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SYSTEMATIC REVIEW

Systematic review and meta-analysis of integrated studies on antimicrobial resistance genes in Africa—A One Health perspective

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Abstract

Background: Increasing antimicrobial resistance (AMR) raises serious health and financial concerns. However, the main drivers of the emergence, spread and subsequent colonisation of resistant bacterial strains between humans, animals and the environment are still poorly understood.

Objective: The aim of this review was to identify molecular studies on AMR in One Health settings in Africa and to determine the prevalence of antimicrobial resistance genes in humans, animals and the environment. Due to the very low number of studies including environmental samples, the meta-analysis only includes data obtained from animals and humans.

Methods: The PubMed, Web of Science and Scopus databases were searched, identifying 10 464 publications on AMR in Africa from January 1st, 2000 until June 1st, 2020. Inclusion criteria were: (i) Integrated studies assessing AMR simultaneously in an animal-human, animal-environment, human-environment or animal-human-environment context, (ii) Genotypic characterisation of AMR and (iii) temporal and spatial relationship between samples from humans and animals. Statistical random-effects model meta-analysis was performed.

Results: Overall, 18 studies met our eligibility criteria and were included in this review. Six studies investigated *Escherichia coli* and *Salmonella* spp. ($N = 6$). The most prevalent AMR genes in animals included *sul1* (36.2%), *sul2* (32.0%), *tetA* (31.5%), *strB* (30.8%) and *blaTEM* (30.0%), whereas *sul2* (42.4%), *tetA* (42.0%), *strB* (34.9%), *blaTEM* (28.8%) and *sul1* (27.8%) were most prevalent in humans. We observed no clear pattern for a higher prevalence in either the animal or the human reservoir.

Conclusion: To date, data on AMR in a One Health perspective in Africa are scarce. Prospective and longitudinal studies using an integrated One Health approach assessing the environment, animals and humans at the same time are needed to better understand the main drivers of AMR sharing in Africa.

Sustainable Development Goal: Good health and wellbeing.

Pascale Vonaesch and Jakob Zinsstag authors contributed equally to this work.

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KEYWORDS
Africa, animals, antimicrobial resistance, environment, humans, One Health, systematic review and meta-analysis

INTRODUCTION

By 2050, 10 million lives could be lost each year to antimicrobial-resistant bacterial strains (AMR) [1]. High selection pressure due to antibiotic overuse, inadequate prescribing [2], massive use to promote growth in livestock production and agricultural use [3] are regarded as the most important drivers. Following the acquisition of resistance, AMR is disseminated by clonal spread of bacteria and horizontal gene transfer (HGT), that is, by plasmids or integrons [4], resulting in accumulation of antimicrobial resistance genes (ARGs) in bacteria. The collection of all ARGs in both pathogenic and non-pathogenic bacteria within an individual organism or a given environment (i.e. surface water, animal or human gastrointestinal tract etc.) is referred to as the resistome [5].

Recent resistome studies demonstrated that environmental reservoirs such as ground and surface water [1, 6] and animal hosts represent an important pool of mobile ARGs [7, 8]. Further, the exchange of ARGs between bacteria from different reservoirs, such as farm animals, farm soil and clinical pathogens, was found to occur via HGT [9, 10]. As an example, extended-spectrum beta-lactamase (ESBL) transmission from livestock to humans has been reported in China [11]. Faeces from livestock, primarily poultry and pig, have been shown to contaminate soil and water mostly with ESBL-*Escherichia coli* [12]. Human faecal excrements have likewise been shown to transfer AMR to the environment (e.g. quinolones (qnr genes)) [13]. Multidrug-resistant (MDR) soil bacteria have been found to contain resistance cassettes with the same nucleotide sequence as resistance genes found in diverse human pathogens [14]. As humans, animals and the environment are in close contact and interconnected in a complex way, AMR is a quintessential One Health issue. AMR research in low-income countries is highly underrepresented and most resistome studies have focused on industrialised settings [9, 10, 15].

In low- and middle-income countries (LMIC), few studies have assessed AMR simultaneously in humans, animals, food and the environment, and those available often suffer from poor design and bias [16] or assess only selected sections of the socio-ecological system (SES). Only one study used a comprehensive SES design combined with a metagenomic analysis but sampled relatively few animals in a cross-sectional study with no clear conclusion on attribution or spread of AMR [17].

A One Health perspective is increasingly needed, especially in Africa, where lack of access to safe drinking water and close contact between animals and humans might lead to a changed landscape compared to more industrialised settings [18]. Strategies targeted at reducing antibiotic misuse in humans and animals in LMICs have been proposed [19]. However, it might be that clonal dissemination plays an even more critical role in AMR spread than antimicrobial selection pressure [20].

This report presents a systematic review of scientific literature published between January 2000 and June 2020 on antimicrobial-resistant bacterial strains in Africa. The objective of this review was to identify studies targeting genotypic characterisation of antimicrobial resistance genes simultaneously in animals, humans and the environment, examine the prevalence of shared resistance genes between these different sources and summarise evidence on the phylogenetic relationship of the assessed bacterial strains.

