

Review

# Genetic Environments of Plasmid-Mediated *bla*<sub>CTX-M-15</sub> Beta-Lactamase Gene in Enterobacteriaceae from Africa

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**Abstract:** The most widely distributed *bla*<sub>CTX-M</sub> gene on a global scale is *bla*<sub>CTX-M-15</sub>. The dissemination has been associated with clonal spread and different types of mobile genetic elements. The objective of this review was to describe the genetic environments of the *bla*<sub>CTX-M-15</sub> gene detected from Enterobacteriaceae in published literature from Africa. A literature search for relevant articles was performed through PubMed, AJOL, and Google Scholar electronic databases; 43 articles from 17 African countries were included in the review based on the eligibility criteria. Insertion sequences were reported as part of the genetic environment of *bla*<sub>CTX-M-15</sub> gene in 32 studies, integrons in 13 studies, and plasmids in 23 studies. In this review, five insertion sequences including *ISEcp1*, IS26, *orf447*, IS903, and IS3 have been detected which are associated with the genetic environment of *bla*<sub>CTX-M-15</sub> in Africa. Seven different genetic patterns were seen in the *bla*<sub>CTX-M-15</sub> genetic environment. Insertion sequence *ISEcp1* was commonly located upstream of the end of the *bla*<sub>CTX-M-15</sub> gene, while the insertion sequence *orf477* was located downstream. In some studies, *ISEcp1* was truncated upstream of *bla*<sub>CTX-M-15</sub> by insertion sequences IS26 and IS3. The class 1 integron (*Int11*) was most commonly reported to be associated with *bla*<sub>CTX-M-15</sub> (13 studies), with *Int11/dfrA17-aadA5* being the most common gene cassette array. IncFIA-FIB-FII multi-replicons and IncHI2 replicon types were the most common plasmid replicon types that horizontally transferred the *bla*<sub>CTX-M-15</sub> gene. Aminoglycoside-modifying enzymes, and plasmid-mediated quinolone resistance genes were commonly collocated with the *bla*<sub>CTX-M-15</sub> gene on plasmids. This review revealed the predominant role of *ISEcp1*, *Int11* and IncF plasmids in the mobilization and continental dissemination of the *bla*<sub>CTX-M-15</sub> gene in Africa.



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**Keywords:** antimicrobial resistance; *bla*<sub>CTX-M-15</sub>; genetic environment; mobile genetic elements; Africa

## 1. Introduction

The most widely distributed *bla*<sub>CTX-M</sub> gene on a global scale is *bla*<sub>CTX-M-15</sub>, especially in the enterobacterial species such as *Escherichia coli*, *Klebsiella* spp. and *Salmonella enterica* [1,2]. The global dissemination of the *bla*<sub>CTX-M-15</sub> gene has been associated with the clonal spread of *E. coli* O25: H4-ST131 strains and different types of mobile genetic elements (MGEs) such as insertion sequences, transposons, integrons, phage elements, and conjugative plasmids [1–3]. Of these MGEs, insertion sequences (IS) are of special concern because this mobile element can facilitate the independent transposition with insertion mutation and genetic rearrangements in Enterobacteriaceae [4–6]. Several types of IS elements have been recognized; however, *ISEcp1*, IS26, *orf447* and *ISCR1* have been frequently found to be responsible for the mobilization and expression of different antimicrobial resistance genes [7]. *ISEcp1* is the most frequently reported IS type [7]. *ISEcp1* is a member of the IS1380 family and was first identified on the plasmid pST01 in *E. coli* strain 79 but has now been globally disseminated in association with different *bla*<sub>CTX-M</sub> phylogenetic clusters [8].

The roles of *ISEcp1* and other MGEs in the genetic environments of *bla*<sub>CTX-M</sub> genes have been well described [7,9,10]. *ISEcp1* is commonly located upstream of the *bla*<sub>CTX-M-15</sub> gene

and is responsible for the downstream mobilization and transposition of itself, adjacent genes, and the *bla*<sub>CTX-M-15</sub> gene. IS26 has commonly been found to be located upstream of the *bla*<sub>CTX-M-15</sub> alone or in association with *ISEcp1* [1,7]. *ISCR1*, on the other hand, has been associated with class 1 integron, forming a transposition complex for the mobilization of *bla*<sub>CTX-M-15</sub> and other beta-lactamase genes [8]. Integrons are site-specific recombination systems that capture various arrays of gene cassettes within the conserved regions and can integrate one or several non-functional gene cassettes and convert these into functional genes [6]. Molecular characterization and replicon typing of various plasmid groups have facilitated the recognition and location of *bla*<sub>CTX-M-15</sub> genes co-existing with other AMR genes on both narrow host-range and, to a lesser extent, broad-host-range plasmids [11].

Genetic environments of *bla*<sub>CTX-M</sub> genes have been described and reported in enterobacterial species from different parts of the world, however variation in genetic patterns exists from region to region [10]. Additionally, analysis of genetic environments of *bla*<sub>CTX-M</sub> gene and associated MGEs on a continental scale may provide necessary information on the diversity and complexity of the genetic environments as well as provide opportunities for better understanding of the epidemiology of this globally disseminated resistance gene. This study aimed to review and describe the genetic environments of *bla*<sub>CTX-M-15</sub> genes and associated MGEs in Enterobacteriaceae in published literature from Africa.

