 doi:10.20944/preprints202012.0144.v1

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

Babafela B. Awosile[1], Agbaje Michael[2]

[1]Department of Health Information and Performance, Health PEI, Charlottetown, Canada

[2]College of Veterinary Medicine, Federal University of Agriculture Abeokuta, Nigeria.

Dr. Babafela B. Awosile
Department of Health Information and Performance, Health PEI, Charlottetown Canada
bawosile@upei.ca

 doi:10.20944/preprints202012.0144.v1

Abstract

The most widely distributed *bla*$_{\text{CTX-M}}$ gene on a global scale is *bla*$_{\text{CTX-M-15}}$. 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*$_{\text{CTX-M-15}}$ 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*$_{\text{CTX-M-15}}$ 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*$_{\text{CTX-M-15}}$ in Africa. Seven different genetic patterns were seen in *bla*$_{\text{CTX-M-15}}$ genetic environment. Insertion sequence *ISEcp1* was commonly located upstream of the end of the *bla*$_{\text{CTX-M-15}}$ gene while insertion sequence *orf477* was located downstream. In some studies, *ISEcp1* was truncated upstream of *bla*$_{\text{CTX-M-15}}$ by insertion sequences *IS26* and *IS3*. Class 1 integron (*Intl1*) was most reported to be associated with *bla*$_{\text{CTX-M-15}}$ (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*$_{\text{CTX-M-15}}$ gene. Aminoglycoside modifying enzymes, and plasmid-mediated quinolone resistance genes were commonly collocated with *bla*$_{\text{CTX-M-15}}$ gene on plasmids. This review revealed the predominant role of *ISEcp1*, *Intl1*and *IncF* plasmid in the mobilization and continental dissemination of the *bla*$_{\text{CTX-M-15}}$ gene in Africa.

Keywords: Antimicrobial resistance, *bla*$_{\text{CTX-M-15}}$, genetic environment, mobile genetic elements, Africa

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 December 2020 doi:10.20944/preprints202012.0144.v1

Introduction

The most widely distributed *bla*$_{\text{CTX-M}}$ gene on a global scale is *bla*$_{\text{CTX-M-15}}$, most especially in the enterobacterial species such as *Escherichia coli, Klebsiella* spp. and *Salmonella enterica*. The global dissemination of *bla*$_{\text{CTX-M-15}}$ 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]. IS*Ecp1* is a member of the family IS*1380* and was first identified on the plasmid pST01 in *E. coli* strain 79 but has now been globally disseminated in association with different *bla*$_{\text{CTX-M}}$ phylogenetic clusters [8].

The roles of *ISEcp1* and other MGEs in the genetic environments of *bla*$_{\text{CTX-M}}$ genes have been well described [7,9,10]. *ISEcp1* is commonly located upstream of *bla*$_{\text{CTX-M-15}}$ gene, and it's responsible for the downstream mobilization and transposition of itself, adjacent genes and *bla*$_{\text{CTX-M-15}}$ gene. *IS26* have been commonly found to be located upstream of *bla*$_{\text{CTX-M-15}}$ 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*$_{\text{CTX-M-15}}$ 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

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 December 2020 doi:10.20944/preprints202012.0144.v1

replicon typing of various plasmid groups have facilitated the recognition and location of *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 *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 *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 *bla*$_{CTX-M-15}$ gene and associated MGEs in *Enterobacteriaceae* in published literature from Africa.

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: *bla*$_{CTX-M-15}$ gene AND Africa OR *bla*$_{CTX-M-15}$ AND genetic environment AND Africa. A literature search was also conducted based on studies reporting the detection of *bla*$_{CTX-M-15}$ from each African country, e.g., *bla*$_{CTX-M-15}$ AND Nigeria, *bla*$_{CTX-M-15}$ AND Egypt, *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 *bla*$_{CTX-M-15}$ in *Enterobacteriaceae* from different African countries.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 December 2020 doi:10.20944/preprints202012.0144.v1

For studies to be included in the qualitative description, the studies must have reported genetic environment of *bla*$_{\text{CTXM-15}}$ 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*$_{\text{CTX-M-15}}$ 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*$_{\text{CTX-M-15}}$ 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*$_{\text{CTX-M-15}}$ 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*$_{\text{CTX-M-15}}$ gene with insertion sequence *orf477* located downstream (*ISEcp1- bla*$_{\text{CTX-M-15}}$ *- orf477)*. Twenty-three studies [20–42] found *ISEcp1* to be the only insertion sequence located upstream of the *bla*$_{\text{CTX-M-15}}$ gene (*ISEcp1-bla*$_{\text{CTX-M-15}}$). Also, two studies [16,42] reported the location of *ISEcp1* upstream of *bla*$_{\text{CTX-M-15}}$

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 December 2020 doi:10.20944/preprints202012.0144.v1

truncated by *IS26* without any downstream *IS* element (*ISEcp1-IS26- bla*$_{CTX-M-15}$). In one these two studies [16], *IS26* was located upstream of *bla*$_{CTX-M-15}$ with *orf447* located downstream in an Enterobacterial isolate. In another two studies [12,43], *ISEcp1* was truncated upstream of *bla*$_{CTX-M-15}$ by *IS26* (*ISEcp1- IS26- bla*$_{CTX-M-15}$ *-orf477*). While in one study [42], *ISEcp1* was truncated upstream of *bla*$_{CTX-M-15}$ by *IS26,* with *IS903* located downstream (*ISEcp1-IS26- bla*$_{CTX-M-15}$ *- IS903*), however novel *IS3* [16], was reported in a study to truncate *ISEcp1* upstream the start of *bla*$_{CTX-M-15}$ gene (*ISEcp1-IS3- bla*$_{CTX-M-15}$). 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 *bla*$_{CTX-M-15}$ gene.

