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Research Article

Characterization of TEM and CMY-2 beta-lactamases in *Enterobacteriaceae* strains isolated at the Brazzaville University and hospital center in Congo

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Abstract

This study aimed to characterize the genes coding for ESBLs in TEM and CMY-2 *Enterobacteriaceae*. 65 strains of *Enterobacteriaceae* were isolated from 65 patients, of which 32.43% came from outpatients and 67.56% from hospitalized patients. The study was carried out over 6 months. The samples (urine, pus, and blood) were collected from hospitalized and external patients at the Brazzaville University Hospital. Strains were identified by API20E. An antibiogram was by diffusion in agar medium (MH) according to CA-SFM. The ESBL phenotype was detected by synergy. The plasmid cephalosporinase phenotype was determined by decreasing the diameter of inhibition around the cefoxitime disc in a strain resistant to ESBL inhibitors. Antibiotic resistance genes were characterized by PCR and sequencing. Sequences were assembled by Codon Code Aligner and compared by BlastX with Genbank, NCBI, and ARGANNOT. Phylogenetic gene trees were constructed using MEGA 7 software. 65 strains of *Enterobacteriaceae* were isolated from 65 patients, of which 32.43% came from outpatients and 67.56% from hospitalized patients. Except for imipenem, colistin; the amikacin and fosfomycin, tested antibiotics show high resistance to most of the beta-lactam, as well as resistance to very frequent aminoglycosides, sulfamides, tetracyclines, and Fluoroquinolones. PCR reveals that 97.29% possessed the TEM gene and 5.40% produced the CMY-2 gene. 64% of the isolates were isolated from urine samples, with a predominance of *Enterobacter cloacae* strains on ESBL production (75%). 60% of ESBL strains were isolated in the service of metabolic diseases. Sequencing of the amplification products revealed that the blaCTX-M1 strains were all TEM-1. Une conservation des motifs SxxK en positions ABL 71 à 74 était observée pour l'alignement des sequences du groupe TEM. This study revealed the presence of the TEM and CMY-2 genes at disturbing frequencies. It proves the need to promote an infection prevention program with the regulation of antibiotic therapy in hospitals in Congo Brazzaville.

Keywords *Enterobacteriaceae*, ESBL, Antibiotic resistance, CHU, Brazzaville

Introduction

The introduction of semi-synthetic penicillins in the 1960s was soon followed by the appearance of Ambler narrow-spectrum Ambler class A beta-lactamase strains with the

active serine site (SXXX) (Henderson et al., 1997), named TEM-1, TEM-2, and SHV-1 (Jacoby, 2009). These enzymes, encoded by plasmid genes, have spread to different species of enterobacteria (Jacoby, 2009). The resistance to amoxicillin and the first-generation cephalosporins they cause has favored

the prescription of aminoglycosides, quinolones, and especially third-generation cephalosporins (C3G).

However, this exposure to C3G led to the appearance in the 1980s of extended-spectrum beta-lactamases (ESBL), class A enzymes, destroying most beta-lactams except for cephamycin and carbapenems (Jacoby, 2009). At the same time, resistance genes to fluoroquinolones and aminoglycosides (*qnr* or *aac(6')-Ib-cr*) have spread within these same bacterial populations following the widespread use of these antibiotics.

Thus, prescribers have used beta-lactam of the latest generation: carbapenems. Their use was soon followed by the appearance of the carbapenemase-producing strains, especially in *K. pneumoniae*, then in other species of enterobacteria. These carbapenemases are of different types: metallo- β -lactamases (IMP, VIM, NDM), beta-lactamases class A (KPC, GHG, SME) and class D (OXA-48) (Bush & Jacoby, 2010). Class D essentially corresponds to the oxacillinase type enzymes comprising OXA-48, which have 5 variants (OXA-162, OXA-163, OXA-181, OXA-204, OXA-232 and the recently described enzymes OXA-244 and OXA-245 (Ouedraogo & Prévance, 2017; Potron et al., 2011).

The OXA-48 gene first described in *K. pneumoniae* is one of the most recently described carbapenemases, structurally different from the previous ones and essentially identified in Mediterranean countries (Nordmann et al., 2013; Poirel & Nordmann, 2012)

These enzymes strongly hydrolyze carbapenems but little or no third-generation cephalosporins (except for OXA-163) (Ouedraogo et al., 2016). They are resistant to suicide inhibitors of β -lactamases. However, their presence is often coupled with the presence of ESBL, which leads to a multi-resistance of these secretory strains (Poirel et al., 2011, Potron & Nordmann, 2012).

