Molecular mechanisms of colistin resistance in Africa: A systematic review of literature

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Abstract

Introduction **Updated and comprehensive data on the mechanism underlying colistin resistance is lacking in Africa.**

Literature search **Herein, we aimed to review available literature on the molecular mechanisms of colistin resistance in Africa. PubMed, Google Scholar, and African Journal online databases were searched on the 15th of January 2020 for original research articles that reported mechanisms of colistin resistance in any of the 54 African countries.**

Review **Of the 1473 studies identified through initial database search, 36 met the inclusion criteria. Colistin resistance was mostly observed in *Escherichia coli* isolated from human clinical samples. Plasmid-mediated colistin resistance mechanism (26; 72.2%) was the most frequently reported resistance mechanism. About three-quarters (27; 75.0%) of the 36 studies were done in North Africa. In this zone, the mobilized colistin resistance (*mcr)* genes were mostly detected in *E. coli* harboring three plasmid types, *IncHI2*, *IncI2*, and *IncX4*, from animal samples (n=9; 42.8%). Of the six studies performed in Southern Africa, four reported *mcr-1* mostly detected from human samples (n=2; 50.0%) in *E. coli* isolates carrying *IncHI2*, *IncI2*, and *IncX4* with diverse range of STs. One hitherto unknown mutation, the mutation in the *I527N* gene was detected in colistin resistant isolates in this region, which was absent in colistin susceptible isolates. In West and Central Africa, two and one studies, respectively, reported *mcr-1* gene exclusively in *Escherichia coli* isolates.**

Conclusions **Transferable plasmid mediated colistin resistance is rapidly emerging in Africa with *mcr-1* as the predominant genetic variant in human, animals, and environmental samples.**

Keywords **Colistin resistance, mechanisms, mobilized colistin resistance, Gram-negative bacteria, Africa.**

Introduction

The emergence of multidrug resistant bacterial infections is one of the greatest threats today to the global public health.[1] It arises naturally as one of the direct consequences of antibiotic use.[2] Its abuse particularly in animal production and aquaculture has further driven the emergence and spread of antibiotic resistance, leading healthcare practice towards a post-antibiotic era.[3] Resistance to all important classes of antibiotics including carbapenems, has been reported particularly among the clinically important pathogens, the ESCAPE pathogens, with substantial impact on morbidity, mortality and attendant increase in healthcare cost.[4] Further exacerbating the problem is the lack of new antibiotics classes in the pipeline, owing to decline in research and development of new effective anti-infective agents.[5] Consequent upon this, old antibiotics such as colistin, which were initially abandoned due to patient safety concerns, were recalled as a life-saving and last resort measure against serious Gram-negative bacterial infections.[6]

Colistin is one of the five polymyxin antibiotics originally isolated in 1947 from the

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soil bacterium *Paenibacillus polymyxa* subsp. *Colistinus*.[7] It is a polycationic lipopolypeptide that acts by competitively displacing divalent cations, Mg^{2+} and Ca^{2+}, from the phosphate group of lipopolysaccharides of Gram-negative cell envelope, thereby disrupting cell membrane integrity and leading to leakage of important cellular components and ultimately bacterial cell death.[7] It has also been shown to act by inhibiting a key respiratory enzyme, type II NADH-quinone oxidoreductases (NDH-2).[7] Colistin is highly and rapidly bactericidal against susceptible bacterial species particularly *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and most members of Enterobacteriaceae family with the exception of *Providencia* spp., *Morganella morganii*, *Proteus* spp., *Serratia marcescens*, among others which are naturally resistant.[8]

Until recently, acquired resistance to colistin has been mostly due to chromosomal mutation in the *PmrA/PmrB* and *PhoP/PhoQ* two-component regulatory systems, or through increased production of capsular polysaccharide.[8] Mutational inactivation of *mgrB*, a negative regulator of the *PhoP/PhoQ* signaling system has also been identified in several studies as a basis for colistin resistance.[8–10] The transferable plasmid encoded colistin resistance (the mobilized colistin resistance or *mcr-1*) emerged in China in late 2015.[11] Today, nine other families of *mcr* genes have been detected from various hosts and pathogens range.[9,10,12] The *mcr* genes have now been globally disseminated and it continues to be increasingly reported worldwide.[13]

While the molecular mechanisms underlying colistin resistance have been described considerably in North America, Europe and more particularly in Asia, updated and comprehensive data on the different mechanisms of colistin resistance are lacking in Africa. We therefore aimed to systematically review available literature on the molecular mechanisms of colistin resistance in African countries, to determine the most prevalent colistin resistance mechanisms, the circulating colistin resistant Gram-negative bacteria clones and hosts in Africa.