Integron was associated with *bla*$_{CTX-M-15}$ gene in13 studies [12,15,18,19,21,21,25,31,32,34,42,44,45]; class 1 integron (*Intl1*) was commonly reported from the 13 studies, while class 2 integron (*Intl2*) 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; *Intl2/dfrA1-sat-aadA1* was detected in *Intl2* in this review from only one study. However, with the exception of 2 studies, different gene cassette arrays were detected in variable regions of *Intl1,* with *Intl1/dfrA17–aadA5* and *Intl1/aadA1* being the most commonly detected gene cassettes (Table 1). Different types of plasmid incompatibility groups were reported to transfer *bla*$_{CTX-M-15}$ 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 *bla*$_{CTX-M-15}$ gene (Table 1). Antimicrobial resistance genes including the narrow-spectrum *bla*$_{OXA-1}$ and *bla*$_{TEM-1}$ beta-lactamases, tetracycline resistance genes (*tetA* and *tetB*), sulfonamide resistance

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 December 2020 doi:10.20944/preprints202012.0144.v1

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 *bla*$_{\text{CTX-M-15}}$ gene on plasmids.

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

Authors	Country	Sample sources	Enterobacterial species	Genetic Environment Pattern	Additional resistance genes	Mobile genetic eleme	
						Integron/gene cassettes	
Adelowo et al[12]	Nigeria	Environment	*Escherichia coli*	*ISEcp1-IS26-orf477, ISEcp1-orf477*		*Intl1/dfrA17-aadA5, Intl1/dfrA32-ereA-aadA2, Intl1/dfrA16-aadA2, Intl1/aadA1, Intl1/dfrA7, Int2*	
Aibinu et al[20]	Nigeria	Human	*Escherichia coli*	*ISEcp1*	*aac-(6')-lb-cr, QnrB1, QnrA1*		
Aibinu et al[44]	Nigeria	Human	*Enterobacter cloacae, Pantoea agglomerans*		*aadA1, aph, aac-(6')-Ib), sul1, cat1, QnrB1, tet(A), tet(E)*	*Intl1, Intl2*	
Alabi et al[21]	Nigeria	Human	*Proteus mirabilis*	*ISEcp1*	*aac(6')-Ib-cr, QnrA, bla*$_{\text{TEM-1}}$	*Int1, Int2, aadA1, aadA1-qacH, aadB-aadA2, aadA5, dfrA7, dfrA15, dfrA17, dfrA17-aadA5*	
Fortini et al[47]	Nigeria	Human	*Escherichia coli*		*aac(6')-Ib-cr, QnrS1, QnrB1, QepA1, bla*$_{\text{OXA-1}}$, *bla*$_{\text{TEM-1}}$, *bla*$_{\text{CMY-2}}$		*Inc I I*
Fortini et al[46]	Nigeria	Chicken, pig	*Escherichia coli*		*QnrS1, bla*$_{\text{TEM-1}}$		
Inwezerua et al[42]	Nigeria	Human	*Escherichia coli*	*IsEcp1, ISEcp1-IS26, ISEcp1-IS26-IS903*	*QnrB, aac(6')-lb-cr, bla*$_{\text{TEM-1}}$	*Int1/aadA1, int1/dfrA17-aadA5*	*Inc*
Iroha et al[13]	Nigeria	Human	*Escherichia coli*	*ISEcp1-orf477*	*aac(6')-Ib-cr, bla*$_{\text{OXA-1}}$, *bla*$_{\text{SHV}}$, *bla*$_{\text{TEM-1}}$		
Ogbolu et al[48]	Nigeria	Human	*Escherichia coli, Klebsiella spp.*		*CTXM-2, OXA-1, SHV, bla*$_{\text{TEM-1}}$, *bla*$_{\text{AmpC}}$		
Ojo et al[43]	Nigeria	Chicken	*Escherichia coli*	*ISEcp1-IS26-orf477*	*aac(3)-IIa, aac(6')-Ib-cr, dfrA5, dfrA12, strA, strB, sul1, sul2, tet(A), tet(B), bla*$_{\text{OXA-1}}$, *bla*$_{\text{TEM-1}}$	*Intl1/aadA2-orfF-dfrA12*	*Inc I*
Raji et al[22]	Nigeria	Human	*Escherichia coli, Klebsiella* spp., *Proteus mirabilis*	*ISEcp1*	*bla*$_{\text{TEM}}$, *bla*$_{\text{SHV}}$		
Soge et al[23]	Nigeria	Human	*Klebsiella* spp.	*ISEcp1*	*Tet(A), aac(3)-II, aac(6')-Ib*		
Agyekum et al[14]	Ghana	Human	*Escherichia coli, Klebsiella* spp.	*ISEcp1- orf477*	*bla*$_{\text{TEM}}$, *aac(3)-II, OXA-30*		*Inc*
Kudirkiene et al[49]	Ghana	Human	*Salmonella* Poona		*bla*$_{\text{TEM-1B}}$, *bla*$_{\text{OXA-1}}$, *QnrB1, aac(6')Ib-cr, tet(A), dfrA15, sul2, catB3, strA,*		*T*

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 December 2020 doi:10.20944/preprints202012.0144.v1

