Journal of Global Antimicrobial Resistance 41 (2025) 39–43

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Review

Environmental mediation of colistin resistance in the African context. A systematic scoping review

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ARTICLE INFO

Article history:
Received 25 July 2024
Revised 28 November 2024
Accepted 7 December 2024
Available online 14 December 2024

Editor: Stefania Stefani

Keywords:
Colistin
Mcr gene
Enterobacteriaceae
Cationic antimicrobial agent
Gram-negative
Human

ABSTRACT

Objectives: The prevalence of antimicrobial resistance (AMR) among Gram-negative bacteria is a major global health concern. Resistance to last-resort antibiotics like colistin is particularly alarming. This study reviews how environmental factors have contributed to colistin resistance in the African context, where reports of colistin-resistant Gram-negative organisms are emerging.

Methods: A systematic review was conducted using multiple databases to identify articles on environmental mediation of colistin resistance in Africa. Search terms included "environment," "colistin," "mobile colistin resistance gene," and related keywords. Articles from 2015 to 2021 focusing on Africa were included. Data on country, genes detected, methods used, and bacterial species were extracted.

Results: Out of 847 articles identified, 26 were included in the final review. Studies were predominantly from Tunisia, Algeria, South Africa, Egypt, Nigeria, and Congo. The mobile colistin resistance (*mcr-1*) gene was the most common genetic variant detected. *Escherichia coli* (*E. coli*) was the predominant organism spreading *mcr* genes. Colistin-resistant genes were found in humans, animals, and environmental samples including manure, soil, water bodies, and wildlife.

Conclusions: This review confirms the rapid spread of plasmid-mediated colistin-resistant genes in humans, animals, and the environment across Africa. The movement of resistant genes between these reservoirs is alarming. There is a need for more research into colistin resistance mechanisms and implementation of continent-wide antibiotic stewardship programs to address this emerging threat in Africa. © 2024 The Author(s). Published by Elsevier Ltd on behalf of International Society for Antimicrobial Chemotherapy.

1. Introduction

The global development and dissemination of antimicrobial resistance (AMR) in bacteria is a universal threat to humans, animals, and the environment. It is an established fact that although this phenomenon is unpreventable, taking informed and proactive steps can mitigate its menace [1]. AMR is the ability of a microbe to resist the effects of a medication that was initially effective against it. The term "antibiotic resistance" (ABR) is a subset of AMR and applies only to bacteria developing resistance to antibiotics, thus rendering them ineffective [2].

The most obvious cause of ABR is the use of antibiotics in humans, especially when antibiotics are used inappropriately (e.g. overuse of broad-spectrum antibiotics, or administration of non-targeted antibiotics, and the factor of non-compliance in humans) [2]. The use of antibiotics in animals, both for the treatment and prevention of disease, contribute significantly to the problem because some organisms have the ability to colonize both humans and domestic animals [3]. For several decades, antibiotics have

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https://doi.org/10.1016/j.jgar.2024.12.002

transformed health delivery systems universally, bringing relief to clinicians and veterinarians, particularly with reference to the treatment of tenacious bacterial infections. Antimicrobial resistance threatens to overturn all the benefits of antibiotics in contemporary medicine.

Mobile genetic elements, such as plasmids, confers resistance by moving across and between bacterial species [4]. The external environment serves as a major pool for resistant genes. These genes contaminate environmental elements, such as natural water bodies, and thereby come into contact with human and animal life [5].

The increased use of antibiotics has led to a rise in resistance among various microbes and complicated the treatment of infectious diseases, such as those caused by Gram-negative bacteria, including *Enterobacteriaceae, Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. This often makes the infections untreatable or necessitates the use of last resort antibiotics, such as colistin [6].

Globally, both humans and animals are colonized by commensal organisms that are potentially pathogenic colistin-resistant organisms/mobile colistin resistance (*mcr*) gene-containing bacteria [7–9] and this has left the world with limited therapeutic options [10], that are fast becoming ineffective [11]. The advent and spread of *mcr* genes have significantly jeopardized the efficacy of colistin.

