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Posted Date: 14 November 2023

doi: 10.20944/preprints202311.0872.v1

Keywords: One Health Debate; Colistin; Food-Producing Animals

 doi:10.20944/preprints202311.0872.v1

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Is Colistin Essential for the Treatment and Metaphylaxis of Infections in Food-Producing Animals; One Health Debate

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Abstract: Colistin [polymyxin E] is a veterinary exclusive antimicrobial and one of the oldest antibiotics that is currently recognised as one of the highest priority critically important antimicrobials for humans. It is extensively used for multiple medical and non-medical purposes particularly for growth promotion, prophylaxis/metaphylaxis and therapeutic in food animals. As a result, colistin resistance was widespread along the food-chain linking to multidrug resistant bacterial infections in humans reflected by greater use of colistin in healthcare settings resulted in different types of bans/restrictions in food-producing animals, around the world. This report debates the testimonies of 23 countries representing the bulk of global food producing animal production, providing robust evidence on the essential need for colistin in animal production.

Introduction

Colistin [polymyxin E] is one of the oldest antibiotics, in regular use since the 1950's, and has undergone a major shift in public health importance. A veterinary exclusive antimicrobial, for growth promotion, prophylaxis/metaphylaxis and therapeutic use in food animals, has regained importance in human medicine for serious and critical multi-resistant infections [1], to be recognised by the World Health Organization [WHO] as one of the highest priority critically important antimicrobials [HP-CIAs]. Alternatively, the World Organization for Animal Health [WOAH, founded as *OIE*] has consistently not listed colistin as critically important for animals.

Since 2015, the rapid global spread of colistin resistance was reported in bacteria from animals and humans worldwide [2,3]. Furthermore, colistin resistance was widespread along the food-chain linking to human clinical infections, including the environment, food-producing animals, retail meat, asymptomatic human individuals and patients without previous exposure to colistin, especially young children [4]. Since the first report of the plasmid-mediated, colistin-resistant [*mcr-1*] gene in *Escherichia coli* in China, different variants of this gene, and other numerous subvariants of mcr-2 to mcr-10 have been reported [2,5-7]. The phylogeny and spread of *mcr-1~10* genes and variants vary greatly suggesting different evolutionary advantages worldwide [8]. The higher prevalence of mobile *mcr* genes among animal bacterial isolates combined with the markedly higher use of colistin in livestock, compared with human medicine, in several countries is of major public health concern as it facilitates the rapid global spread of antimicrobial resistance between different bacterial species as well as between animals and humans [9,10]. Conversely, several independent studies have confirmed that major reductions of colistin use in food-producing animals, and not human medicine, have resulted in significant reductions in colistin-resistant bacteria in both food-producing animals and humans, including both asymptomatic human carriers and infected individuals [6,11-14].

Use of Colistin in veterinary practice

In the European Union [EU], colistin is marketed for "Treatment and metaphylaxis of enteric infections caused by non-invasive *Escherichia coli* susceptible to colistin sulfate." for most food-producing animal species. In some other non-EU regions, colistin is marketed for both colibacillosis and Salmonella in food-producing animals. In pet animals, minor uses of other polymyxins are administered alone or in combination with other antibiotics for eye and ear infections. In horses/foals, off-label uses of human polymyxin B formulations are given at sub-therapeutic intravenous concentrations for endotoxemia.

In young food-producing animals, *E. coli* diseases are typically manifested as gastrointestinal infections, known as colibacillosis, where only orally administered colistin achieves high gastrointestinal concentrations as it is not appreciably bioavailable to the systemic circulation. In chickens, colibacillosis differs in that common signs are either localized [e.g. omphalitis] or systemic [e.g. colisepticemia], where orally administered colistin does not attain therapeutic concentrations at the site of infection [15]. Colistin is effective for primary diarrheal colibacillosis, which is rare in chickens. This suggests an alternative use of colistin is to decolonise the gastrointestinal tract of *E. coli* and thus reduce indoor *E. coli*-laden dust levels, the likely common cause of chicken colibacillosis.