## 2. Materials and Methods

The literature search was conducted in the PubMed, AJOL and Google Scholar electronic databases between June 2018 and January 2019 for the purpose of this narrative and non-systematic review. The following terms were used for the literature search: *bla*<sub>CTX-M-15</sub> gene AND Africa OR *bla*<sub>CTX-M-15</sub> AND genetic environment AND Africa. A literature search was also conducted based on studies reporting the detection of *bla*<sub>CTX-M-15</sub> from each African country, e.g., *bla*<sub>CTX-M-15</sub> AND Nigeria, *bla*<sub>CTX-M-15</sub> AND Egypt, *bla*<sub>CTX-M-15</sub> and Kenya, etc. The reference lists of all eligible articles were further reviewed and used to carry out a supplementary literature search. The articles were further screened after the removal of duplicates by titles and abstracts for their relevance to the study objectives and purpose. The primary outcomes of interest were to describe the genetic environment of *bla*<sub>CTX-M-15</sub> in Enterobacteriaceae from different African countries.

For studies to be included in the qualitative description, the studies must have reported the genetic environment of the *bla*<sub>CTX-M-15</sub> resistance gene with special reference to the associated insertion sequences. The data were abstracted onto an Excel (Microsoft Office Excel 2010) spreadsheet. For each eligible study, data extracted included: first author details, year of publication, country from which the study was conducted, sources of the samples (animal, human or environment), enterobacterial species in which the *bla*<sub>CTX-M-15</sub> gene was detected, insertion sequences associated with the genetic environment, additional data on other mobile genetic elements including type of integron and associated gene cassette arrays, plasmid and associated replicon types, as well as additional antimicrobial resistance genes associated with the *bla*<sub>CTX-M-15</sub> gene on different plasmids.

## 3. Results

From the literature search, 43 articles from 17 African countries were included in the review based on the eligibility criteria (Table 1). Thirty-nine studies were based on *bla*<sub>CTX-M-15</sub>-producing Enterobacteriaceae isolated from human clinical cases, three studies from animals, and one study from the environment. Bacteria of Enterobacteriaceae reported were *Escherichia coli* alone (19 studies), *Klebsiella* spp. alone (8 studies), *Salmonella enterica* (6 studies), *E. coli* and *Klebsiella* spp. (4 studies), as well as combinations of other enterobacterial species (6 studies). Insertion sequences were reported in 32 of the 43 studies (Table 1). Seven different genetic patterns were observed among these studies (Figure 1). In eight studies [12–19], the insertion sequence *ISEcp1* was located upstream of the end of the *bla*<sub>CTX-M-15</sub> gene with insertion sequence *orf477* located downstream (*ISEcp1-bla*<sub>CTX-M-15-orf477</sub>). Twenty-three studies [20–42] found *ISEcp1* to be the only insertion sequence located

upstream of the *bla*<sub>CTX-M-15</sub> gene (*ISEcp1*-*bla*<sub>CTX-M-15</sub>). Additionally, two studies [16,42] reported the location of *ISEcp1* upstream of *bla*<sub>CTX-M-15</sub> truncated by IS26 without any downstream IS element (*ISEcp1*-IS26-*bla*<sub>CTX-M-15</sub>). In one these two studies [16], IS26 was located upstream of *bla*<sub>CTX-M-15</sub> with *orf477* located downstream in an enterobacterial isolate. In another two studies [12,43], *ISEcp1* was truncated upstream of *bla*<sub>CTX-M-15</sub> by IS26 (*ISEcp1*-IS26-*bla*<sub>CTX-M-15</sub>-*orf477*). In one study [42], *ISEcp1* was truncated upstream of *bla*<sub>CTX-M-15</sub> by IS26, with IS903 located downstream (*ISEcp1*-IS26-*bla*<sub>CTX-M-15</sub>-IS903); however, novel IS3 type [16] was reported in one study to truncate *ISEcp1* upstream of the start of *bla*<sub>CTX-M-15</sub> gene (*ISEcp1*-IS3-*bla*<sub>CTX-M-15</sub>). The promoter region (−35 and −10) of 48 bp [14,23,24,29,37], V and W promoter region of 127 bp [31], and other unspecified promoter regions of 400–1800 bp [17,19,26,35] of *ISEcp1* were located upstream between the left end of *ISEcp1* and the start codon of the *bla*<sub>CTX-M-15</sub> gene.

