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Molecular epidemiology of antimicrobial resistance in central africa: A systematic review

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Abstract

Background. In Central Africa, it is difficult to tackle antibiotic resistance, because of a lack of data and information on bacterial resistance, due to the low number of studies carried out in the field. To fill this gap, we carried out a systematic review of the various studies, and devised a molecular epidemiology of antimicrobial resistance from humans, animals and the environmental samples.

Method. A systematic search of all publications from 2005 to 2020 on bacterial resistance in Central Africa (Gabon, Cameroon, Democratic Republic of Congo, Central African Republic, Chad, Republic of Congo, Equatorial Guinea, São Tomé and Príncipe, Angola) was performed on Pubmed, Google scholar and African Journals Online (AJOL). All circulating resistance genes, prevalence and genetic carriers of these resistances were collected. The study area was limited to the nine countries of Central Africa.

Results. A total of 517 studies were identified through a literature search, and 60 studies carried out in eight countries were included. Among all articles included, 43 articles were from humans. Our study revealed not only the circulation of beta-lactamase and carbapenemase genes, but also several other types of resistance genes. To finish, we noticed that some studies reported mobile genetic elements such as integrons, transposons, and plasmids.

Conclusion. The scarcity of data poses difficulties in the implementation of effective strategies against antibiotic resistance, which requires a health policy in a 'One Health' approach.

DATA SUMMARY

No data was reused or generated.

INTRODUCTION

Antimicrobial resistance is currently considered an emerging global threat and a major public health problem [1]. The epidemiology of antibiotic resistance among clinical pathogens is essential, particularly for therapeutic management [2]. However, limited

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Keywords: resistance genes; genetic carriers; Central Africa; One Health.
Abbreviations: AJOL, African Journals Online; CAR, Central African Republic; CLSI, Clinical and Laboratory Standards Institute; CPE, carbapenemase-producing *Enterobacteriaceae*; CRPA, ceftazidime-resistant *Pseudomonas aeruginosa*; DRC, Democratic Republic of Congo; ESBL-PE, extended-spectrum beta-lactamase-producing enterobacteriaceae; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HGT, horizontal gene transfer; MRB, multi-resistant bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.
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data are available in Central Africa [3]. Currently, the main multi-resistant bacteria (MRB) responsible for infectious diseases are methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-PE) or cephalosporinase-producing Enterobacteriaceae, ceftazidime-resistant *Pseudomonas aeruginosa* (CRPA), ESBL-producing *Acinetobacter baumanii*, vancomycin-resistant enterococci (VRE), and carbapenemase-producing Gram-negative bacilli (Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter baumanii*) [4].

It should be noted that ESBL-PE are now the most predominant MRBs in many countries [5]. They frequently have resistance to other antibiotics such as fluoroquinolones and aminoglycosides [6]. Carbapenemases are an heterogeneous group of enzymes whose spectrum of activity covers at least one of the carbapenems. In Africa, this type of resistance remains scarce but is related to the risk of therapeutic impasse. Indeed, carbapenems have often been used as the treatment of choice for infectious diseases due to ESBL-PE. This has led to the emergence of carbapenemase-producing Enterobacteriaceae (CPE), which are enzymes hydrolysing all beta-lactams, even carbapenems which are the last line in the treatment for ESBL-PE [7, 8]. There are limited data assessing the impact of different factors on the current rate of antimicrobial resistance in low-income countries [9–11].

While reliable data exist in Europe, the United States, Latin America [12] and Asia [13, 14], very little is available in sub-Saharan Africa [3], particularly in Central Africa where, despite efforts, research on antibiotic resistance is still very weak.

There are two factors in the development of antibiotic resistance, both interdependent and linked to human activity: the excessive use of antibiotics in human and animal health, which leads to the selection of the most resistant bacteria, and the spread of the selected resistant bacteria, through direct transmission within humans and animals ('cross-transmission'), and indirectly through the environment [15]. Horizontal gene transfer (HGT) contributes significantly to the rapid spread of resistance. Multiple mechanisms of HGT liberate genes from normal vertical inheritance. Conjugation by plasmids, transduction by bacteriophages, and natural transformation by extracellular DNA each allow genetic material to jump between strains and species. Thus, HGT adds an important dimension to infectious disease whereby an antibiotic resistance gene can be the agent of an outbreak by transferring resistance to multiple unrelated pathogens [16]. Thus, the use of antibiotics in veterinary medicine and the discharge of antibiotics into the environment contribute to the emergence of new multidrug-resistant bacterial strains. To combat antibiotic resistance, it is necessary to follow a 'One Health' approach that joins efforts of the human, animal and environmental health compartments [17].

In Africa, antimicrobial resistance is increasing to worrisome proportions. Salah *et al*. demonstrate, between 2010 and 2017, an increase in antibiotic resistance of Enterobacteriaceae isolated at the National Institute of Hygiene of Lomé. During this period, the rate of resistance to ceftazidime of *Escherichia coli* strains increased significantly from 18.69–39.26% (P<0.0001); from 1.68–40.22% to ceftriaxone (P<0.0001) and from 42.37–63.23% (P<0.0001) to ciprofloxacin. Resistance of *Klebsiella* spp. strains to ceftazidime increased significantly from 25.26–42.54% (P<0.0001) and to ceftriaxone from 2.17–41.79% (P<0.0001) [18]. It is therefore becoming imperative, in order to combat effectively against the emergence of these resistances, to control the favouring factors and the epidemiology of the different circulating resistance genes and their genetic supports. In this study, we carried out a systematic review of the literature, to collect and compile available data on bacterial resistance in Central Africa, in order to map the circulating resistance genes and their carriers in humans, animals and the environment.

BIBLIOGRAPHICAL METHODS

Study strategy

For this systematic review, we used methodology suggested by the Preferred Reporting Items for Systematic Reviews and meta-analyses as described [19]. Thus, we performed a systematic search of databases such as Medline (Pubmed), Google scholar and African Journals Online (AJOL). Our research focused on the collection of research articles related to antimicrobial resistance in Central Africa published between January 2005 and September 2020. In order to ensure a full search, including all available studies on the topic and in the study area, we have used a combination of keywords. Search terms were 'antibiotic resistance genes', or 'ESBLs', or 'antimicrobial drug resistance' associated with the name of a study area country (Central Africa) as search strategies. The aim was to identify all the circulating resistance genes in the Sub-Saharan region, their prevalence rates and genetic supports (plasmid or chromosome).

Study area

Our study concerns Central Africa, and this Sub-Saharan region of Africa according to the United Nations is made up of nine countries including Gabon, Cameroon, Democratic Republic of Congo (DRC), Central African Republic (CAR), Chad, Republic of Congo, Equatorial Guinea, São Tomé and Príncipe, Angola (Fig. 1). The Central Africa region covers an overall area of 6613000 km^2 and in 2017, the population was estimated around 163495000. In this area, the mean population density of 25 inhabitants per km^2 [20].

Criteria for inclusion in the review and for ineligibility

All studies on bacterial resistance (in English or French), in humans, animals and the environment, which were published within January 2005 to September 2020 were selected. We therefore included studies whose methodology allowed the identification of resistance genes and/or genetic supports.

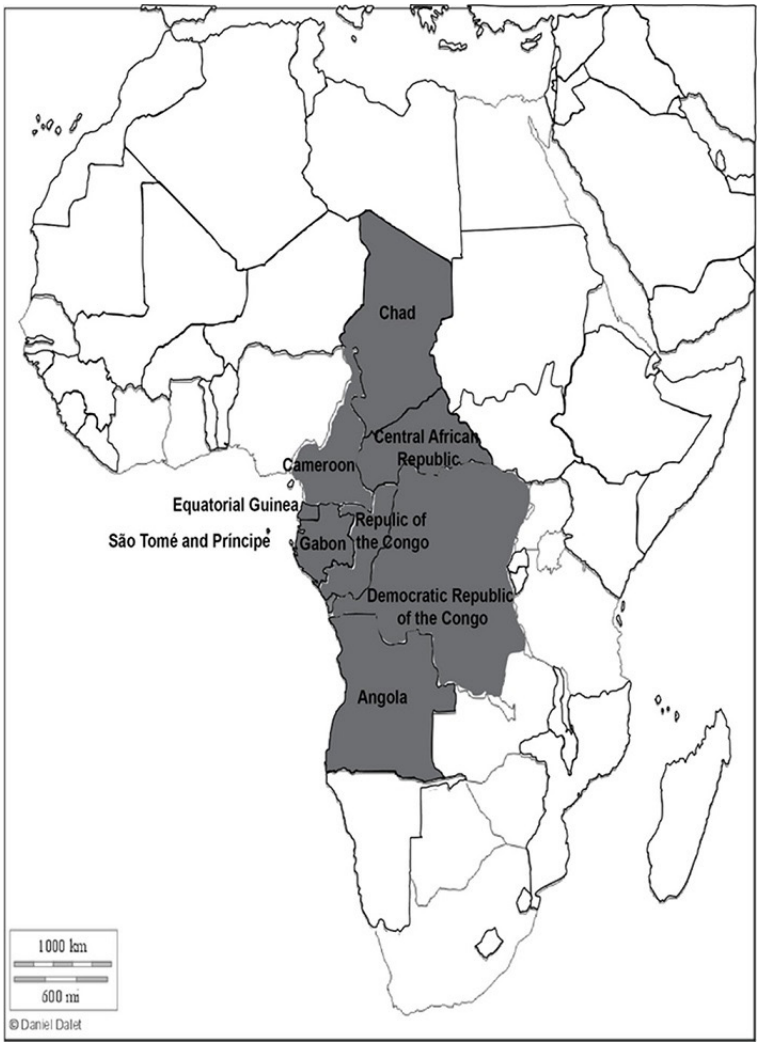

Fig. 1. African card ■ Study area (Central Africa)

We did not include studies carried out in countries outside the study area (Central Africa), and studies that reported only the results of antibiotic susceptibility testing or antimicrobial resistance monitoring, with no molecular tests to characterize resistance genes and/or genetic supports.

