Genetic environments of plasmid-mediated *bla*\textsubscript{CTXM-15} beta-lactamase gene in *Enterobacteriaceae* from Africa

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Abstract

The most widely distributed $bla_{CTX-M}$ gene on a global scale is $bla_{CTX-M-15}$. The dissemination has been associated with clonal spread and different types of mobile genetic elements. This study aimed to review and describe the genetic environments of $bla_{CTX-M-15}$ gene detected from Enterobacteriaceae in published literature from Africa. A literature search for relevant articles was done through PubMed, and Google Scholars 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 $bla_{CTX-M-15}$ 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 associated with the genetic environment of $bla_{CTX-M-15}$ in Africa. Seven different genetic patterns were seen in $bla_{CTX-M-15}$ genetic environment. Insertion sequence $ISEcp1$ was commonly located upstream of the end of the $bla_{CTX-M-15}$ gene while insertion sequence $orf477$ was located downstream. In some studies, $ISEcp1$ was truncated upstream of $bla_{CTX-M-15}$ by insertion sequences $IS26$ and $IS3$. Class 1 integron ($Intl1$) was most reported to be associated with $bla_{CTX-M-15}$ (13 studies), with $Intl1/dfrA17–aadA5$ 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 transfer $bla_{CTX-M-15}$ gene. Aminoglycoside modifying enzymes, and plasmid-mediated quinolone resistance genes were commonly collocated with $bla_{CTX-M-15}$ gene on plasmids. This review revealed the predominant role of $ISEcp1$, $Intl1$ and $IncF$ plasmid in the mobilization and continental dissemination of the $bla_{CTX-M-15}$ gene in Africa.

Keywords: Antimicrobial resistance, $bla_{CTX-M-15}$, genetic environment, mobile genetic elements, Africa
Introduction

The most widely distributed $bla_{CTX-M}$ gene on a global scale is $bla_{CTX-M-15}$, most especially in the enterobacterial species such as $Escherichia coli$, Klebsiella spp. and Salmonella enterica. The global dissemination of $bla_{CTX-M-15}$ gene has been associated with the clonal spread of $E. coli$ O25: H4-ST131 strain 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 family IS1380 and was first identified on the plasmid pST01 in $E. coli$ strain 79 but has now been globally disseminated in association with different $bla_{CTX-M}$ phylogenetic clusters [8].

The roles of $ISEcp1$ and other MGEs in the genetic environments of $bla_{CTX-M}$ genes have been well described [7,9,10]. $ISEcp1$ is commonly located upstream of $bla_{CTX-M-15}$ gene, and it’s responsible for the downstream mobilization and transposition of itself, adjacent genes and $bla_{CTX-M-15}$ gene. $IS26$ have been commonly found to be located upstream of $bla_{CTX-M-15}$ 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 $bla_{CTX-M-15}$ and other beta-lactamase genes [8]. Integrons is 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 \textit{bla}_{CTX-M-15} gene co-existing with other AMR genes on both narrow host-range and to a lesser extent broad-host-range plasmids [11].

While genetic environments of \textit{bla}_{CTX-M} genes have been described and reported in enterobacterial species from different parts of the world, variation in genetic patterns however exist from region to region. Also, analysis of genetic environments of \textit{bla}_{CTX-M} 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 \textit{bla}_{CTX-M-15} gene and associated MGEs in \textit{Enterobacteriaceae} in published literature from Africa.

