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Tracking *bla*$_{CTX-M}$ Transmission Through Transposable Elements in Uropathogenic and Commensal *E. coli*

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Abstract

Aim: To investigate the nucleotide sequences associated with transposable elements carrying *bla*$_{CTX-M}$ allelic variants as potential markers for the transmission of antimicrobial resistance genes between domestic animals, humans and the environment.

Materials & Methods: We conducted whole-genome sequencing and analyzed the nucleotide sequences of most abundant *bla*$_{CTX-M}$ allelic variants (*bla*$_{CTX-M-27}$, *bla*$_{CTX-M-55}$, and *bla*$_{CTX-M-65}$) in commensal *Escherichia coli* (n = 20) from household members in Quito and uropathogenic *E. coli* (UPEC) (n = 149) isolated from nine clinics in Quito, Ecuador.

Results: The Ecuadorian commensal *E. coli* and UPEC displayed identical nucleotide sequences surrounding the *bla*$_{CTX-M}$ gene and the synteny was similar to those found in other parts of the world; however phylogenetic analysis indicated that the genetic environments in Ecuadorian isolates were unique.

Conclusion: These findings suggest that the nucleotide sequences flanking the *bla*$_{CTX-M}$ genes may be useful for resolving ARG transmission pathways, especially inter- regional analyses.

PLAIN LANGUAGE SUMMARY

Bacteria can share small bits of DNA with each other using a type of DNA vehicle, known as a plasmid. The intestinal bacteria of domestic animals can also spread to humans. Some of these bacteria may share genes with human bacteria that make them resistant to antibiotics. It is hard to know how many of these genes move from animal to human bacteria because they are linked

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to pieces of DNA that let them jump around inside bacteria. This makes it harder to track how resistance genes spread. This study looks at one type of resistance gene called *bla*$_{CTX-M}$ which makes bacteria resistant to antibiotics called cephalosporins, used to treat serious infections. We found that the DNA around this gene was the same in bacteria from both humans and domestic animals in Quito, Ecuador. However, the DNA was different from what is found in other parts of the world. We suggest that this DNA near the *bla*$_{CTX-M}$ gene could help us understand how antibiotic resistance spreads between animals and humans in different regions.

Keywords

Transposable elements; *bla*$_{CTX-M}$ gene; antimicrobial resistance; horizontal gene transfer; 3rd generation cephalosporins; one health; plasmids; chromosome; E. coli; UPEC; commensal

1. Introduction

Antimicrobial resistance (AMR) in bacteria was responsible for an estimated 1.27 million deaths worldwide in 2019 and the trend is increasing [1]. The AMR crisis has been fueled by the use and overuse of antimicrobials in both human medicine and food-animal production, augmenting the ability of bacteria to transmit antimicrobial resistance genes [2]. To effectively control AMR, it is critical to understand the sources and transmission mechanisms of drug-resistant bacteria and antimicrobial resistance genes (ARGs). There has been ongoing debate regarding the primary source of antimicrobial resistant bacteria and ARGs for the human population, with some experts implicating food-animal production, while others argue that food animals play a very limited role [3, 4, 5].

The difficulty of determining sources and sinks of ARGs in bacterial populations within the environment could be attributed to the large diversity of: 1) antimicrobial resistance genes; 2) mobile genetic elements (MGEs) that carry and move these genes; and 3) drug resistant bacterial strains. This is further complicated by our lack of understanding about how these elements interplay. Most ARGs are transmitted among bacteria through horizontal gene transfer, where plasmids or bacteriophages carrying ARGs or naked DNA mobilize these genes to genetically related and unrelated bacteria [6]. Some of the most active carriers of ARGs are transposable elements. Transposable elements (TEs) are among the most active carriers of ARGs. These mobile genetic elements facilitate the transfer of ARGs across diverse genetic platforms, including plasmids, chromosomes, and bacteriophages [6]. In some cases, ARGs have been disseminating for a very long time [7] and are probably more homogenously distributed in *E. coli* populations than ARGs that began to disseminate in the 1990s or 2000s, such as *bla*$_{CTX-M}$ or the *mcr-1* [8, 9, 10]. In this case, identifying ARGs that have recently started to disseminate may be better indicators of antimicrobial selective pressure and the potential sources of these genes in an ecosystem [11,12].