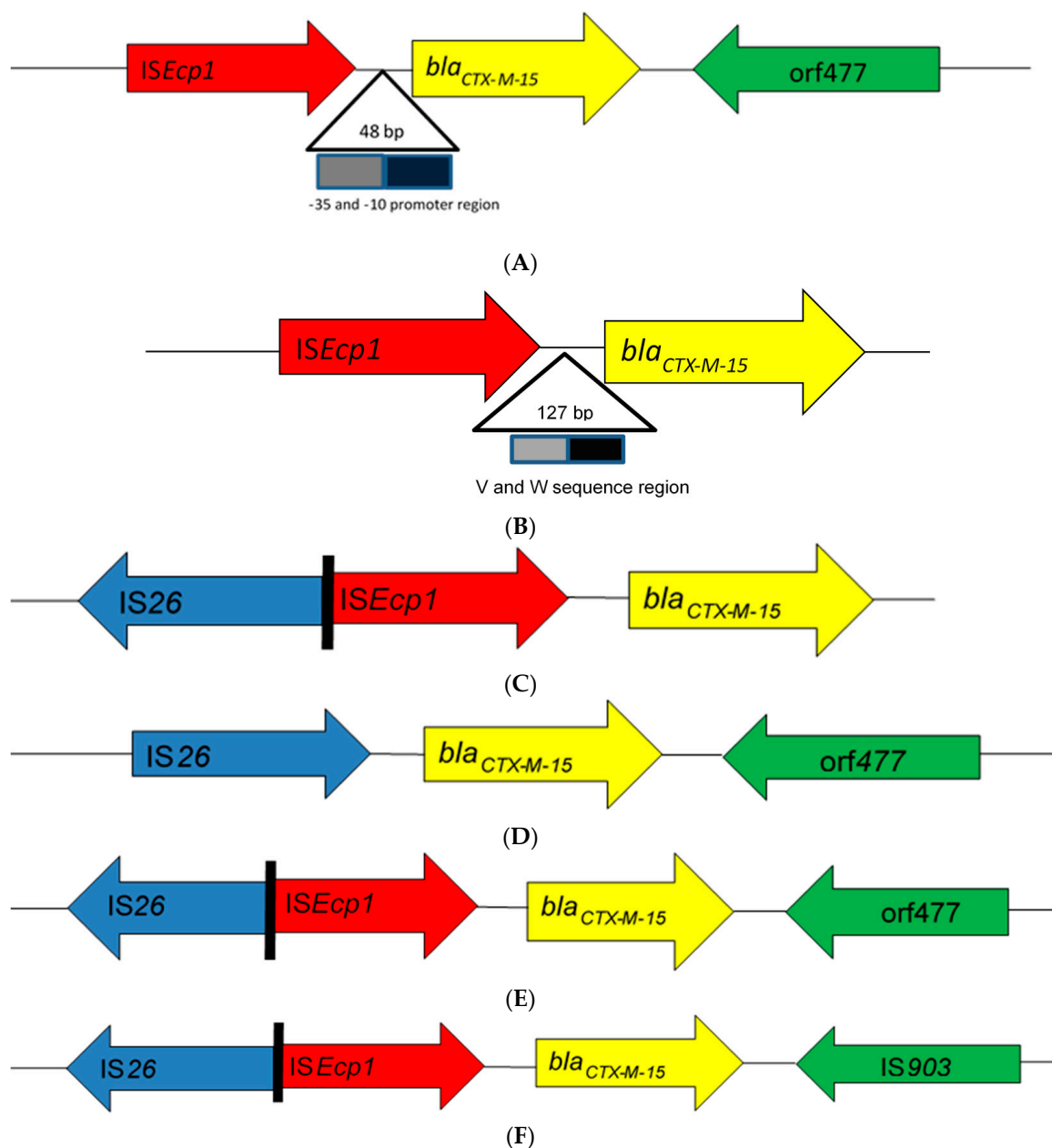
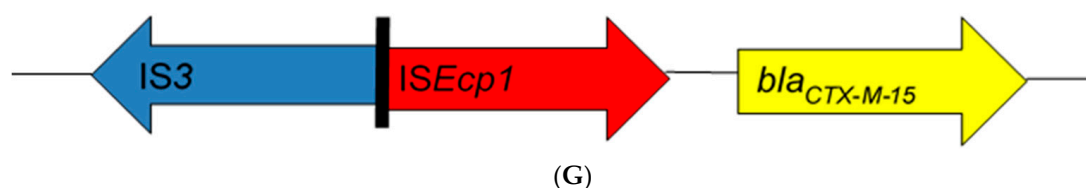


Figure 1. Cont.



**Figure 1.** Schematic representations of different genetic environments of *bla*<sub>CTX-M-15</sub> reported in the literature from Africa. (A) The insertion sequence *ISEcp1* was located upstream of the end of the *bla*<sub>CTX-M-15</sub> gene with insertion sequence *orf477* located downstream. (B) The *ISEcp1* is the only insertion sequence located upstream of the *bla*<sub>CTX-M-15</sub> gene. (C) *ISEcp1* located upstream of *bla*<sub>CTX-M-15</sub> truncated by IS26 without any downstream IS element. (D) IS26 was located upstream of *bla*<sub>CTX-M-15</sub> with *orf447* located downstream. (E) *ISEcp1* was truncated upstream of *bla*<sub>CTX-M-15</sub> by IS26 while *orf477* was located downstream. (F) *ISEcp1* was truncated upstream of *bla*<sub>CTX-M-15</sub> by IS26, with IS903 located downstream. (G) Novel IS3 type truncated *ISEcp1* upstream the start codon of *bla*<sub>CTX-M-15</sub> gene.