\textbf{Methods}

The literature search was conducted in PubMed, AJOL and Google Scholars’ electronic databases between June 2018 and January 2019 for the purpose of narrative and non-systematic review. The following terms were used for literature search: \textit{bla}_{CTX-M-15} gene AND Africa OR \textit{bla}_{CTX-M-15} AND genetic environment AND Africa. A literature search was also conducted based on studies reporting the detection of \textit{bla}_{CTX-M-15} from each African country, e.g., \textit{bla}_{CTX-M-15} AND Nigeria, \textit{bla}_{CTX-M-15} AND Egypt, \textit{bla}_{CTX-M-15} 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 removal of duplicates by titles and abstracts for their relevance to the study objectives and purpose. The primary outcomes of interest were to describe genetic environment of \textit{bla}_{CTX-M-15} in \textit{Enterobacteriaceae} from different African countries.
For studies to be included in the qualitative description, the studies must have reported genetic environment of $bla_{CTX-M-15}$ resistance gene with special reference to the associated insertion sequences. The data were abstracted onto 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), Enterobacteriaceae species from which $bla_{CTX-M-15}$ gene was detected in, insertion sequences associated with 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 $bla_{CTX-M-15}$ gene on different plasmids.

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 $bla_{CTX-M-15}$ 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. In eight studies [12–19], the insertion sequence $ISEcp1$ was located upstream of the end of the $bla_{CTX-M-15}$ gene with insertion sequence orf477 located downstream ($ISEcp1- bla_{CTX-M-15} - orf477$). Twenty-three studies [20–42] found $ISEcp1$ to be the only insertion sequence located upstream of the $bla_{CTX-M-15}$ gene ($ISEcp1- bla_{CTX-M-15}$). Also, two studies [16,42] reported the location of $ISEcp1$ upstream of $bla_{CTX-M-15}$
truncated by IS26 without any downstream IS element (ISEcp1-IS26-blaCTX-M-15). In one of these two studies [16], IS26 was located upstream of blaCTX-M-15 with orf447 located downstream in an Enterobacterial isolate. In another two studies [12,43], ISEcp1 was truncated upstream of blaCTX-M-15 by IS26 (ISEcp1-IS26-blaCTX-M-15-orf477). While in one study [42], ISEcp1 was truncated upstream of blaCTX-M-15 by IS26, with IS903 located downstream (ISEcp1-IS26-blaCTX-M-15-IS903), however novel IS3 [16], was reported in a study to truncate ISEcp1 upstream the start of blaCTX-M-15 gene (ISEcp1-IS3-blaCTX-M-15). The promoter region (-35 and -10) of 48bp [14,23,24,29,37], V and W sequences of 127bp [31], and other unspecified promoter regions of 400-1800bp [17,19,26,35] of ISEcp1 were located upstream between the left end of ISEcp1 and the start codon of blaCTX-M-15 gene.

Integron was associated with blaCTX-M-15 gene in 13 studies [12,15,18,19,21,25,31,32,34,42,44,45]; class 1 integron (IntI1) was commonly reported from the 13 studies, while class 2 integron (IntI2) was reported in 3 studies together with class 1 integron. Class 3 integron was not reported in all the studies reviewed, one gene cassette arrangement; IntI2/dfrA1-sat-aadA1 was detected in IntI2 in this review from only one study. However, with the exception of 2 studies, different gene cassette arrays were detected in variable regions of IntI1, with IntI1/dfrA17–aadA5 and IntI1/aadA1 being the most commonly detected gene cassettes (Table 1). Different types of plasmid incompatibility groups were reported to transfer blaCTX-M-15 gene horizontally. These include IncF, IncH, IncN, IncY, IncK, IncX, IncI, IncA/C, and IncL/M [14,16,25,30,32–36,38,39,42,43,45–54]. However, IncFIA-FIB-FII multi-replicons and IncHI2 replicon types were the most common plasmids associated with blaCTX-M-15 gene (Table 1). Antimicrobial resistance genes including the narrow-spectrum blaOXA-1 and blaTEM-1 beta-lactamases, tetracycline resistance genes (tetA and tetB), sulfonamide resistance
genes (sul2 and sul3) and plasmid-mediated quinolone resistance genes including aminoglycoside-modifying enzymes (aac-(6′)-lb-cr), QnrA, QnrB, and QnrS were commonly associated with blaCTX-M-15 gene on plasmids.