The most common traditional uses of colistin is for post-weaning diarrhea [PWD] in piglets, followed by colibacillosis in other food producing animal species. PWD is a multifactorial condition occurring within the first 14 days after weaning where diarrhea [i.e. defecation with increased rate, volume and water content] results from a combination of risk factors [e.g. breed, age/weight at weaning, colostrum intake/quality, previous vaccination, heat/cold stress, diet characteristics, mixing unfamiliar animals] commonly enhanced by an infection with specific pathogens, especially enterotoxigenic *E. coli* [ETEC] [16]. However, PWD without detectable ETEC is also common, where intestinal dysbiosis from the weaning process and diet changes can lead to intestinal inflammation and diarrhea [16]. Rotavirus and coronavirus gastrointestinal infections can be contributing pathogens. Evidence-based research studies provide several husbandry management tools to either prevent PWD or reduce the incidence/severity [17]. Furthermore, Raasch *et al*. assessed the effectiveness of alternative measures in pig production, such as improvement of biosecurity, vaccination, improved feeding, and health care, and found a significant reduction in colistin consumption as the result of the implementation of different measures [18]. Widely available *E. coli* vaccines, for preventing colibacillosis in many food producing animal species, are marketed for third trimester pregnant animals, to boost colostral quality/immunity, or to be given to neonates prior to weaning. Live apathogenic *E. coli* vaccines are available as well as inactivated *E. coli* vaccines and vaccines against *E. coli* components [e.g. fimbrial adhesin antigens] that provide *E. coli* strains with selective advantages to attach to the intestinal wall and cause disease. Estonia is an example of a country with significant pig production that previously had low sales of doses of *E. coli* vaccines, but high sales of colistin [almost doubled from 2010-2013] [19]. A change in national policy lead to a dramatic increase in sales of *E. coli* vaccines followed by a proportional decrease in colistin sales by 92.5% in total. It was shown on a national population scale that the consumption of colistin in pigs decreased on average by 0.23 mg/PCU [95% confidence interval: 0.06-0.39] for every 10,000 *E. coli* vaccine doses sold, over ten years [19]. The population correction unit, referred to as PCU, is a standardized denominator for European animal sales data [PCU in 1,000 tonnes] and serves to normalize the total quantities of antibiotic active substance sold in each country by the animal population that could be potentially treated.

Use of Colistin in the Public health sector

The critical need for colistin as a last-resort treatment in human medicine continues to grow. Infections caused by multidrug resistant [MDR] Gram-negative bacteria are an increasing global healthcare threat, as reflected by greater use of colistin in hospitals/ICUs for the treatment of infections caused by carbapenem-resistant Enterobacterales, MDR-*Acinetobacter* spp., MDR-*Klebsiella* spp. and MDR-*Pseudomonas* spp [1]. Colistin is also increasingly administered by inhalation for the treatment of infections in cystic fibrosis patients and in patients with ventilator-associated pneumonia. In 2015, infections caused by carbapenem-resistant Gram-negative bacteria were associated with high levels of mortality with an estimated 2,500 deaths due to colistin-resistant Gram-negative bacteria in the EU/EEA [17]. MDR-*Acinetobacter* spp and MDR-*Klebsiella pneumonia* are also

 doi:10.20944/preprints202311.0872.v1

reported from human clinical samples from developing countries expressing colistin resistance-carbapenemase producing phenotypes [20].

Global concerns about Colistin use in veterinary medicine

Major concerns about agriculture colistin use have resulted in different types of bans/restrictions in food-producing animals, around the world. Some countries have banned colistin for use as growth promoters [feed additives], including Brazil, Chile, Uruguay, China, Japan, South Korea, Nepal, South Africa, Vietnam and Thailand [21]. Thailand, has gone a step further and from the start of 2017, the Department of Livestock and Development has further prohibited prophylactic use of colistin sulfate for food-producing animals [11].

Several countries have taken the final decision to not allow colistin for all types of use, including therapeutic, for major food-producing animal populations. This has been achieved by either totally banning colistin use in animals, never granting a national marketing authorisation for colistin use in food-producing animals, or heavy restrictions [voluntary or otherwise] for major food-producing animal species that has resulted in substantial national reductions in colistin sales in animals [Table 1].

In 2016, the European Commission [EC] announced the withdraw of all marketing authorisations for veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally, with no reported negative impact on European food animal production. Although sales of monotherapy colistin have decreased in Europe, 136.5 tonnes of colistin were sold in 2021, of which 99.3% sales were oral mass medication formulations marketed for food-producing animals [e.g. premixes, oral powders/granules/solutions for drinking water] administered to both healthy and diseased animals [European Medicines Agency [22]. This corresponded to an overall, aggregated EU colistin sales, in animals, of 2.2 mg/PCU in 2021, as compared to approximately 0.06 mg/PCU for the European human population polymyxin consumption, based on previous reports [23].