In communities near Quito, Ecuador, we have identified several distinct *E. coli* clones, each carrying the same *bla*$_{CTX-M}$ allelic variant with identical flanking sequences that are consistently bracketed by the same TEs, but located on different plasmids or chromosomes [13]. This is a strong indication that these TEs are central to mobilizing *bla*$_{CTX-M}$ genes moving between different plasmids. Thus, prospectively analyzing *bla*$_{CTX-M}$ genes

alongside associated sequences linked to TEs, could enhance data stratification, enabling the detection of potential spillover of these genes between bacterial populations of different ecosystems. In this study, we compared common *bla*$_{\text{CTX-M}}$ allelic variants *bla*$_{\text{CTX-M-27}}$, *bla*$_{\text{CTX-M-55}}$ and *bla*$_{\text{CTX-M-65}}$ and their genetic environment within commensal *E. coli* (from humans and domestic animals) from a semi-urban community close to Quito and uropathogenic *E. coli* (UPEC) from Quito and compared them with *E. coli* with the same *bla*$_{\text{CTX-M}}$ allelic variants in other parts of the world.

2. Materials & methods

2.1. *E. coli* isolates and DNA extraction

Ceftriaxone resistant *E. coli* isolates (n=149) from urinary tract infections were collected from 9 clinics in Quito and over a period from May 2014 to May 2015 and analyzed in the Diagnostic Microbiology Laboratory of the Microbiology Institute, Universidad San Francisco de Quito. Each bacterial isolate was cultured on Chromocult agar® to identify *E. coli* through β-D-glucuronidase activity and was stored at −80°C in Brain Heart Infusion (BHI) medium, supplemented with 20% glycerol. A single bacterial colony was selected and inoculated into 3 ml of trypticase soy broth (TSB) at 37°C for 18–24 hours. DNA from the bacterial isolates was extracted with the DNeasy Blood & Tissue kit (QIAGEN) according to the manufacturer's protocol. The concentrations and quality of bacterial DNA were measured using the NanoDrop Microvolume Spectrophotometer. All the protocols were approved by the USFQ bioethics committee (code 2015–167T). We also used 20 nucleotide sequences from 20 ceftriaxone resistant commensal *E. coli* obtained (form 6 children and 14 domestic animals) obtained in a previous study conducted within communities of Quito [5].

2.2. Whole genome sequencing

We used Illumina NextSeq 2000 and assembled the UPEC genomes using SPAdes v3.15.5 (https://ablab.github.io/spades/index.html). Contigs were joined into scaffold with a fixed gap size of 100 bp. [14]. The nucleotide sequences were submitted to GenBank and the accession number is SUB14757366.

2.3. Strain genotyping

The assembled UPEC genomes were analyzed using Multi-Locus Sequence Typing (MLST) (version 2.0.9) [15] an online tool provided by the Center for Genomic Epidemiology (CGE). This tool identifies and classifies each bacterial isolate based on the sequences of seven housekeeping genes (*adk, fumC, gyrB, icd, mdh, purA and recA*). These genes were evaluated for their identity and coverage to assign a specific sequence type (ST) to each bacterial isolate (Supplementary information Table S1).

2.4. Antibiotic resistance genes

Antimicrobial resistance genes were identified using the ABRicate tool (version 1.0.1) with the Resfinder, CARD y NCBI databases. Each sequence carrying the *bla*$_{\text{CTX-M}}$ variant was analyzed and trimmed using Geneious Prime (version 2024.0.5) and Unipro UGENE 50.0 [16]. Other ARGs are shown in the Supplementary materials Table S2.

2.5. Nucleotide sequences of *bla*$_{CTX-M}$ variants

Each sequence carrying the *bla*$_{CTX-M}$ variant (in UPECs) was annotated using the following tools: Prokka (version 1.14.6) [17], Prokaryotic Genome Annotation Pipeline (PGAP) and the Pathosystems Resource Integration Center (PATRIC) [18] and confirmed with BLAST.

The GenBank (gbk) files acquired were manually modified based on the data obtained from annotation tools for the identification of mobile genetic elements such as: MobileElementFinder (version 1.0.6) [19] ISEScan (version 1.7.2.3) [20] and ISfinder [21]. A comparison of the genomic structure was performed with the nucleotide sequences of bacterial isolates that had the same *bla*$_{CTX-M}$ allelic variant using Easyfig (version 3.0.0) [22].