Integrations were associated with *bla*<sub>CTX-M-15</sub> genes in 13 studies [12,15,18,19,21,25,31,32,34,42–45]; a class 1 integron (*Int1*) was reported in 13 studies, while a class 2 integron (*Int2*) was reported in 3 studies together with a class 1 integron. A class 3 integron was not reported in all the studies reviewed, one gene cassette arrangement; *Int2/dfrA1-sat-aadA1* was detected in *Int2* in this review from only one study. However, with the exception of two studies, different gene cassette arrays were detected in variable regions of *Int1*, with *Int1/dfrA17-aadA5* being the most reported gene cassette from 6 out of 43 studies reviewed (Table 1). Different types of plasmid incompatibility groups were reported to transfer *bla*<sub>CTX-M-15</sub> gene horizontally. These plasmid groups include IncF, IncH, IncN, IncY, IncK, IncX, IncI, IncA, IncC, IncL, and IncM [14,16,25,30,32–36,38,39,42,43,45–54]. However, IncF plasmid was the most reported plasmid associated with *bla*<sub>CTX-M-15</sub> gene from 17 out of the 43 studies reviewed (Table 1). Antimicrobial resistance genes including the narrow-spectrum *bla*<sub>OXA-1</sub> and *bla*<sub>TEM-1</sub> beta-lactamases, tetracycline resistance genes (*tetA* and *tetB*), sulfonamide resistance genes (*sul2* and *sul3*) and plasmid-mediated quinolone resistance genes *qnrA*, *qnrB*, and *qnrS* and aminoglycoside-modifying enzyme encoding genes (*aac*-(6′)-*lb-cr*), were reportedly associated with *bla*<sub>CTX-M-15</sub> genes on plasmids.

**Table 1.** Genetic environment of CTXM-15 genes in enterobacterial species from Africa.

| References | Country | Sample Sources | Enterobacterial Species                                  | Genetic Environment Pattern   | Additional Resistance Genes   | Mobile Genetic Elements  |   |
|------------|---------|----------------|--|---|---|--|---|
|            |         |                |  |   |   | Integron/Gene Cassettes  | Plasmids  |
| [12]       | Nigeria | Environment    | <i>Escherichia coli</i>                                  | <i>ISEcp1</i> -IS26- <i>orf477</i> ,<br><i>ISEcp1</i> - <i>orf477</i> |   | <i>Int1/dfrA17-aadA5</i> ,<br><i>Int1/dfrA32-ereA-aadA2</i> ,<br><i>Int1/dfrA16-aadA2</i> ,<br><i>Int1/aadA1</i> ,<br><i>Int1/dfrA7</i> , <i>Int2</i>                            |   |
| [20]       | Nigeria | Human          | <i>Escherichia coli</i>                                  | <i>ISEcp1</i>   | <i>aac</i> -(6′)- <i>lb-cr</i> , <i>qnrB1</i> ,<br><i>qnrA1</i>   |  |   |
| [44]       | Nigeria | Human          | <i>Enterobacter cloacae</i> , <i>Pantoea agglomerans</i> |   | <i>aadA1</i> , <i>aph</i> ,<br><i>aac</i> -(6′)- <i>lb</i> , <i>sul1</i> , <i>cat1</i> ,<br><i>qnrB1</i> , <i>tet</i> (A), <i>tet</i> (E)                                     | <i>Int1</i> , <i>Int2</i>  |   |
| [21]       | Nigeria | Human          | <i>Proteus mirabilis</i>                                 | <i>ISEcp1</i>   | <i>aac</i> (6′)- <i>lb-cr</i> , <i>qnrA</i> ,<br><i>bla</i> <sub>TEM-1</sub>  | <i>Int1</i> , <i>Int2</i> , <i>aadA1</i> ,<br><i>aadA1-qacH</i> ,<br><i>aadB-aadA2</i> , <i>aadA5</i> ,<br><i>dfrA7</i> , <i>dfrA15</i> , <i>dfrA17</i> ,<br><i>dfrA17-aadA5</i> |   |
| [47]       | Nigeria | Human          | <i>Escherichia coli</i>                                  |   | <i>aac</i> (6′)- <i>lb-cr</i> , <i>qnrS1</i> ,<br><i>qnrB1</i> , <i>qepA1</i> ,<br><i>bla</i> <sub>OXA-1</sub> , <i>bla</i> <sub>TEM-1</sub> ,<br><i>bla</i> <sub>CMY-2</sub> |  | IncFIA-FIB-FII,<br>IncHI2, IncY,<br>IncX, IncX2,<br>IncI2 |
| [46]       | Nigeria | Chicken, pig   | <i>Escherichia coli</i>                                  |   | <i>qnrS1</i> , <i>bla</i> <sub>TEM-1</sub>  |  | IncN  |

Table 1. Cont.