Antimicrobials [antibiotics, antifungals, antiprotozoals, and antivirals] designated for human use only in the European Union

The EU was the latest region to consider banning certain antimicrobials for use in animals. This was done through the establishment of a list of antimicrobials designated for human-use only, specified in an EC implementing act [EU 2022/1255] [eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32022R1255]. The criteria for establishing the list was based on a European Parliament [EP] Delegated Act [EU 2021/1760] [eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32021R1760], whereby conditions were applied to assess if an antimicrobial/antimicrobial class fulfills all three established criteria [A-High importance for human health, B-Risk of transmission of resistance from animals to humans, C-Non-essential need for animal health] to be designated for human-use only.

Although this EU-approach lead to the conclusion that colistin did not qualify for the human-reserved list, based on not fulfilling Criterion C, it is still worthwhile to re-examine colistin from a global One Health perspective, since the Criteria are published public information and represent the latest high-level government scheme to assess if antimicrobials are essential for animal health.

Discussion

A growing global community of countries either heavily restrict or do not allow the use of colistin in major food animal populations [Table 1]. Combined, these countries represent the majority of the global food producing animal production. There are no associated reports from these nations of any issues with animal health and welfare secondary to the cessation of colistin use in major food producing animal populations. There might be more countries considering or have implemented similar restrictions of colistin for food animals. Thus, with a wider global perspective then the combined decision of 23 countries [Table 1] provides robust evidence that colistin is not essential for food-producing animals.

Together these nations are shaping the global One Health actions and efforts for antimicrobial use in food producing animals. Moreover, *Finland*, Iceland and Norway report consistently no sales of colistin to the European Surveillance of Veterinary Antimicrobial Consumption [EMA/ESVAC] [European Medicines Agency [EMA] [22]. Combined, Denmark and Spain represent the majority of EU pig production, and without the use of colistin, based on different novel approaches to eliminate colistin consumption [Table 1]. Other countries such as France, Italy, Netherlands, Estonia have set national targets for veterinary colistin reductions, based on recommendations [24] and exceeded those targets [22].

The wealth of evidence-based husbandry management tools to either prevent colibacillosis or reduce the incidence/severity, including the use of widely available vaccines and alternative antimicrobials, demonstrates that adequate alternative medicinal products are available as well as sufficient knowledge about good husbandry practices that will reduce infection burdens on intensively driven farming. On their website news stream, the Federation of Veterinarians of Europe [FVE] has taken a position that a ban on veterinary use of colistin would impact animal welfare, based on the need for treating MDR gram-negative infections in food producing animals. However, with the culmination of years of previous colibacillosis husbandry practices leading to MDR *E. coli* strains, then the solution is not the use of more-and-more critically important antimicrobials, but to change husbandry practices towards prevention, including vaccine use. This is especially the case with non-ETEC PWD from intestinal dysbiosis. ESVAC [2022] reports on a European level that although veterinary colistin sales are decreased, it is not matched by increased sales of 3rd/4th generation cephalosporins and fluoroquinolones [22], suggesting that treating MDR *E. coli* strains are a minor issue in food animals. Also, colistin use exerts a major selection pressure on animal bacterial populations for co-selection of resistance to other antibiotic classes. Mobilised colistin resistance has been identified in a range of different plasmids [IncI2, IncX4 and IncFIA type plasmids] that co-carry *mcr* genes with other resistance genes for aminoglycosides, β-lactamases [penicillins, cephalosporins, carbapenems], fluoroquinolones, sulphonamides, tetracyclines, and trimethoprim [25]. Thus, One Health perspectives of colistin use in agriculture must recognise that increases in mass medication practices corresponds to increased colistin multi-resistant bacteria that negatively impacts public health.

Table 1. Countries/Regions that have either banned, heavily restricted or never marketed colistin for therapeutic use in food-producing animals.