2.6 Phylogenetic Analysis of Genetic Environment

Nucleotide sequences from the genetic environments (i.e. flanking region) of *bla*$_{CTX-M-27}$, *bla*$_{CTX-M-55}$, and *bla*$_{CTX-M-65}$ within the Ecuador sequences were subjected to BLAST and the 35 highest hits were retrieved and used to construct phylogenetic trees. To construct the phylogenetic trees, we used MEGA11 software with the Maximum Likelihood method. Additionally, we analyzed the 100 most similar sequences from configurations worldwide, obtained from GenBank using BLAST. (Supplementary information Figure S1 and Table S3).

3. RESULTS

3.1. Genetic environment of *bla*$_{CTX-M}$ genes

The genetic environment of the *bla*$_{CTX-M-65}$ allelic variant was formed by IS*26*-*flipA*-HP (hypothetical protein)-IS*Ecp1*-*bla*$_{CTX-M-65}$-IS*26* in 5 commensal *E. coli*; IS*26*-*flipA*-HP (hypothetical protein) -IS*Ecp1*-*bla*$_{CTX-M-65}$-IS*102*-*tonB*-PAS (methyl accepting protein sensor-IS*26*, in 4 commensal *E. coli* and 10 UPEC isolates; although the commensals had one additional nucleotide between IS*26* and *flipA* (Figure 1). The allelic variant *bla*$_{CTX-M-55}$ showed 3 different genetic environments: IS*26*-IS*Ecp1*- *bla*$_{CTX-M-55}$-*wbuC*-TnA-*bla*$_{TEM}$ -IS*26* in 9 commensal *E. coli* and 4 UPECs; IS*26*-IS*Ecp1*- *bla*$_{CTX-M-55}$-*wbuC*-TnA-*bla*$_{TEM}$ -HP (hypothetical protein) in 1 UPEC; IS1380-HP- *bla*$_{CTX-M-55}$-*wbuC* (fused to *yagA*)-HP in 2 UPECs. The same nucleotide sequences associated with *bla*$_{CTX-M}$ genes in UPECs and commensal *E. coli* from humans were also observed in commensal isolates from domestic animals (Figures 1–3). The *wbuC* gene encodes a cupin fold of metalloproteinase. The *yagA* gene encodes an integrase core domain-containing protein (Figure 2). The allelic variant *bla*$_{CTX-M-27}$, was found in 4.96% (n=7) of the strains, IS*26*-IS*Ecp1*- *bla*$_{CTX-M-27}$-IS*102*-*tonB*-DUF4158-IS*26* in 2 commensals and 4 UPECs (contigs of 2 additional UPECs showed the same configuration but incomplete due to the size of the contig); IS*26*-IS*Ecp1*-*bla*$_{CTX-M-27}$-IS*102*-*tonB*-DUF4158-phage integrase-TEM-IS*6* in one UPEC. The DUF4158 is a gene coding for phage integrase (Figure 3). We also analyzed the genetic environment of 100 *bla*$_{CTX-M}$ genes from various regions worldwide, observing diverse configurations with different associated genes and transposable elements (Supplementary information Figure S1 and Table S3).

3.2. Phylogenetic analysis of the *bla*$_{CTX-M}$ genetic environments

Nucleotide sequence alignments of Ecuadorian configurations of the genetic environments for the 3 *bla*$_{CTX-M}$ allelic variants showed 99–100 identity (0–4 SNPs) within each variant. A phylogenetic analysis of the Ecuadorian genetic environments with highest hits in Blast and identical configuration (synteny), revealed that allelic variant sequences from different countries clustered in different groups (Figure 4).

4. Discussion

In this study we observed that nucleotide sequences of the genetic environment (comprising *bla*$_{CTX-M-55}$, *bla*$_{CTX-M-65}$, and *bla*$_{CTX-M-27}$, TEs and intervening sequences) are most often identical in Ecuadorian isolates but different from sequences from other countries showing identical synteny (Figure 1). This similarity was also found in Korean isolates that demonstrated a similar genetic environment of *bla*$_{CTX-M-27}$ (Figure 3A). The results of this study suggest that TEs carrying *bla*$_{CTX-M-55}$, *bla*$_{CTX-M-65}$, and *bla*$_{CTX-M-27}$ genes, are probably mobilizing frequently among different *E. coli* strains in different communities across the globe, which is something that was previously observed in *bla*$_{CTX-M-55}$ genes [23]. The nucleotide sequences of TEs (and associated genetic sequences), even those showing identical configuration (synteny), seem to be geographically structured (Figure 4) and have a strong potential to be used as epidemiological tools to determine spillover of these important ARGs from different biotic or abiotic components of an ecosystem. Additionally, there were diverse configurations of the genetic environment associated with *bla*$_{CTX-M}$ genes (different TEs and genes) in other countries (Supplementary information Figure S1 and Table S3).