METHODS

Search strategy

The literature search was performed in PubMed, Scopus and Web of Science between May and June 2020. The search was performed by two independent reviewers and compared. The following search terms, with a publication limit of 1st January 2000–1st June 2020, were used to retrieve relevant articles published: *("antimicrobial resistance" OR "antibiotic resistance" OR "antimicrobial susceptibility" OR "Resistome") AND (Africa OR "Horn of Africa" OR Ethiopia OR Eritrea OR Somalia OR Djibouti OR Kenya OR Sudan OR Nigeria OR Egypt OR Congo OR "South Africa" OR Tanzania OR Algeria OR Morocco OR Uganda OR Mozambique OR Ghana OR Angola OR "Ivory coast" OR Madagascar OR Cameroon OR Niger OR "Burkina Faso" OR Mali OR Malawi OR Zambia OR Senegal OR Chad OR Zimbabwe OR Rwanda OR Tunisia OR Guinea OR Benin OR Burundi OR Togo OR "Sierra Leone" OR Libya OR "Central African Republic" OR Liberia OR Mauritania OR Namibia OR Botswana OR Lesotho OR Gambia OR Gabon OR Mauritius OR Eswatini OR Comoros OR "Cape Verde" OR Seychelles).* Only publications in English were included. EndNote X9 was used to manage citations. Duplicate entries were identified by considering the title of the article, the author and the year of publication.

Selection criteria

Articles were reviewed separately by two independent reviewers. After removing duplicates, the remaining 6754 articles were screened based on title and abstract. The following inclusion criteria were defined as follows: (i) Integrated: Studies assessing AMR simultaneously in an animal-human, human-environment, animal-environment or human-animal-environment context; (ii) Genotypic characterisation of AMR: Studies applying genotypic methods to target specific ARGs either by polymerase chain reaction (PCR) or whole-genome sequencing (WGS).

In total, 6677 studies were excluded, because they did not use genetic methods for the detection of ARGs studied AMR

in an isolated manner for human, animal or environmental samples only, featured an ineligible geographic location or resistance in other microorganisms (viruses, protozoa or helminths). Five of the 77 studies remaining after title/abstract screening were not accessible online and could not be retrieved by contacting the authors. The remaining 72 studies were included for full-text analysis. Subsequently, articles were filtered for studies where samples from different environments were temporally and spatially related and phylogenetic relationships were assessed. This led to the exclusion of another 45 articles. From the remaining 32 articles, another fourteen articles were excluded due to methodological reasons, such as missing information on the origin of the samples, genotypic assessment of only a single bacterial strain, or inconsistency in results (results mentioned in text were different from results shown in a figure/table). 18 articles were finally included in the systematic review. Figure 1 summarises the flowchart of selection steps and articles retained.

Data extraction

Data from selected studies were extracted under the following parameters: (i) Study identifier: first author, year of publication, country, sampling population (specific animal, human or environmental source/host), reservoirs studied (animal-human, animal-environment, human-environment); (ii) methods: antimicrobial susceptibility testing, genotyping method for detection of ARGs; (iii) results: bacterial species isolated, number of bacterial isolates from each source (animal, human, environment) and number of each ARG found for each strain. Data extraction was performed by two independent researchers and compared.

