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Epidemiology and prevalence of extended-spectrum β -lactamase- and carbapenemase-producing *Enterobacteriaceae* in humans, animals and environments in West and Central Africa

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Abstract

Extended-spectrum β -lactamase-producing *Enterobacteriaceae* (ESBL-PE) and carbapenemase-producing *Enterobacteriaceae* (CPE) are widespread. Here, we used the “One Health” approach to determine the knowledge gaps on ESBL-PE and CPE in West and Central Africa. We searched all articles on ESBL-PE and CPE in these African regions published in PubMed, African Journals Online, and Google Scholar from 2000 onwards. Among the 1201 articles retrieved, we selected 168 studies (West Africa n=121, and Central Africa n=47) with data from 22 of the 26 West and Central Africa countries. Concerning the settings, 137 articles focused only on humans (carriage and/or infection), 6 articles on humans and animals, 12 on animals, 8 on humans and environments, one on environments, and one on humans, animals and environments. ESBL-PE prevalence ranged from 11% to 72% in humans, and from 7% to 79% in aquatic environments (wastewater). In animals, ESBL-PE prevalence hugely varied: 0% in cattle, 11-36% in chickens, 20% in rats, 21-71% in pigs, and 32-75% in dogs. The *bla*_{CTX-M-15} gene was the predominant ESBL-encoding gene and was associated with plasmids of the incompatibility groups F, H, K, Y, N, II and R. CPE were studied only in humans. Class B metallo- β -lactamases (NDM) and class D oxacillinases (OXA-48 and OXA-181) were the most common carbapenemases. Our results show major knowledge gaps, particularly on ESBL and CPE in animals and environments, that might limit antimicrobial resistance management in these regions. They also emphasize the urgent need to improve active surveillance programs in each country and to support antimicrobial stewardship.

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77 1. Introduction

78 Beta-lactams are the most widely used antibiotics for the treatment of bacterial infections.
79 Their misuse and abuse are the main cause of resistance in *Enterobacteriaceae* worldwide [1,
80 2], in community and healthcare settings, and are associated with high mortality and
81 morbidity [3,4].

82 The most prevalent mechanism by which bacteria acquire resistance to β -lactam antibiotics is
83 the production of enzymes (β -lactamases) that hydrolyze these antibiotics [5,6]. Currently,
84 extended spectrum β -lactamases (ESBL), such as the SHV, TEM and CTX-M variants, and
85 carbapenemases (MBL, KPC, and class D oxacillinases) are the most common β -lactamases
86 detected in *Enterobacteriaceae*, particularly in *Escherichia coli* and in *Klebsiella*
87 *pneumoniae*. ESBLs are enzymes that can hydrolyze penicillins, cephalosporins and
88 aztreonam, but neither cephamycins nor carbapenems, and are inhibited by β -lactamase
89 inhibitors, such as clavulanic acid [7,8]. Therefore, carbapenems have been used as the
90 treatment of choice for infections due to ESBL-producing *Enterobacteriaceae* (ESBL-PE),
91 resulting in the emergence of carbapenemase-producing *Enterobacteriaceae* (CPE) [4,9].
92 During the last decade, ESBL-PE and CPE have increasingly been reported worldwide in
93 different ecosystems [7,10–12].

94 Resistance genes can spread by vertical transfer (e.g., transmission of the ESBL-producing *E.*
95 *coli* sequence type 131) or by horizontal transfer of mobile genetic elements, such as plasmids
96 of different incompatibility (Inc) groups (e.g., IncF, IncX3), transposons or integrons, within
97 and between humans, animals and environments [13, 14]. Consequently, only a “one health
98 approach” can help to understand the emergence and transmission of these genes. However,
99 data collection and surveillance of multidrug-resistant Enterobacteria are often limited,
100 particularly in middle and low income countries, such as many African countries.

The aim of this review is to provide an overview of the epidemiology of ESBL-PE and CPE circulating in humans, animals and environments in West and Central Africa. For that, we systematically reviewed data published from 2000, on bacterial species, genotypes and genetic mechanisms of resistance of ESBL-PE and CPE isolated in humans, animals and environments.