The genetic environment of *bla*$_{CTX-M-55}$, *bla*$_{CTX-M-65}$, and *bla*$_{CTX-M-27}$ in *E. coli* commensal isolates from humans and from domestic animals were identical to those found in UPECs in the same communities of Quito, Ecuador (Figures 1–3). The data suggest that the *bla*$_{CTX-M-27}$, *bla*$_{CTX-M-55}$, and *bla*$_{CTX-M-65}$ genes from commensal *E. coli* (originating from humans or domestic animals) are being transferred to UPECs in humans, or vice versa. These results underscore the importance of adopting a One Health perspective—integrating human, environmental, and animal health—to better understand the transmission of antimicrobial resistance. Furthermore, the presence of these genes in a similar genetic configuration across other bacterial species, such as *Salmonella, Klebsiella, Acinetobacter, Citrobacter,* and *Proteus*, indicates that these genetic structures are likely being mobilized among different bacterial taxa via TEs. The main limitation of this study was the use of short-read sequencing (Illumina NextSeq), which resulted in incomplete recovery of many genetic environments (Figures 1–3). Consequently, additional variations in these configurations may have been missed. Nevertheless, the information obtained was sufficient to discriminate sequences from Ecuadorian isolates and those obtained from other parts of the world.

We argue that the nucleotide sequences of the genetic environment surrounding the *bla*$_{CTX-M}$ genes provide enough information to study the transmission of these genes among geographic locations, although it is unclear whether directionality can be determined. We also argue that this approach may be more efficient than other methods. Plasmid sequencing

for example, which typically requires plasmid enrichment steps and long-read sequencing, would significantly increase the cost of such analyses. Additionally, a previous study conducted in an Ecuadorian community revealed that obtaining whole plasmid sequences provided limited insights because transposable elements (i.e. those carrying *bla*$_{\text{CTX-M}}$ genes) appeared to move across a highly heterogeneous plasmid population [13]. Similarly, relying solely on whole genome sequencing to study antimicrobial resistance (AMR) gene transmission in the One Health context overlooks horizontal gene transfer, leading to an underestimation of the true extent of AMR gene transmission among bacteria from different animal species [13].

The majority of TEs associated with *bla*$_{\text{CTX-M}}$ genes were located on plasmids (Figures 1–3), supporting the idea that TEs are more prevalent in plasmids than in chromosomes [6, 24]. The greater prevalence of TEs in plasmids may be caused by natural selection. [24].

The information about the genetic environment associated with TEs may be useful for other clinically important AMR genes. For instance, Tn*125* has been shown to mobilize *bla*$_{\text{NDM-1}}$, a gene that confers resistance to carbapenem antibiotics from the potential origin *Acinetobacter* spp. [25]; an unknown TEs mobilized the *bla*$_{\text{KPC}}$ gene from the potential original environmental bacteria *Chromobacterium* spp. [26]. IS*Apl1* mobilized the *mcr*-1 gene (causing resistance to colistin) from the potential original commensal bacteria *Moraxella spp.* [27]. IS*Epec-1* was shown to likely mobilize *bla*$_{\text{CTX-M}}$ genes from *Kluyvera* spp., [28], and the transposon IS*1999* may have moved the *bla*$_{\text{OXA-48}}$ gene from the environmental bacteria *Shewanella* spp. [29]. Once arriving at a new bacterial species, other TEs, such as IS*26* or Tn*4401*, may take a more dominant role in mobilization [30, 31, 32]. Finally, the use and overuse of antimicrobials likely increases the mobility of TEs [33].