Attributably to its toxic effects on the kidneys and nervous system, the use of colistin was abandoned in human medicine in the 1970s, however, it remained in use in the production of livestock in Africa and even globally [12]. The use of colistin in human medicine resurfaced in the 2000s when there was an increase in infectious diseases caused by multi- and extensively drug resistant organisms. It is projected that 10 million human lives could be lost worldwide annually by 2050 due to AMR infections [13].

Mcr gene-containing bacteria (MGCB) have been disseminated by horizontal/lateral transfer into diverse ecosystems [14]. The propagation of *mcr* genes is attributed to the inappropriate use of polymyxin in clinical practice [15], livestock production [16], and aquaculture [17].

1.1. Rationale for review

The burgeoning status of AMR in Gram-negative organisms is an issue of great medical significance with repercussions that would inevitably impact multiple socioeconomic factors on a global scale. The rapid dissemination of *mcr* genes among Gram-negative bacteria is an especially worrisome phenomena because they confer resistance to organisms that acquire resistance to highly conserved and last-resort antibiotics, such as colistin.

The distribution of *mcr* genes to and from the resistome is a perpetual occurrence that must be studied within the contexts of colistin resistance in sub-Saharan Africa. As such, a scoping review of published literature covering the prevalence of colistin resistance in environmental samples, alongside the methods of detection utilized would guide future research and pinpoint emerging issues warranting immediate interventions.

2. Methods

A specific systematic search of the literature was conducted on PubMed, Science Direct, MEDLINE, EMBASE, Scopus, and Google Scholar using random tandems of the key terms, such as “environment,” “colistin in humans and animals,” “aquatic-based foods,” mobile colistin resistance gene,” “plasmid-mediated colistin resistance gene,” “plasmid-borne colistin resistance,” “water,” “bacterial isolates,” “mobile colistin resistance,” “enterobacteria,” “Gram-negative bacilli,” “wildlife,” “wild animals,” “soil sewages,” and “fish” with particular interest in Africa. The date filter was turned to scope studies between 2015 and 2021. All reviews, non-English articles, and papers not describing diagnostic or detection methods in Africa were discarded following the initial searches. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed in searching, screening, and including papers for this review (Fig. 1). The following data were extracted from the included articles: the country where the study was performed, the *mcr* gene detected, the diagnostic tool or methods used, and the types and sample size of bacterial species used for the evaluation, sensitivity, and specificity.

3. Results

A total of 847 articles were identified based on these search terms, out of which 26 peer reviewed articles were chosen for the study. Eight of the articles were from Tunisia with seven being from Algeria. The remaining studies were conducted in South Africa, Egypt, Nigeria, and Congo**.**

3.1. Environment (humans and animals)

Humans consciously and unconsciously interfere with animal and environmental ecosystems. Consequently, they can deposit (through various anthropogenic activities) and acquire (through consumption of and contact with contaminated foods, fomites, and environment) antimicrobial-resistant organisms from the natural environment. The main route of transmission of *mcr* containing genes in Africa is by contact with *mcr*-harbouring reservoirs, transportation of foods, and consumption of contaminated food/animal. Colistin resistance among *Enterobacteriaceae* recovered from human and animal sources associated with multiple genetic mechanisms have been reported in Nigeria by Ngbede et al. [18]. The study was conducted between January 2016 and April 2019, where animals, humans, and clinical and hospital environmental samples were collected. A study conducted by Anyanwu et al. [19] discussed how the unregulated use of colistin in livestock for over the past 6 decades has immensely contributed to colistin resistance in Africa. In Africa, *mcr-1, mcr-2, mcr-3, mcr-5, mcr-8*, and *mcr-9* have been detected from animals, humans, food of animal origin, and the environment [19].

The study conducted in the porcine sector in South Africa reported that pigs are a potential reservoir for MGCB. They possessed the *mcr-1* genes, and *ESBL* and *PMQR* genes among others. VAGs, including *ast* encoding heat-stable enterotoxin 1 associated with human diarrhoea were also identified, thus suggesting that the South African pig industry is a potential reservoir for virulent multi- to extensively drug-resistant organisms [19].