					strB, aac(3)-Iia		
Sallem et al[15]	Mauritania	Human	*Escherichia coli*	*ISEcp1-orf477*	*aac(6')-Ib-cr, tet(A), sul2, sul3, strA, strB, bla*$_{OXA-1}$, *bla*$_{TEM-1B}$	*intI/dfrA17-aadA5*	
Soleimanian et al[24]	Niger	Human	*Morganella morganii*, *Citrobacter freundii*	*ISEcp1*	*bla*$_{DHA}$, *CIT, bla*$_{TEM-1}$		
Woerther et al[50]	Niger	Human	*Escherichia coli*		*bla*$_{CMY-2}$, *bla*$_{SHV-44}$		*F*
Harrois et al[51]	Senegal	Human	*Salmonella enterica*		*QnrB1, Aac(6')-Ib-cr*		*In*
Ruppe et al[25]	Senegal	Human	*Escherichia coli*	*ISEcp1*	*bla*$_{TEM-1}$, *bla*$_{OXA-1}$, *aac(6)-Ib-cr, tet(A)*	*intI/dfrA17-aadA5*	*Inc*
Weill et al[26]	Senegal	Human	*Salmonella* Kentucky	*ISEcp1*	*bla*$_{TEM-1}$, *bla*$_{OXA-30}$		
Poirel et al[52]	Sao Tome and Principle	Human	*Escherichia coli*		*bla*$_{OXA-181}$, *bla*$_{TEM-1}$, *RmtB*		
Phoba et al[27]	DRC	Human	*Salmonella* Typhi	*ISEcp1*	*bla*$_{TEM-1D}$, *sulI, dfrA7*		
Rafai et al[53]	Central African Republic	Human	*Escherichia coli, Enterobacter cloacae*		*aac(6')-Ib-cr, QnrB, QnrS*		
Lonchel Mangoue et al[28]	Cameroon	Human	*Escherichia coli*	*ISEcp1*	*bla*$_{OXA-181}$, *bla*$_{TEM-1}$, *aac(6')Ib-cr*		
Founou et al[54]	Cameroon	Human	*Klebsiella* spp.		*sul1, fosA, oqxA, oqxB, bla*$_{TEM-1B}$, *dfrA15, strA, strB*		
Khalaf et al[29]	Egypt	Human	*Escherichia coli*	*ISEcp1*	*bla*$_{TEM-1}$		
Naas et al[30]	Algeria	Human	*Salmonella* Infantis	*ISEcp1*	*armA, bla*$_{TEM-1}$		
Messai et al[31]	Algeria	Human	*Klebsiella* spp.	*ISEcp1*	*bla*$_{TEM-1}$	*Int1*	
Ribeiro et al[16]	Angola	Human	*Escherichia coli, Klebsiella* spp.	*ISEcp1-orf477, IS26-orf447, ISEcp1-IS3-orf477*	*bla*$_{OXA-1}$, *bla*$_{TEM-1}$, *aac-6'-Ib-cr*		*Inc* *Inc*
Albrechtova et al[45]	Angola	Dog	*Escherichia coli*		*qepA, qnrS1, qnrB19, aac(6')-Ib-cr*	*Intl1/dfrA17-aadA5, Intl1/dfrA1-aadA1, Intl2/dfrA1-sat-aadA1*	*F*
Rakotonirina et al[32]	Madagascar	Human	*Escherichia coli, Klebsiella* spp.	*ISEcp1*	*bla*$_{TEM-1}$, *bla*$_{OXA-1}$, *aac(6')-Ib-cr, sul1-sul2, tet(A), qnrB*	*Intl1/ aadA1-aadA2-aadA4-aadA5-dfrA5-dfrA22*	*Inc*
Barguigua et al[17]	Morocco	Human	*Klebsiella* spp.	*ISEcp1-orf477*	*bla*$_{TEM-1B}$, *bla*$_{OXA-1}$, *aac(6')-Ib-cr, qnrB1*		
Villa et al[33]	Morocco	Human	*Klebsiella* spp.	*ISEcp1*	*qnrB1, bla*$_{NDM-1}$		
Kariuki et al[34]	Kenya	Human	*Salmonella* Typhimurium	*ISEcp1*	*bla*$_{TEM-1}$, *bla*$_{OXA-1}$, *aac(6')-Ib, sul1, sul2, aadA1*	*Intl1/dfrA14-catA1*	*In*
Mshana et al[35]	Tanzania	Human	*Escherichia coli*	*ISEcp1*	*bla*$_{TEM-1}$		
Mshana et al[41]	Tanzania	Human	*Enterobacter* spp.	*ISEcp1*			

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 December 2020 doi:10.20944/preprints202012.0144.v1

Mshana et al[36]	Tanzania	Human	*Klebsiella* spp.	*ISEcp1*	*bla*TEM-1, *bla*SHV-11		
Rejiba et al[37]	Tunisia	Human	*Escherichia coli*	*ISEcp1*	*bla*TEM-1, *bla*SHV-12		
Ben slama et al[18]	Tunisia	Human	*Escherichia coli*	*ISEcp1-orf477*	*bla*TEM-1, *bla*OXA-1, *aac(3)-II, aac(6')-Ib-cr, strA, strB, sul2, tet(B)*	*Intl1/ dfrA17–aadA5, Intl1/ dfrA12–orfF–aadA2, Intl1/aadA2*	
Chouchani et al[38]	Tunisia	Human	*Escherichia coli*	*ISEcp1*	*bla*TEM-52		
Elhani et al[39]	Tunisia	Human	*Klebsiella* spp.	*ISEcp1*	*bla*TEM-1, *bla*SHV-12		*In*
Ayari et al[40]	Tunisia	Human	*Escherichia coli*	*ISEcp1-IS26*			
Abbassi et al[19]	Tunisia	Human	*Klebsiella* spp.	*ISEcp1- orf477*	*bla*TEM-1, *bla*OXA-1, *bla*SHV-1	*Intl1/ dfrA17–ereA2, Intl1/aadA*	

Discussion

This review was carried out to describe the genetic environment of internationally disseminated *bla*CTX-M-15 gene in *Enterobacteriaceae* from Africa. The majority of the studies in this review were from human clinical settings which suggest *bla*CTX-M-15 -producing *Enterobacteriaceae* is a challenge to healthcare facilities in Africa. *bla*CTX-M-15 gene has been associated with pandemic *E. coli* O25: H4 ST131 clone that causes both community and human healthcare infections globally. Review of the genetic environments of *bla*CTX-M-15 in *Enterobacteriaceae* revealed five *IS*s including *ISEcp1, IS26, orf447, IS903,* and *IS3* had been detected in Africa. With the exception of novel *IS3* that was reported from Angola [16], all the other *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, *ISEcp1* was located upstream of *bla*CTX-M-15 gene. This *IS* often encodes transposase that facilitates the mobilization of *bla*CTX-M-15 gene among integrons, transposons, plasmids, and chromosomes as well as provides promoters that can activate the weakly expressed state of *bla*CTX-M-15 [56–58]. This *IS* has been reported to be contributing to the global dissemination of *bla*CTX-M-15 gene in association with other MGEs [1,59,60]. The *ISEcp1/ bla*CTX-M-15 genetic

