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Review Article

Bridging Policy and Practice for Colistin Use in Veterinary Settings: A One Health Approach for Resource-Limited Regions

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ABSTRACT

Antimicrobial resistance (AMR) is an important public health problem worldwide in humans and animals. Colistin is extensively used in veterinary medicine to control and treat enteric infections in poultry and swine, emphasizing the need to consider a One Health approach when dealing with colistin resistance. The present study aimed to provide a concise overview of the global antimicrobial resistance burden and the critical status of colistin within the World Health Organization (WHO) and European Medicines Agency (EMA) frameworks. The WHO classifies colistin in its Access, Watch, and Reserve (AWaRe) class reserve group, and the EMA restricts its use in veterinary medicine, categorizing colistin as restricted (Category B). The discovery of plasmid-mediated colistin-resistance (*mcr-1*) genes and their worldwide transmission to humans, animals, food, and the environment in 2015 increased urgent concerns about the continued use of colistin. The present study analyzed 44 open-access articles published between 2015 and 2025, sourced from PubMed, Scopus, and WHO/EMA databases. It investigated resistance to colistin in *Escherichia coli*, the spread and control of *mcr* genes, particularly in Africa and North America. Colistimethate sodium is for human use, and colistin sulfate is more commonly used in veterinary medicine. Over 10 variants of the *mcr-1* gene have been detected in humans, animals, food, and environmental samples. In North Africa, *mcr*-positive isolates have been identified in both poultry and humans, reflecting the interconnected risks. The findings illustrated a persistent gap between global policies and local practice, driven by limited alternatives, weak diagnostic capacity, and uneven regulatory enforcement. As a result, colistin continues to be used despite the increasing risks of resistance.

A practical One Health approach is essential to preserve this critical antibiotic. This approach should strengthen diagnostic tools, improve surveillance systems, provide training for farmers and veterinarians, and harmonize global policies with local needs, aligning with WHO AWaRe and EMA guidelines.

1. Introduction

Antimicrobial resistance (AMR) is an urgent global health issue. In 2019, AMR was estimated to have contributed to approximately 4.95 million deaths across all age groups and regions worldwide[1]. Colistin remains one of the few antibiotics available as a last-line treatment against infections caused by multidrug-resistant Gram-negative bacteria[2]. Recognizing its importance, the World Health Organization (WHO) has classified colistin under the Reserve group of its Access, Watch, and Reserve (AWaRe) program. This designation indicated that colistin use in humans should be restricted to situations where no alternatives exist and should be managed by strict stewardship protocols[3,4].

From a veterinary and regulatory perspective, the European Medicines Agency (EMA), through the antimicrobial advice ad hoc expert group (AMEG), have developed a framework, categories A to D, to guide the cautious use of antibiotics in animals. Colistin was classified as restricted (Category B). This colistin category highlighted that veterinarian should limit its use, avoid it for prevention,

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choose safer alternatives whenever possible, and focus on farm-level prevention efforts[5]. The discovery of the plasmid-mediated colistin-resistance gene (*mcr-1)* in 2015 was a pivotal point in the AMR landscape, demonstrating that resistance to colistin, a last-resort antibiotic, can be transmitted horizontally across bacterial species and environmental sites[6]. Detection of *mcr-1* and its variants has been reported globally across humans, livestock, wildlife, food products, and environmental reservoirs, indicating the urgent need for an integrated One Health approach[7]. The threat posed by *mcr-1*-mediated colistin resistance is particularly important in resource-limited settings, where therapeutic alternatives to colistin are rare, diagnostic tools to detect *mcr* genes are limited, and antimicrobial medicines are hard to find in local resources. The present study aimed to determine the global burden of antimicrobial resistance, highlight the critical status of colistin in the WHO and EMA, and summarize the international and regional (North African) epidemiology of *mcr-1* and its public health implications.

2. Materials and Methods

The present narrative review was conducted exclusively using open-access, peer-reviewed literature and official reports published from 2015 to 2025. Investigations were carried out in PubMed and Scopus using different combinations of the following keywords. Colistin, polymyxins, *mcr*, mobilized colistin resistance, One Health, veterinary, and regional qualifiers such as Africa and North Africa. Policy documents and technical guidelines were obtained from the WHO's AwaRe classifications and Global antimicrobial resistance and use surveillance system (GLASS), EMA, and AMEG portals. Priority was given to recent systematic reviews, surveillance reports, and primary studies covering the human, animal, and environmental sectors. Among all screened studies, 44 met the eligibility criteria and were included in the present study. No new data were generated or analyzed during the present study.

