30% of practitioners' responses to diarrhoea [5].

Colistin usage is widespread (Fig. 1). Despite the non-representativeness of certain studies and the lack of harmonisation in the quantification of antimicrobial usage (Table 1), colistin usage has proved frequent in most reporting countries, with high percentages of users or prescribers. A harmonised quantification methodology [6] recently revealed wide variations, even between European countries.

3. Prevalence and occurrence of colistin resistance

3.1. Methodological difficulties

Data regarding colistin resistance in bacteria from animals and food of animal origin are relatively scarce. It was not until 2014, for example, that colistin was included in the Enterobacteriaceae

* Corresponding author. Ploufragan-Plouzané Laboratory, ANSES (French Agency for Food, Environmental and Occupational Health & Safety), Université Bretagne Loire, Ploufragan, France. Fax: 33 2 96 01 62 73.
E-mail address: isabelle.kempf@anses.fr (I. Kempf).

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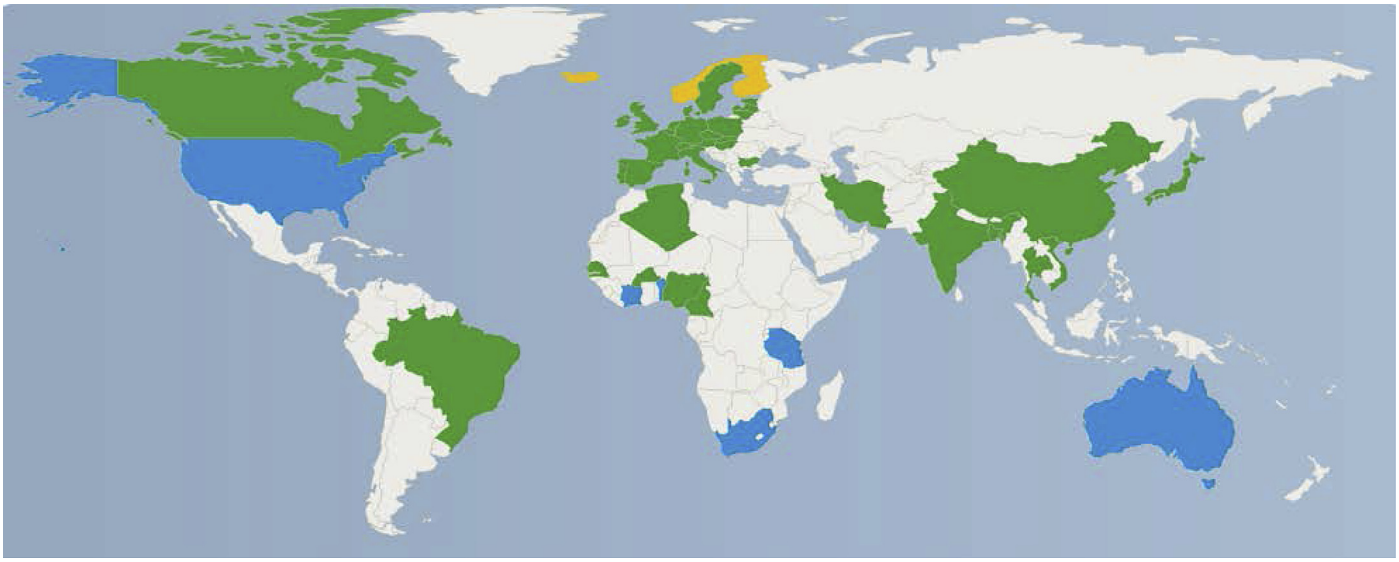

Fig. 1. Countries where usage of colistin (green) or polymyxins (blue) has been reported in farm animals [1–38]. For three European countries (yellow), no polymyxin/colistin sales were reported [7]. For other countries (white), no information on antimicrobial usage or colistin/polymyxin usage in farm animals was found.

mandatory antimicrobial panel of the European surveillance of bacteria of animal origin (Commission Implementing Decision 2013/652/EU) and, to our knowledge, polypeptides were not considered in the antimicrobial resistance monitoring schemes of many other countries until quite recently. Several reasons may be advanced to explain this situation. First, the absence or limited use of colistin in either humans or animals in many countries probably played a role in the exclusion of polypeptides in epidemiological studies and surveillance systems of bacteria of animal origin in these countries. Next, the fact that colistin resistance was thought to be limited in Enterobacteriaceae (which are the main indicators of resistance in Gram-negative bacteria) and, up to the end of 2015 [1], was only caused by chromosomal mutations probably led veterinarians and scientists to hypothesise that clonal expansion of a colistin-resistant (CST-R) isolate or co-selection of colistin resistance by other antimicrobials were rare, and finally to neglect colistin resistance surveillance. However, the increasing role of colistin in humans as a last-resort antimicrobial has prompted more accurate and careful monitoring of resistance to this polypeptide.