2. Methods

2.1 Literature search

A systematic search was carried out in PubMed, African Journals Online, and Google Scholar using the search terms “ESBL” and/or “carbapenemases”, “*Enterobacteriaceae*”, “West Africa” or “Central Africa”, “antimicrobial” or “antibiotic”, “resistance”, and “susceptibility” or “sensitivity”, combined with the names of the different West and Central African countries. According to the United Nation geographical region definition of the Central and West Africa region [15], this region includes the following countries: Angola, Cameroon, Central African Republic (CAR), Chad, Congo-Brazzaville, Democratic Republic of the Congo (DRC), Equatorial Guinea, Gabon, and São Tomé et Príncipe in Central Africa, and Benin, Burkina Faso, Cape Verde, Côte d’Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Saint Helena, Senegal, Sierra Leone and Togo in West Africa. All studies (in English or French) on ESBL-PE and/or CPE in humans, animals, food, or environment published between January 2000 and January 2019 were included.

2.2 Data extraction

After excluding irrelevant and duplicate studies, the remaining studies were fully read to extract data for this review: name of the first author, year of publication, country where the study was carried out, study design, and settings (hospital or community, animals, food, environment), *Enterobacteriaceae* species, ESBL-PE and CPE prevalence, method of analysis

(phenotypic, molecular, or genomic), resistance genes, genetic support of resistance determinants, and genetic diversity.

3. Results

3.1 Studies selected for the analysis

A total of 1366 articles were identified. After review of titles and abstracts, 1201 articles were excluded (irrelevant and duplicate studies), and 165 articles were fully read. These 165 articles (West Africa n=118 and Central Africa n=47) focused on 23 of the 26 countries that constitute the West and Central African region (Figure 1): Nigeria (n=57), Senegal (n=16), Cameroon (n=14), Ghana (n=12), Burkina Faso, Chad, Gabon and Mali (n=7/country), DRC and CAR (n=6/country), Benin (n=5), Angola and Togo (n=4/country), Côte d'Ivoire (n=3), Mauritania, Niger and Sierra Leone (n=2/country), Congo-Brazzaville, Equatorial Guinea, Gambia, Guinea, Guinea-Bissau and São Tomé and Príncipe (n=1/country), and Benin and Togo together (n=1). No article was found on ESBL-PE and/or CPE in Cape Verde, Liberia and Saint Helena (Data and all references in table S1, S2 and S3 in supplemental material).

Concerning the settings, 136 articles focused only on humans (carriage and/or infection), 6 articles on humans and animals, 13 on animals/foods, one on humans and environment, 8 on the environment, and one on humans, animals and environment. The characteristics of the included studies are presented in Table 1, and Tables S1, S2 and S3 in supplemental material.

3.2 Prevalence and genetic determinants of ESBL-PE in humans, animals, animal food and environments

Among the 152 studies on ESBL-PE in humans, 54 identified ESBL-PE isolates using phenotypic tests based on synergy between indicators and inhibitors, but without resistance

gene identification, 92 used molecular tests for the identification of resistance genes, and 6 were based on whole genome sequencing.

ESBL-PE prevalence varied among countries, and within countries it increased over time. For example, in Nigeria, ESBL-PE prevalence increased from 11% in 2009 to 72% in 2011. Overall, the highest ESBL-PE rate (79%) was detected in *Enterobacteriaceae* isolates from children in Senegal in 2017, and the lowest rate (4%), in clinical *Enterobacteriaceae* isolates from CAR in 2006 (Table 1).

The *bla*_{CTX-M-15} gene (60 to 100%) was the most frequent ESBL-encoding gene detected in ESBL-PE isolates from 17 countries (n=67 studies), followed by *bla*_{SHV-12} (2 to 30%) in 10 countries (n=13 studies), *bla*_{CTX-M-1} (3 to 6%) in 4 countries (n=13 studies), *bla*_{CTX-M-3} (3 to 4%) in 3 countries (2 studies), and *bla*_{CTX-M-14} in 4 (2 studies) (Table 1). These ESBL-encoding genes were detected in different *Enterobacteriaceae* species, especially in *E. coli*, *K. pneumoniae*, *Salmonella*, *Enterobacter*, *Morganella*, *Proteus* and *Providencia*.

The few studies on the resistance genetic support identified several genetic elements (e.g. transposons and/or plasmids) involved in the mobility of resistance genes. In humans, the frequency of plasmids associated with ESBL was as follows: IncF (30 to 100%), IncNT (0 to 100%), IncY (0 to 100%), IncH and IncK (Table 1). The *bla*_{CTX-M-15} gene was commonly detected in insertion sequences (ISEcp1), and was associated mainly with IncF (90%) plasmids, but also with IncN, IncY, IncH, and IncK plasmids (Table 1).