| References | Country                  | Sample Sources | Enterobacterial Species  | Genetic Environment Pattern                   | Additional Resistance Genes   | Mobile Genetic Elements   |                                    |
|------------|--------------------------|----------------|--|---|---|---|------------------------------------|
|            |                          |                |  |   |   | Integron/Gene Cassettes   | Plasmids                           |
| [42]       | Nigeria                  | Human          | <i>Escherichia coli</i>  | ISEcp1, ISEcp1-IS26, ISEcp1-IS26-IS903        | <i>qnrB</i> , <i>aac</i> (6')-Ib-cr, <i>bla</i> <sub>TEM-1</sub>  | <i>Int1/aadA1</i> , <i>int1/dfrA17-aadA5</i>                                      | IncFIA, IncFIB, HI2 IncK           |
| [13]       | Nigeria                  | Human          | <i>Escherichia coli</i>  | ISEcp1-orf477                                 | <i>aac</i> (6')-Ib-cr, <i>bla</i> <sub>OXA-1</sub> , <i>bla</i> <sub>SHV</sub> , <i>bla</i> <sub>TEM-1</sub>  |   |                                    |
| [48]       | Nigeria                  | Human          | <i>Escherichia coli</i> , <i>Klebsiella</i> spp.                           |   | <i>bla</i> <sub>CTXM-2</sub> , <i>bla</i> <sub>OXA-1</sub> , <i>bla</i> <sub>SHV</sub> , <i>bla</i> <sub>TEM-1</sub> , <i>bla</i> <sub>AmpC</sub>   |   | IncF                               |
| [43]       | Nigeria                  | Chicken        | <i>Escherichia coli</i>  | ISEcp1-IS26-orf477                            | <i>aac</i> (3)-IIa, <i>aac</i> (6')-Ib-cr, <i>dfrA5</i> , <i>dfrA12</i> , <i>strA</i> , <i>strB</i> , <i>sul1</i> , <i>sul2</i> , <i>tet</i> (A), <i>tet</i> (B), <i>bla</i> <sub>OXA-1</sub> , <i>bla</i> <sub>TEM-1</sub> | <i>Int1/aadA2-orfF-dfrA12</i>   | IncFIB, IncFIA-IncFIB-IncI1        |
| [22]       | Nigeria                  | Human          | <i>Escherichia coli</i> , <i>Klebsiella</i> spp., <i>Proteus mirabilis</i> | ISEcp1  | <i>bla</i> <sub>TEM</sub> , <i>bla</i> <sub>SHV</sub>   |   |                                    |
| [23]       | Nigeria                  | Human          | <i>Klebsiella</i> spp.   | ISEcp1  | <i>tet</i> (A), <i>aac</i> (3)-II, <i>aac</i> (6')-Ib   |   |                                    |
| [14]       | Ghana                    | Human          | <i>Escherichia coli</i> , <i>Klebsiella</i> spp.                           | ISEcp1- orf477                                | <i>bla</i> <sub>TEM</sub> , <i>aac</i> (3)-II, <i>bla</i> <sub>OXA-30</sub>   |   | IncFII-FIA-FIB, IncFIK             |
| [49]       | Ghana                    | Human          | <i>Salmonella</i> Poona  |   | <i>bla</i> <sub>TEM-1B</sub> , <i>bla</i> <sub>OXA-1</sub> , <i>qnrB1</i> , <i>aac</i> (6') Ib-cr, <i>tet</i> (A), <i>dfrA15</i> , <i>sul2</i> , <i>catB3</i> , <i>strA</i> , <i>strB</i> , <i>aac</i> (3)-Iia              |   | TrfA-IncHI2-IncHI2A                |
| [15]       | Mauritania               | Human          | <i>Escherichia coli</i>  | ISEcp1-orf477                                 | <i>aac</i> (6')-Ib-cr, <i>tet</i> (A), <i>sul2</i> , <i>sul3</i> , <i>strA</i> , <i>strB</i> , <i>bla</i> <sub>OXA-1</sub> , <i>bla</i> <sub>TEM-1B</sub>   | <i>int1/dfrA17-aadA5</i>  |                                    |
| [24]       | Niger                    | Human          | <i>Morganella morganii</i> , <i>Citrobacter freundii</i>                   | ISEcp1  | <i>bla</i> <sub>DHA</sub> , <i>bla</i> <sub>CIT</sub> , <i>bla</i> <sub>TEM-1</sub>   |   |                                    |
| [50]       | Niger                    | Human          | <i>Escherichia coli</i>  |   | <i>bla</i> <sub>CMY-2</sub> , <i>bla</i> <sub>SHV-44</sub>  |   | FII/FIA/FIB, FII/I1/Iγ,            |
| [51]       | Senegal                  | Human          | <i>Salmonella enterica</i>   |   | <i>qnrB1</i> , <i>aac</i> (6')-Ib-cr  |   | IncHI2, IncN, IncFII               |
| [25]       | Senegal                  | Human          | <i>Escherichia coli</i>  | ISEcp1  | <i>bla</i> <sub>TEM-1</sub> , <i>bla</i> <sub>OXA-1</sub> , <i>aac</i> (6)-Ib-cr, <i>tet</i> (A)  | <i>int1/dfrA17-aadA5</i>  | IncFIA-FIB-FII                     |
| [26]       | Senegal                  | Human          | <i>Salmonella</i> Kentucky   | ISEcp1  | <i>bla</i> <sub>TEM-1</sub> , <i>bla</i> <sub>OXA-30</sub>  |   |                                    |
| [52]       | Sao Tome and Principe    | Human          | <i>Escherichia coli</i>  |   | <i>bla</i> <sub>OXA-181</sub> , <i>bla</i> <sub>TEM-1</sub> , <i>rmtB</i>   |   | IncX3                              |
| [27]       | DRC                      | Human          | <i>Salmonella</i> Typhi  | ISEcp1  | <i>bla</i> <sub>TEM-1D</sub> , <i>sul1</i> , <i>dfrA7</i>   |   |                                    |
| [53]       | Central African Republic | Human          | <i>Escherichia coli</i> , <i>Enterobacteriaceae</i>                        |   | <i>aac</i> (6')-Ib-cr, <i>qnrB</i> , <i>qnrS</i>  |   | IncF                               |
| [28]       | Cameroon                 | Human          | <i>Escherichia coli</i>  | ISEcp1  | <i>bla</i> <sub>OXA-181</sub> , <i>bla</i> <sub>TEM-1</sub> , <i>aac</i> (6') Ib-cr   |   |                                    |
| [54]       | Cameroon                 | Human          | <i>Klebsiella</i> spp.   |   | <i>sul1</i> , <i>fosA</i> , <i>oqxA</i> , <i>oqxB</i> , <i>bla</i> <sub>TEM-1B</sub> , <i>dfrA15</i> , <i>strA</i> , <i>strB</i>  |   | ColIRNAI, IncFIB (K), IncFIA (HI1) |
| [29]       | Egypt                    | Human          | <i>Escherichia coli</i>  | ISEcp1  | <i>bla</i> <sub>TEM-1</sub>   |   |                                    |
| [30]       | Algeria                  | Human          | <i>Salmonella enterica</i> ser Infantis                                    | ISEcp1  | <i>armA</i> , <i>bla</i> <sub>TEM-1</sub>   |   | IncL, IncM                         |
| [31]       | Algeria                  | Human          | <i>Klebsiella</i> spp.   | ISEcp1  | <i>bla</i> <sub>TEM-1</sub>   | <i>Int1</i>   |                                    |
| [16]       | Angola                   | Human          | <i>Escherichia coli</i> , <i>Klebsiella</i> spp.                           | ISEcp1-orf477, IS26-orf447, ISEcp1-IS3-orf477 | <i>bla</i> <sub>OXA-1</sub> , <i>bla</i> <sub>TEM-1</sub> , <i>aac</i> -6'-Ib-cr  |   | IncFII, IncFIK6, IncHI2 and IncY   |
| [45]       | Angola                   | Dog            | <i>Escherichia coli</i>  |   | <i>qepA</i> , <i>qnrS1</i> , <i>qnrB19</i> , <i>aac</i> (6')-Ib-cr  | <i>Int1/dfrA17-aadA5</i> , <i>Int1/dfrA1-aadA1</i> , <i>Int12/dfrA1-sat-aadA1</i> | IncFIB, IncY, IncN, IncI1          |