3. Colistin in human and veterinary medicine

3.1. Mechanism of action and clinical formulations

Colistin (polymyxin E) is a cationic cyclic lipopeptide that targets the lipid A component of lipopolysaccharides (LPS) in the outer membrane of Gram-negative bacteria[8]. By displacing divalent cations such as Ca^{2+} and Mg^{2+}, colistin destabilizes the bacterial outer membrane, resulting in rapid cell death[9]. Colistin is administered primarily as colistin methanesulfonate (CMS) in human clinical practice. The CMS is a prodrug that is hydrolyzed in the body and biological fluids into its active form, colistin, along with other inactive methanesulfonated byproducts[10]. This hydrolysis provides antibacterial activity, but it can alter how the drug circulates and remains in the bloodstream, causing nephrotoxicity in clinical use[11].

veterinarians commonly administer colistin sulfate orally or apply it topically to treat intestinal infections, particularly in swine and poultry, where it is effective against *Escherichia coli (E. coli)*-associated diarrhea[12]. Despite its broad clinical use, colistin has limitations, including the potential for heteroresistance and bacterial regrowth when the dosage is not adequate. Therefore, it is essential to use the appropriate pharmacokinetic/pharmacodynamic-guided dosing to maintain long-term antibiotic efficacy[13].

In human medicine, nephrotoxicity is the primary dose-limiting side effect. Nephrotoxicity often appears as acute kidney injury and necessitates close therapeutic monitoring and careful adjustment of the dosage to avoid renal damage[14]. Neurotoxic effects, including dizziness and paresthesia, are less frequently observed but may occur, particularly with intravenous administration, which is associated with the highest risk of nephrotoxicity and neurotoxicity[15]. The extensive use of colistin in animals has raised significant concerns about resistance, prompting strict regulations and guidelines, especially in Europe. The EMA classified polymyxins, including colistin, as restricted (Category B). These regulations enforce strict protocols, limiting veterinary use of these medicines, to preserve their effectiveness for the future[16,17].

3.2. Emergence and global spread of mcr genes

After the discovery of *mcr* genes, the clinical use of colistin declined. The *mcr* genes encode phosphoethanolamine transferases, which modify the lipid A component of lipopolysaccharides, thereby reducing colistin binding [16]. In 2015, the first *mcr-1* gene was reported in China, where the gene was detected on transferable plasmids in *E. coli* isolated from pigs, retail meat, and hospitalized patients[18]. This finding helped in understanding colistin resistance by revealing that it could be mediated not only by chromosomal mutations but also through horizontal gene transfer among different bacterial species[19]. Since its first discovery, *mcr-1* has spread rapidly worldwide, with reports of its presence in humans, animals, environmental sources, and food products[20,21]. The *mcr* genes (*mcr-1* to *mcr-10*) are located on plasmids, which facilitate their transfer among different bacteria, species, and even between continents[22,23]. Considerable diversity exists in the structures of the plasmids and their bacterial hosts, reflecting ongoing genetic evolution and adaptation[24-26].

North Africa has experienced an increasing prevalence of *mcr*-positive *E. coli* in clinical and veterinary settings[27,28]. A recent study highlighted high *mcr* prevalence rates, which affected the environment, animal, and human health in Algeria and Tunisia, two key countries in North Africa[29]. In Tunisia, a notably high prevalence of *mcr-1* (41.5%) was detected in 195 broiler chickens screened using PCR, highlighting the widespread issue of colistin resistance in poultry production[30]. Furthermore, there is an urgent need to improve antimicrobial resistance surveillance systems in resource-limited areas. Current gene detection diagnostic methods generally do not meet international standards, which delays effective antimicrobial interventions[31].

3.3. Policy-to-practice gap in low-resource settings

Building on the observed global and regional patterns of *mcr* dissemination, it is evident that a significant disparity exists between internationally advocated AMR policies and their implementation in low-resource settings[32]. Reports submitted to the WHO GLASS platform and recent global analyses indicated significant differences in laboratory coverage, testing quality, and information about how antibiotics are used. These systemic deficiencies undermine the management of antimicrobial resistance, especially *mcr* genes[33,34]. A major issue contributing to this gap is the limited availability of therapeutic alternatives. Although global policies promote restricted colistin use, affordable and effective alternatives such as carbapenems or tigecycline are often inaccessible or prohibitively expensive in many low-income regions[9]. Consequently, colistin remains a last-resort or even first-line treatment in certain situations. In Africa, veterinary practitioners heavily rely on colistin to manage enteric infections in poultry and livestock, directly opposing international recommendations[35]. For instance, in Blantyre, Malawi, veterinary healthcare outlets provide access to colistin and other essential antibiotics without prescription[35]. This unrestricted availability fosters selective pressure and ultimately weakens antimicrobial principles[34].