Data extraction

After removing studies not fulfilling the eligibility criteria and the duplicates, and after a full reading of each selected article, an essential database for the review was created, including: country, sample source, resistance genes found, prevalence rate of resistance, genetic support for resistance genes, and year of the study, (Tables 1–3) referring to studies in humans, animals and the environment, respectively.

DISTRIBUTION AND CHARACTERISTICS OF THE INCLUDED STUDIES

A total of 517 articles were identified through the search. After reviewing each abstract, 457 articles that did not fulfil eligibility criteria were excluded. The remaining 60 articles were fully and thoroughly reviewed to extract data on bacterial resistance in Central Africa (Fig. 2). The selected articles concerned eight of the nine countries in the region.

With 13 articles each, Gabon and Cameroon had the most, followed by DRC (12), Angola (9), CAR (6), Chad and the Republic of Congo (three each), and São Tomé and Príncipe (2). It should be noted that one paper is counted twice, as the study was carried out in both Angola and São-Tomé and Príncipe. No studies fulfilling the eligibility criteria were found in Equatorial Guinea.

Table 1. Data on bacterial resistance in humans in Central Africa

Country	no. of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemase genes	Rate of CPE (%)	Other resistance genes	Rate of other resistance genes (%)	Genetic elements	Study period	References
Gabon	11	Clinic and	*CTX-M, CTX-M15,*	3–100	*NDM-7*	5.1	**Methicillin**	0.97–96	Transposon	2012 (*n*=1)	[43–45]
		carriage	*CTX-M1, CTX-M8,*		*OXA-48*		*mecA*		IncX3	2013 (*n*=3)	[46–53]
			CTX-M27, TEM,				**Aminoglycosides**		Integrons classes 1 et 2 (IntI1, IntI2)	2014 (*n*=4)	
			TEM-104, SHV,				*aac(6')-ib, aac(3)-IIa*		SCCmec IV	2016 (*n*=3)	
			SHV-12, SHV-28,				*ant(3), aac(3)*		SCCmec V		
			OXA, OXA-9,				*aadA1, aphA-3*		SCCmec non-typable		
			OXA-30, blaZ,				**Sulfonamides**				
			act-17, ampR,				*sul1, sul2, folA*				
			lap-2				**Trimethoprin**				
							dhfr 1, dfrA,				
							dfrG, dfrK +G, dfrB				
							Tetracyclines				
							tetA-2, tetD,				
							tetK, tetM				
							Quinolones				
							qnrS1				
							Fosfomycin				
							fosA				
							Rifampicin				
							arr-ms				
							Macrolides				
							mphA,				
							mpbBM, msr(A)				
							Chloramphenicol				
							cat				
Angola	8	Clinic and	*CTX-M15, CTX-M55,*	22.2–28	*OXA-181,*	27.4 à 78	**Methicillin**	2.5–56	IncX3, IncFIA,	2006 (*n*=1)	[54–56]

Continued

Table 1. Continued

Country	no. of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemase genes	Rate of CPE (%)	Other resistance genes	Rate of other resistance genes (%)	Genetic elements	Study period	References
		carriage	*TEM-1,*		*NDM-1,*		*mecA*		IncA/C,	2011 (*n*=1)	[57–61]
			OXA-1, blaP1		*NDM-5*		**Aminoglycosides**		IncFIB, IncL/M, IncN,	2015 (*n*=1)	
							armA, rmtB		IncY, IncFII, IncHI2	2016 (*n*=2)	
							rmtC, aadA1		Integrons classes		
							aadA8, aph		one et 2 (int1 and int2)		
							Streptomycin		Plasmide non-typable		
							strA, strB		p3iANG		
							Quinolones		SCCmec Iva		
							aac(6')-ib-cr,		SCCmec V		
							qnrB, qnrS,				
							Trimethoprin				
							dfrA1, dfrA15,				
							dfrA18				
							Sulfonamides				
							sul1, sul2				
							Tetracyclines				
							tetG				
							Chloramphenicol				
							cat1, floR				
Cameroon	11	Clinic and	*CTX-M15, OXA-1,*	2–96	*NDM-1, NDM-4*		**Aminoglycosides**	1.79–85.71	pYC-5b, pYC-14	2005 (*n*=2)	[62–64]
		carriage	*OXA-9, OXA-30,*				*aacA4, aac(3)-Iia,*		IncFIA, CoIRNAI,	2012 (*n*=3)	[65–67]
			OXA-50, OXA-395,				*aadA1, aac(6')-Ib,*		IncFIB(K), IncFIA(HI1),	2016 (*n*=1)	[68–70]
			OXA-486, TEM-1,				*aac(3)-Iid, aadA16*		IncHI1B, IncR, CoI,	2018 (*n*=2)	[71, 72]
			TEM_1A, TEM-1B,				*aph(3')-IIb, aph(3')-Ib,*		IncY,	2020 (*n*=3)	
			TEM-116, SHV-1,				*aph(6')-Id, rmtB*		Integron class 1 (int 1)		
			SHV-11, SHV-12,				**Streptomycin**		Transposons		
			SHV-134, PSE-1,				*strA, strB*		(Tn4651, Tn4652)		

Continued

Table 1. Continued

Country	no. of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemase genes	Rate of CPE (%)	Other resistance genes	Rate of other resistance genes (%)	Genetic elements	Study period	References
			PAO, SCO-1				**Quinolones**				
							oqxA, oqxB,				
							QnrB1, aac(6')-Ib-cr,				
							crpP, gyrA, parC,				
							parE, QnrS1				
							Sulfonamides				
							sul1, sul2, sul3				
							Trimethoprim				
							dfrA15, dfrA27,				
							dfr12, dfr7,				
							dfr1a, dfrA14				
							dfrA1				
							Fosfomycin				
							fosA				
							Tetracyclines				
							tetA, tetB, tetD, tetG, tetR				
							Chloramphenicol				
							catA2, cat1,				
							cat2, catB7,				
							catB9, cmlA, floR				
							Rifampicyn				
							ARR-3				
							macrolides				
							mph(A)				
							Glycopeptides				
							vanW				

Continued

Table 1. Continued

Country	no. of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemase genes	Rate of CPE (%)	Other resistance genes	Rate of other resistance genes (%)	Genetic elements	Study period	References
Chad	3	Clinic and carriage	*CTX-M15, CTX-M27, CTX-M9, CTX-M14, OXA-1, TEM-1*	48	*NDM-5* *OXA-181*	2.5–6.5	**Aminoglycosides** *armA, rmtB, rmtC* **Quinolones** *qnrS, qnrB, qnrD, oqxAB, aac(6′)-Ib-cr, qepA*	0.97–94	IncX3, IncF, IncR non-typeable plasmid, Mobp 5–3 plasmid	2019 (*n*=3)	[73–75]
Democratic Republic of Congo	6	Clinic and carriage	*CTX-M15, SHV-12, OXA-1, TEM-1 SHV-2a, TEM-1b, CMY*	10	NA	–	**Aminoglycosides** *AAC3, ANT2, ANT3, APH3, APH6, aac(6′), aph(2″) aph(3′), ant(4′), aac(6′)-Iaa* **Quinolones** *aac(6′)-Ib-cr, qnrB, qnrB1, qnrS, gyrA* **Tetracyclines** *tetA, tetB, tetD, tetM, tetK* **Sulfonamides** *folP, sul1, sul2* **Macrolides** *mphA, erm(A), erm(B), erm, erm(T)* **Chloramphenicol** *cat, catA, catB, catA1* **Rifampicyn**	–	IncFIB69, IncFII105, IncFII107, SCCmecV	2012 (*n*=1) 2013 (*n*=1) 2015 (*n*=2) 2017 (*n*=1) 2019 (*n*=1)	[76–78] [79–81]