Table 1. Cont.

| References | Country    | Sample Sources | Enterobacterial Species                             | Genetic Environment Pattern | Additional Resistance Genes   | Mobile Genetic Elements   |                           |
|------------|------------|----------------|---|-----------------------------|---|---|---------------------------|
|            |            |                |   |                             |   | Integron/Gene Cassettes   | Plasmids                  |
| [32]       | Madagascar | Human          | <i>Escherichia coli</i> ,<br><i>Klebsiella</i> spp. | ISEcp1                      | <i>bla</i> <sub>TEM-1</sub> , <i>bla</i> <sub>OXA-1</sub> ,<br><i>aac</i> (6')-Ib-cr,<br><i>sul1-sul2</i> , <i>tet</i> (A),<br><i>qnrB</i>                              | <i>Int11</i> /<br><i>aadA1-aadA2-aadA4-</i><br><i>aadA5-dfrA5-dfrA22</i>                          | IncFII-FIA-FIB,<br>IncHI2 |
| [17]       | Morocco    | Human          | <i>Klebsiella</i> spp.                              | ISEcp1-orf477               | <i>bla</i> <sub>TEM-1B</sub> , <i>bla</i> <sub>OXA-1</sub> ,<br><i>aac</i> (6')-Ib-cr,<br><i>qnrB1</i>  |   |                           |
| [33]       | Morocco    | Human          | <i>Klebsiella</i> spp.                              | ISEcp1                      | <i>qnrB1</i> , <i>bla</i> <sub>NDM-1</sub>  |   | IncH                      |
| [34]       | Kenya      | Human          | <i>Salmonella</i><br><i>Typhimurium</i>             | ISEcp1                      | <i>bla</i> <sub>TEM-1</sub> , <i>bla</i> <sub>OXA-1</sub> ,<br><i>aac</i> (6')-Ib, <i>sul1</i> , <i>sul2</i> ,<br><i>aadA1</i>  | <i>Int11/dfrA14-catA1</i>   | IncFII, IncHI2            |
| [35]       | Tanzania   | Human          | <i>Escherichia coli</i>                             | ISEcp1                      | <i>bla</i> <sub>TEM-1</sub>   |   | IncFIA- FIB               |
| [41]       | Tanzania   | Human          | <i>Enterobacter</i><br>spp.                         | ISEcp1                      |   |   |                           |
| [36]       | Tanzania   | Human          | <i>Klebsiella</i> spp.                              | ISEcp1                      | <i>bla</i> <sub>TEM-1</sub> , <i>bla</i> <sub>SHV-11</sub>  |   | IncFII, IncFIA            |
| [37]       | Tunisia    | Human          | <i>Escherichia coli</i>                             | ISEcp1                      | <i>bla</i> <sub>TEM-1</sub> , <i>bla</i> <sub>SHV-12</sub>  |   |                           |
| [18]       | Tunisia    | Human          | <i>Escherichia coli</i>                             | ISEcp1-orf477               | <i>bla</i> <sub>TEM-1</sub> , <i>bla</i> <sub>OXA-1</sub> ,<br><i>aac</i> (3)-II,<br><i>aac</i> (6')-Ib-cr, <i>strA</i> ,<br><i>strB</i> , <i>sul2</i> , <i>tet</i> (B) | <i>Int11/ dfrA17-aadA5</i> ,<br><i>Int11/</i><br><i>dfrA12-orfF-aadA2</i> ,<br><i>Int11/aadA2</i> |                           |
| [38]       | Tunisia    | Human          | <i>Escherichia coli</i>                             | ISEcp1                      | <i>bla</i> <sub>TEM-52</sub>  |   | IncA, IncC                |
| [39]       | Tunisia    | Human          | <i>Klebsiella</i> spp.                              | ISEcp1                      | <i>bla</i> <sub>TEM-1</sub> , <i>bla</i> <sub>SHV-12</sub>  |   | IncFII, IncL,<br>IncM     |
| [40]       | Tunisia    | Human          | <i>Escherichia coli</i>                             | ISEcp1-IS26                 |   |   |                           |
| [19]       | Tunisia    | Human          | <i>Klebsiella</i> spp.                              | ISEcp1- orf477              | <i>bla</i> <sub>TEM-1</sub> , <i>bla</i> <sub>OXA-1</sub> ,<br><i>bla</i> <sub>SHV-1</sub>  | <i>Int11/ dfrA17-ereA2</i> ,<br><i>Int11/aadA</i>   |                           |