Table 1: Genetic environment of CTX-M-15 gene in enterobacterial species from Africa

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Sample sources</th>
<th>Enterobacterial species</th>
<th>Genetic Environment Pattern</th>
<th>Additional resistance genes</th>
<th>Mobile genetic elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aibinu et al[20]</td>
<td>Nigeria</td>
<td>Human</td>
<td>Escherichia coli</td>
<td>ISEcp1</td>
<td></td>
<td>Intl2</td>
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<tr>
<td>Aibinu et al[44]</td>
<td>Nigeria</td>
<td>Human</td>
<td>Enterobacter cloacae, Pantoea agglomerans</td>
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<td>Fortini et al[47]</td>
<td>Nigeria</td>
<td>Human</td>
<td>Escherichia coli</td>
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<tr>
<td>Fortini et al[46]</td>
<td>Nigeria</td>
<td>Human</td>
<td>Escherichia coli</td>
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<tr>
<td>Inwezerua et al[42]</td>
<td>Nigeria</td>
<td>Human</td>
<td>Escherichia coli</td>
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<td>Ogbolu et al[48]</td>
<td>Nigeria</td>
<td>Human</td>
<td>Escherichia coli, Klebsiella spp.</td>
<td>CTXM-2, OXA-1, SHV, blatEM1, blaAMPC</td>
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<td>Ojo et al[43]</td>
<td>Nigeria</td>
<td>Chicken</td>
<td>Escherichia coli</td>
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<tr>
<td>Raji et al[22]</td>
<td>Nigeria</td>
<td>Human</td>
<td>Escherichia coli, Klebsiella spp., Proteus mirabilis</td>
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<td>Nigeria</td>
<td>Human</td>
<td>Klebsiella spp.</td>
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<td>Tet(A), aac(3)-II, aac(6′)-lb</td>
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<td>Kudirkene et al[49]</td>
<td>Ghana</td>
<td>Human</td>
<td>Salmonella Poona</td>
<td></td>
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<tr>
<td>Author et al.</td>
<td>Country</td>
<td>Species</td>
<td>Species Description</td>
<td>plasmid/insertion element</td>
<td>Antibiotics Resistant</td>
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<tr>
<td>Sallem et al. [15]</td>
<td>Mauritania</td>
<td>Escherichia coli</td>
<td>ISEcp1-orf477</td>
<td>strB, aac(3)-Iia</td>
<td>aac(6)'Ib-cr, tet(A), sul2, sul3, strA, strB, blaOXA-1, blaTEM-1B</td>
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<td>Soleimanian et al. [24]</td>
<td>Niger</td>
<td>Morganella morganii</td>
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<td>bladSHA, CIT, blaTEM-1</td>
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<td>Woerther et al. [50]</td>
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<td>Escherichia coli</td>
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<td>blacMY-2, blasHV-44</td>
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<td>Harrios et al. [51]</td>
<td>Senegal</td>
<td>Salmonella enterica</td>
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<td>Ruppe et al. [25]</td>
<td>Senegal</td>
<td>Escherichia coli</td>
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<td>blaTEM-1, blaOXA-1, aac(6)Ib-cr, tet(A)</td>
<td>intI/dfrA17-aadA5</td>
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<tr>
<td>Weill et al. [26]</td>
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<td>Salmonella Kentucky</td>
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<td>Poirel et al. [52]</td>
<td>Sao Tome and Principle</td>
<td>Escherichia coli</td>
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<tr>
<td>Phoba et al. [27]</td>
<td>DRC</td>
<td>Salmonella Typhi</td>
<td>ISEcp1</td>
<td>blatem-1D, sulII, dfRA7</td>
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<td>Rafai et al. [53]</td>
<td>Central African Republic</td>
<td>Escherichia coli</td>
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<td>Lonchel Mangoue et al. [28]</td>
<td>Cameroon</td>
<td>Escherichia coli</td>
<td>ISEcp1</td>
<td>biaOXA-1H, blatem-1H, RmtB</td>
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<tr>
<td>Founou et al. [54]</td>
<td>Cameroon</td>
<td>Klebsiella spp.</td>
<td></td>
<td>sulI, foxA, qoxA, qoxB, blatem-1H, dfrA15, strA, strB</td>
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<tr>
<td>Khalaf et al. [29]</td>
<td>Egypt</td>
<td>Escherichia coli</td>
<td>ISEcp1</td>
<td>blatem-1</td>
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</tr>
<tr>
<td>Naas et al. [30]</td>
<td>Algeria</td>
<td>Salmonella Infantis</td>
<td>ISEcp1</td>
<td>arm4, blatem-1</td>
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<tr>
<td>Messai et al. [31]</td>
<td>Algeria</td>
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<td>biaOXA-1H, blatem-1H, aac(6)Ib-cr</td>
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<td>Ribeiro et al. [16]</td>
<td>Angola</td>
<td>Escherichia coli</td>
<td>ISEcp1-orf477, IS26-orf447, ISEcp1-1S3-orf477</td>
<td>biaOXA-1, blatem-1H, aac(6)Ib-cr</td>
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<tr>
<td>Albrechtova et al. [45]</td>
<td>Angola</td>
<td>Dog</td>
<td>Escherichia coli</td>
<td>gep4, qnrS1, aac(6)Ib-cr</td>
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<td>Rakotonirina et al. [32]</td>
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<td>Escherichia coli</td>
<td>ISEcp1</td>
<td>biaOXA-1H, biaOXA-1, aac(6)Ib-cr, sul1- sul2, tet(A), qnrB</td>
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<td>Villa et al. [33]</td>
<td>Morocco</td>
<td>Klebsiella spp.</td>
<td>ISEcp1</td>
<td>qnrB1, blNDM-1</td>
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<td>Kariuki et al. [34]</td>
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<td>Salmonella Typhimurium</td>
<td>ISEcp1</td>
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<td>Mshana et al. [35]</td>
<td>Tanzania</td>
<td>Escherichia coli</td>
<td>ISEcp1</td>
<td>blatem-1</td>
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<td>Mshana et al. [41]</td>
<td>Tanzania</td>
<td>Enterobacter spp.</td>
<td>ISEcp1</td>
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</table>
This review was carried out to describe the genetic environment of internationally disseminated \( \text{bla}_{\text{CTX-M-15}} \) gene in \textit{Enterobacteriaceae} from Africa. The majority of the studies in this review were from human clinical settings which suggest \( \text{bla}_{\text{CTX-M-15}} \)-producing \textit{Enterobacteriaceae} is a challenge to healthcare facilities in Africa. \( \text{bla}_{\text{CTX-M-15}} \) gene has been associated with pandemic \textit{E. coli} O25: H4 ST131 clone that causes both community and human healthcare infections globally. Review of the genetic environments of \( \text{bla}_{\text{CTX-M-15}} \) in \textit{Enterobacteriaceae} revealed five \text{IS}s including \text{ISEcp1}, \text{IS26}, \text{orf477}, \text{IS903}, \text{and IS3} had been detected in Africa. With the exception of novel \text{IS3} that was reported from Angola \[16\], all the other \text{IS}s have been reported from other parts of the world to be associated with the genetic environment of different type of AMR genes in general \[7,8,55\]. From all the studies reviewed, \text{ISEcp1} was located upstream of \( \text{bla}_{\text{CTX-M-15}} \) gene. This \text{IS} often encodes transposase that facilitates the mobilization of \( \text{bla}_{\text{CTX-M-15}} \) gene among integrons, transposons, plasmids, and chromosomes as well as provides promoters that can activate the weakly expressed state of \( \text{bla}_{\text{CTX-M-15}} \) \[56–58\]. This \text{IS} has been reported to be contributing to the global dissemination of \( \text{bla}_{\text{CTX-M-15}} \) gene in association with other MGEs \[1,59,60\]. The \text{ISEcp1}/ \( \text{bla}_{\text{CTX-M-15}} \) genetic