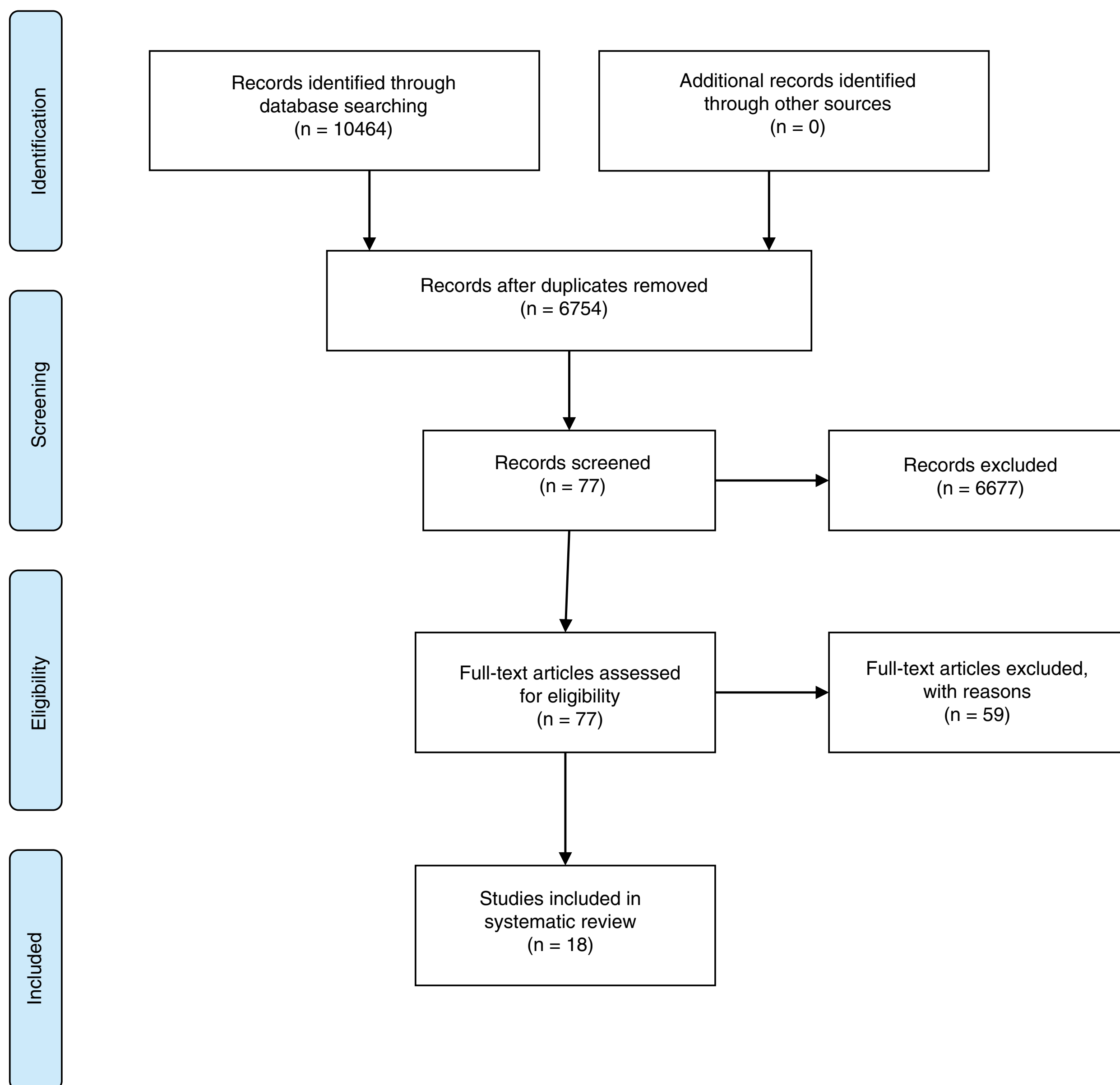

FIGURE 1 Search Strategy and PRISMA flow diagram

Selection of resistance genes studied

For the analysis, only genes that were studied in at least two different studies were considered. The following genes occurred only in a single study and were, therefore, not included in the final analysis: *vanB*, *vanA*, *tet(L)*, *blaACT*, *blaNDM*, *blaMOX-CMY*, *aac(6')-aph(2'')*, *aac(3)-IId*, *aac(3')-IIa*, *aac(3')-Iva*, *aph(6)-Id*, *aph(3')-Via*, *aph(3'')-Ib*, *aph(3')-Ic*, *aph(3')-Ia*, *dfrC*, *drfA18*, *drfA10*, *mph(c)*, *dhfr1*, *dhfr5*, *dhfr12*, *dhfr13*, *dfrG*, *norA*, *rpoB(H481N9)*, *aadD*, *spc*, *ant(4')-Ib*, *ampC*, *mrx*, *ere(B)*, *tet(X)*, *ant2*, *int1*, *int2*, *arsB-mob*, *qacE-delta1*, *qacL*, *mrs(A)*, *mrs(E)*, *mph(E)*, *parE(D434N9)*, *inu(F)*, *ere(A)*, *oqxA*, *oqxB*, *blaEC*.

Statistical analysis

We included in this meta-analysis studies reporting the number of samples and the number of AMR positive samples to estimate the relative risk. Studies were grouped on the basis of bacterial species. A pooled risk ratio (RR) was then calculated if for the given bacterial species if the gene was tested in at least two different studies. Heterogeneity was assessed by the I^2 and τ^2 statistics. We exclusively used random-effects models, irrespective of whether heterogeneity was present or not. For all statistical analyses, we used the R software environment version 4.0.3 and the 'meta' package version 4.14-0. We used the function 'metabin' using the Mantel-Haenszel method with inverse variance weighting for pooling [21].

RESULTS

Overview of the selected studies

Based on the eligibility criteria, a total of 18 original studies with a count of 1988 isolated bacterial strains (981 *Escherichia* sp., 316 *Campylobacter* spp., 278 *Staphylococcus* spp., 413 *Salmonella* spp.) were included for this systematic review and meta-analysis. An overview of the selected studies is given in Figure 2. Selected studies and study identifiers are listed in Table 1. Although the time interval searched was between 2000 and 2020, the earliest study that met the eligibility criteria was from 2014, and the number of studies per year increased in recent years (Figure 2c). Studies were available from ten different countries: Tunisia, Algeria, Egypt, Nigeria, Ghana, Ethiopia, Uganda, Zambia, Botswana and South Africa (Figure 2a), and included data from four bacterial genera: *Escherichia* sp., *Salmonella* spp., *Staphylococcus* spp. and *Campylobacter* spp., with six, six, four and two studies respectively (Figure 2b). The majority of the studies (15/18) detected ARGs by PCR, however, five studies applied WGS, with some studies applying both methods (Figure 2e). In 15/18 studies, samples were collected from human and animal sources (Figure 2d). Only three studies included