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 December 2020 doi:10.20944/preprints202012.0144.v1

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 *bla*$_{\text{CTX-M}}$ genes and other beta-lactamase resistance genes [10,59]. Of the genetic environments associated with *bla*$_{\text{CTX-M}}$ genes, *ISEcp1* is one of the most commonly detected *IS* element in the genetic environment of *bla*$_{\text{CTX-M}}$ genes suggesting a possible co-evolutionary relationship between the *ISEcp1* and *bla*$_{\text{CTX-M}}$ 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 *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 *bla*$_{\text{CTX-M-15}}$ gene as previously described [7,9,10]. *IS26* was another *IS* described in Africa. However, this *IS* element was located upstream of *bla*$_{\text{CTX-M-15}}$ disrupting *ISEcp1* element in all the studies reporting the presence of the *IS26* in the genetic environment of *bla*$_{\text{CTX-M-15}}$. *IS26* has also been reported from other parts of the world to be associated with *bla*$_{\text{CTX-M}}$ genes alone without *ISEcp1*[64], or associated with *bla*$_{\text{CTX-M}}$ genes together with and located upstream to *ISEcp1* [55,56,66] or located truncating *ISEcp1* [55,64] in genetic arrangements with *bla*$_{\text{CTX-M}}$ 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 ISEcp1/ *bla*$_{\text{CTX-M-15}}$ complex on plasmids [63,67].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 December 2020 doi:10.20944/preprints202012.0144.v1

Genetic environment downstream the *bla*$_{\text{CTX-M-15}}$ revealed the flanking of the *bla*$_{\text{CTX-M-15}}$ gene by two different types of insertion sequences *orf447* and *IS903*. Both *IS* elements are the major *IS* elements commonly reported downstream of *bla*$_{\text{CTX-M}}$ genetic environments [8,68,69]. However, based on this review, *orf447* is the major *IS* element downstream of *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. *ISEcp1- bla*$_{\text{CTX-M-15}}$ *- orf477* genetic pattern has been reported from European and Indian strains of *Enterobacteriaceae* [55,61,66]; *ISEcp1 bla*$_{\text{CTX-M-15}}$ has been reported from Spain, Canada, India, and Poland [64,70–73]; *ISEcp1-IS26- bla*$_{\text{CTX-M-15}}$ *- orf447* has also been reported from France [55,74]; while the *ISEcp1-IS3 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 *bla*$_{\text{CTX-M}}$ and other beta-lactamase genes [8,61,75]. These genetic patterns from Africa reveal how genetic environment of *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 *bla*$_{\text{CTX-M-15}}$. Similar genetic environments of *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 *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 *IS* elements such as *ISEcp1* and *ISCR1,* often located adjacent to these *IS* elements and functions in the mobilization and transposition of *bla*$_{\text{CTX-M-15}}$ gene [8]. In addition, some AMR genes associated with *bla*$_{\text{CTX-M-15}}$ are captured within the conserved regions of class

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 December 2020 doi:10.20944/preprints202012.0144.v1

1 integron. 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 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 *bla*$_{\text{CTX-M-15}}$ gene. Similar to this review, several studies have found that narrow-host range plasmid *IncF* is the predominant plasmid groups that harbor *bla*$_{\text{CTX-M-15}}$ gene [77]. The *IncF* plasmid is mainly restricted to *Enterobacteriaceae* with support mechanisms such as lower fitness cost, transferability properties, plasmid addiction and stability system that favor (i) higher prevalence of *bla*$_{\text{CTX-M-15}}$ in *Enterobacteriaceae* compared to other Gram-negative bacteria and (ii) global dissemination of *bla*$_{\text{CTX-M-15}}$ in association with other mobile genetic elements [11,59,78]. The *IncFII-FIA-FIB* multi-replicons plasmids were more commonly associated with *bla*$_{\text{CTX-M-15}}$ 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 *bla*$_{\text{CTX-M-15}}$ gene. Another important finding of this review was the presence of other antimicrobial resistance associated with *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 *bla*$_{\text{OXA-1}}$ and *bla*$_{\text{TEM-1}}$ 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*)

 doi:10.20944/preprints202012.0144.v1

were found to be consistently associated with *bla*$_{\text{CTX-M-15}}$ from different studies in the review. These AMR genes have been previously reported to be co-located on *IncFII-FIA-FIB* plasmid replicons in association with *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 *bla*$_{\text{CTX-M-15}}$ 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*$_{\text{CTX-M-15}}$ 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 *bla*$_{\text{CTX-M-15}}$ beta-lactamase gene in *Enterobacteriaceae* from Africa.

Funding: None
Competing interests: None declared
Ethical approval: Not required

 doi:10.20944/preprints202012.0144.v1

Reference

1. Cantón R, González-Alba JM, Galán JC. CTX-M Enzymes: Origin and Diffusion. Frontiers in Microbiology. 2012;3. doi:10.3389/fmicb.2012.00110.

2. Peirano G, Pitout JDD. Molecular epidemiology of Escherichia coli producing CTX-M β-lactamases: the worldwide emergence of clone ST131 O25:H4. International Journal of Antimicrobial Agents. 2010;35(4):316–321.

3. Pitout JD, Laupland KB. Extended-spectrum β-lactamase-producing Enterobacteriaceae: an emerging public-health concern. The Lancet Infectious Diseases. 2008;8(3):159–166.

4. Lee H, Doak TG, Popodi E, Foster PL, Tang H. Insertion sequence-caused large-scale rearrangements in the genome of *Escherichia coli*. Nucleic Acids Research. 2016;gkw647.