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Setting</th>
<th>Species</th>
<th>IS Type</th>
<th>AMR Genes</th>
<th>MGEs</th>
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<td>Mshana et al.</td>
<td>Tanzania</td>
<td>Human</td>
<td>Klebsiella spp.</td>
<td>ISEcp1</td>
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<td>Rejiba et al.</td>
<td>Tunisia</td>
<td>Human</td>
<td>Escherichia coli</td>
<td>ISEcp1</td>
<td>( \text{bla}<em>{\text{TEM-1}}, \text{blas}</em>{\text{SHV-12}} )</td>
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<tr>
<td>Ben slama et al.</td>
<td>Tunisia</td>
<td>Human</td>
<td>Escherichia coli</td>
<td>ISEcp1-orf477</td>
<td>( \text{bla}<em>{\text{TEM-2}}, \text{blas}</em>{\text{OXA-1}}, \text{aac(3)-II}, \text{aac(6')-Ib-cr}, \text{strA}, \text{strB}, \text{sul2}, \text{tet(B)} )</td>
<td>\text{Intl1/ dfrA17–aadA5}, \text{Intl1/ dfrA12–orfF–aadA2}, \text{Intl1/aadA2}</td>
</tr>
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<td>Chouchani et al.</td>
<td>Tunisia</td>
<td>Human</td>
<td>Escherichia coli</td>
<td>ISEcp1</td>
<td>( \text{bla}_{\text{TEM-52}} )</td>
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<tr>
<td>Elhani et al.</td>
<td>Tunisia</td>
<td>Human</td>
<td>Klebsiella spp.</td>
<td>ISEcp1</td>
<td>( \text{bla}<em>{\text{TEM-1}}, \text{blas}</em>{\text{SHV-12}} )</td>
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<tr>
<td>Ayari et al.</td>
<td>Tunisia</td>
<td>Human</td>
<td>Escherichia coli</td>
<td>ISEcp1-AS26</td>
<td>( \text{bla}<em>{\text{TEM-1}}, \text{blas}</em>{\text{OXA-1}}, \text{aadA2} )</td>
<td>\text{Intl1/ dfrA17–ereA2}, \text{Intl1/aadA2}</td>
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<td>Abbassi et al.</td>
<td>Tunisia</td>
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<td>ISEcp1-orf477</td>
<td>( \text{bla}<em>{\text{TEM-1}}, \text{blas}</em>{\text{SHV-1}} )</td>
<td></td>
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</table>