Continued

Table 1. Continued

Country	no. of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemase genes	Rate of CPE (%)	Other resistance genes	Rate of other resistance genes (%)	Genetic elements	Study period	References
							Arr				
							Trimethoprim				
							DHFR, dfrG,				
							dfrK, dfrA1				
							Methicillin				
							mecA				
							Streptomycin				
							strA, strB				
Republic of	3	clinic	*CTX-M15, TEM-1,*	9.30–74.42	*OXA-181*	6.97	**Methicillin**	22.22–60	NA	2019 (*n*=3)	[82–84]
Congo			*SHV-1, SHV-85*				*mecA*				
							Colistin				
							mcr-1				
Central	6	Clinic and	*CTX-M15, CTX-M3,*	–	NA	–	**Aminoglycosides**	13–97	IncF, IncHI2,	2006 (*n*=1)	[85–87]
African Republic		carriage	*CTX-M27, CTX-M127*				*aac(6')-Ib, aacC3,*		IncFIB, IncQ1	2007 (*n*=1)	[88–90]
			TEM-1, OXA-1, OXA30,				*aadA1, aadA2,aadA5*			2014 (*n*=1)	
			SHV-2a, SHV-12				*tmrB*			2015 (*n*=1)	
							Streptomycin			2016 (*n*=1)	
							strA, strB			2019 (*n*=1)	
							Chloramphenicol				
							catB3, catA1				
							Trimethoprim				
							dfrA14, dfrA7,				
							dfrA1, dfrA5, dfrA2d				
							dfr12, dfrA17				
							Sulfonamides				
							sul1, sul2, sul3				

Continued

Table 1. Continued

Country	no. of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemase genes	Rate of CPE (%)	Other resistance genes	Rate of other resistance genes (%)	Genetic elements	Study period	References
							Tetracyclines				
							tetA, tetB, tetD				
							Quinolones				
							aac(6')-Ib-cr, qnrB,				
							qnrB1, qnrS, oqxA,				
							oqxB, qepA, qnrS1				
São Tome and	2	carriage	*CTX-M15, TEM-1*	–	*Oxa-181*	44	**Methicillin**	2.78–16	SCCmec Iva	2018 (*n*=2)	[59, 91]
Príncipe							*mecA*		IncX3		
							Aminoglycosides		IncX4		
							rmtB				
							Colistin				
							mcr-1				

ESBL: Extended Spectrum Beta-lactamase; ESBL-PE: Extended Spectrum Beta-lactamase-Producing Enterobacteriaceae; CPE: Carbapenemase-Producing Enterobacteriaceae; %: Percentage
N.B: One study, carried out in both countries, was recorded in Angola and Sao Tome and Principe.

Table 2. Data on bacterial resistance in animals in Central Africa

Country	Number of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemase genes	Rate of CPE (%)	Other resistance genes	Rate of other resistance genes (%)	Genetic elements	Study period	References
Gabon	3	Gorilla	*CTX-M1, CTX-M14,*	5.9–41.2	NA	–	**Aminoglycosides**	50	NA	2014 (*n*=1)	[49, 92]
		Chicken	*CTX-M15, CTX-M32*				*aac(6′)-ib, acc(3)-II*			2015 (*n*=1)	[93]
		Bat	*TEM, SHV, SHV-11*				*aadA1, aadA2,*			2020 (*n*=1)	
							aadA5				
Angola	2	Cow	*CTX-M15*	25–75	NA	–	**Streptomycin**	56	IncFIB, IncY,	2014 (*n*=1)	[60, 94]
		Pig	*TEM-1*				*strA*		IncN, IncI1,	2015 (*n*=1)	
		Chicken	*OXA-1*				**Quinolones**		IncFIIk6,		
							aac(6′)-ib-cr, qepA,		IncFII36		
							qnrB, qnrS				
							Tetracyclines		Integrons classes		
							tetA, tetB, tetD		one et 2 (int1,int2)		
							Sulfonamides				
							sul1, sul2				
							Trimethoprin				
							dfrA15				
							Chloramphenicols				
							catA1, cmlA				
Cameroon	2	Pig	, *CTX-M15*	21.52	NA	–	**Methicillin**	–	SCCmectypeVc	2018 (*n*=2)	[67, 95]
			TEM-116, SHV-1, TEM-1B,				*mecA*		CoIRNAI, CoIE10,		
			SHV-27, SHV-28,				**Macrolides**		IncFIB (K),		
			blaZ, SCO-1				*ermB, ermC,*		IncFIA(HI1),		
							mph(A)		IncY, IncFII(K), IncR, CoIE10		
							Tetracyclines				
							tetA, tetK,				

Continued

Table 2. Continued

Country	Number of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemase genes	Rate of CPE (%)	Other resistance genes	Rate of other resistance genes (%)	Genetic elements	Study period	References
							tetL, tetM				
							Aminoglycosides				
							aac(3')-IIa, aadA1				
							Streptomycin				
							strA, strB				
							Quinolones				
							oqxA, oqxB,				
							QnrB1				
							Fosfomycin				
							fosA				
							Sulfonamides				
							sul1, sul2				
							Trimethoprim				
							dfrA15				
							Chloramphenicols				
							catA1				
Central	1	gorillas,		–	NA	–	**Aminoglycosides**	–	NA	2014	[87]
African		Agile mangabeys	*CTX-M2, CTX-M15, TEM-1, SHV-62*				*aadA1, aadA2,*				
Republic		chimpanzees,					*aadA5*				
		African buffalos,					**Quinolones**				
		Forest elephants,					*qnrB33, qnrB17,*				
		Red River hogs,					*qnrB28, oqxA,*				
		duikers,					*qepA, qnrS1*				
		Lowland bongos,					**Sulfonamides**				
		Sitatunga					*sul1, sul2*				

Continued

Table 2. Continued

Country	Number of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemase genes	Rate of CPE (%)	Other resistance genes	Rate of other resistance genes (%)	Genetic elements	Study period	References
							Tetracyclines				
							tetA, tetB				
							Chloramphenicols				
							catA1				
							Trimethoprim				
							dfr12, dfrA17,				
							dfrA7				
							Streptomycin				
							strA, strB				

ESBL: Extended Spectrum Beta-lactamase; ESBL-PE: Extended Spectrum Beta-lactamase-Producing Enterobacteriaceae; CPE: Carbapenemase-Producing Enterobacteriaceae; %: Percentage

Table 3. Data on bacterial resistance in the environment in Central Africa

Country	Number of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemasegenes	Rate of CPE (%)	Other resistancegenes	Rate of other resistances (%)	Genetic elements	Studyperiod	References
Angola	1	Floors, walls wastewater treated water for humanconsumption water for animalconsumption urbansewer line river	*CTX-M15* *TEM-1* *OXA-1*	30	NA	–	**Quinolones** *aac(6')-ib-cr*	–	IncFII36 IncHI2 IncY chromosome (CTX-M15)	2015 (*n*=1)	[60]
Cameroon	1	wastewater	*CARB3*, *CARB5*, *CfxA6, CMY1*, *CMY59, GES21*, *NPS, AER1*, *OXA1, OXA164*, *OXA212, OXA226*, *OXA232, OXA256*, *OXA347, OXA-46*, *OXA-5, OXA-9*, *SHV100, TEM126*, *VEB-3, LCR1*	5.2–15	AIM1 *IMP11, IMP12*	–	**Aminoglycosides** *aac(6')–29a, aac(6')Iia*, *aad(6), aadA*, *aac(6')-Ib7, aadA13*, *aadA15, aadA16*, *aac(6')-Ie-aph(2'')-Ia*, *aadA4, aadA7*, *ant(2'')-Ia, ant(3')-Ii*, *aac(6')-Iid, ant(4')Ib*, *ant(4')-Iib, ant(6)Ia*, *ant(6)-Ib, ant(9)-Ia*, *aph(3')-Ia, aph(3'')Ib*, *aph(3'')-Ic, aph(3')Iic*, *aph(3')-IIIa, aph(6)Id*,	2.8–80	CoIE,IncA/C, IncB/O/K/Z. Inc FIA, IncFIB, IncFIC, IncFII, IncH, IncH, IncI, IncI, IncN, IncP, IncB, IncR, IncT, IncU, IncY, IncW, IncX	2019 (*n*=1)	[96]

Continued

Table 3. Continued

Country	Number of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemasegenes	Rate of CPE (%)	Other resistancegenes	Rate of other resistances (%)	Genetic elements	Studyperiod	References
							armA				
							Chloramphenicol				
							Cat, catB3,				
							catI, catQ,				
							cat-TC, flor				
							Rifampicyn				
							ARR-3				
							Quinolones				
							oqxA, oqxB,				
							qnrB41, qnrD2,				
							qnrS6, qnrVC1,				
							qnrVC4				
							Macrolides				
							ereA2, ereB,				
							erm(33), erm(47),				
							ermB, ermC,				
							ermF, ermG,				
							ermQ, ermT,				
							ermX, lnuA,				
							lnuB, lnuC,				
							mefA, mefB,				
							mefCmphA,				
							mphE, mphG				
							Phosphonicantibiotics				
							fosA2, fosA5,				
							fosB				