Work on the production of ESBLs and carbapenemases in enterobacteria in Africa has been limited in North Africa. Data on West and Central Africa are scarce and scattered. Some studies have reported the presence of ESBL and carbapenemases in Nigeria (Oduyebo, 2015), Senegal (Sire et al., 2007), and Burkina Faso (Ouedraogo et al., 2016).

Data on Central Africa are scarce and scattered. Some studies have been reported in Cameroon (Gangoue et al., 2005) and in Gabon (Yala et al., 2016).

In Congo Brazzaville, no studies on the characterization of ESBL genes and OXA-48 carbapenemases have been reported. This justifies the framework of the present study which aimed to genotypically characterize ESBL and OXA-48 carbapenemase gene variants harbored by strains of enterobacteria isolated in portage and in infectious processes at the CHU of Brazzaville.

Materials and methods

Patients and samples

It is a prospective descriptive study, carried out over six months from May to September 2018. It focused on enterobacterial strains isolated from inpatients and outpatients from diagnostic specimens at Brazzaville University Hospital. The samples corresponded to the various sites of colonization (urine, pus, and blood cultures), essentially isolated to the various services of general Surgery, Cardiology, Pediatric, Metabolic Disease, Rheumatology, Urology, Pediatric Intensive Care, Gastroenterology, and Infectious Diseases.

Some epidemiological data such as age, sex, and origin of service were first identified for each patient. Duplicates (same strain in the same patient for the duration of the study) were eliminated. Samples for pus were taken by a swab, this technique consists of having a sterile swab moistened with sterile distilled water at the site of pathological colonization. The strains were isolated according to conventional techniques and identified by the API20E system (Biomérieux, Marcy-l'Etoile, France).

The collection of strains was made at the laboratory of bacteriology -virology of the Hospital and University Center of Brazzaville and the genotypic study was conducted at the laboratory of Cellular and Molecular Biology, Faculty of Science and Technology Marien Ngouabi University and Institute for Research in Exact and Natural Sciences (IRSEN), Brazzaville.

Study of the sensitivity

Antibiotic susceptibility testing was carried out for each strain by the method of diffusion in agar medium on Mueller-Hinton medium (Becton Dickinson, The Bridge of Claix, France) according to the recommendations of the Committee of the Antibiogram of the French Society of Microbiology (CA-SFM) (Bonnet et al., 2010). The agar plates were inoculated with a swab from a culture inoculum calibrated at 0.5 McFarland before the deposit of the disks impregnated with antibiotic (Bio-Rad, Marnes-La-Coquette, France). After incubation of agar plates at 37 ° C for 18h to 24h inhibition diameters, due to antibiotic concentration gradients established from the disc, were compared to the critical values given by CA-SFM, thus allowing the define the susceptibility or resistance of a strain to an antibiotic.

ESBL production was confirmed phenotypically according to CA-SFM recommendations, including the MH agar synergy test between the clavulanic acid disc and cephalosporin discs of the 3rd (ceftriaxone: CRO, cefepime: FEP). The phenotype cephalosporinase CMY-2 was determined when there was a decrease in the diameter of inhibition around the cefoxitine disc on MH agar in a strain resistant to ESBL inhibitors such as amoxicillin / clavulanic acid. 16 antibiotics

were tested: amoxicillin AMX (25µg), amoxicillin / clavulanic acid AMC (20 / 10µg), cefepime FEP (30µg), Piperacillin-Tazobactam TZP (75 / 10µg), cefalotin CF (30µg), ceftriaxone CRO (30µg) ERT ertapenem (10 µg), imipenem IMP (10 µg), fosfomycin FF (50 µg), nitrofurantoin FNitro (300 µg), trimethoprim + Sulphamethazole SXT (1.25 / 23.75 µg), amikacin (30 µg), ciprofloxacin CIP (5 µg), doxycycline DO (30UI), CT colistin (50µg) and gentamycin GEN (15µg). The different strains tested were classified into sensitive (S) and Resistant (R) categories. *E. coli* ATCC 25922 strain was used as a sensitive reference for antibiogram.