Methods

Literature search

A systematic literature search was conducted to identify articles reporting colistin resistance in Africa. Multiple searches were conducted in PubMed, Google Scholar, and African Journal online (AJOL). Our search strategy uses different relevant keywords: "colistin resistance" OR "mobilized colistin resistance gene" OR "mcr" AND Africa, or names of the 54 African countries. The present study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14]

Study selection

Publications identified were considered up to January 15, 2020. Searches undertaken were not restricted by language. Two authors independently performed the literature search. After removing duplicates, the studies identified in the initial search were first screened by title and abstract and retained if they met the predefined inclusion criteria, as follows: (i) original article published or accepted in a peer-reviewed journal, (ii) studies that described mechanism of colistin resistance in humans, animals and environment, and (iii) studies conducted in any of the 54 Africa countries. Full text of the articles that met the inclusion criteria were retrieved and further screened. Studies that reported phenotypic prevalence of colistin resistance without investigation of molecular basis underlying the resistance were excluded. Also, studies conducted outside the specified period of this systematic review were excluded. The screening process was documented in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of the study selection.

Data extraction

Two reviewers independently extracted the relevant data, using a standardized collection form to extract data from the included articles. The following data were extracted from each study: name of country in which the study was conducted, the first author's name, year of publication, sources of isolates

(human/animal/environment), bacterial species, plasmid type, genes detected, number of *mcr* positive bacteria, sequences types (ST), number of isolates exhibiting colistin resistance, medical condition (for human), and result of antibiotic susceptibility testing.

Data analysis

The data collected, including the countries, sources of isolates, bacterial species, plasmid type, genes detected, number of *mcr* genes positive bacteria, and sequences types (ST), were analysed using Microsoft Excel 2013. Descriptive statistics including frequencies and percentages were used in the analysis.

Results

Literature search and study selection

A total of 1493 non duplicate, potentially relevant studies were identified and retrieved from the databases. After screening of the titles and abstracts, 1414 articles were considered irrelevant and excluded. Of the 59 full text articles considered of interest and assessed for eligibility, only 36 articles met the inclusion criteria and were included in the final analysis (Figure 1). Based on the included studies, the first article on colistin resistance in Africa was published in 2014.

Characteristics and distribution of studies describing colistin resistance in Africa

This systematic review involved a total of 36 studies conducted in seven countries namely Tunisia (n=7), South Africa (n=6), São Tomé and Príncipe (n=1), Nigeria (n=2), Libya (n=1), Egypt (n=8), and Algeria (n=11) (Figure 2). The studies were published between 2014 and 2019. The studies documented colistin resistance mechanisms in bacterial isolates obtained from humans (21; 58.3%), animals (10; 27.8%) and environmental samples (3; 8.3%). In the included studies, colistin resistance mechanism was described in mainly three bacterial species comprising *A. baumannii*, *Escherichia coli* and *Klebsiella pneumoniae*. Colistin resistance was most frequently observed in *E. coli* isolated from human clinical samples. Both chromosomal and plasmid mediated mechanisms were reported, with plasmid-mediated colistin resistance mechanism (26; 72.2%) most frequently reported (Figure 3).

Overall, the studies described colistin resistance in 904 bacterial isolates, 188 (20.79%) of which harbored various *mcr* genes. Of the 188 *mcr* genes detected, *mcr-1* was the most prevalent. Among the 188 isolates in which the presence of *mcr* genes has been reported, 88 (46.80%) reported the types of plasmid. The *mcr* genes were mostly harbored on an *IncHI2* plasmid (n=50; 56.82%), followed by *IncI2* (n=19; 21.59%).