Continued

Table 3. Continued

Country	Number of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemasegenes	Rate of CPE (%)	Other resistancegenes	Rate of other resistances (%)	Genetic elements	Studyperiod	References
							Streptogramins				
							vgaC				
							Sulfonamides				
							sul1, sul2, sul3				
							Trimethoprin				
							dfrA1, dfrA10,				
							dfrA12, dfrA14,				
							dfrA16, dfrA19,				
							dfrA23, dfrA3,				
							dfrA8, dfrB3,				
							dfrC, dfrD,				
							dfrE, dfrF,				
							dfrG				
							Tetracyclines				
							tet31, tet32,				
							tet33, tet36,				
							tet38, tet39,				
							tet40, tet44,				
							tetA(P), tetB(P),				
							tetC, tetD,				
							tetE, tetG,				
							tetH, tetK,				
							tetL, tetM,				
							tetO, tetQ,				
							tetS, tetT,				
							tetV, tetW,				

Continued

Table 3. Continued

Country	Number of reports	Source of samples	ESBL and other β-lactamases genes	Rate of ESBL-PE (%)	Carbapenemasegenes	Rate of CPE (%)	Other resistancegenes	Rate of other resistances (%)	Genetic elements	Studyperiod	References
							tetX, tetY,				
							tetZ				
							Nucleosideantibiotics				
							sat-1, sat-4				
Democratic	6	Wastewater +	*CTX-M1* group,	5.3–7.4	*OXA-48, KPC,*	–	**Aminoglycosides**	–	NA	2012 (*n*=2)	[97, 98]
Republic of Congo		drinking water	*CTX-M, TEM,*		*VIM, IMP,*		*aadA*			2016 (*n*=1)	[99, 100]
			SHV-2, SHV-18		*NDM*		**Sulfonamides**			2019 (*n*=1)	[101, 102]
			SHV, OXA,				*sul1, sul2, sul3*			2020 (*n*=2)	
							Tetracyclines				
							tetB				
Republic of Congo	2	householdwastewater	*TEM-1*	9.30–74.42	NA	–	**Methicillin**	47.36	NA	2019 (*n*=2)	[82, 84]
			CTX-M15, SHV-1, SHV-85				*mecA*				

ESBL: Extended Spectrum Beta-lactamase; ESBL-PE: Extended Spectrum Beta-lactamase-Producing Enterobacteriaceae; CPE: Carbapenemase-Producing Enterobacteriaceae; %: Percentage

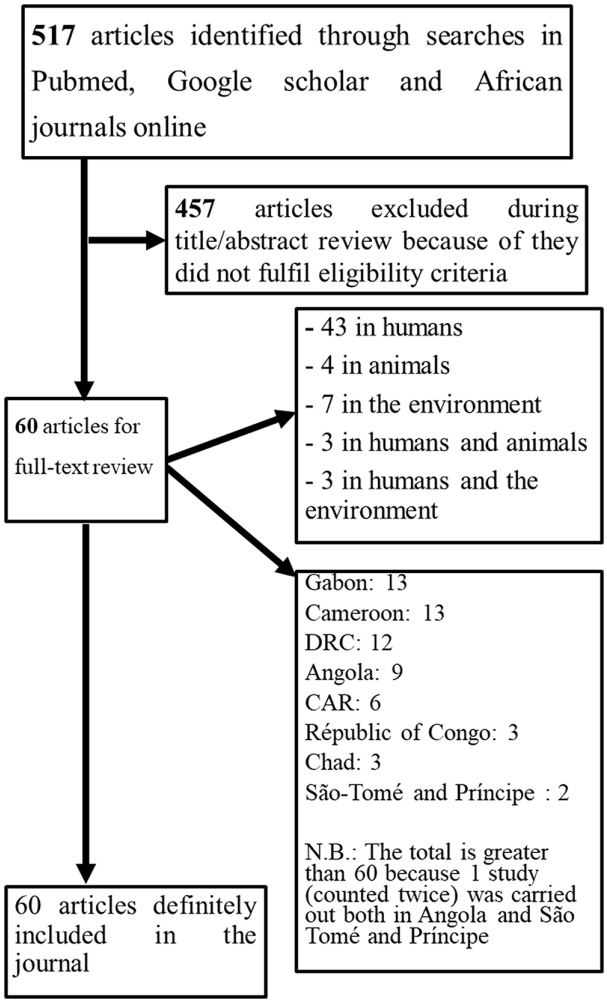

Fig. 2. Flow chart of article selection process

Among the 60 included studies, 43 were carried out in humans, four in animals, seven in the environment, three in humans and animals, three in humans and the environment.

An antimicrobial susceptibility testing was performed in 48 studies, of which 38 used the agar disc diffusion method, eight used the automated system Vitek two compact (BioMérieux, Marcy-l'Etoile France), and two studies used both methods. For 23 studies, antimicrobial susceptibility testing was performed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines, 20 studies used the Clinical and Laboratory Standards Institute (CLSI) guidelines, while five studies used both.

RESISTANCE RATES, CIRCULATING GENES AND GENETIC SUPPORTS IN HUMANS

Among the included studies, 49 were carried out in humans (Table 1).

The highest prevalence rate of ESBL in humans (100%) was reported in Gabon from carriage isolates, and the lowest (2%) in Cameroon from clinical isolates. The *CTX-M15* gene was predominant in 31 studies (31/49), followed by *TEM* (25/49), *OXA* (20/49), *SHV* (16/49), *CTX-M1* (4/49), *CTX-M14* and *CTX-M27* (3/49 each), *CTX-M3* and *CTX-M9* (2/49 each), *CTX-M8*, *CTX-M32*, *CTX-M55*, *CTX-M127*, *act-17*, *ampR*, and *lap-2* (1/49 each).

The prevalence rate of clinical or carriage carbapenemase-producing enterobacteriaceae (CPE) ranged from 2.5–78%. *NDM-1, NDM-4, NDM-5*, and *NDM-7* metallo-beta-lactamase genes were reported in eight studies in Cameroon, Chad, Angola, and Gabon, *OXA-48* and *OXA-181* oxacillinase genes were reported in seven studies in Gabon, Angola, Chad, Republic of Congo, and São Tomé and Príncipe. The *OXA-181* gene, a variant of *OXA-48*, was the most predominant carbapenemase gene in five

studies from four countries (Angola, Chad, Republic of Congo, São-Tome and Príncipe). We did not find, in the timeframe of this study, any presence of carbapenemase coding genes in DRC and CAR studies.

Many ESBL (bla_{CTX-M}) and carbapenemase (bla_{NDM} and bla_{OXA}) genes were carried by mobile genetic elements, such as transposons (Tn4651, Tn4652), class 1 and 2 integrons (Int1, Int2), non-typeable plasmids and plasmids (IncX3, IncX3, In cX4, IncFIA, IncA/C, IncFIB, IncL/M, IncN, IncY, IncFII, IncHI2, IncHIIB, IncR, CoI, CoIRNAI, IncF, IncFIB69, IncFII105, IncFII107, IncQ1). In addition to the genes for resistance to the β-lactams and to carbapenems, other genes were observed in humans, namely those for resistance to meticillin (*mecA*), aminoglycosides (*armA, rmtB*, *rmtC, aac(6′)-Ib, aa [3]-IIa, ant [3], aac [3], aadA1, aadA8, aphA-3*), sulphonamides (*sul1, sul2, sul3, folA*), trimethoprim (*dhfr1, dfrA, dfrG, dfrK +G, dfrB*) tetracycline (*tetA, tetD, tetG, tetK, tetM, tetR*), quinolones (*aac(6′)-Ib-cr, qnrB, qnrD, qnrS, qepA, oqxA, oqxB, crpP, gyrA, parC, parE*), fosfomycin (*fosA, ARR-3*), macrolides (*mph(A), mpbBM, msrA, erm(A), erm(B), erm(C), erm(T)*), chloramphenicol (*cat, floR, cmIA*), streptomycin (*strA, strB*), glycopeptides (*vanW*), colistin (*mcr-1*). These other resistances had prevalence rates that ranged from 0.97–96%. The *mecA* gene was commonly associated with the chromosomal cassette SCCmecIV, SCCmecV or non-typeable SCCmec.

RESISTANCE RATES, CIRCULATING GENES AND GENETIC SUPPORTS IN ANIMALS

Out of the 60 studies included, eight were in animals and carried out in Gabon (3), Cameroon (2), Angola (2), and CAR (1) (Table 2). The prevalence rates ranged from 5.9–75% for ESBL and 50–56% for other resistances, and were observed in gorillas, chickens, bats, pigs, cows, forest elephants, African buffaloes, chimpanzees, pigs, agile mangabeys, duikers, lowland bongos, sitatungas.

Among the β-lactamase genes, *CTX-M15* was the most predominant. *CTX-M1, CTX-M2, CTX-M14, CTX-M32, TEM, SHV, OXA, blaZ, SCO-1* were also reported.

None of the included studies revealed any carbapenemase genes but, as in humans, other genes that confer resistance to tetracycline, aminoglycosides, streptomycin, quinolones, sulphonamides, trimethoprim, chloramphenicol, methicillin, macrolides were reported.

Mobile genetic elements such as transposons, integrons (class 1 and 2) and plasmids supported the genes, except for the mecA gene, which was associated with the SCCmec Vc-type chromosomal cassette.