5. Conclusion

In this manuscript, we demonstrated that the nucleotide sequences flanking TEs and *bla*$_{\text{CTX-M}}$ genes may provide valuable epidemiological insights into the source and transmission of these resistance genes among different hosts in geographical regions. This analysis adds additional evidence that resistance to 3rd generation cephalosporins is transmitted between *E. coli* in domestic animals and extraintestinal pathogenic *E. coli* (ExPEC) in humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Article Highlights

- Studying the horizontal transmission of antimicrobial resistance genes between bacterial commensals in humans, domestic animals, and human pathogens is often challenging.
- We sequenced genomes from ceftriaxone resistant uropathogenic *E. coli* and commensal *E. coli* (from humans and domestic animals) and analyzed the contigs containing the $bla_{\text{CTX-M}}$ genes
- The study provides evidence that transmission of the $bla_{\text{CTX-M}}$ gene is often associated with specific transposable elements (TEs) that move the gene among plasmids or from plasmid to chromosomes among commensals and pathogens.
- The nucleotide sequences and genetic environments flanking the $bla_{\text{CTX-M}}$ gene, including TEs, were found to vary across different regions of the world, and these flanking regionsconsequently, can be used to gain insights into transmission networks of ARGs.

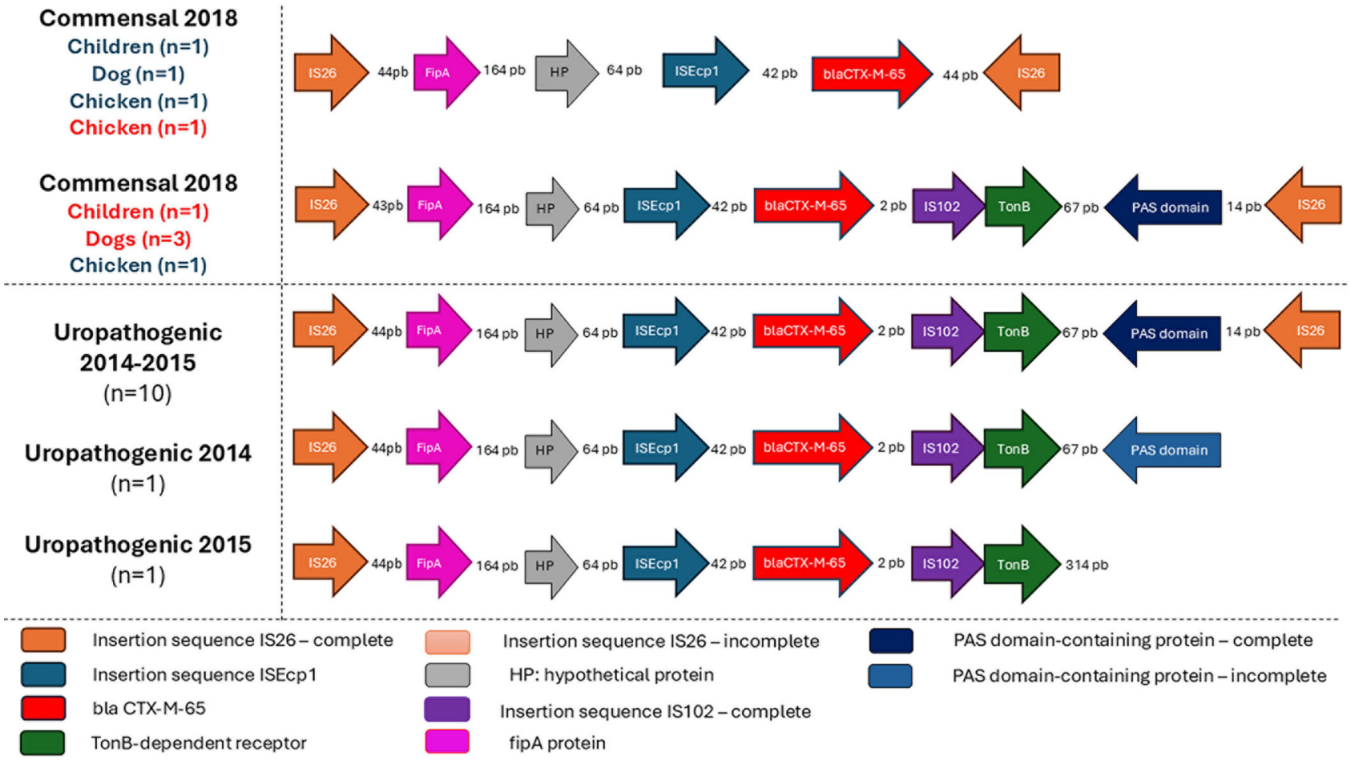

Figure 1.