Molecular detection of antibiotic resistance genes

DNA extraction

The bacterial strains were cultured overnight on MacConkey agar at 37 °C. Then, the colonies were removed using a sterile plastic loop of 1µl and transferred into 200 µl of sterile water. The extraction of total DNA from the ESBL and AmpC enterobacteria strains was carried out using the Qiagen kit: mini Kit (Qiagen, Hilden, Germany) according to the conditions specified by the suppliers.

The DNA was eluted in a final volume of 100 µL. The extracted DNA was stored at -20 °C for further analysis.

Detection by PCR of CMY-2 and blaTEM

Molecular gene detection was performed on all strains using the conventional PCR technique using a T100 thermocycler (Bio-Rad, France) using the specific primer pairs for the blaTEM genes (Kruger et al., 2004) and CMY-2 (Souana, 2011) shown in Table 1.

Each conventional PCR reaction was carried out in a 50 µL reaction mixture containing 36.75 µL of sterile distilled water, 1 µl of each primer (20 µM), 1 µl of dNTP, 5 µl of 10X PCR reaction buffer and 0.25 µl of Taq DNA polymerase (Eurogentec, Belgium) and 5 µL of extract raw DNA.

The conventional PCR conditions consisted of an initial denaturation step at 95 ° C for 15min; followed by 35 cycles of amplifications each comprising a hybridization step at 55 ° C for 50 seconds, an elongation step at 72 ° C for 1 minute, and a final extension step at 72 ° C for 7 minutes.

The amplification products were detected by electrophoresis using 1.5% SYBR-safe agarose gels (Invitrogen, Leek, The Netherlands), as well as a DNA molecular weight marker (BenchTop pGEM). @DNAMarker, Promega, Madison, Wisconsin, USA). Visualization of the gels was performed using the leaning ADNPPEM marker (Promega, Madison, Wisconsin, USA) under ultraviolet illumination.

DNA sequencing

Classical PCR products positive for ESBL were purified using the NucleoFast 96 PCR plate (Machery-Nagel EURL, France) and sequenced using BigDye terminator chemistry on a ABI3730 Automatic Sequencer (Applied Biosystems, Foster City, California, USA).

The sequences obtained were assembled and corrected with Codon Code Aligner software version 8. Sequence alignment and analyses were performed using the basic local alignment search tool (BLAST) software available on the website of the National Information Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov>).

Phylogenetic and molecular evolutionary analyses were conducted using MEGA version 7 (Kumar et al., 2017).

Statistical Analysis

The data were captured using the GraphPad Prism 7 software. The Chi² (X²) test was used to compare the production frequencies of ESBL genes between enterobacterial strains isolated from inpatients and outpatients. The confidence interval was 95% with a degree of freedom of 1. The difference between the frequencies was considered significant when the *p*-value was less than 0.05.

Results

A total of 65 enterobacterial strains were selected on MacConkey agar with reduced β-lactams susceptibility. Bacterial identification by API 20E reveals 29 *Escherichia coli*, 23 *K. pneumoniae*, 4 *Serratia marcescens*, 4 *Enterobacter cloacae*, 3 *Citrobacter freundii* and 2 *Proteus mirabilis* isolates.

The antibiotic susceptibility testing on 16 different antibiotics shows that 96.92 % (n= 63) were resistant to amoxicillin (Table 2), 87.69% (n=57), of the isolates were resistant to amoxicillin/acid clavulanic, 75.38% (n=49), resistant to cefalotin, and 47.69% (n=31) resistant to ceftriaxone. Low level of resistance to Piperacillin-Tazobactam was observed with 6.15% of the isolates (n= 4); 23.07% (n=15) to cefepime, 6.15% (n=4) to Ertapenem (*K. pneumoniae* only) and 9.23% (n=4) to Colistin mainly in *Serratia marcescens* (naturally resistant). In contrast, all strains (100%) were sensitive to imipenem and fosfomycin sensitivity was observed for 98.47% of isolates (Table 2). Regarding aminoglycosides, there is a fairly strong resistance was observed against gentamicin and amikacin with 33.84% (n=22) and 1.53% (n=1) respectively. In addition, against fluoroquinolones, average resistance of 52.30% (n=34) was detected for ciprofloxacin; 67.69% (n=20) for tetracyclines and 38.46 (n=25) furans remain resistant; as for the sulfonamides, the latter remain resistant to 89.23 % (n=58) of the strains studied (Table 2).