RESISTANCE RATES, CIRCULATING GENES AND GENETIC SUPPORTS IN THE ENVIRONMENT

Among the 60 selected studies, ten revealed the presence of resistant bacteria in the environment. These studies were carried out in the Republic of Congo [2], DRC [6], Cameroon [1] and Angola [1] (Table 3). Some studies revealed the presence of carbapenemase coding genes, but none of them determined the prevalence of CPE.

ESBL-PE prevalence rate in the environment ranged from 5.2–74.42%, and that for other types of resistance ranged from 2.8–80%. Resistant bacteria were detected in wastewater, soil, walls, treated water for human consumption, water for animal consumption, urban sewage, domestic sewage and drinking water. The genes responsible for these resistances were β-lactamases (*CTX-M15, CTX-M1* group, *TEM, OXA, SHV, CARB, Cfx, CMY, GES, NPS, AER, VEB-3, LCR1*), carbapenemases (*AIM, IMP, VIM, NDM, OXA-48, KPC*) and all other resistance genes observed in humans and animals. The β-lactamases and carbapenemases genes were generally carried by plasmids. Only one *CTX-M15* gene, in Angola, was carried by a chromosome. As in humans and animals, the *CTX-M15* gene was the most predominant β-lactamase.

DISCUSSION

Antimicrobial resistance is an increasing problem for public and animal health worldwide, particularly in Africa. In Central Africa, despite the regularity of annual epidemiological reports on antibiotic resistance, there is a paucity of molecular studies, and only limited data on resistance genes are available. This absence of information on antimicrobial resistance makes it difficult to control and monitor bacterial resistance in the subregion. In fact, more knowledge of antimicrobial resistance and reasonable antibiotic use could contribute significantly to diminishing the spread of antimicrobial resistance in this region [3]. So, in order to avoid a deterioration of the health situation in the region, it is very necessary that the healthcare system adopts antimicrobial resistance surveillance strategies and implements an antibiotic use and control programme. Such strategies limit the use of antibiotics to situations where they are essential, in order to prevent antimicrobial resistance making current treatments ineffective.

Studies were carried out on several host groups (humans, animals and the environment), the most representative being studies on humans (81.67%, 49/60) compared with those on animals (13.33%, 8/60) and the environment (16.67%, 10/60). Our observations corroborate the previous studies which reported also a short number of studies concerning the prevalence of ESBL-PE and CPE in West and Central Africa in animals and environment [21]. The presence of same genes in different

habitats (humans, animals and environment) could suggest the potential horizontal transmission of these genes between the three domains. Although there are few studies on animals and the environment, high rates of resistance were reported, ranging from 5.9–75% for animals, and from 5.2–74.42% for the environment. This high burden could be explained by excessive use of antibiotics as growth stimulants and preventive treatment in animals [22], and on other hand, to anthropogenic activities that leads to antibiotic pollution of the environment [23]. In this review, the prevalence of extended-spectrum beta-lactamases (ESBL) in carriage and in infectious processes ranged from 3–100%, and from 0.97–96% for other resistance genes. These resistance rates are similar to those found by Ouedraogo *et al*. in West Africa, where prevalences ranged from 10–100% for ESBLs [24]. ESBL rates found in Chad (48%) are also close to those found in East Africa (42% in average) [25] and China (46%) [26], but significantly higher than those found in 2012 in Germany (10–15%) [27] or the USA (4–12%) [28]. These differences in prevalence may be due to overuse associated with a lack of antibiotic use policy in most African and Asian countries, unlike those in the Western countries (Europe and USA). Among all the resistance genes identified, our literature review revealed high rates of isolates carrying one or more resistance genes, inducing high rates of antibiotic resistance with damaging effects on human health. Indeed, the diseases caused by these drug-resistant bacteria are lethal, due most often to the absence of effective treatments. Guillemot *et al*. established that during the past 50 years, the permanent increase in bacterial resistance has led to modifications in therapeutic recommendations [29]. For example, in response to the increased number of *Haemophilus influenzae* strains producing β-lactamase, guidelines for the treatment of otitis have favoured a combination of aminopenicillin and a β-lactamase inhibitor [30–32]. For pneumococcal meningitis, increased resistance to β-lactams has resulted in the recommendation of an injectable third-generation cephalosporin (cefotaxime or ceftriaxone) first-line prescription in combination [33] with a glycopeptide (vancomycin) [34]. In the same way, at the physician level, restricting the use of antimicrobial agents, providing locally adapted guidelines for the prudent use of antibiotics, and implementing quality control of antimicrobial therapy within a hospital, in particular within the intensive care unit, might help to minimize the selection of multidrug-resistant bacteria [35].

In the reviewed literature, among the β-lactamase genes, $bla_{CTX\text{-}M15}$ gene was the most predominant in humans, animals and the environment. In all the three cases it was usually carried by plasmids, which made its spread easier and therefore increased the prevalence rate of ESBL-PE in humans, animals and the environment, leading to the spread of multidrug-resistant pathogens responsible for human and animal infectious diseases [36].

There were no reports of carbapenemase genes in animals, unlike previous studies which reported bla_{KPC}, $bla_{OXA\text{-}48}$, bla_{NDM}, bla_{VIM}, bla_{IMP} genes in animal samples [37]. However, carbapenemase genes were reported in humans and in the environment, highlighting pollution of the environment by human activities.

In addition to β-lactamase and carbapenemase genes, other resistance genes were reported, such as resistance genes to meticillin, aminoglycosides, quinolones, tetracycline, streptomycin, sulfonamides, trimethoprim, fosfomycin, chloramphenicol, rifampicyn, macrolides, glycopeptides, colistin, phosphonic antibiotics, streptogramins, nucleoside antibiotics, which were detected in human, animal and environmental isolates (Tables 1–3 referring to studies in humans, animals and the environment, respectively).

The included studies in this review did not allow us to identify clones.

However, the presence of the same resistance genes in all three sectors showed evidence of resistant species and clones spread between humans, animals and the environment. For example, the mecA gene, carried by the SCCmec cassette, which confers β-lactam resistance (MRSA) to *Staphylococcus aureus*, is in our review one of those distributed in the three sectors. Previous studies reported the presence of the same ST5 clone of *S. aureus* (*S. aureus* ST5) in South Africa from humans [38], in Senegal from pigs [39] and in Tunisia from the environment [40]. This means that this *S. aureus* ST5 clone was disseminated in Africa in humans, animals and the environment. Antibiotics discharged into the environment contribute to the development of antibiotic resistance in the animals that involuntarily consume them in their food. Moreover, studies have shown that the use of antibiotics in the animal sector constitutes a selection pressure and promotes the transmission of resistant mutants to humans either by direct contact or through food [41, 42]. All this proves that the struggle against antibiotic resistance can only be effective within a framework that combines human, animal and environmental health, a 'One Health approach'.

CONCLUSION

This systematic review has confirmed the scarcity of thorough studies on bacterial resistance in the Central Africa. Thus, despite the increasing prevalence rates of resistant bacteria, and the spreading of several resistance gene types in humans, animals and the environment, not enough attention is given to the monitoring of antimicrobial resistance in the subregion. This leads to a lack of data and information to efficiently tackle the increase of antimicrobial resistance. We believe that the struggle is necessarily based on the implementation of a national health policy for each country, including measures for environmental hygiene, more adequate prescription and consumption of antibiotics in human and animal health. Intersectoral collaboration (human, animal and environmental health) is essential in order to combat antibiotic resistance.

LIMITATION

Annual epidemiological reporting on antibiotic resistance from most of parts of Africa is common practice. But in many countries of Central Africa, our study area, these epidemiological reports, even when they exist, do not often include data on the molecular basis of this resistance (genes). This makes it difficult to monitor antibiotic resistance.

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Author contributions
N.E.B. conceived the study. D.A.C. and O.R. designed the study. D.A.C. searched published work, reviewed published papers and made the primary selection of eligible papers. D.A.C. and G.S. resolved disagreements regarding the eligibility of papers. D.A.C. and B.L. compiled the data. M.L.G. and D.A.C. analysed the data. All authors contributed to the writing of the report and have seen and approved the final version.

Conflicts of interest
All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical statement
This research is in full compliance with ethical standards and moreover, neither human nor animal subjects were used while conducting this research.

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Peer review history

VERSION 4

Editor recommendation and comments

https://doi.org/10.1099/acmi.0.000556.v4.3
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Rubén de Dios; Brunel University London, Life Sciences, UNITED KINGDOM

Date report received: 21 July 2023
Recommendation: Accept

Comments: All suggestions and considerations have been fulfilled. Therefore, this manuscript is accepted for publication. Congratulations!

SciScore report

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iThenticate report

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Author response to reviewers to Version 3

Dear editors and reviewers

thank you for your comments on our manuscript.

We will take your recommendations into consideration and use them to optimize the quality of our manuscript.

Yours faithfully

Point-by-point response to reviewers

Reviewer 1

· Comment 2: We added a "Limitation" section on line 358 in the manuscript, in order to explain why only few data on resistance genes are availablefor the review.

· Comment 9 : We changed "gene-carrying molecular elements" for "genetic elements" in the tables of the review.