Genetic environment of *bla*$_{\text{CTX-M-65}}$ found in ceftriaxone resistant UPECs and commensal *E. coli* in Quito. Arrows indicate different genes (showing in different colors) and transcriptional direction; numbers indicate the distance in base pairs (bp) between genes. Toned down colors indicate the presence of incomplete genes (because of contig size). Text written in blue and red colors indicate *bla*$_{\text{CTX-M-65}}$ in chromosomes or plasmids respectively. The IS*26* is probably the TE that is moving the *bla*$_{\text{CTX-M-65}}$ gene.

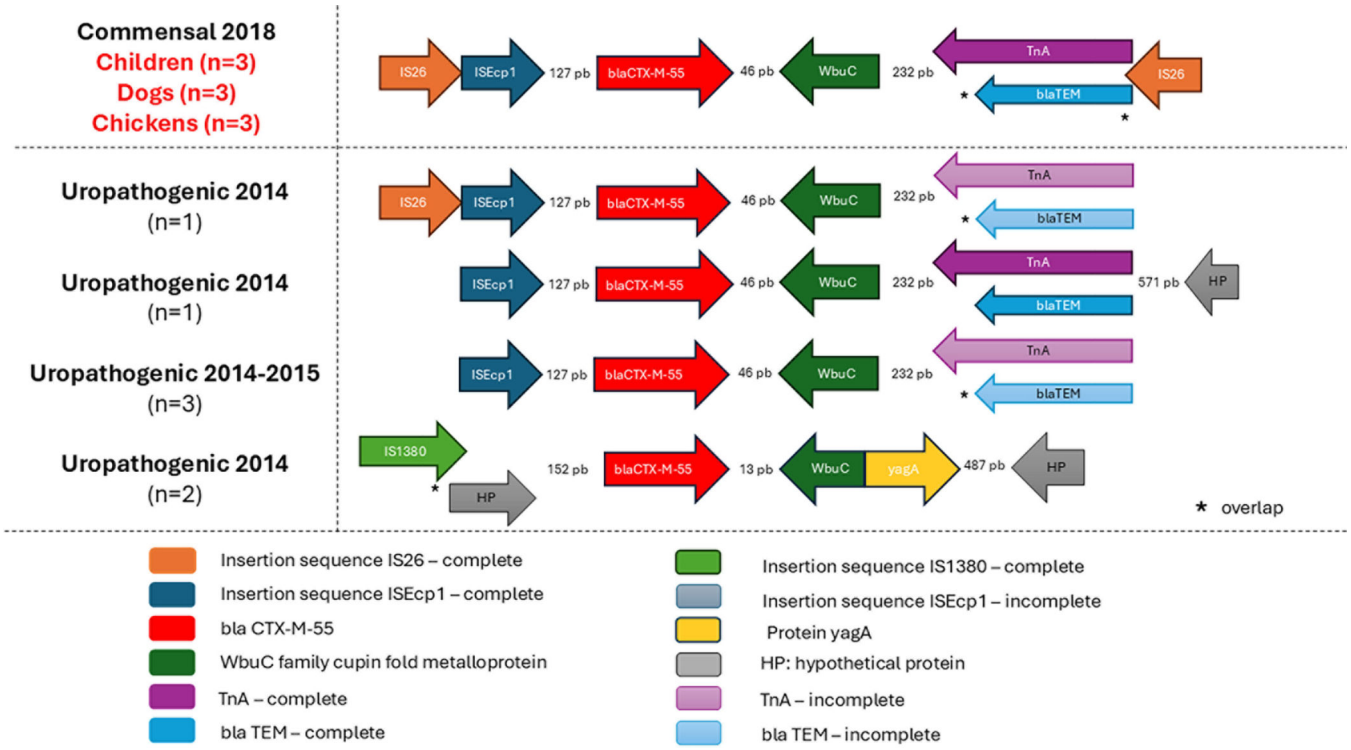

Figure 2.

Genetic environment of *bla*$_{\text{CTX-M-55}}$ found in ceftriaxone resistant UPECs and commensal *E. coli* in Quito. Arrows indicate different genes (showing in different colors) and transcriptional direction, and numbers indicate the distance in base pairs (bp) between genes. Tone down colors indicate incomplete genes (because of contig size). The IS*26* is probably the TE that is moving the *bla*$_{\text{CTX-M-55}}$ gene.