5. Nzabarushimana E, Tang H. Insertion sequence elements-mediated structural variations in bacterial genomes. Mobile DNA. 2018;9(1). doi:10.1186/s13100-018-0134-3.

6. Mahillon J, Chandler M. Insertion Sequences. Microbiology and Molecular Biology Reviews. 1998;62(3):725–774.

7. Poirel L, Naas T, Nordmann P. Genetic support of extended-spectrum β-lactamases. Clinical Microbiology and Infection. 2008;14:75–81.

8. Zhao W-H, Hu Z-Q. Epidemiology and genetics of CTX-M extended-spectrum β-lactamases in Gram-negative bacteria. Critical Reviews in Microbiology. 2013;39(1):79–101.

9. Karim A, Poirel L, Nagarajan S, Nordmann P. Plasmid-mediated extended-spectrum Î²-lactamase (CTX-M-3 like) from India and gene association with insertion sequence ISEcp1. FEMS Microbiology Letters. 2001;201(2):237–241.

10. Lartigue M-F, Poirel L, Nordmann P. Diversity of genetic environment of blaCTX-M genes. FEMS Microbiology Letters. 2004;234(2):201–207.

11. Carattoli A. Resistance Plasmid Families in Enterobacteriaceae. Antimicrob Agents Chemother. 2009;53(6):2227–2238.

12. Adelowo OO, Caucci S, Banjo OA, Nnanna OC, Awotipe EO, Peters FB, et al. Extended Spectrum Beta-Lactamase (ESBL)-producing bacteria isolated from hospital wastewaters, rivers and aquaculture sources in Nigeria. Environmental Science and Pollution Research. 2018;25(3):2744–2755.

13. Iroha IR, Esimone CO, Neumann S, Marlinghaus L, Korte M, Szabados F, et al. First description of Escherichia coli producing CTX-M-15- extended spectrum beta lactamase (ESBL) in out-patients from south eastern Nigeria. Annals of Clinical Microbiology and Antimicrobials. 2012;11(1):19.

14. Agyekum A, Fajardo-Lubián A, Ansong D, Partridge SR, Agbenyega T, Iredell JR. blaCTX-M-15 carried by IncF-type plasmids is the dominant ESBL gene in Escherichia coli and Klebsiella pneumoniae at a hospital in Ghana. Diagnostic Microbiology and Infectious Disease. 2016;84(4):328–333.

15. Sallem RB, Slama KB, Estepa V, Cheikhna EO, Mohamed AM, Chairat S, et al. Detection of CTX-M-15-producing *Escherichia coli* isolates of lineages ST410-A, ST617-A and ST354-D in faecal samples of hospitalized patients in a Mauritanian hospital. Journal of Chemotherapy. 2015;27(2):114–116.

16. Ribeiro TG, Novais Â, Peixe L, Machado E. Atypical epidemiology of CTX-M-15 among Enterobacteriaceae from a high diversity of non-clinical niches in Angola: Table 1. Journal of Antimicrobial Chemotherapy. 2016;71(5):1169–1173.

17. Barguigua A, El Otmani F, Talmi M, Reguig A, Jamali L, Zerouali K, et al. Prevalence and genotypic analysis of plasmid-mediated β-lactamases among urinary Klebsiella pneumoniae isolates in Moroccan community. The Journal of Antibiotics. 2013;66(1):11–16.

18. Ben Slama K, Ben Sallem R, Jouini A, Rachid S, Moussa L, Sáenz Y, et al. Diversity of Genetic Lineages Among CTX-M-15 and CTX-M-14 Producing Escherichia coli Strains in a Tunisian Hospital. Current Microbiology. 2011;62(6):1794–1801.

19. Abbassi MS, Torres C, Achour W, Vinué L, Sáenz Y, Costa D, et al. Genetic characterisation of CTX-M-15-producing Klebsiella pneumoniae and Escherichia coli strains isolated from stem cell transplant patients in Tunisia. International Journal of Antimicrobial Agents. 2008;32(4):308–314.

20. Aibinu I, Odugbemi T, Koenig W, Ghebremedhin B. Sequence Type ST131 and ST10 Complex (ST617) predominant among CTX-M-15-producing Escherichia coli isolates from Nigeria* *This study has been partially presented during the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Chicago, IL, September 2011. Clinical Microbiology and Infection. 2012;18(3):E49–E51.

21. Alabi OS, Mendonça N, Adeleke OE, Da Silva GJ. Molecular screening of antibiotic-resistant determinants among multidrug-resistant clinical isolates of *Proteus mirabilis* from SouthWest Nigeria. African Health Sciences. 2017;17(2):356.

22. Raji MA, Jamal W, Ojemeh O, Rotimi VO. Sequence analysis of genes mediating extended-spectrum beta-lactamase (ESBL) production in isolates of Enterobacteriaceae in a Lagos Teaching Hospital, Nigeria. BMC Infectious Diseases. 2015;15(1). doi:10.1186/s12879-015-1005-x.

23. Soge OO, Queenan AM, Ojo KK, Adeniyi BA, Roberts MC. CTX-M-15 extended-spectrum β-lactamase from Nigerian Klebsiella pneumoniae. Journal of Antimicrobial Chemotherapy. 2006;57(1):24–30.

24. Soleimanian S, Gordon NC, Wareham DW. Polymicrobial necrotizing fasciitis involving enterobacteria producing CTX-M-15 extended-spectrum -lactamases. Journal of Medical Microbiology. 2011;60(1):135–137.

25. Ruppe E, Woerther P-L, Diop A, Sene A-M, Da Costa A, Arlet G, et al. Carriage of CTX-M-15-Producing Escherichia coli Isolates among Children Living in a Remote Village in Senegal. Antimicrobial Agents and Chemotherapy. 2009;53(7):3135–3137.