**Discussion**

This review was carried out to describe the genetic environment of internationally disseminated \( \text{bla}_{\text{CTX-M-15}} \) gene in \textit{Enterobacteriaceae} from Africa. The majority of the studies in this review were from human clinical settings which suggest \( \text{bla}_{\text{CTX-M-15}} \)-producing \textit{Enterobacteriaceae} is a challenge to healthcare facilities in Africa. \( \text{bla}_{\text{CTX-M-15}} \) gene has been associated with pandemic \textit{E. coli} O25: H4 ST131 clone that causes both community and human healthcare infections globally. Review of the genetic environments of \( \text{bla}_{\text{CTX-M-15}} \) in \textit{Enterobacteriaceae} revealed five \text{IS}s including \text{ISEcp1}, \text{IS26}, \text{orf477}, \text{IS903}, \text{and IS3} had been detected in Africa. With the exception of novel \text{IS3} that was reported from Angola \[16\], all the other \text{IS}s have been reported from other parts of the world to be associated with the genetic environment of different type of AMR genes in general \[7,8,55\]. From all the studies reviewed, \text{ISEcp1} was located upstream of \( \text{bla}_{\text{CTX-M-15}} \) gene. This \text{IS} often encodes transposase that facilitates the mobilization of \( \text{bla}_{\text{CTX-M-15}} \) gene among integrons, transposons, plasmids, and chromosomes as well as provides promoters that can activate the weakly expressed state of \( \text{bla}_{\text{CTX-M-15}} \) \[56–58\]. This \text{IS} has been reported to be contributing to the global dissemination of \( \text{bla}_{\text{CTX-M-15}} \) gene in association with other MGEs \[1,59,60\]. The \text{ISEcp1}/ \( \text{bla}_{\text{CTX-M-15}} \) genetic...
association observed in this review has been reported previously from other parts of the world including India, France, Turkey, Poland, Canada, United Kingdom, Spain, and China [8–10,55,56,58,61–64]. This IS element has also been commonly found associated with other \( \text{bla}_{\text{CTX-M}} \) genes and other beta-lactamase resistance genes [10,59]. Of the genetic environments associated with \( \text{bla}_{\text{CTX-M}} \) genes, \( \text{ISEcp1} \) is one of the most commonly detected IS element in the genetic environment of \( \text{bla}_{\text{CTX-M}} \) genes suggesting a possible co-evolutionary relationship between the \( \text{ISEcp1} \) and \( \text{bla}_{\text{CTX-M}} \) genes [9,52,61,65].