Distribution of *mcr* genes in various Africa regions

North Africa

About three-quarters (27; 75.0%) of the 36 studies were done in North Africa. The prevalence of *mcr* genes was 17.53% among colistin resistant isolates. A total of 21 studies reported *mcr* genes in three countries: Tunisia (n=5), Egypt (n=8), and Algeria (n=8) (Figure 2). The *mcr* genes included *mcr-1* (n=18; 85.9%), *mcr-1* and *mcr-2* (n=1; 4.7%), *mcr-1* and *mcr-3* (n=1; 4.7%), and *mcr-8* (n=1; 4.7%). The *mcr* genes were equally detected from samples obtained from animals (n=9; 42.8%) and humans (n=9; 42.8%). The presence of *mcr* genes was reported in only *Escherichia coli* and *Klebsiella pneumoniae*. Four plasmid types were reported. All of them were reported from *Escherichia coli* and harbored *mcr-1* with *IncHI2* (n=3) as the most prevalent *mcr* associated plasmid encountered in North Africa (Table 1).

The most commonly reported sequence type was ST10 reported in all three countries. Tunisia reported the most diverse range of STs (8 types), followed by Algeria (5 types). The presence of *mgrB* mutation was detected in *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Acinetobacter baumannii*.

Southern Africa

In Southern African, six (16.6%) of the 36 studies were conducted in the region. The prevalence of *mcr* genes was 31.85% among