#### 4. Discussion

This review was carried out to describe the genetic environments of the internationally disseminated *bla*<sub>CTX-M-15</sub> gene in Enterobacteriaceae from Africa. Most of the studies in this review were from human clinical settings, which suggests that *bla*<sub>CTX-M-15</sub>-producing Enterobacteriaceae are a challenge to healthcare facilities in Africa. The *bla*<sub>CTX-M-15</sub> gene has been associated with the pandemic-initiating *E. coli* O25: H4 ST131 clone that causes both community and human healthcare infections globally [2]. Review of the genetic environments of *bla*<sub>CTX-M-15</sub> in Enterobacteriaceae revealed five ISs including *ISEcp1*, IS26, *orf447*, IS903, and IS3 which had been detected in Africa. With the exception of a novel IS3 type that was reported from Angola [16], all the other ISs have been reported from other parts of the world to be associated with the genetic environment of different AMR genes in general [7,8,55]. From all the studies reviewed, *ISEcp1* was typically located upstream of *bla*<sub>CTX-M-15</sub> gene. This IS often encodes a transposase that facilitates the mobilization of *bla*<sub>CTX-M-15</sub> gene among integrons, transposons, plasmids, and chromosomes, as well as provides promoters that can activate the weakly expressed state of *bla*<sub>CTX-M-15</sub> [56–58]. This IS has been reported to contribute to the global dissemination of *bla*<sub>CTX-M-15</sub> genes in association with other MGEs [1,59,60]. The *ISEcp1/ bla*<sub>CTX-M-15</sub> genetic association observed in this review has previously been reported from other parts of the world including India, France, Turkey, Poland, Canada, the United Kingdom, Spain, and China [8–10,55,56,58,61–64]. This IS element has also been commonly found associated with other *bla*<sub>CTX-M</sub> genes and other beta-lactamase resistance genes [10,59]. Of the genetic environments associated with *bla*<sub>CTX-M</sub> genes, *ISEcp1* is one of the most commonly detected IS elements in the genetic environment of *bla*<sub>CTX-M</sub> genes, suggesting a possible co-evolutionary relationship between the *ISEcp1* and *bla*<sub>CTX-M</sub> genes [9,52,61,65].

The insertion site of *ISEcp1* was different from study to study in this review; this may be due to the variation in bacterial strains, IS promoter types, and other factors associated with genetic environments of the *bla*<sub>CTX-M-15</sub> gene. Three studies provided information on the promoter regions in this review; the –35 and –10 putative promoter regions (48 bp) were

reported in five studies, while V and W sequences (127 bp) were in one study. In all cases, these promoter regions are important in the transcription, mobilization, and expression of the *bla*<sub>CTX-M-15</sub> gene as previously described [7,9,10]. IS26 was another IS described in Africa. However, this IS element was located upstream of *bla*<sub>CTX-M-15</sub>, disrupting *ISEcp1* elements in all studies reporting the presence of IS26 and *ISEcp1* in the genetic environment of *bla*<sub>CTX-M-15</sub>. IS26 has also been reported from other parts of the world to be associated with *bla*<sub>CTX-M</sub> genes alone without *ISEcp1* [64] or associated with *bla*<sub>CTX-M</sub> genes together with and located upstream of *ISEcp1* [55,56,66], or located truncating *ISEcp1* [55,64] in genetic arrangements with *bla*<sub>CTX-M</sub> genes similar to the findings of this review. In all these genetic arrangements involving IS26, the IS was suggested to be associated with transposition and stabilization of the *ISEcp1*/*bla*<sub>CTX-M-15</sub> complex on plasmids [63,67].