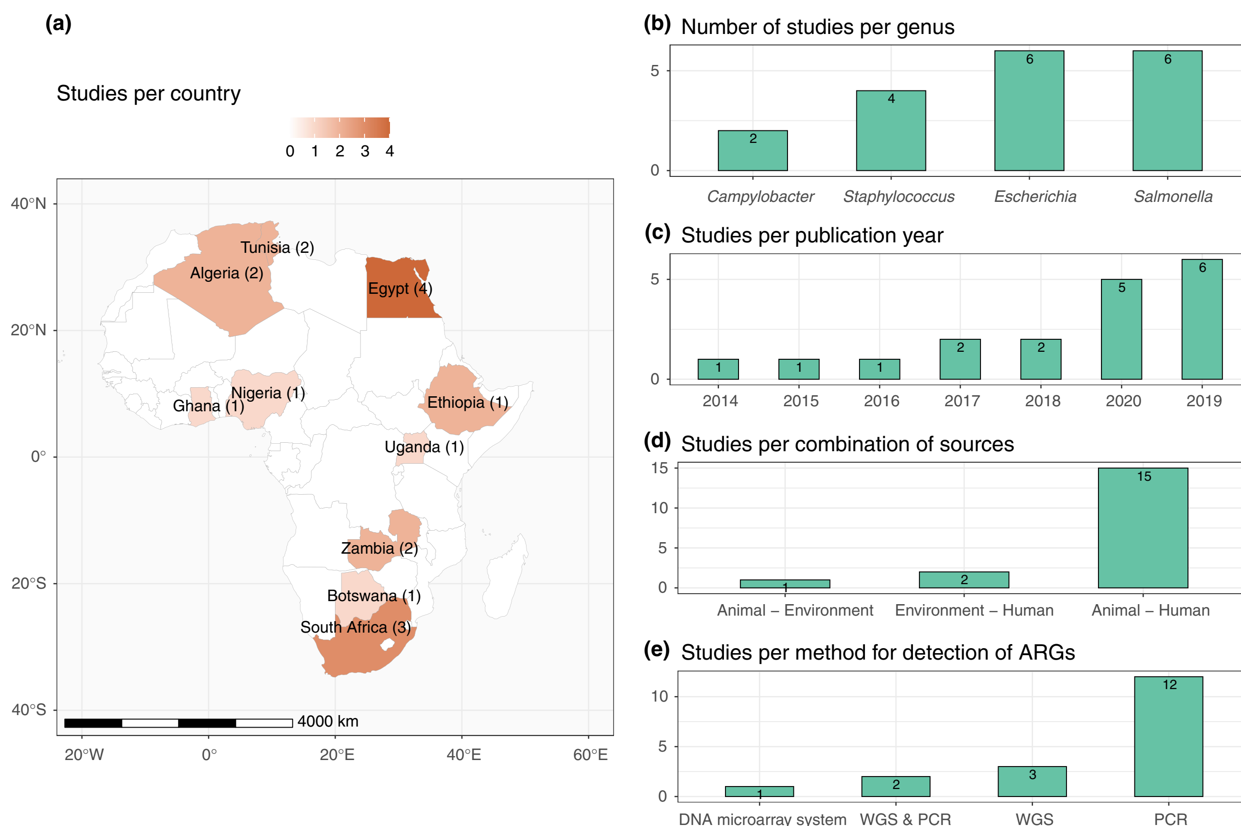

FIGURE 2 Summary of the selected studies showing number of studies (a) per country, (b) per bacterial genus, (c) per combination of sources and (e) applied methods for detection of ARGs

TABLE 1 Overview of the selected studies

ID	Reference	Country	Pathogen	Source	Detection ARGs	ARGs tested	Phylogeny	*n*
1	Agabou, A.; Clonal relationship between human and avian ciprofloxacin-resistant Escherichia coli isolates in North-Eastern Algeria (2015)	Algeria	*Escherichia*	Human, chicken	PCR	*blaKPC, blaOXA-48-like, blaVIM, blaIMP,* and *blaNDM, blaTEM, blaSHV, blaCTX, qnrA, qnrB, qnrS, qepA, aac(6')-Ib-cr, oqxAB*	MLST	94
2	Ahmed, H.A.; Characterizationof Virulence-Associated Genes, Antimicrobial Resistance Genes, and Class 1 integrons in Salmonella enterica serovar Typhimurium Isolates from Chicken meat and Humans in Egypt (2016)	Egypt	*Salmonella*	Chicken meat, humans	PCR	*blaTEM, aadB, aadC, aadA, floR, tetA(A), tetA(B), sul1,invA, avrA, mgtC, stn, bcfC*	gyrA gene sequencing	78
3	Ajayi, A.; Molecular diversity and antibiotic resistance gene profile of Salmonella enterica serovars isolated from humans and food animals in Lagos, Nigeria (2019)	Nigeria	*Salmonella*	Humans, food animals (cattle, sheep, chicken)	PCR	*qnrA, qnrB, qnrS, gyrA, blaSHV, blaCTX, blaTEM, tet(B), tet(A)*	gyrA gene sequencing	71
4	Amoako, D. G.; Genomic analysis of methicillin-resistant Staphylococcus aureus isolated from poultry and occupational farm workers in Umgungundlovu District, South Africa (2019)	South Africa	*Staphylococcus*	Poultry, occupational farm workers	Whole genome Sequencing, PCR	*mecA, blaZ, aac(6')-aph(2''), aadD, spc, ant(4')-Ib, erm(A), erm(C), msr(A) and mph(C), tet(M), tet(K), dfr(C), gyrA*	MLST, spa typing, clonal complex prediction	145
5	Chukwu, M. O.; Antibiotic resistance profile and clonality of E. coli isolated from water and paediatric stool samples in the north-west, province South Africa (2019)	South Africa	*Escherichia*	Pediatric stool samples, water	PCR	*blaCTX, blaSHV, blaCMY, blaDHA*	ERIC-PCR	240
6	Chukwu, M. O.; Characterization and Phylogenetic Analysis of Campylobacter Species Isolated from Paediatric Stool and Water Samples in the Northwest Province, South Africa (2019)	South Africa	*Campylobacter*	Pediatric stool samples, water	PCR	*gyrA, tetO*	ERIC-PCR	257
7	De vries, S. P. W.; Phylogenetic analyses and antimicrobial resistance profiles of Campylobacter spp. from diarrhoeal patients and chickens in Botswana (2018)	Botswana	*Campylobacter*	Humans with diarrhea, chickens	whole genome sequencing	*tetO, gyrA, blaOXA*	Core genome alighments, SNP based tree	90
8	Dhaouadi, S.; Prevalence of meticillin-resistant and -susceptible coagulase-negative staphylococci with the first detection of the mecC gene among cows, humans and manure in Tunisia (2020)	Tunisia	*Staphylococcus*	Cows with mastitis, humans, manure	PCR	*mecA, mecC, blaZ, tet(K), erm(A), erm(B)*	PFGE	49