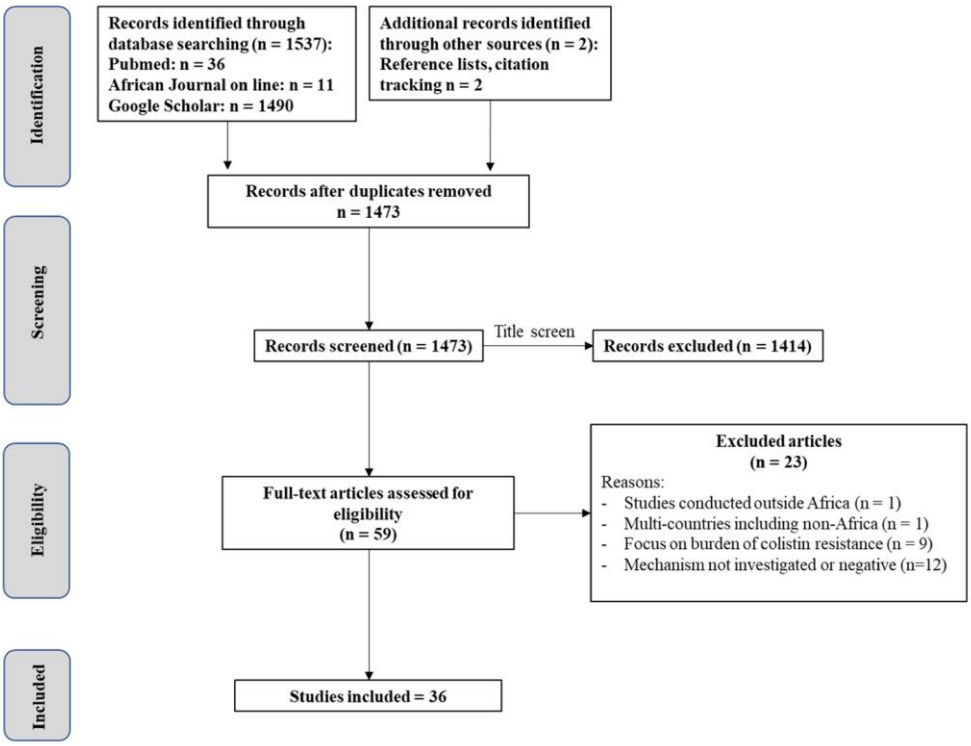

Figure 1. Literature research and study selection

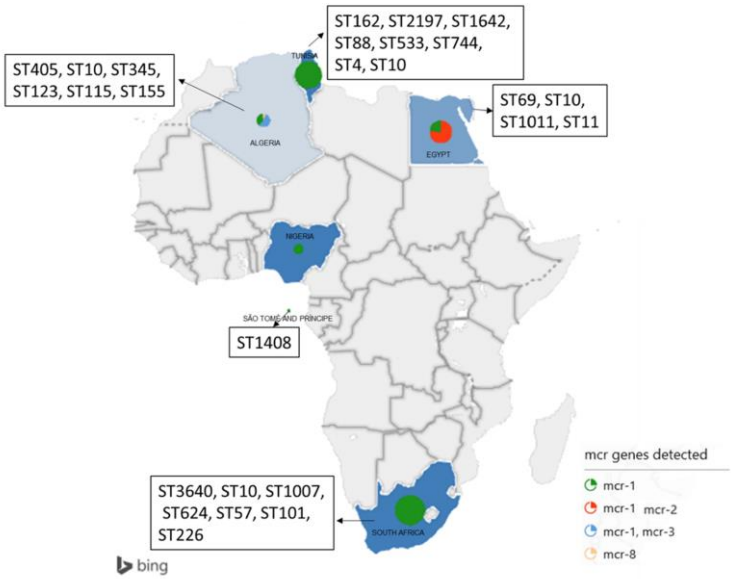

Figure 2. Geographical distribution of the study countries

colistin resistant isolates. Four studies reported *mcr* genes, exclusively *mcr*-1. They were mostly detected from human samples (n=2; 50.0%) followed by animal sample (n=1; 25.0%), environment sample (n=1; 50%) and food (n=1; 4.4%). Diverse range (8 types) of STs including ST1, ST10, ST14, ST57, ST101, ST226, ST624, ST1007 were reported. The presence of *mcr-1* genes was reported in *Escherichia coli* and *Klebsiella pneumoniae*. Three plasmid types including *IncHI2*, *IncI2*, and *IncX4* were reported. The three plasmids were contained in *E. coli*

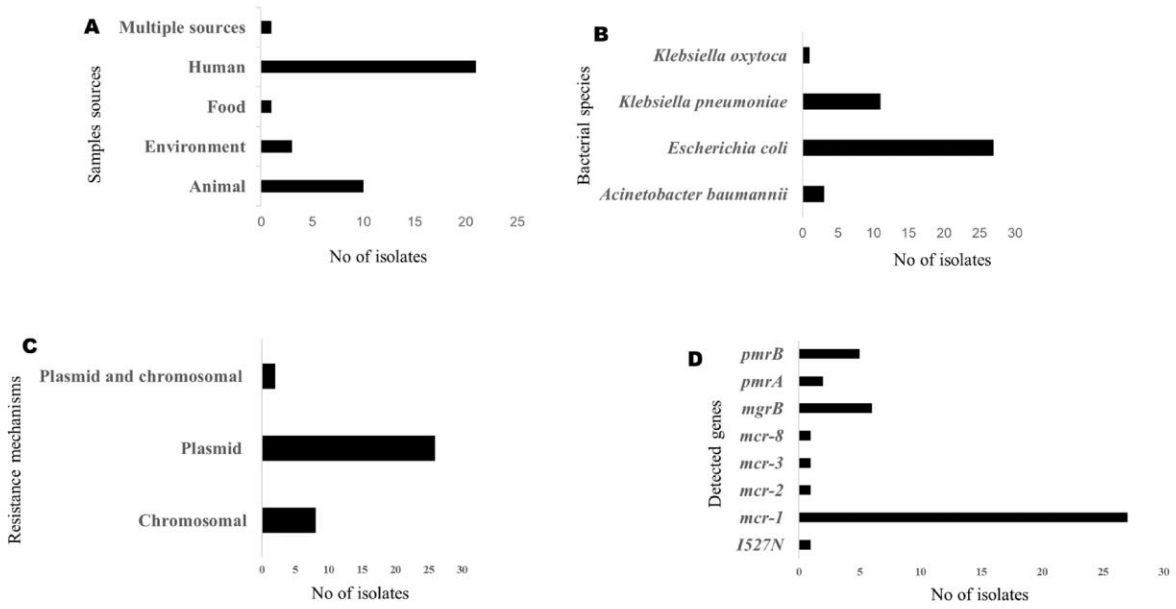

Figure 3. Characteristics of colistin resistance in Africa

isolates and harbored *mcr*-1 (Table 2). Interestingly, one hitherto unknown mutation, the mutation in the *I527N* was detected in colistin resistant isolates in this region, which was absent in colistin susceptible isolates. Since then, this gene has not been detected in other regions.