The distribution of Enterobacteriaceae stains according to the production of ESBL shows a predominance of *Enterobacter cloacae* strains (75%) despite the low number, followed (75%) despite the low number, followed *Citrobacter freundii* (66.66%), *Escherichia coli* (62.06 %), *Klebsiella pneumoniae* (52.17%), *Proteus mirabilis* (50%) and *Serratia marcescens* (25%) (Table 6).

The production of ESBL enzymes results in the appearance of a synergistic image in the funnel (A) and champagne cork (B) between the AMC discs and the C3Gs (Fig 1).

Most ESBL Enterobacteriaceae strains were isolated from urine 32 (64%), pus samples come second 4 (36.36%) and blood samples take last place 1 (25%) (Table 4).

The prevalence of EBLSE strains was higher in the Metabolic Diseases department (60%), followed by Surgery. The departments of Urology, Cardiology, Internal Medicine (50%), Gastroenterology, and Pediatric Intensive Care took third place and in last place (50%) came Pediatrics (42.85%) (Table 5) Most of the strains were isolated from hospitalized patients (67.56%).

The frequency of ESBL Enterobacteriaceae strains was higher in hospitals (67.56%) than in community settings (32.43%). Even though the difference in ESBL production between the hospital and community environment is not statistically significant with $p\text{-value} > 0.05$ ($p = 0.05$) nevertheless a relatively high risk was observed on their isolation in a hospital environment (RR = 1.10) (Table 6) Of the 37 patients infected with a strain of ESBL Enterobacteriaceae, 20 (54.05) were male and 17 (45.94%) female. The sex ratio was 1.17 and a relative risk less than 37 strains of enterobacteria isolated in this study were found to produce beta-lactamases gene: 97.29% (n = 36) had blaTEM gene and 5.40% (n = 2) had CMY-2 gene.

TEM-type ESBLs were generally found in most of the strains studied. With a prevalence of 55.38% of strains possessing this blaTEM gene (Fig 2). Two strains produced CMY-2 gene (Fig 3). This gene was found only in *Escherichia coli* and most of it was co-expressed with other ESBLs genes.

Sequencing of PCR amplification products blaTEM and after comparison based on NCBI data revealed that: all 36 blaTEM-positive strains were all TEM-1 AAR25033.1.

The multiple alignment of the protein sequences of class A beta-lactamase genes has made it possible to demonstrate the conservation of the sequences presenting the SxxK motifs in ABL positions 71 to 74 for the TEM group (Fig 4). These SxxK motifs represent the catalytic tetrad for these beta-lactamase genes.

The genetic tree (Fig 5) clearly shows the kinship relationships between our TEM beta-lactamase genes (colored in blue) and their counterparts (black). Thus,

representing a monophyletic group or group with common ancestor and all its descendants.

Discussion

This study assessed the antibacterial activity of antibiotics on Enterobacteriaceae. Between May and September 2018; 65 strains of enterobacteria were collected for their resistance to beta-lactams at the Bacteriology and Virology Laboratory of the Brazzaville University Hospital.

These bacteria were isolated from different departments and outpatients from diagnostic samples at the Brazzaville University Hospital.

In our study, Enterobacteriaceae were found in all types of services. However, some specialties appeared to be more concerned, including surgery and urology with 13.84% and 12.30% respectively. These results agree with those of Souna in Algeria who reports surgery as being the specialty most concerned (Souna, 2011).

Of all the isolated Enterobacteriaceae, *Escherichia coli* remains the most frequent species (44.61%), followed by *Klebsiella pneumoniae* (35.38%), as reported by several studies (Messai et al., 2007; Nadmia et al., 2010). While, *Citrobacter freundii* and *Proteus mirabilis* occupy the last place with almost identical isolation rates of 4.61 % and 3.07% respectively. The same classification was reported by Nijssen et al. (2004) (Nijssen et al., 2004) and Souna (2011) but with a last place occupied by *Enterobacter cloacae* and *Proteus mirabilis*.