(Continues)

TABLE 1 (Continued)

ID	Reference	Country	Pathogen	Source	Detection ARGs	ARGs tested	Phylogeny	n
9	Djeffal, S.; Prevalence and clonal relationship of ESBL-producing Salmonella strains from humans and poultry in northeastern Algeria (2017)	Algeria	*Salmonella*	Humans, poultry	PCR	*blaCTX*, *blaTEM*	MLST	83
10	Eguale, T.; Genetic markers associated with resistance to beta-lactam and quinolone antimicrobials in non-typhoidal Salmonella isolates from humans and animals in central Ethiopia (2017)	Ethiopia	*Salmonella*	Cattle, poultry, swine, human	PCR, sequencing	*blaTEM*, *blaSHV*, *blaPER*, *blaPSE*, *blaOXA*, *gyrA*, *gyrB*, *parC*, *parE*, *qnrA*, *qnrB*, *qnrD*, *qnrS*, *qepA*, *aac(6')-Ib-cr*, *blaCMY*, *blaCTX*	MLST	72
11	Egyir, B.; Whole genome sequence profiling of antibiotic resistant Staphylococcus Aureus isolates from livestock and farm attendants in Ghana (2020)	Ghana	*Staphylococcus*	Livestock, farm attendants	Whole genome sequencing, PCR	*mecA*, *mecC*	MLST	25
12	Elhariri, M.; Virulence and Antibiotic Resistance Patterns of Extended-Spectrum Beta-Lactamase-Producing Salmonella enterica serovar Heidelberg Isolated from Broiler Chickens and Poultry Workers: A Potential Hazard (2019)	Egypt	*Salmonella*	Broiler chickens, poultry workers	PCR	*blaCMY*, *blaTEM*, *blaSHV*, *blaOXA*, *blaPSE*, *blaCTX*, *amoC*	invA gene sequencing	33
13	Gwida, M.; Microarray-based detection of resistance and virulence factors in commensal Escherichia coli from livestock and farmers in Egypt (2020)	Egypt	*Escherichia*	Farmers, livestock	DNA microarray system	*aadA*, *strA*, *strB*, *aac(3')-Iva*, *ant2*, *qnrA*, *qnrS*, *tet(A)*, *tet(B)*, *tet(X)*, *sul1*, *sul2*, *sul3*, *dfrA*, *aar*, *mph(A)*, *mrx*, *ereB*, *cmlA*	Split network tree construction, detected by microarray	47
14	Iramiot, J. S.; Whole genome sequences of multi-drug resistant Escherichia coli isolated in a Pastoralist Community of Western Uganda: Phylogenomic changes, virulence and resistant genes (2020)	Uganda	*Escherichia*	Cattle, humans in pastoralis community	Whole genome sequencing	*blaOXA*, *blaTEM*, *catA*, *clmA*, *drfA*, *oqxB*, *qacL*, *qacE*, *qnrS*, *sul1*, *sul2*, *sul3*, *tet(A)*, *tet(B)*	SNP based tree	42
15	Kalai, W.; Antimicrobial susceptibility and MLVA analysis of S. Typhimurium strains isolated from human and poultry samples in Tunisia (2018)	Tunisia	*Salmonella*	Poultry, humans	PCR	*blaTEM*, *blaSHV*, *blaCTX*, *tet(A)*, *tet(B)*, *tet(C)*, *tet(D)*, *tet(E)*, *tet(G)*, *sul1*, *sul2*, *gyrA*, *parC*, *qnrA*, *qnrB*, *qnrS*, *aac(c')-Ib*, *oqxAB*, *qepA*	MLVA	45

(Continues)

TABLE 1 (Continued)

ID	Reference	Country	Pathogen	Source	Detection ARGs	ARGs tested	Phylogeny	*n*
16	Mainda, G.; Whole Genome Sequence Analysis Reveals Lower Diversity and Frequency of Acquired Antimicrobial Resistance (AMR) Genes in E. coli From Dairy Herds Compared With Human Isolates From the Same Region of Central Zambia (2019)	Zambia	*Escherichia*	Human, dairy Herds	Whole genome sequencing	*strB*, *strA*, *sul2*, *tet(A)*, *tet(B)*, *sul2*, *blaTEM*, *aadA*	SNP based tree	296
17	Ramadan, H.; Antimicrobial Resistance, Genetic Diversity and Multilocus Sequence Typing of Escherichia coli from Humans, Retail Chicken and Ground Beef in Egypt (2020)	Egypt	*Escherichia*	Humans, retail chicken, ground beef	PCR	*blaCTX*, *blaTEM*, *blaCMY*, *blaSHV*, *blaOXA*, *catA1*, *catA2*, *floR*, *tetA*, *tetB*, *sul1*, *sul2*, *strA*, *strB*, *dhfr1*, *dhfr5*, *dhfr12*, *dhfr13*, *mphA*	PFGE, MLST	120
18	Youn, J. H.; Prevalence and characterization of Staphylococcus aureus and Staphylococcus pseudintermedius isolated from companion animals and environment in the veterinary teaching hospital in Zambia, Africa (2014)	Zambia	*Staphylococcus*	Companion animals, environment in veterinary teaching hospital	PCR	*catA*, *ermA*, *ermB*, *ermC*, *aac(6')-Ie-aph(2'')-Ia*, *mecA*, *blaZ*, *tet(K)*, *tet(L)*, *tet(M)*, *tet(O)*, *vanA*, *vanB*	MLST, spa typing	48

sampling from environmental sources, with one study examining animal and environmental samples and two studies assessing human and environmental samples. There was not a single study meeting our inclusion criteria that covered all three domains.