The insertion site of \( \text{ISEcp1} \) 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 \( \text{bla}_{\text{CTX-M-15}} \) gene. Three studies provided information on the promoter regions in this review; the -35 and -10 putative promoter regions (48bp) were reported in five studies while V and W sequences (127bp) in one study. In all cases, these promoter regions are important in the transcription, mobilization, and expression of \( \text{bla}_{\text{CTX-M-15}} \) gene as previously described [7,9,10]. \( \text{IS26} \) was another IS described in Africa. However, this IS element was located upstream of \( \text{bla}_{\text{CTX-M-15}} \) disrupting \( \text{ISEcp1} \) element in all the studies reporting the presence of the \( \text{IS26} \) in the genetic environment of \( \text{bla}_{\text{CTX-M-15}} \). \( \text{IS26} \) has also been reported from other parts of the world to be associated with \( \text{bla}_{\text{CTX-M}} \) genes alone without \( \text{ISEcp1} \)[64], or associated with \( \text{bla}_{\text{CTX-M}} \) genes together with and located upstream to \( \text{ISEcp1} \) [55,56,66] or located truncating \( \text{ISEcp1} \) [55,64] in genetic arrangements with \( \text{bla}_{\text{CTX-M}} \) genes similar to the findings of this review. In all these genetic arrangements involving \( \text{IS26} \), the IS was suggested to be associated with transposition and stabilization of \( \text{ISEcp1/ bla}_{\text{CTX-M-15}} \) complex on plasmids [63,67].
Genetic environment downstream the \textit{bla}$_{\text{CTX-M-15}}$ revealed the flanking of the \textit{bla}$_{\text{CTX-M-15}}$ gene by two different types of insertion sequences \textit{orf447} and \textit{IS903}. Both \textit{IS} elements are the major \textit{IS} elements commonly reported downstream of \textit{bla}$_{\text{CTX-M}}$ genetic environments [8,68,69]. However, based on this review, \textit{orf447} is the major \textit{IS} element downstream of \textit{bla}$_{\text{CTX-M-15}}$ gene in Africa. In this review, seven different genetic patterns were observed; four of the five genetic patterns have been previously reported. \textit{ISEcp1} - \textit{bla}$_{\text{CTX-M-15}}$ - \textit{orf477} genetic pattern has been reported from European and Indian strains of Enterobacteriaceae [55,61,66]; \textit{ISEcp1} \textit{bla}$_{\text{CTX-M-15}}$ has been reported from Spain, Canada, India, and Poland [64,70–73]; \textit{ISEcp1-IS26} - \textit{bla}$_{\text{CTX-M-15}}$ - \textit{orf447} has also been reported from France [55,74]; while the \textit{ISEcp1-IS3} \textit{bla}$_{\text{CTX-M-15}}$ pattern was reported to be novel from Angola [16]. Other genetic patterns have been reported in the genetic environments of other types of \textit{bla}$_{\text{CTX-M}}$ and other beta-lactamase genes [8,61,75]. These genetic patterns from Africa reveal how genetic environment of \textit{bla}$_{\text{CTX-M-15}}$ is consistent what has been reported on the global scales. Also, immigration, global migration and traveling for tourism purposes could also have contributed to these global genetic patterns of \textit{bla}$_{\text{CTX-M-15}}$. Similar genetic environments of \textit{bla}$_{\text{CTX-M-15}}$ reported in this review and other novel genetic patterns have been previously reported from travelers returning to the United Kingdom from the Middle East, Africa and Asian countries which suggest possible overseas acquisition of these genetic patterns [66].