Methodological difficulties have also hampered the analysis of bacterial susceptibility to colistin, a cyclic decapeptide bound to a fatty acid chain that does not therefore diffuse well in agar. Consequently, the inhibition zones (IZs) around the colistin disk are small, making it difficult to differentiate colistin-susceptible from CST-R strains. Colistin also binds to plastic panels, which results in uncertainties on the active concentration in the medium. The use of surfactants to lessen this adhesion through broth microdilution (BMD) has been proposed, but the need for a reliable, standardised method continues to be emphasised [45]. Finally, Agersø et al. [46] have reported the distribution of colistin minimum inhibitory concentrations (MICs) for several thousands of *Salmonella* isolates belonging to different serotypes, showing that *Salmonella enterica* serotype Dublin and *S. enterica* serotype Enteritidis isolates had higher colistin MICs than other *Salmonella* serotypes, such as *S. enterica* serotype Typhimurium. As the epidemiological cut-off value of 2 mg/L proposed by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for *Salmonella* (and *Escherichia coli*) is within the MIC distributions of *S.* Dublin and *S.* Enteritidis, a high percentage of *S.* Dublin isolates, and to a lesser extent *S.* Enteritidis isolates, are classified as CST-R. The prevalence of colistin resistance in *Salmonella* must therefore be examined in relation to the proportions of intrinsically CST-R serotypes in the tested isolates.

3.2. Salmonella

Data regarding colistin resistance in *Salmonella* are presented in Table 2. Few data concern isolates from clinical animal cases, but certain studies based on disk diffusion (DD) report alarming ratios of CST-R isolates [58,60]. However, colistin resistance appears relatively limited in *Salmonella* from healthy pigs in Europe and Japan, with a maximum of 6.3% of CST-R strains [47–52]. Worryingly, a CST-R *Salmonella* isolated from a pig was also resistant to ampicillin, cefotaxime, chloramphenicol, gentamicin, tetracycline and trimethoprim/sulfamethoxazole [47]. Higher levels of resistance are sometimes observed in other countries [53]. Few data are available on cattle: no *Salmonella* from healthy cattle in Japan had an MIC > 8 mg/L [51], whilst a Swedish report mentions 5% CST-R *Salmonella* out of 77 *Salmonella* isolates mainly from cattle, but including cats and wild animals, a high proportion of which were identified as *S.* Typhimurium (43/77). The percentages vary in isolates obtained from chickens or chicken products: no resistance was detected using DD in 111 *Salmonella* strains in Iran [57], whilst in Japan no isolate from chickens had an MIC >8 mg/L [51]. The resistance percentage increased to 5.5% for 673 isolates from broiler meat in Europe studied by BMD in the framework of European monitoring in 2014 according to Decision 2013/652/EU. Colistin resistance was as high as 31.6% for 76 *S.* Enteritidis isolates, but 0/147 for *S. enterica* serotype Infantis and only 1/69 for *S.* Indiana. For isolates from broilers, the resistance rate was 7.6% but varied markedly between member states and serotypes tested: 40.4% of *S.* Enteritidis strains were CST-R but the levels of resistance were much lower for *S. enterica* serotype Kentucky and *S.* Infantis. Similarly, the quite high level of resistance found among 792 isolates from laying hens (10.5%) could be related to the sizeable proportion of *S.* Enteritidis (210/792). Thus, as underlined in the European report [55], 72% and 80% of CST-R isolates from, respectively, broilers and layers involved *S.* Enteritidis, a serovar that is intrinsically CST-R at higher levels than others. The percentage of resistance for 726 isolates from turkeys in nine member states was limited (1.8%) [55].