Assessment of shared ARGs

We calculated the average prevalence for every single resistance gene from animal and human sources separately (Figure S1). For human isolates, *tetA* was the gene with the highest prevalence, followed by *sul2*, *floR*, *strB* and *sul1*. For animal samples, *blaZ* was the most prevalent gene (detected uniquely in Staphylococcus spp.), followed by *tetK*, *sul1*, *floR* and *sul2*. The average frequency for most of the genes is similar between the isolates from human and animal sources, highlighting the high number and degree of shared resistance genes between the two compartments. For most of the bacterial species, the number of studies and sample size was small. The analysis for *Campylobacter* spp. included 316 samples from 2 studies, the analysis for *Staphylococcus* spp. included a total of 278 isolates across 4 studies, and for *Salmonella* spp. 413 samples across 6 studies were included. For *Escherichia* sp., the sample size was bigger, with a total of 981 isolates across 6 studies.

Resistance genes found in *Escherichia* sp

Although here we summarised studies by genus, the selected studies for *Escherichia* sp. exclusively examined *E. coli* isolates. Six studies on *E. coli* met our eligibility criteria, in which a total of 981 isolates were examined. From animal sources, the following resistance genes were found most frequently: *sul1* (36.2%), *sul2* (32.0%), *tetA* (31.5%), *strB* (30.8%) and *blaTEM* (30.0%). In human isolates, resistance genes have been detected following a similar frequency pattern: *sul2* (42.4%), *tetA* (42.0%), *strB* (34.9%), *blaTEM* (28.8%), *sul1* (27.8%). Subsequently, we assessed if genes were more frequently detected in human or in animal isolates using random effect models. No clear pattern emerged for the majority of the genes (Figure 3). The range of observed prevalence among studies inter-study differences was substantial, whereas some studies reported higher prevalence in humans and others in animals for the same gene. There were two genes with consistent trends: The aminoglycoside adenylyl-transferase gene *aadA1* was detected more frequently in animal isolates across all studies, with a pooled risk ratio (RR) of 2.83 (95% confidence interval (CI): 1.13–7.11, Figure 3a). The opposite was found for the chloramphenicol acetyl-transferase *catA1*, which was consistently higher amongst *E. coli* isolated from humans, with a pooled RR of 0.39 (CI: 0.15–1.00), and no heterogeneity ($I^2 = 0\%$, $\tau^2 = 0$, Figure 3c). For the other genes, no clear pattern was detected, with most of the genes having a pooled RR close to 1, suggesting a similar probability of occurrence in humans and animals (Figure 3c–f).