26. Weill F-X, Perrier-Gros-Claude J-D, Demartin M, Coignard S, Grimont PAD. Characterization of extended-spectrum-Î²-lactamase (CTX-M-15)-producing strains of *Salmonella enterica* isolated in France and Senegal. FEMS Microbiology Letters. 2004;238(2):353–358.

27. Phoba M-F, Barbé B, Lunguya O, Masendu L, Lulengwa D, Dougan G, et al. Salmonella enterica serovar Typhi Producing CTX-M-15 Extended Spectrum β-Lactamase in the Democratic Republic of the Congo. Clinical Infectious Diseases. 2017;65(7):1229–1231.

28. Lonchel Magoué C, Melin P, Gangoué-Piéboji J, Assoumou M-CO, Boreux R, De Mol P. Prevalence and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae in Ngaoundere, Cameroon. Clinical Microbiology and Infection. 2013;19(9):E416–E420.

29. Khalaf NG, Eletreby MM, Hanson ND. Characterization of CTX-M ESBLs in Enterobacter cloacae, Escherichia coli and Klebsiella pneumoniae clinical isolates from Cairo, Egypt. BMC Infectious Diseases. 2009;9(1). doi:10.1186/1471-2334-9-84.

30. Naas T, Bentchouala C, Cuzon G, Yaou S, Lezzar A, Smati F, et al. Outbreak of Salmonella enterica serotype Infantis producing ArmA 16S RNA methylase and CTX-M-15 extended-spectrum β-lactamase in a neonatology ward in Constantine, Algeria. International Journal of Antimicrobial Agents. 2011;38(2):135–139.

31. Messai Y, Iabadene H, Benhassine T, Alouache S, Tazir M, Gautier V, et al. Prevalence and characterization of extended-spectrum β-lactamases in Klebsiella pneumoniae in Algiers hospitals (Algeria). Pathologie Biologie. 2008;56(5):319–325.

32. Rakotonirina HC, Garin B, Randrianirina F, Richard V, Talarmin A, Arlet G. Molecular characterization of multidrug-resistant extended-spectrum β-lactamase-producing Enterobacteriaceae isolated in Antananarivo, Madagascar. BMC Microbiology. 2013;13(1):85.

33. Villa L, Poirel L, Nordmann P, Carta C, Carattoli A. Complete sequencing of an IncH plasmid carrying the blaNDM-1, blaCTX-M-15 and qnrB1 genes. Journal of Antimicrobial Chemotherapy. 2012;67(7):1645–1650.

34. Kariuki S, Okoro C, Kiiru J, Njoroge S, Omuse G, Langridge G, et al. Ceftriaxone-Resistant Salmonella enterica Serotype Typhimurium Sequence Type 313 from Kenyan Patients Is Associated with the *bla* $_{\text{CTX-M-15}}$ Gene on a Novel IncHI2 Plasmid. Antimicrobial Agents and Chemotherapy. 2015;59(6):3133–3139.

35. Mshana SE, Imirzalioglu C, Hain T, Domann E, Lyamuya EF, Chakraborty T. Multiple ST clonal complexes, with a predominance of ST131, of Escherichia coli harbouring blaCTX-M-15 in a tertiary hospital in Tanzania. Clinical Microbiology and Infection. 2011;17(8):1279–1282.

36. Mshana SE, Hain T, Domann E, Lyamuya EF, Chakraborty T, Imirzalioglu C. Predominance of Klebsiella pneumoniaeST14 carrying CTX-M-15 causing neonatal sepsis in Tanzania. BMC Infectious Diseases. 2013;13(1). doi:10.1186/1471-2334-13-466.

37. Réjiba S, Mercuri PS, Power P, Kechrid A. Emergence and Dominance of CTX-M-15 Extended Spectrum Beta-Lactamase Among *Escherichia coli* Isolates from Children. Microbial Drug Resistance. 2011;17(2):135–140.

38. Chouchani C, Salabi A, Marrakchi R, Ferchichi L, Walsh TR. Characterization of IncA/C conjugative plasmid harboring bla TEM-52 and bla CTX-M-15 extended-spectrum β-lactamases in clinical isolates of Escherichia coli in Tunisia. European Journal of Clinical Microbiology & Infectious Diseases. 2012;31(6):1081–1087.

39. Elhani D, Bakir L, Aouni M, Passet V, Arlet G, Brisse S, et al. Molecular epidemiology of extended-spectrum β-lactamase-producing Klebsiella pneumoniae strains in a university hospital in Tunis, Tunisia, 1999–2005. Clinical Microbiology and Infection. 2010;16(2):157–164.

40. Ayari K, Bourouis A, Chihi H, Mahrouki S, Naas T, Belhadj O. Dissemination and genetic support of broad-spectrum beta-lactam-resistant *Escherichia coli* strain isolated from two Tunisian hospitals during 2004-2012. African Health Sciences. 2017;17(2):346.

41. Mshana SE, Gerwing L, Minde M, Hain T, Domann E, Lyamuya E, et al. Outbreak of a novel Enterobacter sp. carrying blaCTX-M-15 in a neonatal unit of a tertiary care hospital in Tanzania. International Journal of Antimicrobial Agents. 2011. doi:10.1016/j.ijantimicag.2011.05.009.

42. Inwezerua C, Mendonça N, Calhau V, Domingues S, Adeleke OE, Da Silva GJ. Occurrence of extended-spectrum beta-lactamases in human and bovine isolates of Escherichia coli from Oyo state, Nigeria. The Journal of Infection in Developing Countries. 2014;8(06). doi:10.3855/jidc.3430.

43. Ojo OE, Schwarz S, Michael GB. Detection and characterization of extended-spectrum β-lactamase-producing Escherichia coli from chicken production chains in Nigeria. Veterinary Microbiology. 2016;194:62–68.