Also, these species are distributed differently depending on the services and collection sites. Urinary tract infection is a common pathology in everyday practice. The main bacterial species involved in this infection is *Escherichia coli*, since it represents 50 to 80% of the causative agents (Matute et al., 2004). This corresponds to the results obtained in our study with a rate of 76.92%. This is related to the pathophysiology of urinary tract infection, which is generally ascending, and there is a strong colonization of the perineum by Enterobacteria of digestive origin, and *Escherichia coli*. In addition, there are specific uropathogenicity factors.

Thus, *Escherichia coli* has adhesins, capable of binding the bacteria to the urinary epithelium and preventing its elimination. *Klebsiella* and *Proteus* secrete a urease which alkalizes urine whose pH, naturally acidic, prevents the proliferation of germs (Sekhsokh, 2008). Indeed, *Klebsiella pneumoniae* is much more isolated from the respiratory tract (50%) and is the causative agent of pneumonia (Paterson & Bonomo, 2005).

It should also be noted that the *Enterobacter cloacae* strains are essentially isolated from samples of surgical wounds, is 100%; these species often behave as opportunistic pathogens.

Table 1. Primers used for classical PCR and sequencing

Gene	Accession number	Primer	Sequence \rightleftharpoons (5' 3')	Target(s)	Product size (pb)	Reference
TEM	KJ939560.1	Forward	ATGAGTATTCAACATTTCCGTG		861	Souna, 2011
		Reverse	TTACCAATGCTTAATCAGTGAG			
CITM	X78117	Forward	TGGCCAGAAGTGCAGGCAAA	CMY-2	462	
		Reverse	TTTCTCCTGAACGTGGCTGGC			

Table 2. Resistance profile of enterobacterial strains

ATB	<i>E. coli</i> (n=29)		<i>K. pneumoniae</i> (n=23)		<i>Ent. Cloacae</i> (n=4)		<i>C. freundii</i> (n=3)		<i>P. mirabilis</i> (n=2)		<i>S. marcescens</i> (n=4)		TOTAL Resistance
	R	S	R	S	R	S	R	S	R	S	R	S	
	%												
AMX	100		95.65	4.34	100		100		50	50	100		96.92
AMC	89.66	10.34	86.95	13.04	100		100			100	100		87.69
TZP	3.45	96.55	13.04	86.95				100		100		100	6.15
CF	75.85	24.13	69.56	30.43	100		100			100	100		75.38
CRO	44.82	55.17	60.86	39.13	25	100	66.66	33.33		100	25	75	47.69
FEP	27.58	72.42	13.39	82.60			66.66	33.33		100	25	75	23.07
ERT		100	17.38	82.60		75		100		100		100	6.15
IMP		100		100		100		100		100		100	
CS		100		100		100		100	100		100		9.23
AK		100	4.34	95.65		100		100		100		100	1.53
GEN	27.58	72.41	43.47	56.52	25	100	66.66	33.33		100	25	75	33.84
CIP	79.31	20.68	26.08	69.56	25	100	33.33	66.66	50	50	50	100	52.30
FF		100	4.34	95.65		75		100		100		100	1.53
F	10.34	89.65	60.87	39.13	75	75		100	100		75	25	38.46
DO	75.86	24.13	65.21	34.78	50	100	100			100	100	100	67.69
SXT	89.65	10.34	95.65	4.34	50	25	100		50	50	100		89.23

AMX : amoxicillin ; AMC : Amoxicillin/Acid clavulanic; TZP : Piperacillin-Tozobactam ; CF : Cefalotin ; CRO : ceftriaxon ; FEP : Cefipim, ERT : Ertapenem ; IMP : Imipenem ; CS : Colestin ; AK : Amykacin ; GEN : Gentamycin ; CIP: Ciprofloxacin; FF: Fosfomicin ; F : Nitrofurantoin ; DO : Doxycillin ; SXT : Trimethoprim+Sulfaphametaxazol.