The presence of diarrhoeagenic *mcr*-harbouring *Escherichia coli* (*E. coli*) in the African food chain is worrisome. This is because the treatment of food-borne diarrhoea, which is one of the most common causes of mortality among rural Africans, could be difficult if associated with MGCB. In Nigeria, *mcr-1*-carrying *Alcaligenes faecalis* was detected among 12 faecal multidrug-resistant isolates (8.3%) recovered in 2016 from the rectum of pigs, suggesting that non-Enterobacteriaceae has been circulating *mcr*-1 in West Africa since at least 2016. Colistin selective pressure in the Nigerian porcine sector is likely due to the use of various antimicrobials (including colistin) without prescription nor with a veterinarian’s supervision [19]. The table below summarizes the detection of mcr in Africa (Table 1).

3.2. Environment (manure/soil, aquatic, and wildlife ecosystems)

A study conducted by Anyanwu et al., [19] reported the environment as the repository of anthropogenic and agricultural wastes laden with AMR organisms constituting a prominent source of fruition of AMR organisms [37]. Six publications reported on

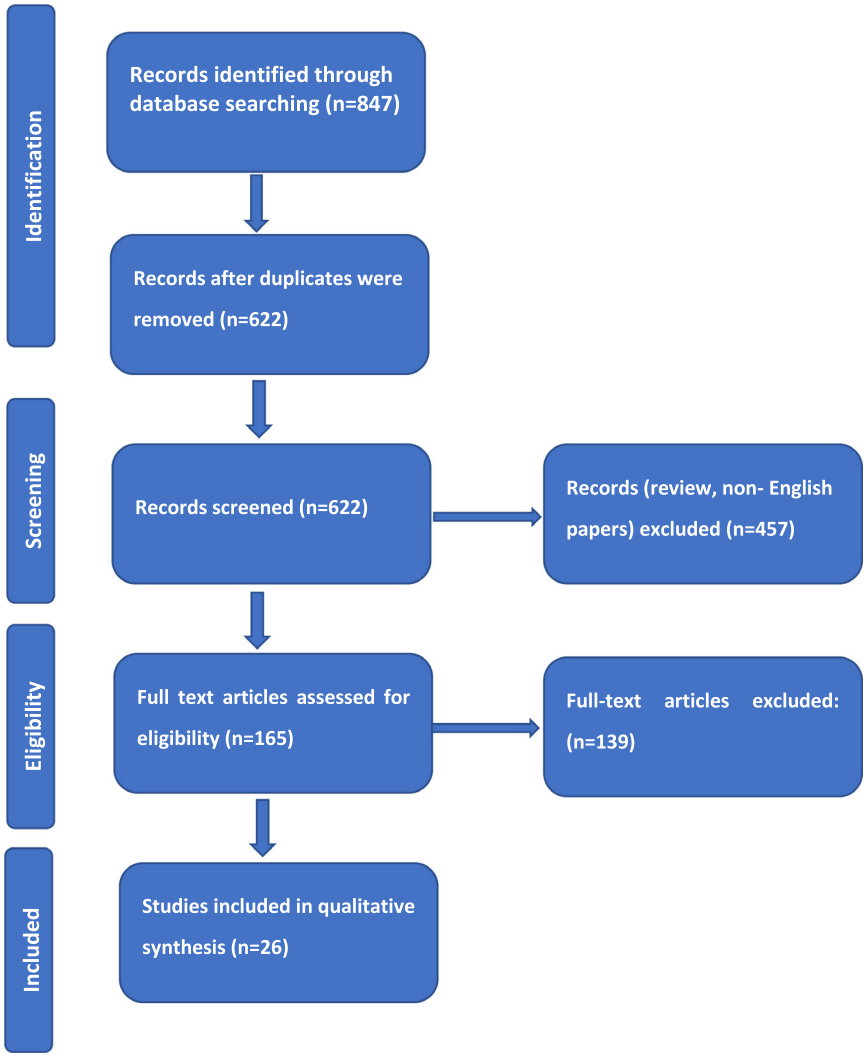

Fig. 1. Literature search and study inclusion.