Among the 165 reviewed articles, only 29 concerned ESBL-PE in animals and/or environments in Angola, Benin, Burkina Faso, Cameroon, Côte d'Ivoire, CAR, DRC, Gabon, Ghana, Guinea, Mali, Nigeria, and Senegal. In animals, ESBL-PE prevalence was investigated in pigs [16–20], dogs [21–23], rats [24,25], chickens or chicken food [19,21,26–31], gorillas [32], cattle [19,20,33], goats and sheep [21]. Only one article described ESBL-PE isolated from drinking water [34] (Table S2 in supplemental material).

ESBL-PE prevalence in animals varied widely: 0% in cattle, 11-36% in chickens, 20% in rats, 21-71% in pigs, and 32-75% in *E. coli* isolated from dogs (Table S2 in supplemental material).

The *bla*_{CTX-M-15} gene (67 to 100%) was the predominant ESBL-encoding gene and was mainly associated with IncF, IncY, IncN, IncI1, and IncR plasmids. The genes encoding CTX-M-1, CTX-M-2, CTX-M-14, CTX-M-27, CTX-M-55, CTX-M-61 and SHV-12 were also detected (Table 1).

In the environment, ESBL-PE were isolated from wastewater [35–41], hospital surfaces [42], and a poultry farm [43]. ESBL-PE prevalence in wastewater varied from 7 to 79%. Like in humans and animals, CTX-M-15 was the predominant ESBL type (Table S3 in supplemental material).

3.3 CPE in humans, animals and environments

CPE were reported by 25 studies in 12 countries, mainly in *E. coli* and *K. pneumoniae* isolates. Ambler class A carbapenemases (KPC and GES), class B metallo- β -lactamases (NDM, VIM and DIM), and class D oxacillinases (OXA-48, OXA-51-Like, OXA-58 and OXA-181) were detected in CPE from different West and Central Africa countries (Figure 2). Specifically, production of NDM-1, -4, -5 and -7 was reported by studies in Angola, Cameroon, Chad, Gabon, Ghana, Nigeria, Senegal, and Sierra Leone. VIM-1 and -2 were detected in Nigeria and Sierra Leone, and DIM-1 only in Nigeria. KPC and GES were identified only in one study in Nigeria. OXA-48 was detected in Nigeria and Senegal, OXA-181 in Angola, Chad, Burkina-Faso, Mali, Nigeria, São Tomé and Príncipe, and Togo, and OXA-51-like and OXA-58 in Sierra Leone (Table 2).

The *bla*_{NDM-1} gene was associated with many broad-host-range plasmid types, including IncA/C, IncH1 and IncF. The *bla*_{OXA-181} and *bla*_{NDM-5} genes were detected on IncX3 plasmids, and *bla*_{OXA-48} and *bla*_{NDM-4} on IncL/M and IncF plasmids, respectively. The plasmid

frequencies and the frequencies of plasmid-enzyme associations are summarized in Table 2.
No article was identified on CPE in food, animals, and/or environments.

4. Discussion

In this systematic review, the “one health” approach was used to analyze literature data on ESBL-PE and CPE prevalence in different ecosystems (humans, animals, food and environment) in Central and West Africa regions. Our results revealed major knowledge gaps that may hinder the management of antimicrobial resistance in these regions.

First, most articles focused mainly on humans (n=136), and only a limited number of published studies investigated ESBL-PE and CPE isolated from animals and environments (n=29). Only one study carried out in Angola [44] analyzed the distribution and molecular epidemiology of ESBL-PE and CPE in different non-clinical ecosystems (healthy individuals, healthy animals, and aquatic environments). Six other studies focused on ESBL-PE isolated from humans and animals: three in Cameroon (ESBL-PE in pigs and humans) [16–18], one in CAR (ESBL-PE isolates in wild mammals and humans) [32], one in Cote d’Ivoire (ESBL-producing *E. coli* in humans, dogs, cats, and wildlife) [22], and one in Nigeria (ESBL-producing *E. coli* isolates in humans and cattle) [33].