· We agree with your suggestion. So we have renamed the "Methods" section to "Bibliographical methods" and, in the "Results" section, we've removed this heading and use the sub-headings as main headings (Lines 160; 182; 218 and 236 in the manuscript) .

· L54: We changed "human" to "humans" on line 50 in the manuscript.

· L94: We agree with you. We have changed the sentence according to your comment and citing the appropriate source. The new sentence is: "Horizontal gene transfer (HGT) contributes significantly to the rapid spread of resistance. Multiple mechanisms of HGT liberate genes from normal vertical inheritance. Conjugation by plasmids, transduction by bacteriophages, and natural transformation by extracellular DNA each allow genetic material to jump between strains and species. Thus, HGT adds an important dimension to infectious disease whereby an antibiotic resistance gene can be the agent of an outbreak by transferring resistance to multiple unrelated pathogens" (Line 90-97 in the manuscript).

· L105, L108: We italicised *Escherichia coli*and *Klebsiella spp*species names on lines 105 and 108, as well as all gene names throughout the manuscript.

· L105: We've rewritten, throughout the manuscript, the first letters of antibiotic names in lowercase.

· L124: As suggested, we removed "dealing with" on line 123 in the manuscript, and replaced by "related to"

· L125-126: According to the comment, we've rephrased the sentence on line 124-125, the proposed is: "In order to ensure a full search, including all available studies on the topic and in the study area"

· On Lines134 and 135, we replaced respectively "concern" by "concerns" and "whose" by "including" as suggested.

· L138, L140: We've written square kilometres with a superindex 2, as followed: Km^2

· L159, L319: we've taken the comment into account and rewritten the sentence as followed: "Table 1, Table 2 and Table 3 referring to studies un humans, animals and the environment, respectively(L156-158; L326-327 on the manuscript)

· L185, L193, L194, L198: We agree with the comments and have rewritten words or sentences as suggested by the reviewer (respectively on lines 186; 194; 195; 199 and 200 in the manuscript).

· L200: On Line 201 in the manuscript and throughout the text, we've rewrittenthe terminology for naming bla genes as bla followed by the specific name (CTX-M, NDM or OXA) in subindex, as followed: $bla_{CTX\text{-}M,}bla_{NDM}$, bla_{OXA}

· L201: We've replaced "Tn 4651 and Tn 4652" by "Tn4651 and Tn4652" (L202 in the text)

· L202-206: In order to clarify the sentence, we've changed it and replaced by the following: "Many ESBL ($bla_{CTX\text{-}M}$) and carbapenemase ($bla_{NDM}$and bla_{OXA}) genes were carried by mobile genetic elements, such as transposons (Tn4651, Tn4652), class 1 and 2 integrons (Int1, Int2), non-typeable plasmids and plasmids (IncX3, IncX3, IncX4, IncFIA, IncA/C, IncFIB, IncL/M, IncN, IncY, IncFII, IncHI2, IncHIIB, IncR, CoI, CoIRNAI, IncF, IncFIB69, IncFII105, IncFII107, IncQ1)". (L201-205 in the manuscript)

· L212, L213, L239, L269, L276, L279, L287, L304: We agree with the comments and have removed or rewritten words or sentences as suggested by the reviewer (respectively on lines 211; 213; 242; 275; 282; 284; 293 and 311 in the review).

· L318: We've removed efflux pumps from the text and tables.

· L324: We've removed *S. aureus*in brackets (L332 in the review)

· L329-330 and L335-336: As rightly suggested, the references to "One Health" have been combined in a unique last sentence, as followed: All this proves that the struggle against antibiotic resistance can only be effective within a framework that combines human, animal and environmental health, a "One Health approach" (L341-343 in the review).

· L341, L342: We've replaced respectively ""genes types" by "gene types"

and "no interest" by "not enough attention" on lines 348 and 349 in the review.

VERSION 3

Editor recommendation and comments

https://doi.org/10.1099/acmi.0.000556.v3.3
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Rubén de Dios; Brunel University London, Life Sciences, UNITED KINGDOM

Date report received: 04 July 2023
Recommendation: Minor Amendment

Comments: In this revised version of the manuscript, Dikoumba et al. have applied all the comments and suggestions previously proposed. The text, as a whole, reads more fluid and clearer, and some inconsistencies have been fixed. Please find below some additional suggestions and minor amendments to apply. • Reviewer 1, comment 2: it would be interesting to add your response to this comment explicitly in the manuscript as a limitation. • Reviewer 1, comment 9: I suggest to change "gene-carrying molecular elements" for "genetic elements", which comprises better chromosomal elements on one hand and mobile genetic elements on the other hand. • As this is a review manuscript, the Methods and Results sections do not contain the usual

methods and results. I would suggest to rename the "Methods" section to "Bibliographical methods" or something similar that conveys that there are no experimental methods. In the case of the "Results" section, I would suggest to remove this heading and use the sub-headings as main headings. This is because there are no actual results obtained from this study (it is a literature review), but this will a structure to the manuscript. • L54: change "human" to "humans" • L94: correct the difference between vertical and horizontal transfer. Vertical transfer is a genetic inheritance after an event of cell division (it is a bit more specific than transferring material between two cells of the same species). On the other hand, horizontal transfer is a genetic acquisition, by different means, from non-sibling cells or the environment. Please adapt these definitions as required citing the appropriate sources. • L105, L108: species names must be italicised, as well as gene names when appropriate according to the conventions. Please correct this throughout the manuscript. • L105 and throughout the manuscript: antibiotic names do not need a first letter in uppercase • L124: Replace "dealing with" by "related to". • L125-126: "In order to ensure…avoid excluding certain studies". This sentence seems a bit unclear and repetitive. Please rephrase and ideally clarify which studies you wanted to avoid excluding. • L134: replace "concern" by "concerns". • L135: replace "whose" by "including". • L138, L140: square kilometres need to be written with a superindex 2. • L159: Tables must be fully named as Table 1, Table 2 and Table 3 (also in L319). At this point, it would be helpful to explicitly mention they refer to studies un humans, animals and the environment, respectively. • L185: replace "most" by "highest" • L193: replace "lactamases" by "lactamase" • L194: replace "OXA-48, OXA-181" by "OXA-48 and OXA-181"; replace "oxacillinases" by "oxacillinase" • L198: replace "found" by "find"; replace "timeframe" by "timeframe of this study"; replace "carbapenemases" by "carbapenemase coding genes" • L200 and throughout the text: the terminology for naming bla genes is bla followed by the specific name (for example CTX-M or OXA) in subindex. Please correct throughout the text. • L201: replace "Tn 4651 and Tn 4652" by "Tn4651 and Tn4652" • L202-206: Please clarify the terminology for plasmids. "Other types of plasmids" means that the previously mentioned mobile genetic elements are plasmids, and they are not. "Non-typeable plasmid" is not a type of plasmid. Differentiating incompatibility groups as it is done here can be understood as if the previously mentioned plasmids do not have any incompatibility. This needs to be fixed. • L212: remove ")" after fosA • L213: replace "chloramphenicole" by "chloramphenicol" • L239: replace "carbapenemases" by "carbapenemase coding genes"; "EPC" would be "CPE" here? • L269: remove "with" after "corroborate" • L276: replace "using" by "use" • L279: replace "in the manuscript" by "in this review" • L287: replace "West" by "Western countries". If this refers to Europe and the USA I would suggest to mention them explicitly • L304: replace "in the review" by "in the reviewed literature" • L318: although efflux pumps are a means of resistance, it seems out of place in this list. Please clarify or remove. • L324: as "Staphylococcus aureus" has been previously mentioned in the manuscript, there is no need to clarify the abbreviation S. aureus in brackets. • L329-330 and L335-336: These two references to "One Health" would read better as only one reference at the end of the paragraph. • L341: replace "genes types" by "gene types" • L342: replace "no interest" by "not enough attention" Please provide a revised version of the manuscript as well as a point-by-point response to these comments within 2 weeks.

SciScore report

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iThenticate report

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Author response to reviewers to Version 2

Dear editors and reviewers

thank you for your comments on our manuscript.

We will take your recommendations into consideration and use them to optimize the quality of our manuscript.

Yours faithfully

Point-by-point response to reviewers

Editor comments:

· The literature database has been set to Vancouver style, as indicated by the editor

· I have changed the term "non-beta-lactamase genes", which is inappropriate, by "other resistance genes".

· We have restored Figure 2 to its correct format

· L51-52: done

· L56: We've taken this into account, and removed chromosomes from the mobile genetic elements

· L154-155, L300: All tables 1, 2 and 3 are cited here because the data referred to in these paragraphs are found in all 3 tables.

· L159-160: eligibility criteria and the reasons to filter out articles are specified in paragraph 2.3 entitled: "Criteria for inclusion in the review and for ineligibility" (L140).

· L199: We've modified the sentence in order to make it clearer.

· L274: changed

· L275-281: We've taken your comments into consideration and revised the sentence to make it more coherent.

· L284: We've modified the sentence

· L286-288: done

· L300-302: done

· Sentences on lines L88, L227-228, L254-256, L256-259, L261, L262-264, L270-271, L314-315 : We've tried to correct the grammar of these sentences to make them more understandable.