West Africa

In the West Africa region, only 2 (5.5%) of the 36 studies reported the mechanism of colistin resistance during the study period. The two studies were conducted in Nigeria and exclusively reported *mcr-1* genes in *Escherichia coli* isolates (Table 3). The prevalence of *mcr* genes was 26.92% among colistin resistant isolates. The genes were detected from human sample (n= 1; 50.0%) and multiple sources sample (n=1; 50.0%). The plasmid and sequence type were not determined.

Central Africa

In this region, only a study conducted in São Tomé and Príncipe reported the mechanism of colistin resistance. This study reported the isolation of an *Escherichia coli* ST1408 isolate from a human sample which harbored *mcr-1* on an *IncX4* plasmid (Table 4).

Discussion

Until recently, acquired resistance to colistin has been mostly due to chromosomal mutation. The transferable plasmid encoded colistin resistance emerged in China in late 2015.[11] Since then, eight other families of *mcr* genes have been detected from various hosts and pathogens range across the world.[9,15] As illustrated in this study, the diversity of colistin resistance mechanisms in the various African countries is also changing.

Our finding showed that *mcr* genes have been reported in six African countries. The lack of data from several African countries may not be unconnected with lack of/inadequate laboratory capacity for their detection. The emergence of these transferable colistin resistance mechanisms may be attributed firstly to the high use of colistin as growth promoters, prophylactic and other agricultural use in many African countries.[16] In a survey conducted by World Organization for Animal Health, 15% of African countries authorized the use of antibiotics including colistin in food animals.[16] Secondly,

the importation of food from countries including France and China where colistin resistance is endemic may have also contributed to the emergence of colistin resistance.[13,17] Importation of antibiotic resistant bacteria across geographical regions has been well documented in the literature.[18] China for example is Africa's leading commercial partner. Thus, there are large travel volumes through which the transferable plasmid encoded colistin resistance could reach the continent. Algeria, Egypt, Nigeria and South Africa were China's most important trading partners in Africa and consequently the countries at highest importation risk.[19]

In this study, the *mcr* genes bearing bacteria were prevalently reported in *Escherichia coli* and *Klebsiella pneumoniae*. The predominance of *Escherichia coli* among the isolates bearing *mcr* genes is consistent with a result of a previously published systematic review of literature on the global burden of *mcr* genes.[13] Similarly, another study systematic review in Latin America and Caribbean showed that *mcr* genes were more predominantly harbored by *Escherichia coli*.[20] The prevalence of *Escherichia coli* and *Klebsiella pneumoniae* among *mcr* bearing isolates in this study may be related to the source of exposure of the isolates to colistin. Colistin contained in food animal's feeds is usually the source of exposure of gut bacteria particularly *Escherichia coli* and *Klebsiella pneumoniae* to colistin.[17]

Similar to reports of studies in Europe,[21] *IncHI2* is the most frequently reported *mcr* bearing plasmid type in African countries. Moreover, *IncHI2* plasmids are especially known for co-localization of various antibiotic resistance determinants.[22] This plasmid has been isolated from contaminated food, animals and water, thereby supporting the fact that the global trade of food and animals is a major vehicle for dissemination of *mcr* genes and other antibiotic resistance genes in Africa.[23] Thirdly, since antibiotic use, no matter how appropriate, contributes to antibiotic resistance, over prescription of polymyxins by health workers as alternative to carbapenem as a last resort agent against MDR Gram-negative bacteria infections may have contributed also to the rapidly emerging transferable colistin resistance in Africa.[13]

Findings from this study show that most of the studies that reported *mcr* genes were performed in North Africa. This may be due beside the aforementioned factors, to the North African countries' collaboration and proximity with Europe, particularly with France. As we all know, these countries are low- or middle-income countries with poor medical and healthcare infrastructure. The proximity to Europe may account for the high prevalence of *mcr* genes in North Africa as the *mcr* bearing bacterial species could be easily imported due to high human and materials traffic between the countries. Also, the cordial collaboration between North Africa and Europe ensures access to state-of-the-art healthcare facility and improved human capacity for detection of this emerging resistance mechanism.