Second, no molecular characterization was performed in some countries (Congo, Equatorial Guinea and Gambia), leading to a serious lack of information on the different resistance genes involved in ESBL-PE and CPE.

Third, no data was available on CPE in animals and environments in Central and West Africa regions, although they were detected in animals and environment in other African countries [12,45,46].

Nevertheless, most of the ESBL-PE prevalence rates in humans in Central and West Africa regions were much higher than in North America [47] and Europe [48], in agreement with studies from other African regions [7] and Asian countries [49]. ESBL-PE prevalence in animals (*E. coli* isolated from dogs, pigs and cattle) and environment (hospital wastewater) also was high, when investigated.

Several factors could explain this alarming situation in West and Central Africa. Indeed, major gaps in the knowledge on antimicrobial resistance in Africa undermine the development and implementation of evidence-based public health policies and medical practice. Moreover, the lack of standardized antimicrobial resistance detection methods and interpretation guidelines do not allow comparing the results of different studies and optimal resistance tracking. In addition, access to reference laboratories and to external quality assessment schemes must be improved by strongly promoting and scaling up the Global Antimicrobial Surveillance System (GLASS) launched by the World Health Organization in 2015 and based on each country's specific priority pathogens [4,10,11].

Some studies (REF) showed that the degree of household antimicrobial usage, as reported by farmers, was higher in humans than in animals, probably because people have more access to human drugs than veterinary drugs. This might increase the risk of ESBL-PE circulation in humans and also between humans and animals. Then, free-roaming animals contribute to the dispersal of multidrug-resistant ESBL-producing bacteria in the community through fecal shedding and environmental contamination. Close contacts between humans and animals, poor household waste disposal methods, poor environmental sanitation and other related factors could facilitate the exchange of antimicrobial resistant bacteria between humans and animals within households. Therefore, a national antimicrobial monitoring program should be put in place to track the marketing and consumption of antimicrobial agents, including the quantity and reasons of antimicrobial drug usage in humans and animals [7,17,21].

The *bla*_{CTX-M-15} gene was the most prevalent ESBL-encoding gene in humans, animals and environment, and was carried by different plasmids, mainly of the IncF group, but also of the IncN, IncY, IncH, and IncK groups. This suggests that *bla*_{CTX-M-15}-carrying plasmids are widely exchanged among humans, animals and environments, and may be responsible for the increasing ESBL-PE rate in this region. This hypothesis should be confirmed by detailed genetic studies.

Despite the data paucity, CPE prevalence among human isolates varied between 4% and 27% in Central and West Africa. CPE were mainly detected in *E. coli* and *K. pneumoniae* isolates, and less frequently in other *Enterobacteriaceae*, such as *Enterobacter cloacae*, *Klebsiella aerogenes*, *Citrobacter freundii* and *Morganella morganii*. Class D carbapenemases (especially OXA-181) were the most reported enzymes in Central and West Africa. All the available publications found that *bla*_{OXA-181} was associated with the IncX3 plasmid. OXA-181, a variant of OXA-48, was first identified in different *Enterobacteriaceae* isolates from Indian patients [50], and has spread in different countries, including Africa [4,51].

Our results also indicate that many variants of the metallo- β -lactamase NDM are produced by different *Enterobacteriaceae* species. NDM-1 was identified in *E. coli* and *K. pneumoniae* isolates from Angola, Nigeria and Ghana [45,46,52–57], NDM-4 in *E. coli* isolates from Cameroon [58], NDM-5 in *E. coli*, *K. pneumoniae* and *E. cloacae* from Angola, Chad and Togo [46,59,60], and NDM-7 in *K. pneumoniae* and *E. cloacae* from Gabon [61]. Hence, NDM-producing *Enterobacteriaceae* are considered to be endemic CPE in North African countries [62]. In addition, other metallo- β -lactamase-encoding genes, such as *bla*_{VIM} and *bla*_{DIM}, were detected only in *E. coli* and *K. pneumoniae* isolates from Nigeria and Sierra Leone [52,53,63]. Unlike North America and Europe where *bla*_{KPC} is the most common β -lactamase gene in CPE isolates, KPC-producing *E. coli* was detected only in Nigeria [52].

5. Conclusions

This review on ESBL-PE and CPE in humans, animals and environments in Central and West Africa confirms the dissemination of β -lactamase-producing *Enterobacteriaceae* in this region of the world.