Table 3. Distribution of Enterobacteriaceae strains according to ESBL production

Espèce	Entérobactéries		Total
	n (%)		
	EBLSE/CMY-2	E non BLSE	
<i>E. coli</i>	18(62.06)	10 (37.93)	29
<i>K. pneumoniae</i>	12(52.17)	11(47.82)	23
<i>Ent. Cloacae</i>	3(75) *	1 (25)	4
<i>C. freundii</i>	2 (66.66)	1 (33.33)	3
<i>P. mirabilis</i>	1(50)	1 (50)	2
<i>Serratia marcescens</i>	1 (25)	3 (75)	4
Total	37	29	65

$\chi^2= 3.178 \quad p=0.672$

Table 4. Distribution of ESBL Enterobacteriaceae strains by sampling

Samples	Enterobacteriaceae		Total
	n (%)		
	EBLSE/CMY-2	E non BLSE	
Urine	32(64)	18 (36)	50
Blood	1(25)	2(50)	4
Pus	4 (36.36)	3 (27.27)	11
Total	37	23	65

$X^2=0.267$ $p=0.875$

Table 5. Distribution of ESBL Enterobacteriaceae strains according to their departments

Services	Enterobacteria		Total
	n (%)		
	EBLSE	E non BLSE	
External patient	15 (75)	5 (25)	20
Surgery	5(55.55)	4(44.44)	9
Urology	4(50)	4 (50)	8
Pediatrics	3(42.85)	4 (57.14)	7
Cardiology	3(50)	3 (50)	6
Metabolic diseases	3 (60)	2 (40)	5
Infectious diseases	2(50)	2(50)	4
Pediatric intensive care	1(50)	1(50)	2
Rheumatology	-	2	2
Gastroenterology	1(50)	1(50)	2
Total	37	26	65

$X^2= 6.329$ ddl: 9 $p=0.7066$

Table 6. Distribution of ESBL Enterobacteriaceae strains according to their origin

Origin	Enterobacteriaceae		Total
	n (%)		
	EBLSE	E non BLSE	
Hospitable	25(67.56)	18 (64.28)	43
Community	12(32.43)	10(35.71)	22
Total	37	28	65