Of the ten families of *mcr* genes detected from various hosts and pathogens range in the world, four including *mcr-1*, *mcr-2*, *mcr-3* and *mcr-8* were detected in Africa. Similar to a report from other regions around the world,[24] ST10 is the dominant ST in both animals and environmental samples. The ST10 bearing bacteria are known to co-produce other antibiotic inactivating enzymes such as ESBLs and carbapenemase.[25,26] This may have wide range implication on the management of infections caused by these bacteria.

This systematic review is limited by a number of factors. First, this review reports data from studies published in electronic databases and indexed in Google Scholar, PubMed and AJOL. Several unpublished theses and dissertations and articles published in traditional local print journals could not be assessed and so they were not included. Secondly, studies reporting the burden of colistin resistance without the corresponding report of the molecular basis of the resistance were excluded. As such, the burden of *mcr* genes in Africa may have been underestimated. Nevertheless, this systematic review is the first to determine the Africa wide burden and distribution of *mcr* genes. It thus provides a baseline data on this rapidly emerging resistance mechanism.

Conclusions

This study shows that the transferable plasmid mediated colistin resistance is rapidly emerging in Africa with *mcr-1* as the predominant genetic variant in human, animals as well as in the environmental samples. This is worrisome in a continent where alternative antibiotics are rarely available. Therefore, there is urgent need to establish African-wide antibiotic stewardship and intensify efforts to preserve the efficacy of colistin as a last resort antibiotic.

Authors' contributions statement: AY and AO conceived and designed the study. AO collected the data. AY analyzed the data; AY and AO drafted and revised the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors – none to declare.

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Table 1. Distribution of the studies describing colistin resistance in North Africa

Country	Year	Source	Organism	Number of isolates exhibiting colistin resistance	Mechanism	Plasmid	Genes detected	Number of isolates positives for *mcr* genes	ST	References
Algeria	2014	Human	*Acinetobacter baumannii*	1	Chromosomal	NA	*PmrB*	NA	ND	[27]
Egypt	2019	Food	*Escherichia coli*	1	Plasmid	IncHI2A and IncHI2	*mcr-1*	1	ST69	[28]
Algeria	2017	Animal	*Escherichia coli*	1	Plasmid	ND	*mcr-1*	1	ST405	[29]
Tunisia	2019	Animal	*Escherichia coli*	5	Plasmid	IncHI2	*mcr-1*	5	ST162	[30]
Tunisia	2019	Animal	*Escherichia coli*	1	Plasmid	IncHI2	*mcr-1*	1	ND	[31]
Algeria	2016	Animal	*Escherichia coli*	5	Plasmid	ND	*mcr-1*	3	ND	[32]
Tunisia	2016	Animal	*Escherichia coli*	37	Plasmid	IncHI2	*mcr-1*	37	ST4	[18]
Tunisia	2018	Animal	*Escherichia coli*	2	Plasmid	IncI1 and incP	*mcr-1*	2	ST2197	[33]
Egypt	2016	Animal	*Escherichia coli*	1	Plasmid	ND	*mcr-1*	1	ST10	[34]
Algeria	2019	Environment	*Escherichia coli*	103	Plasmid	ND	*mcr-1*, *mcr-3*	6	ST10, ST155, ST345 and ST405	[35]
Tunisia	2019	Animal	*Escherichia coli*	4	Plasmid	ND	*mcr-1*	4	ST1642	[36]
Algeria	2016	Human	*Escherichia coli*	1	Plasmid	IncFIB	*mcr-1*	1	ST405	[37]
Algeria	2016	Human	*Escherichia coli*	6	plasmid	ND	*mcr-1*	1	ST405	[38]
Egypt	2016	Human	*Escherichia coli*	1	Plasmid	ND	*mcr-1*	1	ST1011	[39]
Algeria	2019	Human	*Escherichia coli*	1	Plasmid	ND	*mcr-1*	1	ND	[40]
Egypt	2019	Human	*Escherichia coli*	5	Plasmid and chromosomal	ND	*mcr-1*, *pmrA*, *pmrB*	1	ND	[41]
Algeria	2018	Environment	*Escherichia coli*	246	Plasmid	ND	*mcr-1*	2	ND	[42]
Egypt	2019	Human	*Escherichia coli, Klebsiella pneumoniae*	40	Plasmid and chromosomal	ND	*mcr-1*, *mgrb*	2	ST11	[43]
Egypt	2019	Animal	*Escherichia coli, Klebsiella*	34[#]	Plasmid	ND	*mcr-1*,	34	ND	[44]