Our findings highlight the paucity of data on ESBL-PE and CPE in animals and the environment. They also emphasize the urgent need to improve active surveillance programs in each country and to support antimicrobial stewardship.

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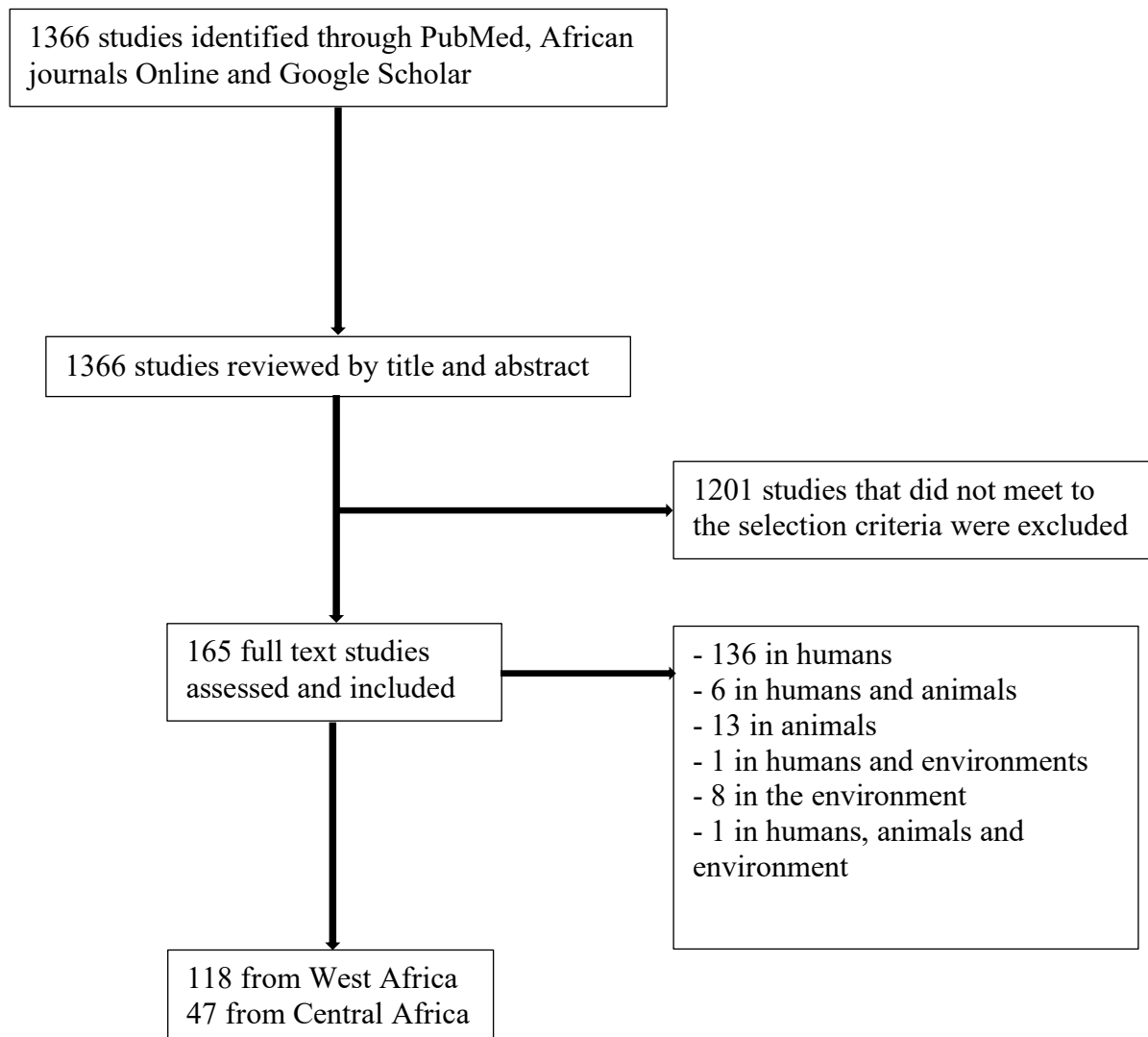


