



Letter to the Editor

On a collision course: The availability and use of colistin-containing drugs in human therapeutics and food-animal farming in Lebanon


Sir,

The emergence and dissemination of plasmid-borne mobile colistin resistance (*mcr*) genes have threatened the clinical use of colistin (polymyxin E), a last-resort antibiotic against multidrug-resistant (MDR) Gram-negative bacterial pathogens. Although reports have documented the emergence of colistin resistance via chromosomal mutations in clinical pathogens, it was the discovery of *mcr-1* in *Escherichia coli* isolated from a pig in China that indicated the possibility of the transmission of colistin resistance via lateral gene transfer [1]. Subsequently, it became apparent that *mcr-1* was not restricted to China and that this gene was spreading globally [2]. Despite global attention, the emergence of *mcr-1* and other *mcr* variants, their distribution and their impact on the treatment of complicated infections in countries with limited resources, weakened infrastructure and undeveloped antimicrobial stewardship still require further assessment. It can be argued that these countries might be the most vulnerable in the fight against MDR bacterial infections and, subsequently, the preservation of colistin efficacy is of paramount importance. Furthermore, the dissemination of *mcr* in vulnerable countries might serve as a reservoir for global dissemination of these genes. In this study, a survey was conducted to assess the availability of colistin for human therapeutics and veterinary and animal farming applications in Lebanon, a country with developing antimicrobial stewardship. The survey focused on different points in the antimicrobial resistance risk chain and mainly targeted (i) direct clinical exposure to colistin (amount of imported colistin for human cases) and (ii) potentially hazardous agricultural practices (colistin use in animal farming). The overall objective was to highlight factors that might be driving the spread of *mcr* and colistin resistance in Lebanon [3,4], which has well-documented post-civil war challenges in infrastructure and resource management.

The survey showed that although most antibiotics are easily accessible (over-the-counter) in Lebanon, colistin is not available in community drug stores and is largely limited to hospital use [Records of the Order of Pharmacists of Lebanon (OPL), 2018]. In Lebanese hospitals, colistin (colistimethate sodium) is administered by inhalation or as an intravenous infusion for the management of *Acinetobacter* spp., extended-spectrum β -lactamase (ESBL)-producing isolates, carbapenem-resistant Enterobacteriaceae, and infections that involve other resistant Gram-negative bacteria. Using OPL records, it was possible estimate that the amount of colistin imported for hospital use has been generally increasing in Lebanon (Supplementary Fig. S1).

Notably, in 2017 the amount of imported colistin was 348 500 flacons (1 MIU of colistin per flacon), which constituted approximately five times the amount imported in 2010 (72 135 flacons) (Supplementary Fig. S1). To estimate the number of patients who might have benefited from the imported colistin in 2017, the following was assumed: (i) since colistin is ordered on demand, then all of the imported quantity was consumed with minimal waste; (ii) the patient population was comprised of adults, which require a loading/maintenance dose of 9 MIU/day (as per standard prescription recommendations); and (iii) colistin treatment was administered over a median of 14 days [5]. Subsequently, the amount of colistin imported in 2017 could address the needs of ca. 2766 critically ill adult patients (0.046% of the Lebanese population). In comparison, the amount of imported colistin was enough to address the needs of ca. 572 patients (0.013% of the population) in 2010. Obviously, the aforementioned numbers of colistin-treated patients are constrained by our assumptions and the robustness of the available data. However, the analysis still represents a proxy for the potential burden of MDR bacterial infections in Lebanon and the importance of colistin as a therapeutic agent in this country.

To assess colistin availability for veterinary and animal farming applications, all major veterinary drug stores across Lebanon were surveyed. Twelve different drug brands that contained colistin (Table 1) and that were readily and legally available in the market without the requirement of a veterinarian's prescription were identified. Notably, these drugs were advertised for the treatment and prevention of diseases mainly in poultry, which is not surprising because the poultry farming industry is among the most developed in Lebanon. The drugs were available in two formulations, either as a liquid or a water-soluble powder, and the route of administration was via drinking water. Furthermore, it was noticed that the treatment instructions (indications) on the packaging of the drugs were in many instances cryptic, non-specific and/or covered a wide range of diseases (Table 1). Although none of the packages recommended the drugs for growth promotion applications, we encountered anecdotal accounts that some of these drugs were sold for the aforementioned purpose were noted. Taken together, these observations documented a notable variety and availability of colistin-containing drugs for poultry farming. In light of previous observations on the widespread resistance to colistin and the high occurrence of *mcr-1* in commensal bacteria isolated from Lebanese poultry [4], a link between the availability of colistin and the emergence of colistin resistance can be suggested. This might be a cause for concern because *mcr* and cognate plasmids have a well-established ability for transmission beyond the farm, especially in the absence of proper monitoring and on-farm control mechanisms.

To our knowledge, this is the first attempt to evaluate colistin consumption in humans and to identify potential risky agricultural

Table 1

A list of colistin-containing drugs that are readily available for use in animal farming in Lebanon. All of the listed drugs are accessible to farmers without the need for a veterinarian's prescription. The information listed in the table was collected from the packaging of each drug. The table shows that colistin is mainly used for poultry to treat and/or prevent a wide range of diseases. In many cases the drugs are recommended for use non-specifically to treat Gram-negative and/or Gram-positive bacterial infections.