Table 1
Summary of *mcr* genes detected in humans and animals in Africa

s/n	Country	*Mcr* gene detected	*Mcr* carrying organisms	Detection method	Source of isolate	Reference
1	South Africa	*Mcr-1*	*E. coli*	qPCR	Human and cattle stool	[20]
2	Algeria	*Mcr-1*	*E. coli* and *Klebsiella pneumoniae*	RT-PCR	Poultry	[21]
3	South Africa	*Mcr-1*	*E. coli*	PCR	Poultry	[22]
4	Tunisia	*Mcr-1*	*E. coli*	PCR and sequencing	Poultry	[23]
5	Egypt	*Mcr-1*	*E. coli*		Animals	[24]
6	South Africa	*Mcr-1*	*E. coli*	PCR and sequencing	Poultry	[22]
7	Global including Algeria	*Mcr-1*	*E. coli* and *Klebsiella pneumoniae*	RT-PCR, sequencing and Pasteur method	Humans and animals	[25]
8	Egypt	*Mcr-1*	*E. coli*		Poultry	[26]
9	South Africa	*Mcr-1*	*E. coli*	Whole genome sequencing	Pig	[27]
10	Egypt	*Mcr-1*	*Enterobacteriaceae*	PCR	Broiler	[28]
11	Tunisia	*Mcr-1*	*E. coli*	PCR	Poultry	[29]
12	Algeria	*Mcr-1*	*E. coli*	RT-PCR and sequencing	Poultry	[30]
13	Tunisia	*Mcr-1*	*E. coli*	PCR and sequencing	Poultry	[31]
14	Tunisia	*Mcr-1*	*E. coli*		Calves	[32]
15	Tunisia	*Mcr-1*	*E. coli* and *Klebsiella pneumoniae*	Multilocus sequencing	Camels	[33]
16	Tunisia	*Mcr-1*	*E. coli*	PCR	Poultry	[34]
17	Morocco	*Mcr-1*		PCR	Poultry	[35]
18	Tunisia	*Mcr-1*	*Enterobacteriaceae*	PCR	Poultry	[36]
19	Nigeria	*Mcr-1.1*, *Mcr-5* and *Mcr-8*	*Enterobacteriaceae* and *Alcaligenes faecalis*	PCR and Whole genome sequencing	Humans and animals	[18]

E. coli, *Escherichia coli*; PCR, polymerase chain reaction; qPCR, quantitative polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction.

Table 2
Summary of *mcr* genes detected in manure/soil, aquatic, and wildlife ecosystems.

	Country	Environment	*Mcr*-gene	Sequence type	*Mcr* carrying organisms	Method of detection	Ref
1	Algeria	Farmland	*Mcr-1* *Mcr-3*	ST10, ST405, ST345 ST155	*E. coli*	RT-PCR and sequencing	[44]
2	South Africa	Wastewater	*Mcr-1*		*E. coli*	PCR	[45]
3	Congo	Wastewater	*Mcr-1*		*Pseudomonas aeruginosa*	PCR	[46]
4	Algeria	Wildlife	*Mcr-1*	ST405	*E. coli*	PCR and sequencing	[43]
5	Algeria	Seawater	*Mcr-1*	M49, M78	*E. coli*	PCR and sequencing	[9]
6	Tunisia	Wastewater	*Mcr-1*	ST131, ST3221, ST8900, ST69, ST2142, ST38, ST2460. ST13	*E. coli* *Klebsiella pneumoniae*	PCR and sequencing	[31]