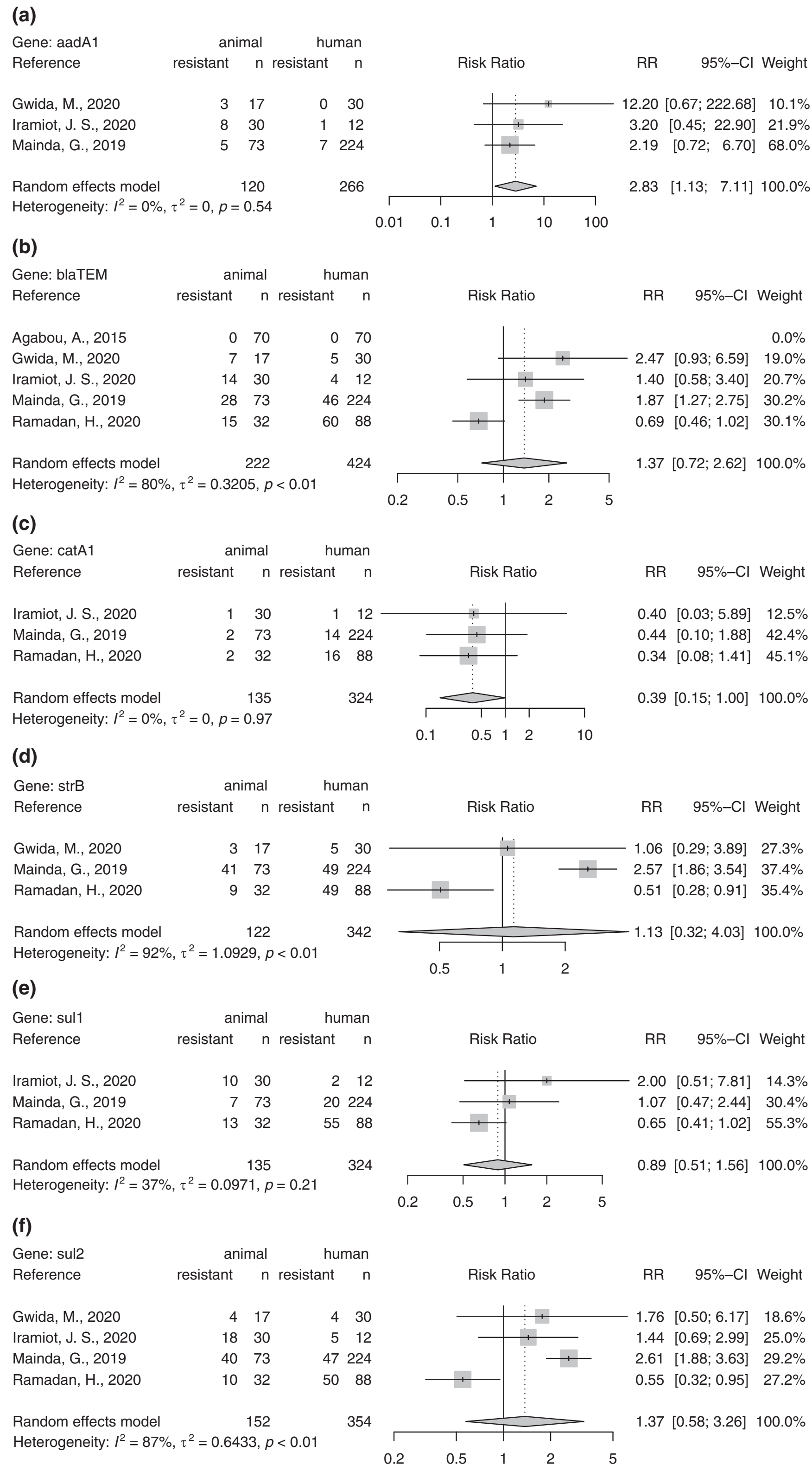

FIGURE 3 Forest plots for (a) aadA1, (b) blaTEM, (c) cat(A), (d) strB, (e) sul1 and (f) sul2

Resistance genes found in *Salmonella* spp

Six studies on *Salmonella* spp. met our eligibility criteria, including 413 isolates. From animal sources, the following resistance genes were found most frequently: *floR* (75%), *aadA2* (70%), *sul1* (50.3%). For human samples, a similar pattern was observed: *floR* (70%), *sul1* (55.6%) and *aadA1* (50%). No clear pattern emerged for the majority of the genes

in the random effect models comparing frequencies in humans and animals (Figure S4), suggesting little evidence that there is a difference between humans and animals. However, due to small sample size, the power is low.

Resistance genes found in *Staphylococcus* spp

Four studies on *Staphylococcus* spp. were included in this review, compromising a total of 278 isolates. In isolates from animal sources, the most frequent genes were *blaZ* (30.9%), *tetK* (28.4%) and *tetM* (16.2%). For human isolates the most frequently detected gene was *catA* (40%), followed by *tetK* (36.7%) and *blaZ* (34%). There was no evidence for a significant difference in occurrence of the genes between human and animal samples (Figure S5).

Resistance genes found in *Campylobacter* spp

Two studies on *Campylobacter* were included in this review, including a total of 316 isolates. In total, only three genes (*blaOXA*, *gyrA*, *tetA*) were detected with the following frequencies in humans 70%, 49.5% and 16.2%, and in animals 40%, 36.6% and 17.1%, respectively. Since the two studies did not include the same genes that were analysed, no pooled RR could be produced and no data for the meta-analysis can be shown.

Overall, these results suggest that many resistance genes co-occur in animal and in human reservoirs with prevalence varying between different studies and settings. However, the co-occurrence of resistance genes does not necessarily mean that these genes share the same origin. Therefore, for this review, we included exclusively studies where samples were spatially and temporally related and where some kind of genetic relationship between samples from different sources was examined.

In the studies identified, the following genetic relationships between samples from different sources were found:

Agabou *et al*. identified seven major clonal groups across human and avian ciprofloxacin-resistant *E. coli* from chickens and their farmers in Algeria, of which four were found simultaneously in human and in chicken isolates. Multilocus sequency typing (MLST) further provided evidence of a genetic linkage of samples belonging to the same clonal group between human and animal isolates, suggesting that these pathogenic resistant strains share the same origin [22]. Iramiot *et al*. [23] used Single Nucleotide Polymorphisms (SNPs) to cluster phylogenomic groups of samples from humans and cattle in pastoralist communities in western Uganda and found that 67% of *E. coli* isolated from cattle were closely related to those found in humans. By using hybridisation profiles, Gwida *et al*. investigated the relationship between multidrug-resistant (MDR) isolates from different food-producing animals (buffalo, cattle) and in-contact farmers. Due to the high similarity of hybridisation patterns between some human and animal isolates, the authors assume a direct transmission between human and animal or vice versa of multi-resistant strains [24]. Ramadan *et al*. determined the existence of sequence types using MLST among *E. coli* isolates from diarrheic patients, retail chicken and beef in Mansoura, Egypt. Across 116 *E. coli* isolates, chicken and beef samples shared six sequence types, and human and animal samples shared two sequence types (one shared between human and chicken and one between human and beef) [25].

On the contrary, a study by Mainda *et al*. [26] tested the relationship between resistance genes in *E. coli* from cattle and humans inhabiting the same region of Zambia by WGS and found no clear evidence for a genetic relationship of the isolates. Knowing that many ARGs are carried by mobile genetic elements such as plasmids, phylogenetic relationship alone may not be enough to infer transmission of ARGs, reiterating the difficulty of establishing transmission routes [13].

Estimates from different studies are significantly different, with some studies reporting higher prevalence of a given AMR gene/resistant bacterial strain in animal isolates and others in human isolates. Due to small sample size and high heterogeneity, none of the pooled effect estimates was found significant. Overall, these results suggest that a high number of frequent ARGs are shared between human and animal sources, however, certain strains and genetic elements might occur preferentially in one of the two compartments with a high variability between different settings and studies.

We last also assessed if there are co-occurrence patterns of specific resistance genes (Figure S6). As the sample sizes of the individual studies differ and it is not always reported if a gene was not found or not reported, the graph shows only weak evidence of co-occurrence of different resistance genes and mainly highlights the need for further molecular studies on integrated AMR studies in Africa.