Figure 1: Flow diagram summarizing article identification and selection

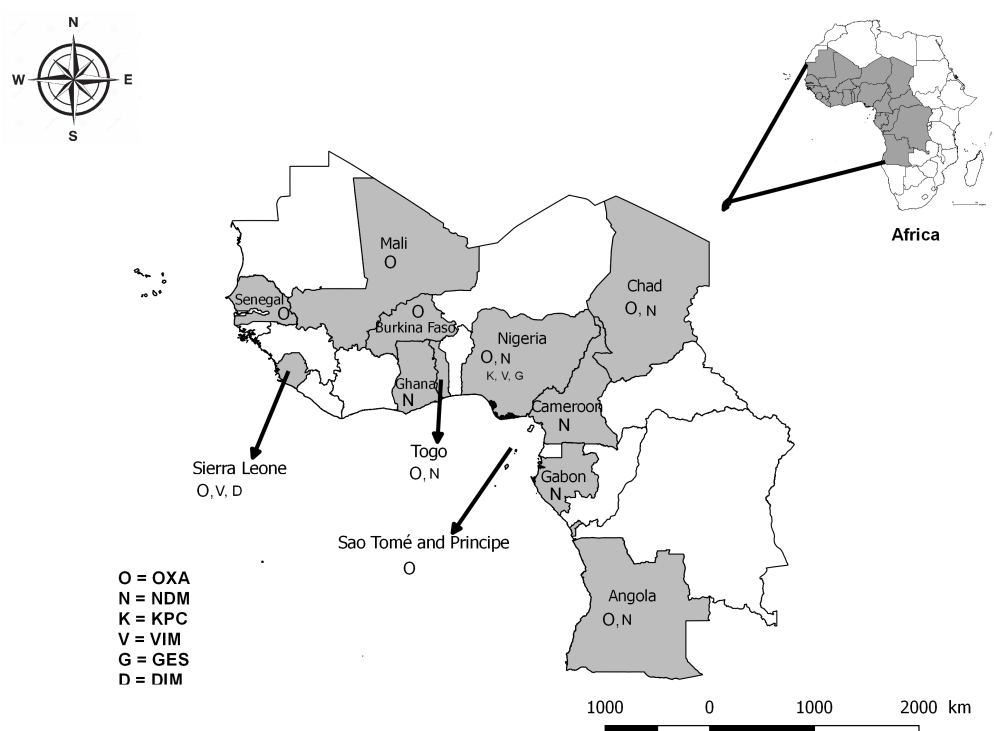


Figure 2: Geographic distribution of carbapenemases produced by *Enterobacteriaceae* isolates in the West and Central Africa region.

Table 1: Prevalence and genetic determinants of extended-spectrum β -lactamase-producing *Enterobacteriaceae* isolated in humans, animals and environments in West and Central Africa.

| ESBL type (%) | Origin | Incompatibility group | ESBL-PE prevalence | Country | References |
|--|--------------|--|--------------------|---------------|------------|
| CTX-M-15 (98%) SHV-12 (2%) | Humans | IncF [30% (100% associated with CTX-M-15)] IncHI2 [15% (100% associated with CTX-M-15)] IncY [20% (100% associated with CTX-M-15)] NT [35% (100% associated with CTX-M-15)] NA | 22% | Angola | [44] |
| CTX-M-15 (100%) | Animals | IncF [45.5% (100% associated with CTX-M-15)] IncY [36.4% (100% associated with CTX-M-15)] NT [18.2% (100% associated with CTX-M-15)] | 75% | | [23,44] |
| CTX-M-15 (100%) | Humans | NA | 35-65% | Benin | [42,47,49] |
| CTX-M | Environments | NA | 15% | | [36,42] |
| CTX-M-15 (94%) SHV-12 (6%) | Humans | NA | 32-58% | Burkina Faso | [64,65] |
| SHV-100 | Environments | NA | NA | | [37] |
| CTX-M-15 (97%) SHV-12 (3%) | Humans | IncF [100% (100% associated with CTX-M-15)] NA | 12-55% | Cameroon | [66–70] |
| CTX-M-15 (100%) | Animals | IncF [100% (100% associated with CTX-M-15)] | 21% | | [16,18] |
| CTX-M-15 (65%) CTX-M-3 (5%) SHV-12 (20%) SHV-2a (10%) | Humans | IncF [89% (100% associated with CTX-M-15)] IncHI2 [4% (100% associated with CTX-M-15)] NT [7% (100% associated with CTX-M-15)] NA NA NA | 4-63% | CAR | [71–74] |
| CTX-M-15 (100%) | Animals | NA | | | [32] |
| CTX-M-15 (96%) CTX-M-9 (4%) | Humans | IncF [100% (100% associated with CTX-M-15)] | 48% | Chad | [59,75,76] |
| CTX-M-15 (98%) | Humans | IncF [24% (100% associated with CTX-M-15)] | 27-56% | Côte d'Ivoire | [22,77] |