Country/Region	Types of Major Colistin Restrictions in Food Animals
Europe	
Denmark	**2016**: Yellow Card Initiative expanded to include an additional 'factor' if certain antimicrobials are administered on farms. A 'factor' 10 was attached to colistin, meaning for every kg of colistin used per farm, 10 kg are recorded on the yellow-card for that farm. This has effectively eliminated the use of colistin for food animals [26].
Ireland	**2021**: Voluntary cessation of all colistin use in the Animal Health sector [27].
Spain	**2016:** The REDUCE program initiative establishes collective agreements between veterinarians, food-producing farmers, cooperative farmer collectives and the Spanish government for voluntary reductions of antimicrobial consumption. Six years later there is virtually 100% reduction in national colistin sales.
Portugal	**2018:** Voluntary ban of colistin by *Portuguese* poultry and rabbit farmers [28].
United Kingdom	**2016**: Voluntary ban of colistin by UK poultry farmers [29]. Also, no sales of colistin in all food animals in 2021 [30].

 doi:10.20944/preprints202311.0872.v1

Asia	
India	**2019**: Central Government of India banned the manufacture, sale and distribution of Colistin and its formulations for food producing animals, poultry, aqua farming and animal feed supplements.
Bangladesh	**2020:** Colistin is banned for veterinary use [all forms of use], including manufacturing and distribution.
Malaysia	**2019**: Colistin has been officially banned for use in food animals [31].
Indonesia	**2019**: Ministry of Agriculture prohibits the use of colistin in animals [32].
Oceania	
Australia	**1992**: Colistin has not been used in Australia since the early 1990s, at which time there was a product approved for use in pigs only. No products currently on the market. Polymyxins have never been approved for use in Australian poultry [33].
New Zealand	Colistin has never been marketed for use in animals.
North America	
USA	**1998**: Colistin has been approved but never been marketed for animals.
Canada	Colistin has never been marketed for use in animals. In 2017, the own-use importation legal 'loophole' was shutdown that could lead to importation of colistin for use in animals [34].
Central America	
Costa Rica	**2021**: Use of colistin not permitted in animals [10].
Nicaragua	**2021**: Use of colistin not permitted in animals [10].
South America	
Peru	**2021**: Under the framework of the 2019–2021 Multi-Sector Plan to Address Antimicrobial Resistance, a Resolution bans the import, trade, manufacture, and development of veterinary products containing the active ingredient colistin [Polymyxin E] [35].
Paraguay	**2019**: Resolution 1,150 has prohibited manufacture, distribution, import and usage of any veterinary product that has colistin as its active principle and its salts [10].
Argentina	**2019**: National Food Safety and Quality Service [Senasa], an independent governmental agency, has banned the 'elaboration, distribution, import, use and possession of veterinary products containing the active ingredient colistin and its salts' [36].
Ecuador	**2020:** Ban on the manufacture, sale, and use of colistin for use in animals [37].
Middle East	
Egypt	**2013**: Ban on the use of colistin as veterinary medicinal products in food animals.
Saudi Arabia	**2019:** Based on committee recommendations and international reports, both a ban and withdraw of all veterinary products with colistin, including withdraw of importation and distribution licence of the listed products [Government Ref no. 4/60162; Ref no. 12/B/541/40].
Lebanon	**2022**: After years of research and governmental meetings, the ban on Colistin import and its use in the agricultural sector in Lebanon has been officially issued, titled Resolution No. 221/1.
Jordan	**2022**: Based on the recommendations of the committee responsible for veterinary medicine, the Jordanian government, by decree [5/5/10/7240], has prohibited manufacture, distribution, import and usage of any veterinary product that has colistin in food animals [38].

Colistin is used in both human and veterinary medicine for serious, potentially life-threatening infections. Prevention strategies, including vaccines, as viable alternatives to colistin use in food-producing animals, are not an option in human medicine for infections critically requiring colistin treatment. These prevention strategies can transform colibacillosis on farms to a disease of limited morbidity and mortality. Thus, there are valid arguments of an overriding public health interest for preserving colistin for critical infections in humans.

In conclusion, colistin is marketed for the treatment and metaphylaxis of colibacillosis in food-producing animals. Alternatives can be used in place of colistin, and several evidence-based preventative strategies are well known for the major food producing animal species to limit the morbidity and mortality from colibacillosis. Testimonies of 23 countries, representing the bulk of global food producing animal production, provide robust evidence that colistin is not essential for its marketed-use, clearly showing that even intensive animal production can be maintained without the use of this antibiotic. Their combined national responses are commensurate with the gravity of colistin's clinical importance in human medicine and associated widespread dissemination of resistance from over-use of colistin in food animals.

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