The genetic environment downstream of the *bla*<sub>CTX-M-15</sub> revealed flanking of the *bla*<sub>CTX-M-15</sub> gene by two different types of insertion sequences, *orf447* and IS903. Both IS elements are the major IS elements commonly reported downstream of *bla*<sub>CTX-M</sub> [8,68,69]. However, based on this review, *orf447* is the major IS element downstream of *bla*<sub>CTX-M-15</sub> gene in Africa. In this review, seven different genetic patterns were observed; four of the five genetic patterns have previously been reported. *ISEcp1*-*bla*<sub>CTX-M-15</sub>-*orf477* genetic pattern has been reported from European and Indian strains of Enterobacteriaceae [55,61,66]; *ISEcp1 bla*<sub>CTX-M-15</sub> has been reported from Spain, Canada, India, and Poland [64,70–73]; *ISEcp1*-IS26-*bla*<sub>CTX-M-15</sub>-*orf447* has also been reported from France [55,74]; while the *ISEcp1*-IS3 *bla*<sub>CTX-M-15</sub> pattern was reported to be novel from Angola [16]. Other genetic patterns have been reported in the genetic environments of other types of *bla*<sub>CTX-M</sub> and other beta-lactamase genes [8,61,75]. These genetic patterns from Africa reveal how the genetic environment of *bla*<sub>CTX-M-15</sub> is consistent with what has been reported on global scales. Additionally, immigration, global migration, and traveling for tourism purposes could also contribute to these global genetic patterns of *bla*<sub>CTX-M-15</sub>. Similar genetic environments of *bla*<sub>CTX-M-15</sub> reported in this review and other novel genetic patterns have previously been reported from travelers returning to the United Kingdom from the Middle East, Africa, and Asian countries, which suggests the possible overseas acquisition of these genetic patterns [66].

Class 1 integrons were more commonly associated with *bla*<sub>CTX-M-15</sub> compared to class 2 integrons; this is consistent with previous reports elsewhere [8,76]. Class 1 integrons are often associated with IS elements such as *ISEcp1* and *ISCR1*. These integrons are often located adjacent to *ISEcp1* and *ISCR1* and function in the mobilization and transposition of *bla*<sub>CTX-M-15</sub> genes [8]. In addition, some AMR genes associated with *bla*<sub>CTX-M-15</sub> are captured within the conserved regions of the class 1 integrons. AMR genes were harbored within the cassette arrays of class 1 integron in different studies in this review. Antimicrobial resistance genes including *dfrA17*, *dfrA5*, *dfrA1*, *aadA5*, *aadA2*, *aadA1* and *catA1* were observed within the conserved region of the class 1 integrons, and these genes often confer multi-drug resistance to trimethoprim, aminoglycosides, and chloramphenicol. Conjugative plasmids are essential for the evolution and global dissemination of the *bla*<sub>CTX-M-15</sub> gene. Similar to this review, several studies have found that the narrow-host range plasmid IncF is the predominant plasmid group that harbors the *bla*<sub>CTX-M-15</sub> gene [77]. The IncF plasmid is mainly restricted to Enterobacteriaceae with support mechanisms such as lower fitness cost, transferability properties, plasmid addiction, and stability systems that favor: (i) the higher prevalence of *bla*<sub>CTX-M-15</sub> in Enterobacteriaceae compared to other Gram-negative bacteria; and (ii) global dissemination of *bla*<sub>CTX-M-15</sub> in association with other mobile genetic elements [11,59,78]. The IncFII-FIA-FIB multi-replicon plasmids were more commonly associated with *bla*<sub>CTX-M-15</sub> in this review and have been widely distributed in the Enterobacteriaceae, especially *E. coli*, globally [79,80]. This replicon group could be maintained and propagated between enterobacterial species and from host to host without antimicrobial selective pressure [59,77]. This may provide some explanation to the rapid and global spread of the *bla*<sub>CTX-M-15</sub> gene. Another important finding of this review was the presence of other antimicrobial resistance associated with *bla*<sub>CTX-M-15</sub> often co-located

on the same plasmid. Different AMR genes commonly co-exist on plasmids, therefore facilitating the co-dissemination of resistance genes and greater survival fitness of bacteria under antimicrobial selective pressure [78]. Antimicrobial resistance genes including the narrow-spectrum *bla*<sub>OXA-1</sub> and *bla*<sub>TEM-1</sub> beta-lactamases, aminoglycoside-modifying enzymes (*aac*-(6')-*lb-cr*), tetracycline resistance genes (*tetA* and *tetB*), sulfonamide resistance genes (*sul2* and *sul3*) and plasmid-mediated quinolone resistance genes (*qnrA*, *qnrB* and *qnrS*) were found to be consistently associated with *bla*<sub>CTX-M-15</sub> from different studies in the review. These AMR genes have previously been reported to be co-located on IncFII-FIA-FIB plasmid replicons in association with *bla*<sub>CTX-M-15</sub>-producing *E. coli* O25:H4-ST131 [81,82], conferring multi-drug resistance to different antimicrobial classes, complicating the genetic environments, and facilitating the global spread of *bla*<sub>CTX-M-15</sub> in Enterobacteriaceae. In addition to the contribution of clonal spread of some bacteria of Enterobacteriaceae, especially *E. coli* and *Klebsiella* spp., the association of *bla*<sub>CTX-M-15</sub> with mobile genetic elements such as insertion sequences, integrons, and conjugative plasmids may explain its global dominance and dissemination. This review has showed the diversity and the complexity of the genetic environments of *bla*<sub>CTX-M-15</sub> beta-lactamase gene in Enterobacteriaceae from Africa. We recognize that a limited number of articles were included in this review, which was a limitation of this review. This is partly due to limited published articles on this subject matter in Africa. Our focus was to provide a narrative review that can serve as baseline literature for a future comprehensive and systematic review and indicate the need for more research on this internationally disseminated beta-lactamase resistance gene.

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