44. Aibinu I, Pfeifer Y, Peters F, Ogunsola F, Adenipekun E, Odugbemi T, et al. Emergence of blaCTX-M-15, qnrB1 and aac(6')-Ib-cr resistance genes in Pantoea agglomerans and Enterobacter cloacae from Nigeria (sub-Saharan Africa). Journal of Medical Microbiology. 2012;61(1):165–167.

45. Albrechtova K, Kubelova M, Mazancova J, Dolejska M, Literak I, Cizek A. High Prevalence and Variability of CTX-M-15-Producing and Fluoroquinolone-Resistant *Escherichia coli* Observed in Stray Dogs in Rural Angola. Microbial Drug Resistance. 2014;20(4):372–375.

46. Fortini D, Fashae K, Garcia-Fernandez A, Villa L, Carattoli A. Plasmid-mediated quinolone resistance and -lactamases in Escherichia coli from healthy animals from Nigeria. Journal of Antimicrobial Chemotherapy. 2011;66(6):1269–1272.

47. Fortini D, Fashae K, Villa L, Feudi C, García-Fernández A, Carattoli A. A novel plasmid carrying blaCTX-M-15 identified in commensal Escherichia coli from healthy pregnant women in Ibadan, Nigeria. Journal of Global Antimicrobial Resistance. 2015;3(1):9–12.

48. Ogbolu DO, Alli OAT, Olanipekun LB, Ojo OI, Makinde OO. Faecal carriage of extended-spectrum beta-lactamase (ESBL)-producing commensal Klebsiella pneumoniae and Escherichia coli from hospital out-patients in Southern Nigeria. 2013;9.

49. Kudirkiene E, Andoh LA, Ahmed S, Herrero-Fresno A, Dalsgaard A, Obiri-Danso K, et al. The Use of a Combined Bioinformatics Approach to Locate Antibiotic Resistance Genes on Plasmids From Whole Genome Sequences of Salmonella enterica Serovars From Humans in Ghana. Frontiers in Microbiology. 2018;9. doi:10.3389/fmicb.2018.01010.

50. Woerther P-L, Angebault C, Jacquier H, Hugede H-C, Janssens A-C, Sayadi S, et al. Massive Increase, Spread, and Exchange of Extended Spectrum -Lactamase-Encoding Genes Among Intestinal Enterobacteriaceae in Hospitalized Children With Severe Acute Malnutrition in Niger. Clinical Infectious Diseases. 2011;53(7):677–685.

51. Harrois D, Breurec S, Seck A, Delauné A, Hello SL, Gándara MP de la, et al. Prevalence and characterization of extended-spectrum β-lactamase-producing clinical Salmonella enterica isolates in Dakar, Senegal, from 1999 to 2009. Clinical Microbiology and Infection. 2014;20(2):O109–O116.

52. Poirel L, Aires-de-Sousa M, Kudyba P, Kieffer N, Nordmann P. Screening and Characterization of Multidrug-Resistant Gram-Negative Bacteria from a Remote African Area, São Tomé and Príncipe. Antimicrobial Agents and Chemotherapy. 2018;62(9). doi:10.1128/AAC.01021-18.

53. Rafaï C, Frank T, Manirakiza A, Gaudeuille A, Mbecko J-R, Nghario L, et al. Dissemination of IncF-type plasmids in multiresistant CTX-M-15-producing Enterobacteriaceae isolates from surgical-site infections in Bangui, Central African Republic. BMC Microbiology. 2015;15(1):15.

54. Founou LL, Founou RC, Allam M, Ismail A, Djoko CF, Essack SY. Genome Sequencing of Extended-Spectrum β-Lactamase (ESBL)-Producing Klebsiella pneumoniae Isolated from Pigs and Abattoir Workers in Cameroon. Frontiers in Microbiology. 2018;9. doi:10.3389/fmicb.2018.00188.

55. Eckert C, Gautier V, Arlet G. DNA sequence analysis of the genetic environment of various blaCTX-M genes. Journal of Antimicrobial Chemotherapy. 2006;57(1):14–23.

56. Ensor VM, Shahid M, Evans JT, Hawkey PM. Occurrence, prevalence and genetic environment of CTX-M β-lactamases in Enterobacteriaceae from Indian hospitals. Journal of Antimicrobial Chemotherapy. 2006;58(6):1260–1263.

57. Gourbeyre E, Siguier P, Chandler M. Bacterial insertion sequences: their genomic impact and diversity. FEMS Microbiology Reviews. 2014;38(5):865–891.

58. Lartigue M-F, Poirel L, Aubert D, Nordmann P. In Vitro Analysis of ISEcp1B-Mediated Mobilization of Naturally Occurring -Lactamase Gene blaCTX-M of Kluyvera ascorbata. Antimicrobial Agents and Chemotherapy. 2006;50(4):1282–1286.

59. Bevan ER, Jones AM, Hawkey PM. Global epidemiology of CTX-M β-lactamases: temporal and geographical shifts in genotype. Journal of Antimicrobial Chemotherapy. 2017;72(8):2145–2155.

60. Cantón R, Coque TM. The CTX-M β-lactamase pandemic. Current Opinion in Microbiology. 2006;9(5):466–475.

61. Singh NS, Singhal N, Virdi JS. Genetic Environment of blaTEM-1, blaCTX-M-15, blaCMY-42 and Characterization of Integrons of Escherichia coli Isolated From an Indian Urban Aquatic Environment. Frontiers in Microbiology. 2018;9. doi:10.3389/fmicb.2018.00382.

62. Shahid M, Sobia F, Singh A, Khan HM. Concurrent Occurrence of blaampC Families and blaCTX-M Genogroups and Association with Mobile Genetic Elements ISEcp1, IS26, ISCR1, and sul1-Type Class 1 Integrons in Escherichia coli and Klebsiella pneumoniae Isolates Originating from India. Journal of Clinical Microbiology. 2012;50(5):1779–1782.

63. Smet A, Van Nieuwerburgh F, Vandekerckhove TTM, Martel A, Deforce D, Butaye P, et al. Complete Nucleotide Sequence of CTX-M-15-Plasmids from Clinical Escherichia coli Isolates: Insertional Events of Transposons and Insertion Sequences. PLoS ONE. 2010;5(6):e11202.