E. coli, Escherichia coli; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction.

plasmid-mediated colistin resistance in 617 isolates from the environment in Africa (Table 2). Per these studies, the farms were reported to be a key reservoir of colistin resistant *E. coli*. Run off from farm soils fertilized with manure in the form of animal droppings might be responsible for the dissemination of AMR genes in the environment. This notion has been reported in certain studies [38]. Such occurrences would undoubtedly further complicate our ability to stall the progression of AMR. Interestingly, a study has reported the ability of anaerobic digestion and composting as effective means of eliminating *mcr* in animal manure [39]; however, a different study has also reported the ability of garbage flies to pick up colistin-resistant organisms from one place and subsequently deposit them on animal manure during feeding or breeding [40]. The ability of certain organisms to transfer *mcr-1* via conjugation further exacerbates the situation at hand. Hence, contact with animal manure and soil as well as direct consumption of raw/undercooked plant products potentially increases the likelihood that *mcr* genes would be dispersed and further strengthen the resistome. Sadly, in Africa, most farmers work with their bare hands without personal protective equipment and vegetables are often consumed raw or undercooked. Therefore, farmers and consumers of raw/undercooked contaminated vegetables/farm crops in Africa are at greater risk of infection by colistin-resistant organisms thriving in manure/soil.

With regard to wastewater treatment plants, its final effluent is a major transfer vehicle for AMR pathogens into the aquatic environment, thus leading to the spread of ABR genes through transfer of genetic material among these pathogens [41]. *E. coli* contamination of water continues to be a persistent problem with undesirable socioeconomic impacts. Hence, the discharge of wastewater (mostly containing *E. coli*) into the environment (farmlands) poses a serious threat to public health [4,42].

A study conducted by Bachiri et al., [43] focused on 86 fresh stool samples collected from January to April 2016 from Barbary macaques (*Macaca sylvanus*). Isolates from the Barbary monkey were found to carry *mcr-1* carrying ST405/ phylogroup D *E. coli* strain implying zoonosis of extraintestinal pathogenic *E. coli* clone circulating colistin resistance in the wild. The presence of genes encoding extended spectrum beta-lactamase (ESBL) and plasmid-mediated quinolone resistance (PMQR) in the strain suggests that wildlife may transmit genes imparting antibiotic resistance as a last resort. It also suggests that the ST405 *E. coli* clone spreads ESBL globally. Direct contact with humans/animals, eating vegetables/fruits, or drinking contaminated water are possible routes through which monkeys acquire the ST405 extraintestinal pathogenic *E. coli* clone.

In Africa, people delight in settling around water bodies and as such make use of the water for their daily activities, such as drinking, bathing/swimming, washing, cooking, and even fishing. Unfortunately, there are reports that surface waters contain colistin-resistant organisms and this poses a considerable threat to public health, especially to those inhabiting the areas surrounding the water bodies [40].

4. Conclusions

Mobile colistin resistance in Africa is an imminent threat that must be dealt with swiftly through proactive steps. Its explosion has the capacity to spread to other continents and, as such, the World Health Organization (WHO) must pay particular attention to this phenomenon.

The review indicated that organisms harbouring the *mcr* genes are widespread among humans, animals, and the environment in the African region. Among these isolates, *E. coli* was the chief culprit responsible for *mcr* transmission, with Tunisia, Algeria, and South Africa having the highest reported rates of transmission.

The use and or abuse of colistin is the clear reason why MGCB is being isolated from natural water bodies in Africa. This has had an inevitable impact on the transmission dynamics of colistin-resistant organisms alongside the evolution rate of plasmid-mediated colistin-resistant strains found in the environment.

Mcr genes have spread into the wild in Africa; implying that the genes are maintained in environmental bacterial populations regardless of environmental selective pressures. This has occurred by means of horizontal/lateral and vertical transfer of the various *mcr* genes (*mcr-1, mcr-2, mcr-3, mcr-5, mcr-8*, and *mcr-9*). Even among enterobacterial clones that are zoonotic and virulent, the transmission of the *mcr* genes is non-clonal.

It is hypothesized that the implicated genes have been exported via international travel and the trade of animal/plant products between the various regions and countries of Africa. These actions further stresses the need for the One Health approaches that are coordinated at the continental and hence international level.

Declaration of competing interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

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