Trade name	Active ingredient (s)	Treated food animals	Treatment objective/indications	Route of administration	Withdrawal time/contraindication	Country of manufacture
Colisultrix (oral powder)	Colistin (500 000 IU/g) Trimethoprim	Poultry, pigs, calves, goats, lambs, rabbits	Infections caused by or associated with organisms susceptible to trimethoprim and colistin	Drinking water or liquid feed	Meat: 7 days. Not to be used in layers producing eggs for human consumption	France
Altibiotic (multi-antibiotic with vitamins)	Erythromycin thiocyanate Chlortetracycline HCL Colistin sulfate (65 g/kg) Amoxicillin trihydrate	Poultry	Prevention and treatment of Gram-negative and Gram-positive bacteria and mycoplasma (PPLO). Specifically against CRD complex, synovitis, coryza, salmonellosis, blue comb, and all kinds of enteritis and stresses	Drinking water	Not indicated	Lebanon (packaged)
Colexin (water-soluble powder)	Colistin sulfate (1.2 MIU/g) Trimethoprim	Poultry, goats, calves, sheep	General bacterial infections especially of the gastrointestinal tract caused by Gram-negative and Gram-positive bacteria in ruminants and poultry	Drinking water	Not indicated	Lebanon (packaged)
Colistin 50% (water-soluble powder)	Colistin sulfate (9 MIU/g)	Poultry	Treatment of intestinal infections caused by Gram-negative bacteria in poultry	Drinking water	Not indicated	Lebanon (packaged)
Colived (water-soluble powder)	Colistin sulfate (1.5 MIU/g)	Poultry	Treatment of intestinal infections caused by Gram-negative bacteria	Drinking water	Not indicated	Lebanon (packaged)
Colived Fort (water-soluble powder)	Colistin sulfate (6 MIU/g)	Poultry	Treatment of intestinal infections caused by Gram-negative bacteria	Drinking water	Not indicated	Lebanon (packaged)
Colisin (water-soluble powder)	Erythromycin thiocyanate Colistin sulfate (500 000 IU/g)	Poultry	Treatment of fowl cholera, CRD, synovitis, omphalitis, coryza and colibacillosis	Drinking water	Not indicated	Lebanon (packaged)
Doxaved C (water-soluble powder)	Doxycycline hyclate Colistin sulfate (20 mg/g)	Poultry	Bacterial infections of the respiratory and gastrointestinal tracts	Drinking water	Not indicated	Lebanon (packaged)
Ampisin (water-soluble powder)	Ampicillin trihydrate Colistin sulfate (500 000 IU/g)	Poultry, calves	Used in cases of bacterial infections caused by Gram-positive and Gram-negative bacteria. Poultry: <i>Streptococcus</i> , <i>Staphylococcus</i> , <i>Corynebacterium</i> , clostridia, <i>Salmonella</i> , <i>Proteus</i> , <i>Brucella</i> , spirochetes and <i>Escherichia coli</i> . Calves: treatment of pneumonia, arthritis, bacterial scour, omphalitis, navel diseases and omphalophlebitis	Drinking water	Meat: 5 days Eggs: 7 days Not to be used for ruminating calves	Jordan
Colisol (colistin 10% liquid)	Colistin sulfate (2 MIU/mL)	Poultry, calves, lambs, other young animals	Treatment of gastrointestinal infections caused by <i>E. coli</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Klebsiella</i> and <i>Pseudomonas</i> in poultry. Also for treatment of diarrhoea in calves and other young animals	Drinking water	Meat: 2 days	Saudi Arabia
Montamox (water-soluble powder)	Amoxicillin trihydrate Colistin sulfate (800 000 IU/g)	Poultry	Treatment of colibacillosis (<i>E. coli</i>), fowl typhoid, pullorum disease (<i>Salmonella Gallinarum</i> , <i>Salmonella Pullorum</i>), fowl cholera (<i>Pasteurella multocida</i>), necrotic enteritis (<i>Clostridium perfringens</i>), paratyphoid infections (<i>Salmonella</i> Enteritidis, <i>Salmonella</i> Typhimurium)	Drinking water	7 days	Saudi Arabia
Rythrocol (water-soluble powder)	Erythromycin thiocyanate Colistin sulfate (500 000 IU/g)	Poultry	Treatment and prevention of fowl cholera (<i>P. multocida</i>), mycoplasmosis or CRD (<i>Mycoplasma gallisepticum</i> , <i>Mycoplasma synoviae</i>), CRD, infectious synovitis, bumblefoot and omphalitis (<i>Staphylococcus</i> spp.), infectious coryza (<i>Haemophilus paragallinarum</i>) and colibacillosis (<i>E. coli</i>)	Drinking water	Meat: 3 days Eggs: 2 days	Saudi Arabia

PPLO, pleuropneumonia-like organisms; CRD, chronic respiratory disease.

and animal farming practices that might lead to increased resistance, which jeopardises the medical efficacy of this important antibiotic in Lebanon. Based on this study, it was concluded that the wide availability of colistin for animal farming might be contributing to the emergence and dissemination of *mcr*-mediated colistin resistance in Lebanon, which threatens effective interventions against MDR bacterial infections in humans. Therefore, the use of colistin in Lebanese animal farming must be carefully

evaluated and legislated in order to preserve the efficacy of colistin for the treatment of MDR bacterial infections in Lebanon. In addition, the establishment of a national surveillance programme on colistin availability and consumption in humans and animals is of paramount importance. This programme should engage and be under the jurisdiction of the Ministries of Health and Agriculture, and it should mandate (i) proper documentation of the import and consumption of colistin on a public server, (ii) illegalisation of the

use of colistin without medical and/or veterinary prescription and (iii) phasing out colistin from controversial animal farming practices.

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Competing interests

None declared.

Ethical approval

Not required.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jgar.2019.01.019>.

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