Reviewer 1

· Comment 2: We agree with you on the regularity of annual epidemiological reports on antibiotic resistance in several African countries. But in many countries of Central Africa, our study area, these epidemiological reports, even when they exist, do not often include data on the molecular basis of this resistance (genes). This makes it difficult to monitor antibiotic resistance.

· Comment 5: It is explained under lines L330 to L336 of this manuscript.

· Comment 9: We prefer use the term "Gene-carrying molecular elements", to refer to all the elements that carry the resistance genes. These can be mobile genetic elements (plasmids, integrons, transposons), but also chromosomes such as the SCCmec chromosomal cassette that carries the MRSA mecA gene.

· Specific comment 1: done

· Specific comment 5: done

· Specific comment 10: We have corrected this paragraph as suggested above (L275-L281).

Reviewer 2

· Comment 3 : done

· Comment 5 : Your comment has been taken into consideration. In fact, since we don't define Ambler's classification in the manuscript, we prefer not to refer to it and remove it.

VERSION 2

Editor recommendation and comments

https://doi.org/10.1099/acmi.0.000556.v2.3
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Rubén de Dios; Brunel University London, Life Sciences, UNITED KINGDOM

Date report received: 11 May 2023
Recommendation: Major Revision

Comments: I would like to thank the authors for providing a revised version of the manuscript. Some changes proposed by the reviewers have been applied. However, the most important suggestions and concerns brought up by the reviewers are still unclear or completely unaddressed. There are many statements that are too vague and do not get to transmit the information. The writing

still needs a major revision, as it is very hard to read many parts of the manuscript. Some examples are: • The literature database with the articles that passed each filter has not been made available. • The term "non-beta-lactamase genes" is not appropriate to group every other antibiotic resistance mechanism different from beta-lactamases, as the rest of antibiotic resistance genes the authors refer to can be completely unrelated from a functional and epidemiologic point of view. • Figure 2 has lost the format in the revised manuscript • L51-52: number should be expressed either in digits or in words. Please homogenise. • L56: chromosomes are not mobile genetic elements. • L154-155, L300: Tables are not correctly cited and it cannot be known what each table refers to here. • L159-160: eligibility criteria and the reasons to filter out articles are still not clear. • L199: "plasmid groups of incompatibility" is not a correct term as it does not refer to a mobile genetic element, which be a plasmid. The incompatibility groups refer to a co-existence of plasmids in the cell and their replication according to compatible replication mechanisms. • L274: "In this study…" Do you mean in the manuscript? The prevalence data you are handling are extracted from other studies, it is not produced by this work. • L275-281: It is mentioned here that ESBL prevalence in Central Africa is 3-100%, and continue to say that is it similar to that of East Africa (42%) and China (46%), and significantly lower than those of Germany and USA (10-15%, 4-12%, respectively). This does not make sense. • L284: "resistance genes with damaging effects on human health". The resistance genes do not cause a disease themselves. • L286-288: this is an example of a vague statement. There is a mention to changes in therapeutic recommendations due to AMR, but it does not exemplify those changes. • L300-302: Another example of a vague sentence. "…" is inappropriate when listing these genes because the reader cannot figure out what follows in the list. Equally, finishing the sentence with "…and many others" does not help the reader to understand which genes the authors mean. Even if they are collected in the tables, their explanation in the text needs to improve. Specific examples (not the only ones) of lines/sentences that need grammar correction or that are difficult to understand are: L88, L227-228, L254-256, L256-259, L261, L262-264, L270-271, L314-315. There are also examples of specific reviewer suggestions that have not been accomplished in all instances throughout the manuscript or not accomplished at all. Examples are: Reviewer 1 • Comment 2, comment 5 and comment 9 not changed. • Specific comment 1 only changed once out of 7 total references to the terminology that was suggested to change. • Specific comment 5: African Journal Online only corrected once in the manuscript. • Specific comment 10: this explanation is hard to reconcile with the fact that the authors give a prevalence range for "non-beta-lactamase genes" in L276. Reviewer 2 • Comment 3 has not been applied to L83 and L252 • Comment 5: The definition of the Ambler's classification has been completely removed from the manuscript. However, its categories are still mentioned (L190, L192) without contextualising what that classification refers to. Please provide a revised version of the manuscript, addressing all these changes and applying the suggestions to the entirety of the manuscript, as well as improving the grammar and the readability. Provide also a point-by-point response to these specific comments.

SciScore report

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iThenticate report

https://doi.org/10.1099/acmi.0.000556.v2.2
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Author response to reviewers to Version 1

Point-by-point response to reviewers

Reviewer 1

General comments

Comment 1: If you are looking to analyze the molecular epidemiology of AMR genes, why are concentrating mainly on ESBLs?

Most of the genes responsible for the resistances mentioned in L64-71 should be analyzed, especially that these are highly prevalent forms of resistances in Africa, not obscure or indolent. I suggest you could either alter the aim of the study to only concentrate on ESBLs or expand the analysis and tables to include other types of resistances that are highly prevalent and equally serious from infection control standpoint. (You should not refer to them as other resistance genes).

Response 1: We take this into account. As we have indicated, the aim of our study was to review the different resistance genes found in Central Africa, in humans, animals and the environment. The data in the various tables show a diversity of resistance genes encountered. However, as noted in line 73-74, extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-PE) are now the most predominant multi-resistant bacteria (MRB) in many countries. In this study, we therefore focus on this

category of MRB, without of course missing the other types of resistances, whose association with beta-lactamases often leads to therapeutic impasses. Considering the threat, the non-beta-lactamases represent for antimicrobial resistance, we have called them "other resistance genes" because of their high diversity, and to differentiate them from beta-lactamases. So, taking into account your remark, we have now called them "non-beta-lactamases genes".

Therefore, the title of our study seems appropriate as it indicates the genetic diversity of antibiotic resistance in Central Africa.

Comment2:L245-247: Please rethink this statement, there may be a dearth in reports to support your particular aim, but annual epidemiological reporting from most of parts of Africa is common practice.

Response 2: Done

Comment3: L116: Could you provide the reasoning behind choosing this timeframe, if it was to cover 15 years, why not make it (2007-2022) to be a more recent investigation.

Response 3: We effectively opted to do this study over 15 years. It was done in 2020, as part of my PhD thesis, which I started in 2017 and finished in July 2021.

Comment 4: The discussion part of the manuscript lacks comparisons with other regions in and out of Africa. It is important to compare the rates in this review with other rates recorded in other regions and discuss the proposed causes of increase or decrease in certain AMR genes.

Response4: Done

Comment5:L314-318: Please expand on your recommendations to better implement One Health policies in central Africa.

Response5: Done

Specific comments

Comment 1: L39: "…to fight against antibiotic resistance" rethink the expression

Response 1: Done

Comment 2: L53-54: Please clarify this sentence

Response 2: We mean that the study, by showing not only the occurrence of beta-lactamase and carbapenemase genes, but also that of non-beta-lactamase genes, demonstrated the multi-drug resistance of the bacteria. Moreover, most of these resistance genes are carried by mobile genetic elements that facilitate their dissemination.

Comment 3: L111: Methodology misspelled.

Response 3: Corrected

Comment 4:L112: Please modify the citation. e.g. by Moher et al (ref no.).

Response 4: Done

Comment 5: L114: African journal online should be capitalized and maybe add the abbreviation AJOL

Response 5: Done

Comment 6: L114: "focused on the collection of research…".

Response 6: Done

Comment 7:L121: do you mean Sub-Saharan Region; this misspell is recurring throughout the manuscript.

Response 7: Corrected

Comment 8: L124-130: Please use references.

Response 8: Done

Comment 9: L173: "genetic supports" do you mean mobile genetic elements? if yes please change accordingly.

Response 9: We use the term "genetic carriers" to refer to all the elements that carry the resistance genes. These can be mobile genetic elements (plasmids, integrons, transposons), but also chromosomes such as the SCCmec chromosomal cassette that carries the MRSA mecA gene.

Comment 10:L205: To be more informative, I would suggest analyzing each resistance separately.

Response 10: During the data collection, we observed that in many studies the identification of a resistance gene was not systematically associated with a prevalence. This did not allow us to analyze each resistance individually.

Comment 11: L254: "The aim of establishing these strategies…"

Response 11: Done

Comment 12: L273: 'and' misspelled.

Response 12: Done

Reviewer 2

Comment 1: Review the paper throughout for efficient use of proper grammar and sentence structure prior to publication.

Response 1: Done. I tried to do it the best I could

Comment 2: In the Methods section (page 2 line 44) list the included list of countries for readers ease of access and interest. It is relevant and crucial to list the origin of the discussed data even in the abstract of the script.

Response 2: Done

Comment 3: Line 64: Consider revising the sentence as " limited data, rather than "few".

Response 3: Done

Comment 4: Line 66: I suggest not describing the "Antimicrobial Resistance" as a "disease", avoid using the emerging global disease term and replace the disease with "threat".

Response 4: Done

Comment 5: Line 74: The sentence that mentions Ambler classification is out of place in the text. Consider revising or moving to more relevant section of the abstract.