64. Pérez-Etayo L, Berzosa M, González D, Vitas A. Prevalence of Integrons and Insertion Sequences in ESBL-Producing E. coli Isolated from Different Sources in Navarra, Spain. International Journal of Environmental Research and Public Health. 2018;15(10):2308.

65. Saladin M. Diversity of CTX-M β-lactamases and their promoter regions from Enterobacteriaceae isolated in three Parisian hospitals. FEMS Microbiology Letters. 2002;209(2):161–168.

66. Dhanji H, Patel R, Wall R, Doumith M, Patel B, Hope R, et al. Variation in the genetic environments of blaCTX-M-15 in Escherichia coli from the faeces of travellers returning to the United Kingdom. Journal of Antimicrobial Chemotherapy. 2011;66(5):1005–1012.

67. Johnson TJ, Danzeisen JL, Youmans B, Case K, Llop K, Munoz-Aguayo J, et al. Separate F-Type Plasmids Have Shaped the Evolution of the *H* 30 Subclone of *Escherichia coli* Sequence Type 131. mSphere. 2016;1(4). doi:10.1128/mSphere.00121-16.

68. Poirel L, Decousser J-W, Nordmann P. Insertion Sequence ISEcp1B Is Involved in Expression and Mobilization of a blaCTX-M -Lactamase Gene. Antimicrobial Agents and Chemotherapy. 2003;47(9):2938–2945.

69. Poirel L, Lartigue M-F, Decousser J-W, Nordmann P. ISEcp1B-Mediated Transposition of blaCTX-M in Escherichia coli. Antimicrobial Agents and Chemotherapy. 2005;49(1):447–450.

70. Gómez-Garcés JL, Saéz D, Almagro M, Fernández-Romero S, Merino F, Campos J, et al. Osteomyelitis associated to CTX-M-15-producing Aeromonas hydrophila: First description in the literature. Diagnostic Microbiology and Infectious Disease. 2011;70(3):420–422.

71. Boyd DA, Tyler S, Christianson S, McGeer A, Muller MP, Willey BM, et al. Complete Nucleotide Sequence of a 92-Kilobase Plasmid Harboring the CTX-M-15 Extended-Spectrum Beta-Lactamase Involved in an Outbreak in Long-Term-Care Facilities in Toronto, Canada. Antimicrobial Agents and Chemotherapy. 2004;48(10):3758–3764.

72. Baraniak A. Ceftazidime-hydrolysing CTX-M-15 extended-spectrum beta-lactamase (ESBL) in Poland. Journal of Antimicrobial Chemotherapy. 2002;50(3):393–396.

73. Upadhyay S, Hussain A, Mishra S, Maurya AP, Bhattacharjee A, Joshi SR. Genetic Environment of Plasmid Mediated CTX-M-15 Extended Spectrum Beta-Lactamases from Clinical and Food Borne Bacteria in North-Eastern India. PLOS ONE. 2015;10(9):e0138056.

74. Fabre L, Delauné A, Espié E, Nygard K, Pardos de la Gandara M, Polomack L, et al. Chromosomal integration of the extended-spectrum beta-lactamase gene blaCTX-M-15 in Salmonella enterica serotype Concord isolates from internationally adopted children. Antimicrobial agents and chemotherapy. 2009;53(5):1808–1816.

75. Wang J, Stephan R, Zurfluh K, HÃ¤chler H, Fanning S. Characterization of the genetic environment of blaESBL genes, integrons and toxin-antitoxin systems identified on large transferrable plasmids in multi-drug resistant Escherichia coli. Frontiers in Microbiology. 2015;5. doi:10.3389/fmicb.2014.00716.

76. Kaushik M, Kumar S, Kapoor RK, Virdi JS, Gulati P. Integrons in Enterobacteriaceae : diversity, distribution and epidemiology. International Journal of Antimicrobial Agents. 2018;51(2):167–176.

 doi:10.20944/preprints202012.0144.v1

77. Lahlaoui H, Ben Haj Khalifa A, Ben Moussa M. Epidemiology of Enterobacteriaceae producing CTX-M type extended spectrum β-lactamase (ESBL). Médecine et Maladies Infectieuses. 2014;44(9):400–404.

78. Woodford N, Carattoli A, Karisik E, Underwood A, Ellington MJ, Livermore DM. Complete Nucleotide Sequences of Plasmids pEK204, pEK499, and pEK516, Encoding CTX-M Enzymes in Three Major Escherichia coli Lineages from the United Kingdom, All Belonging to the International O25:H4-ST131 Clone. Antimicrobial Agents and Chemotherapy. 2009;53(10):4472–4482.

79. Nicolas-Chanoine M-H, Blanco J, Leflon-Guibout V, Demarty R, Alonso MP, Caniça MM, et al. Intercontinental emergence of Escherichia coli clone O25:H4-ST131 producing CTX-M-15. Journal of Antimicrobial Chemotherapy. 2007;61(2):273–281.

80. Rogers BA, Sidjabat HE, Paterson DL. Escherichia coli O25b-ST131: a pandemic, multiresistant, community-associated strain. Journal of Antimicrobial Chemotherapy. 2010;66(1):1–14.

81. Marcadé G, Deschamps C, Boyd A, Gautier V, Picard B, Branger C, et al. Replicon typing of plasmids in Escherichia coli producing extended-spectrum β-lactamases. Journal of Antimicrobial Chemotherapy. 2009;63(1):67–71.

82. Zurfluh K, Glier M, Hächler H, Stephan R. Replicon typing of plasmids carrying blaCTX-M-15 among Enterobacteriaceae isolated at the environment, livestock and human interface. Science of The Total Environment. 2015;521–522:75–78.

 doi:10.20944/preprints202012.0144.v1

 doi:10.20944/preprints202012.0144.v1