The constant use of colistin is also closely attributed to diagnostic restrictions in resource-limited environments. Despite international guidelines emphasizing the need to monitor *mcr* and other plasmid-mediated resistance genes, access to molecular diagnostic methods such as PCR and whole-genome sequencing (WGS) remains limited, even in national reference laboratories[36]. Most clinical and veterinary laboratories still rely on culture-based and phenotypic susceptibility tests, which cannot reliably detect transferable resistance genes or identify underlying genetic mechanisms, such as plasmid-mediated *mcr* variants[16]. Data from the WHO GLASS initiative further highlighted persistent challenges across many African countries, including insufficient laboratory coverage, poor quality, and weak integration of AMR and antimicrobial use datasets[37]. Recent assessments indicated that infrastructure deficiencies, inadequate training, and weak management continued to hinder effective AMR surveillance[38,39]. These deficiencies delay detection and response to emerging resistance threats. Addressing critical diagnostic gaps, such as limited lab capacity, staff shortages, and inadequate control, is essential for making antimicrobial policies actionable. Furthermore, these diagnostic and therapeutic challenges are compounded by weak enforcement and limited regulations in many low-resource areas in Africa[38]. While the WHO's AwaRE framework and EMA and AMEG provided clear guidelines for colistin use, their enforcement at the veterinary level is inconsistent. Except for South Africa, most African countries continue to allow over-the-counter access to colistin without veterinary prescription, despite legal prohibitions[39].

Although the EMA has classified colistin as a Category B (Restrict) antimicrobial, this restriction is not uniformly applied in practice. The European Union's Regulation (EU) 2019/6 mandated prescription and reporting requirements for veterinary antibiotic use[40,41]. However, such measures are rarely mirrored in low-resource settings. For instance, in Nigeria, the widespread use of prophylactic and unregulated use of colistin by farmers continues to drive the emergence and dissemination of *mcr*-positive bacterial strains[39].

3.4. One Health perspective

Addressing colistin resistance requires a comprehensive One Health approach that integrates human, animal, and environmental health. Since *mcr* genes are transmitted across species and ecosystems, limiting resistance to only one sector is not enough[22]. Therefore, integrated surveillance systems covering veterinary, clinical, and environmental areas are essential for detecting emerging resistance at an early stage and informing timely interventions. Countries that coordinate health, agriculture, and environment sectors are already making progress with their AMR action plans. Their successes provide a helpful model for Africa and other resource-limited regions[42]. Strengthening laboratory capacity through regional reference centers should be prioritized to enhance diagnostic methods and data sharing. Furthermore, investment in the training of veterinarians and para-veterinary personnel is vital to close diagnostic gaps. Community education programs are also essential for reducing public misuse of over-the-counter antibiotics[39]. Finally, global frameworks such as the WHO's AWaRe classification and the EMA and AMEG guidelines should be adapted to local contexts through the development of context-sensitive decision tools. Such adaptations ensure that antimicrobial stewardship policies are not merely aspirational but are practically applicable and effectively implemented within diverse resource settings[43,44].

4. Conclusion

Colistin remains the last line of defense against multidrug-resistant Gram-negative pathogens; however, its effectiveness is increasingly undermined by the global dissemination of *mcr* genes. Although international frameworks, such as WHO's AWaRe and EMA and AMEG, have established robust, evidence-based policies to promote the prudent use of colistin, their implementation in resource-limited regions remains inadequate. This shortfall results from limited therapeutic alternatives, insufficient diagnostic capacity, weak regulatory enforcement, and persistent socioeconomic constraints. In Africa, these structural challenges have maintained reliance on colistin as a treatment option, thereby accelerating the emergence and spread of resistance. Addressing this growing threat requires a comprehensive One Health approach that integrates human, veterinary, and environmental health sectors. The One Health approach should be supported by investments in laboratory infrastructure, training healthcare and veterinary personnel, public and farmer

education, and the contextual adaptation of global policies to local realities. Bridging the policy-to-practice gap is essential to preserving the long-term efficacy of colistin and safeguarding the health of humans and animals. Future studies should quantify the environmental resources and transmission routes of *mcr* genes in African agricultural and water systems.

Declarations

Ethical considerations

The present manuscript is original, has not been published elsewhere, is not under consideration for publication in another journal, and does not contain plagiarized material. No chatbots or artificial intelligence were used in the preparation of this manuscript. All writing, analysis, and interpretation were carried out solely by the author, who takes full responsibility for the accuracy, originality, and integrity of the content.

Competing interests

The author stated that there is no conflict of interest.

Author contribution

Mohamed Elamine Benyamina conceived and designed the study, collected and analyzed the relevant literature, interpreted the findings, and drafted, revised, and finalized the manuscript. Mohamed Elamine Benyamina was solely responsible for the scientific content, including conception, analysis, interpretation, and writing. The author has read and approved the final edition of the manuscript.

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Availability of data and materials

All the information in the present review is sourced from publicly accessible, open-access sources available to the general public, and nothing has been generated.

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