Response 5: Done

Comment 6: Line 95: Consider removing this sentence (Furthermore, resistant bacteria and resistance genes can be shared between humans, animals and the environment.), does not add any value since this is already mentioned in the sentence starting in line 87.

Response 6: Done

Comment 7: Line 101: "In Central Africa, antimicrobial resistance is increasing to worrisome proportions. " You must elaborate this statement with clinical and/or epi data added to the section. In fact, consider revising the sections line 101 through 104 by adding available clinical data even if it is p[ersonal communications.

Response 7: Done

Comment 8: Line 135: Doer these studies were peer reviewed, if yes how many?

Response 8: Yes, we only included published studies from journals which all apply the rule of peer review of articles before a final opinion ("accept" or "reject") from the editor-in-chief. There are always two reviewers.

Comment 9: Section 4. Discussions", Line 243: "Antimicrobial Resistance presents an increasing public and animals health across the world... " incomplete sentence, revise and clarify intended statement

Response 9: Done. We have tried to clarify the statement on Line 285-294

Comment 10: Line 257: " Our literature review identified a number of data sources for the epidemiology of antimicrobial resistance in central Africa. Thus, we found especially 517 articles whose only 60 were eligible." Consider removing, this information has been repeated multiple times, focus on the relevancy of collected information from these studies and conclusion being made.

Response 10: Done

Comment 11: Line 264: Consider removing the sentence regarding plasmid transmission, general statement without value.

Response 11: Done

Comment 12: Line 270: Consider removing the sentence regarding One Health, already use as a closing statement for this section.

Response 12: Done

Comment 13: Line 278: "Indeed, the diseases caused by these drug-resistant bacteria are lethal, due most often to the absence of effective treatments." Strong statement without supporting data, either revise as "Could be" or add relevant data to support the claim from the referred publication.

Response 13: Done

Comment 14: Line 282: Again, concept of plasmid transmission is repeated multiple times in numerous sections within the paper, review throughout the paper and remove repetitions of this statement: "In all the three cases it was usually carried by plasmids, which made its spread easier and therefore increased the prevalence rate of ESBL-PE in humans, animals and the environment, leading to the spread of multidrug-resistant pathogens responsible for human and animal infectious diseases [24]."

Response 14: I have removed some phrases that have the same meaning in the text.

Comment 15: Discussions section overall need to be strengthen with the available data from these 60 papers for the importance of the strong AMR threat in Central Africa region.

Response 15: We agree with your suggestion. We have taken this into account and have tried to do so throughout the corrections to the text

VERSION 1

Editor recommendation and comments

https://doi.org/10.1099/acmi.0.000556.v1.5
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Rubén de Dios; Brunel University London, Life Sciences, UNITED KINGDOM

Date report received: 28 March 2023
Recommendation: Major Revision

Comments: In this manuscript, Dikoumba et al. present a systematic review about antimicrobial resistance molecular epidemiology in Central Africa. This work is timely and appropriate, given the lack of comprehensive information about antimicrobial resistance in this region. However, several concerns have emerged after the review process. Please, address the reviewers' suggestions and comments thoroughly, especially those concerning: • Reframing the study to focus on beta-lactamases only (this would entail a change in the title accordingly) or give a comprehensive view of the rest of antibiotic resistance mechanisms mentioned to fulfil the scope of the manuscript. • Making available the literature database used for this study. Ideally, the publications that did not pass the different suitability filters should be provided as well, putting the emphasis on the ones that passed the filters and support this work. Please, provide a revised manuscript containing all suggestions and a point-by-point response to the reviewers' comments within 1 month.

Reviewer 2 recommendation and comments

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Rahsan Erdem; PATH, CVIA, 455 Massachusetts Ave Suite 1000 , Washington , UNITED STATES
https://orcid.org/0000-0002-4397-2606

Date report received: 23 March 2023
Recommendation: Major Revision

Comments: Dear Authors Thank you for the opportunity to review this paper. Please see my suggested revisions below: 1. Review the paper throughout for efficient use of proper grammar and sentence structure prior to publication. 2. In the Methods section (page 2 line 44) list the included list of countries for readers ease of access and interest. It is relevant and crucial to list the origin of the discussed data even in the abstract of the script. 3. Line 64: Consider revising the sentence as " limited data, rather than "few". 4. Line 66: I suggest not describing the "Antimicrobial Resistance" as a "disease", avoid using the emerging global disease

term and replace the disease with "threat". 5. Line 74: The sentence that mentions Ambler classification is out of place in the text. Consider revising or moving to more relevant section of the abstract. 6. Line 95: Consider removing this sentence (Furthermore, resistant bacteria and resistance genes can be shared between humans, animals and the environment.), does not add any value since this is already mentioned in the sentence starting in line 87. 7. Line 101: "In Central Africa, antimicrobial resistance is increasing to worrisome proportions. " You must elaborate this statement with clinical and/or epi data added to the section. In fact, consider revising the sections line 101 through 104 by adding available clinical data even if it is p[ersonal communications. 8. Line 135: Doer these studies were peer reviewed, if yes how many? 9. Section 4. Discussions", Line 243: "Antimicrobial Resistance presents an increasing public and animals health across the world... " incomplete sentence, revise and clarify intended statement. 10. Line 257: " Our literature review identified a number of data sources for the epidemiology of antimicrobial resistance in central Africa. Thus, we found especially 517 articles whose only 60 were eligible." Consider removing, this information has been repeated multiple times, focus on the relevancy of collected information from these studies and conclusion being made. 11. Line 264: Consider removing the sentence regarding plasmid transmission, general statement without value. 12. Line 270: Consider removing the sentence regarding One Health, already use as a closing statement for this section. 13. Line 278: "Indeed, the diseases caused by these drug-resistant bacteria are lethal, due most often to the absence of effective treatments." Strong statement without supporting data, either revise as "Could be" or add relevant data to support the claim from the referred publication. 14. Line 282: Again, concept of plasmid transmission is repeated multiple times in numerous sections within the paper, review throughout the paper and remove repetitions of this statement: "In all the three cases it was usually carried by plasmids, which made its spread easier and therefore increased the prevalence rate of ESBL-PE in humans, animals and the environment, leading to the spread of multidrug-resistant pathogens responsible for human and animal infectious diseases [24]." 15. Discussions section overall need to be strengthen with the available data from these 60 papers for the importance of the strong AMR threat in Central Africa region.

Please rate the quality of the presentation and structure of the manuscript
Satisfactory

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?
No

Is there a potential financial or other conflict of interest between yourself and the author(s)?
No

If this manuscript involves human and/or animal work, have the subjects been treated in an ethical manner and the authors complied with the appropriate guidelines?
Yes

Reviewer 1 recommendation and comments

https://doi.org/10.1099/acmi.0.000556.v1.3
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Anonymous.

Date report received: 02 February 2023
Recommendation: Major Revision

Comments: First and foremost, I would like to commend the authors on the efforts spent in producing this manuscript. This study attempts to shed some light on the AMR picture in central Africa. Upon reviewing this manuscript, I have some comments and questions to be addressed: General comments: 1- If you are looking to analyze the molecular epidemiology of AMR genes, why are concentrating mainly on ESBLs? Most of the genes responsible for the resistances mentioned in L64-71 should be analyzed, especially that these are highly prevalent forms of resistances in Africa, not obscure or indolent. I suggest you could either alter the aim of the study to only concentrate on ESBLs or expand the analysis and tables to include other types of resistances that are highly prevalent and equally serious from infection control standpoint. (You should not refer to them as other resistance genes). 2- L245-247: Please rethink this statement, there may be a dearth in reports to support your particular aim, but annual epidemiological reporting from most of parts of Africa is common practice. 3- L116: Could you provide the reasoning behind choosing this timeframe, if it was to cover 15 years, why not make it (2007-2022) to be a more recent investigation. 4- The discussion part of the manuscript lacks comparisons with other regions in and out of Africa. It is important to compare the rates in this review with other rates recorded in other regions and discuss the proposed causes of increase or decrease in certain AMR genes. 5- L314-318: Please expand on your recommendations to better implement One Health policies in central Africa. Specific Comments: 1- L39: "…to fight against antibiotic resistance" rethink the expression. 2- L53-54: Please clarify this

sentence. 3- L111: Methodology misspelled. 4- L112: Please modify the citation. e.g. by Moher et al (ref no.). 5- L114: African journal online should be capitalized and maybe add the abbreviation AJOL. 6- L114: "focused on the collection of research…". 7- L121: do you mean Sub-Saharan Region; this misspell is recurring throughout the manuscript. 8- L124-130: Please use references. 9- L173: "genetic supports" do you mean mobile genetic elements? if yes please change accordingly. 10- L205: To be more informative, I would suggest analyzing each resistance separately. 11- L254: "The aim of establishing these strategies…" 12- L273: 'and' misspelled.

Please rate the quality of the presentation and structure of the manuscript
Good

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?
No

Is there a potential financial or other conflict of interest between yourself and the author(s)?
No

If this manuscript involves human and/or animal work, have the subjects been treated in an ethical manner and the authors complied with the appropriate guidelines?
Yes

SciScore report

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iThenticate report

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