| | | | | | |
|---|--------------|--|--------|---------------|---------|
| SHV-12 (2%) | | IncN [6% (100% associated with CTX-M-15)] IncR [6% (100% associated with CTX-M-15)] NT [64% (100% associated with CTX-M-15)] NA | | | |
| CTX-M-15 (100%) | Animals | IncF, IncR | 32% | | [22] |
| CTX-M-15 (100%) | Humans | IncY [100% (100% associated with CTX-M-15)] | 50% | DRC | |
| CTX-M-1(100%) | Environments | NA | 7% | | |
| CTX-M-15 (90%) CTX-M-1 (3%) CTX-M-8 (7%) | Humans | NA | 45-51% | Gabon | [78,79] |
| CTX-M-1 (35%) CTX-M-14 (55%) CTX-M-32 (10%) | Animals | NA | 23% | | [80] |
| CTX-M-15 (98%) CTX-M-27 (2%) | Humans | IncF [100% (98% associated with CTX-M-15 and 2% with CTX-M-27)] | 49-62% | Ghana | [81] |
| CTX-M-15 (77%) CTX-M-1 (6%) CTX-M-2 (6%) CTX-M-14 (8%) SHV-12 (3%) | Animals | NA | 36% | | [27,28] |
| CTX-M | Humans | NA | 32% | Guinea Bissau | [82] |
| CTX-M-15 (67%) CTX-M-14 (17%) CTX-M-9(16%) | Animals | IncF [100% (98% and 16% associated with CTX-M-15, CTX-M-14 and CTX-M-9, respectively)] | 20% | Guinea | [24] |
| CTX-M-15 (82%) CTX-M-14 (9%) SHV-12 (8%) SHV-27 (1%) | Humans | NA | 58% | Mali | [83–86] |
| CTX-M-15 (82%) CTX-M-27 (15%) SHV-12 (3%) | Environments | NA | NA | | [38] |
| CTX-M-15 (100%) | Humans | NA | 6% | Mauritania | [87] |
| CTX-M-15 (91%) | Humans | IncF [57% (100% associated with CTX-M-15)] | 31% | Niger | [88] |

| | | | | | |
|--|--------------|--|--------|-----------------------|---------------|
| SHV-12 (3%) | | NT [43% (100% associated with CTX-M-15)] | | | |
| SHV-2a (3%) | | NA | | | |
| SHV-44 (3%) | | NA | | | |
| CTX-M-15 (90%) CTX-M-1 (6%) CTX-M-3 (4%) | Humans | IncF [54.5% (100% associated with CTX-M-15)] IncH [27.3% (100% associated with CTX-M-15)] IncK [18.2% (100% associated with CTX-M-15)] | 11-72% | Nigeria | [33,89–99] |
| CTX-M-14 (4%) CTX-M-15 (92%) CTX-M-27 (2%) CTX-M-55 (2%) | Animals | IncF [100% (100% associated with CTX-M-15)] | 71% | | [20,21,30,31] |
| CTX-M-15 (72%) SHV-12 (14%) SHV-2 (14%) | Environments | IncF [100% (100% associated with CTX-M-15)] | 79% | | [40,41] |
| CTX-M-15 (100%) | Humans | NA | NA | São Tomé and Príncipe | [100] |
| CTX-M-15 (60%) SHV-12 (30%) SHV-2 (10%) | Humans | IncHI2 (50%), IncN (33%), IncF (17%) IncHI2 (100%) IncN (100%) | 26-79% | Senegal | [101–106] |
| CTX-M-15 (100%) | Animals | NA | NA | | |
| CTX-M | Humans | NA | 64% | Sierra Leone | [107] |
| CTX-M | Humans | NA | 22-55% | Togo | [108] |

ESBL-PE: Extended-spectrum β -lactamase- producing *Enterobacteriaceae*; NA: not available; NT: not typeable; CAR: Central Africa Republic ; DRC: Democratic Republic of Congo.