Class 1 integron was more commonly associated with \textit{bla}$_{\text{CTX-M-15}}$ compare to class 2 integron; this is consistent with previous reports elsewhere [8,76]. Class 1 integron is often associated with \textit{IS} elements such as \textit{ISEcp1} and \textit{ISCR1}, often located adjacent to these \textit{IS} elements and functions in the mobilization and transposition of \textit{bla}$_{\text{CTX-M-15}}$ gene [8]. In addition, some AMR genes associated with \textit{bla}$_{\text{CTX-M-15}}$ are captured within the conserved regions of class
1 integron. AMR genes were harbored within the cassette arrays of class 1 integron in different studies in this review. Antimicrobial resistance genes including \textit{dfrA17, dfrA5, dfrA1, aadA5, aadA2, aadA1} and \textit{catA1} were observed within the conserved region of class 1 integron and these genes often confers multi-drug resistance to trimethoprim, aminoglycosides, and chloramphenicol. Conjugative plasmids are essential for the evolution and global dissemination of \textit{bla}_{\text{CTX-M-15}} gene. Similar to this review, several studies have found that narrow-host range plasmid \textit{IncF} is the predominant plasmid groups that harbor \textit{bla}_{\text{CTX-M-15}} gene [77]. The \textit{IncF} plasmid is mainly restricted to \textit{Enterobacteriaceae} with support mechanisms such as lower fitness cost, transferability properties, plasmid addiction and stability system that favor (i) higher prevalence of \textit{bla}_{\text{CTX-M-15}} in \textit{Enterobacteriaceae} compared to other Gram-negative bacteria and (ii) global dissemination of \textit{bla}_{\text{CTX-M-15}} in association with other mobile genetic elements [11,59,78]. The \textit{IncFII-FIA-FIB} multi-replicons plasmids were more commonly associated with \textit{bla}_{\text{CTX-M-15}} in this review and have been widely distributed in the \textit{Enterobacteriaceae} especially \textit{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 \textit{bla}_{\text{CTX-M-15}} gene. Another important finding of this review was the presence of other antimicrobial resistance associated with \textit{bla}_{\text{CTX-M-15}} 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 \textit{bla}_{\text{OXA-1}} and \textit{bla}_{\text{TEM-1}} beta-lactamases, aminoglycoside-modifying enzymes (\textit{aac-(6')-lb-cr}), tetracycline resistance genes (\textit{tetA} and \textit{tetB}), sulfonamide resistance genes (\textit{sul2} and \textit{sul3}) and plasmid-mediated quinolone resistance genes (\textit{QnrA, QnrB} and \textit{QnrS})
were found to be consistently associated with \(\text{bla}_{\text{CTX-M-15}}\) from different studies in the review. These AMR genes have been previously reported to be co-located on \(\text{IncFII-FIA-FIB}\) plasmid replicons in association with \(\text{bla}_{\text{CTX-M-15}}\) 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 \(\text{bla}_{\text{CTX-M-15}}\) in \(\text{Enterobacteriaceae}\). In addition to the contribution of clonal spread of some bacteria of \(\text{Enterobacteriaceae}\), especially \(E.\ coli\) and \(\text{Klebsiella}\) spp., the association of \(\text{bla}_{\text{CTX-M-15}}\) with mobile genetic elements such as insertion sequences, integrons, and conjugative plasmids may explain its global dominance and dissemination. This review showed the diversity and the complexity of the genetic environments of \(\text{bla}_{\text{CTX-M-15}}\) beta-lactamase gene in \(\text{Enterobacteriaceae}\) from Africa.

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