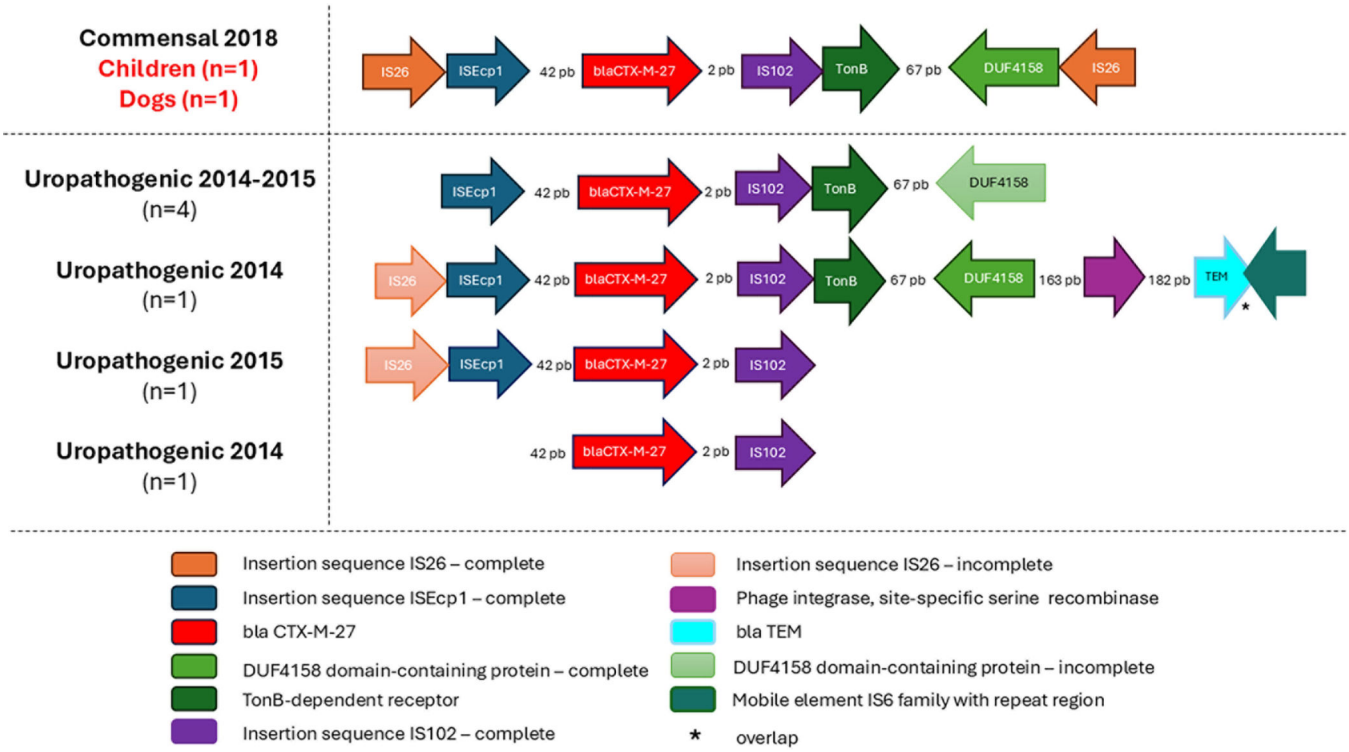

Figure 3.

Genetic environment of *bla*$_{\text{CTX-M-27}}$ found in ceftriaxone resistant UPECs and commensal *E. coli* in Quito. Arrows indicate different genes (showing in different colors) and transcriptional direction, and numbers indicate the distance in base pairs (bp) between genes. Tone down colors indicate incomplete genes (because of contig size). The IS*26* is probably the TE that is moving the *bla*$_{\text{CTX-M-27}}$ gene.