DISCUSSION

Our meta-analysis revealed that while there are few studies assessing sharing of AMR genes between animals and humans, there is no single study with a comprehensive One Health approach focusing simultaneously on animals, humans and their wider environment.

A recent study by Chukwu *et al*. investigated the resistance profiles of *E. coli* pathotypes isolated from paediatric stool samples and drinking water in South Africa and examined the clonality of the isolates. The overall similarity between isolates from water and human sources was estimated between 80% and 90%, suggesting that domestic water plays an important role in the transmission of *E. coli* within the studied community setting [27] and emphasising the need for a comprehensive analysis of AMR in the wider context.

Figure 4 summarises the relationship of humans, livestock, food, excreta, water and the environment reported in the 18 studies. For every related compartment (shown by arrows), we assessed the shared bacterial species and the most prominent type of antimicrobial resistance. Our analysis highlights the lack of data for many of the potential

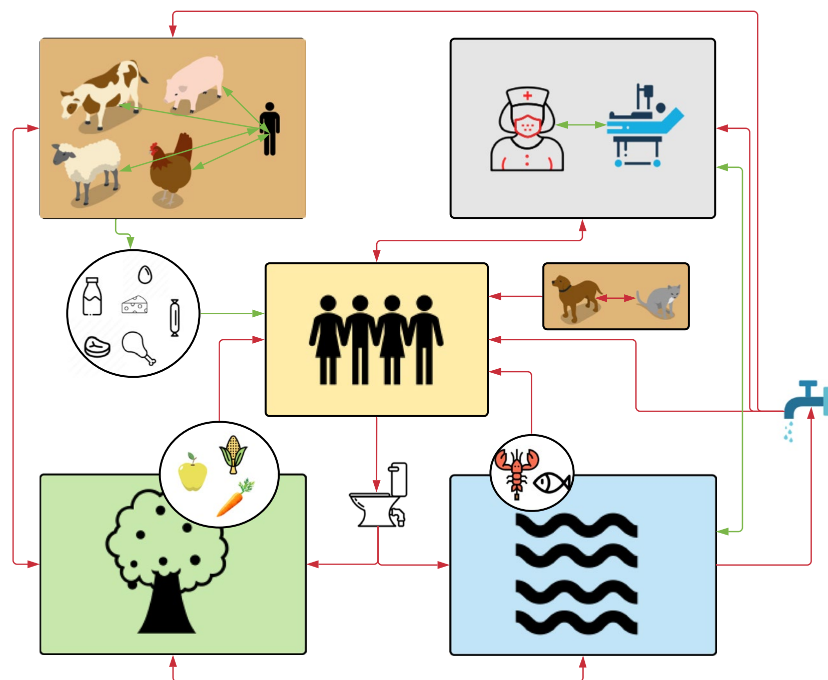

FIGURE 4 A potential schematic of the complex flow of antimicrobial-resistant bacteria in a human- animal-environment system. Green arrows indicate that we identified studies assessing the shared occurrence between the connected reservoirs and red arrows indicate that literature is missing

transmission routes and emphasises the need for targeted One Health studies on AMR resistance.

Our study further highlights that most of the studies performed so far isolated only limited bacterial strains and that strains, which are more difficult to isolate (i.e. Campylobacter spp) are underrepresented. In our review, we could show that AMR prevalence varies widely between the studies and there is no clear trend to higher prevalence of any particular resistance gene in either animals or humans. The small sample size in each study could be, at least partially, responsible for the contradicting results when comparing prevalence in human and animal settings. However, different drivers of AMR emergence and spreading could also lead to divergent results. Future studies should not only have an integrated approach but increase also the number and type of strains assessed for AMR resistance, assessing the overall pool of resistance genes in a given environment ('resistome') as well as the phenotypic resistance of isolated strains.

All of the studies analysed are cross-sectional and there is no temporal dimension. Therefore, while the studies allow for comparison of AMR gene sharing, they do not allow for assessing actual transmission routes. For future research, prospective cohort studies should be considered. For this review, only English publications were considered. Since Africa has many French-speaking countries, this clearly represents a limitation to the study. However, a retrospective search of French publications in PubMed found only 48 articles (compared to 2784 in English) of which none corresponded to the inclusion criteria fixed for this meta-analysis.

This review does not include any studies using culture-free methods such as metagenomics as none of these analysed samples from more than one domain.

The results of our study do not show a clear predominance of AMR genes in animals (cattle, pigs and poultry) compared to humans. Based on the current knowledge, we can argue that livestock production in Africa *per se* is not a major driver for AMR emergence. This means that continuous attention should be paid to antibiotic use in livestock and humans. Antibiotic use in Africa oscillates between persistent lack of supply and un-controlled sale and use. National authorities must urgently regulate the sale and use of antibiotics for humans and animals in a better way.

AMR is a public health problem that transcends species and national borders. New types of AMR strains can disseminate globally following initial endemic emergence, as exemplified by several resistant clones that spread internationally [28, 29]. Indeed, emerging AMR in low-income settings has been shown to be an important source of worldwide spread [30, 31]. To date, a single study on AMR in a low-income setting in Latin America used a comprehensive SES design combined with a metagenomic analysis to determine the resistome. However, the study sampled relatively few animals and as a cross-sectional study did not allow for clear conclusion on acquisition or spread of AMR [17].

The simultaneous approach to human and animal health combined with robust epidemiological study design has a high potential to elucidate understanding of drivers for the emergence and spread of ARGs. Only results from comprehensive One Health approaches, which integrate at the same time humans, animals, and their environment will allow for inferring the most important transmission routes in Africa and for designing more efficient AMR control policies.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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