Country	Year	Source	Organism	Number of isolates exhibiting colistin resistance	Mechanism	Plasmid	Genes detected	Number of isolates positives for *mcr* genes	ST	References
			pneumoniae				*mcr-2*			
Tunisia	2017	Human	*Klebsiella pneumoniae*	7	Chromosomal	NA	*mgrb*	NA	ND	[45]
Tunisia	2018	Human	*Klebsiella pneumoniae*	13	Chromosomal	NA	*mgrb*	NA	ND	[46]
Algeria	2018	Human	*Klebsiella pneumoniae*	3	Chromosomal	NA	*mgrb*, *pmrA/B*	NA	ST101	[47]
Algeria	2019	Human	*Klebsiella pneumoniae*	1	Plasmid	ND	*mcr-8*	1	ND	[15]
Algeria	2018	Human	*Klebsiella pneumoniae*	2	Chromosomal	NA	*mgrb*, *pmrB*	NA	ST2620 and ST3242	[48]
Egypt	2018	Human	*Escherichia coli*, *Klebsiella pneumoniae*	50	Plasmid	ND	*mcr-1*	2	ND	[49]
Egypt	2019	Human	*Escherichia coli*	34	Plasmid	ND	*mcr-1*	1	ND	[50]
Libya	2018	Human	*Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Klebsiella oxytoca*	11	Chromosomal	NA	*mgrb*	NA	ST101	[51]

NA – not applicable; **ND** – not determined; **ST** – sequence type.
#This figure corresponds to the number of resistance genes found because the study didn't specify the exact number of isolates resistant to colistin.

Table 2. Distribution of the studies describing colistin resistance in Southern Africa

Country	Year	Source	Organism	Number of isolates exhibiting colistin resistance	Mechanism	Plasmid	Genes detected	Number of isolates positives for *mcr* genes	ST	References
South Africa	2020	Human	*Acinetobacter baumannii*	26	Chromosomal	NA	*I527N*	NA	ST1	[52]
South Africa	2016	Animal	*Escherichia coli*	108	Plasmid	IncI2	*mcr-1*	19	ND	[53]
South Africa	2016	Human	*Escherichia coli*	7	Plasmid	IncHI2, incI2, IncX4	*mcr-1*	7	ST10, ST1007, ST624, ST57, ST101, ST226	[54]
South Africa	2017	Human	*Escherichia coli, Klebsiella pneumoniae*	19	Plasmid	ND	*mcr-1*	15	ND	[55]
South Africa	2014	Human	*Klebsiella pneumoniae*	1	Chromosomal	NA	*PmrB*	NA	ST14	[56]
South Africa	2018	Environment	*Escherichia coli*	65	Plasmid	ND	*mcr-1*	31	ND	[57]

NA – not applicable; **ND** – not determined; **ST** – sequence type.

Table 3. Distribution of the studies describing colistin resistance in West Africa

Country	Year	Source	Organism	Number of isolates exhibiting colistin resistance	Mechanism	Plasmid	Genes detected	Number of isolates positives for *mcr* genes	ST	References
Nigeria	2019	Human	*Escherichia coli*	21	Plasmid	ND	*mcr-1*	2	ND	[58]
Nigeria	2018	Multiple sources	*Escherichia coli*	5	Plasmid	ND	*mcr-1*	5	ND	[59]

ND – not determined; **ST** – sequence type.

Table 4. Distribution of the studies describing colistin resistance in Central Africa

Country	Year	Source	Organism	Number of isolates exhibiting colistin resistance	Mechanism	Plasmid	Genes detected	Number of isolates positives for *mcr* genes	ST	References
São Tomé and Príncipe	2018	Human	*Escherichia coli*	36	Plasmid	IncX4	*mcr-1*	1	ST1408	[60]

ST – sequence type.