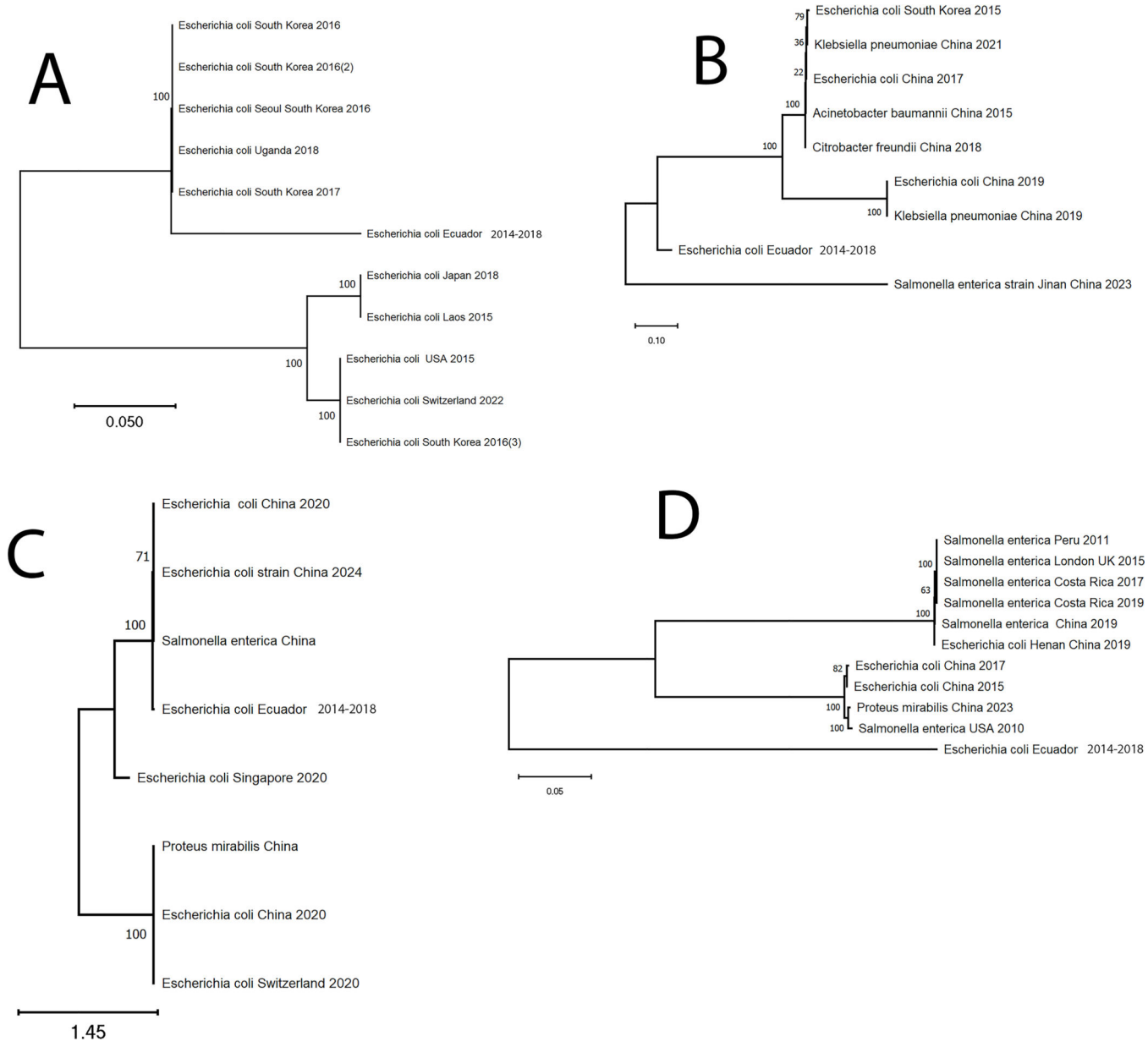

Figure 4.

Phylogenetic tree using Maximum Likelihood of genetic environment of *bla*$_{\text{CTX-M}}$ genes found in Ecuadorian *E. coli* isolates and sequences from different parts of the world that showed the highest hits in blast. A) is *bla*$_{\text{CTX-M-27,}}$ B) is *bla*$_{\text{CTX-M-55,}}$ C) is *bla*$_{\text{CTX-M-65}}$ configuration IS*26*-*flipA*-HP (hypothetical protein)-IS*Ecp1*-*bla*$_{\text{CTX-M-65}}$-IS*26* and, D) *bla*$_{\text{CTX-M-65}}$ configuration IS*26*-*flipA*-HP (hypothetical protein)-IS*Ecp1*-*bla*$_{\text{CTX-M-65}}$-IS*102*-*tonB*-PAS (methyl accepting protein sensor)-IS*26*. Numbers indicate bootstrap values after 100 pseudo-replicates.