$X^2=0.0205$; ddL=1; $p=0.886$ RR=1.10

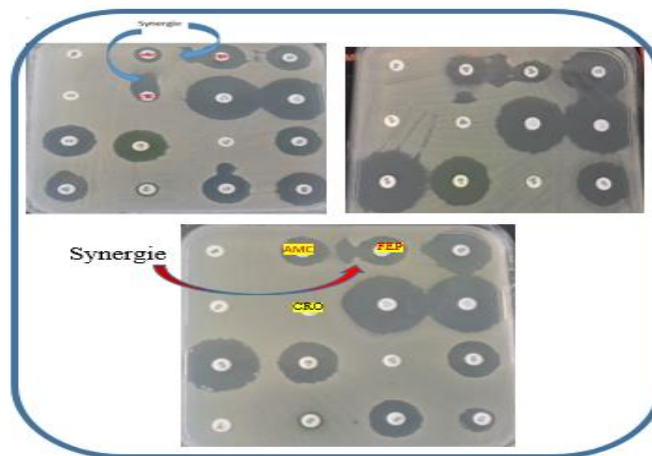


Fig. 1: Synergistic image of *K. pneumoniae* strains

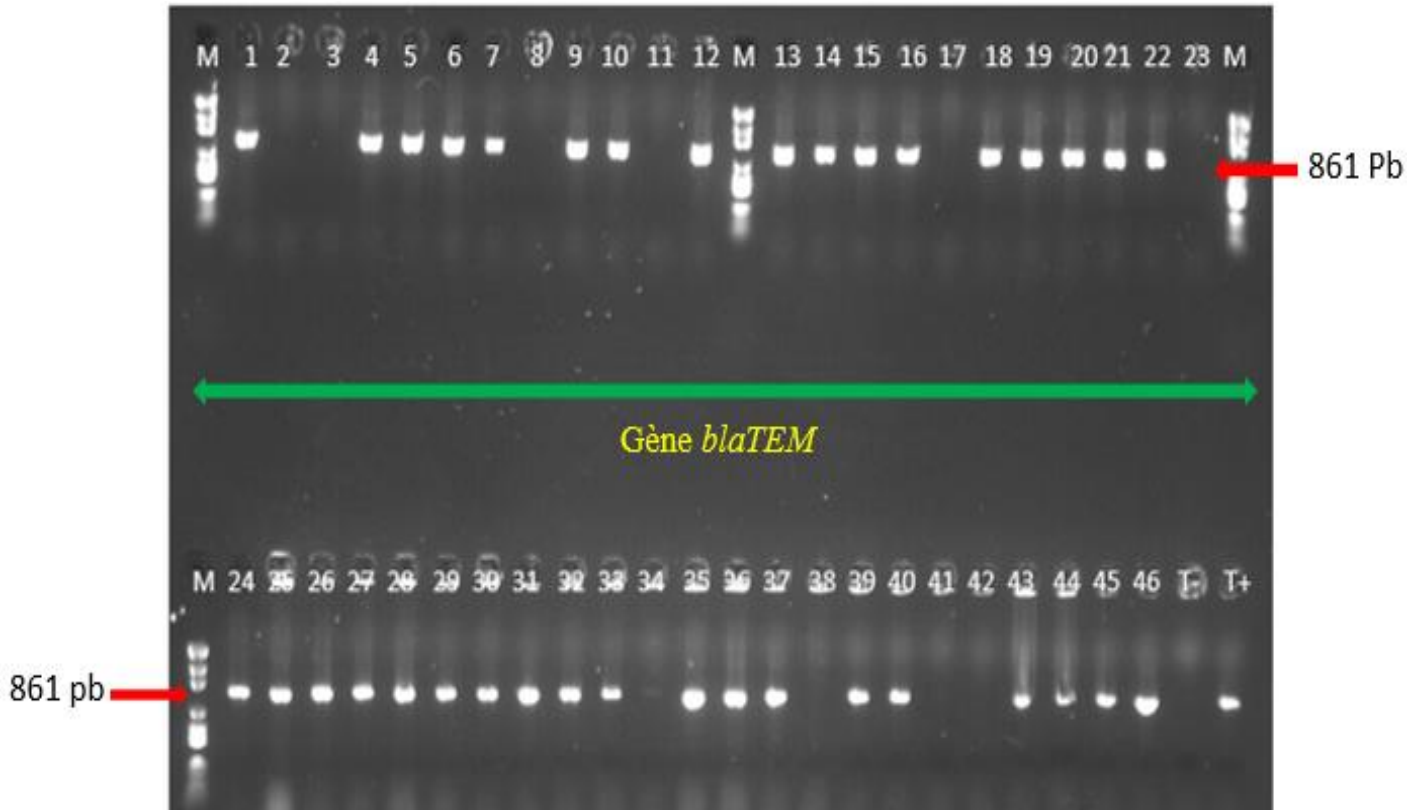


Fig. 2: 1.5% agarose gel electrophoresis of the conventional PCR amplification products of the TEM gene
M : marqueur de poids moléculaire

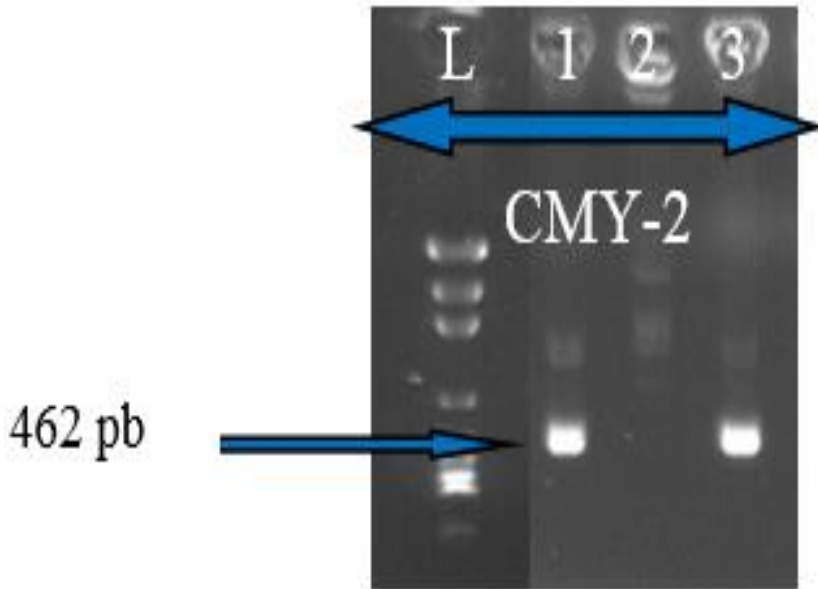


Fig 3: 1.5% agarose gel electrophoresis of the conventional PCR amplification products of the CMY-2 gene

L: Molecular weight marker

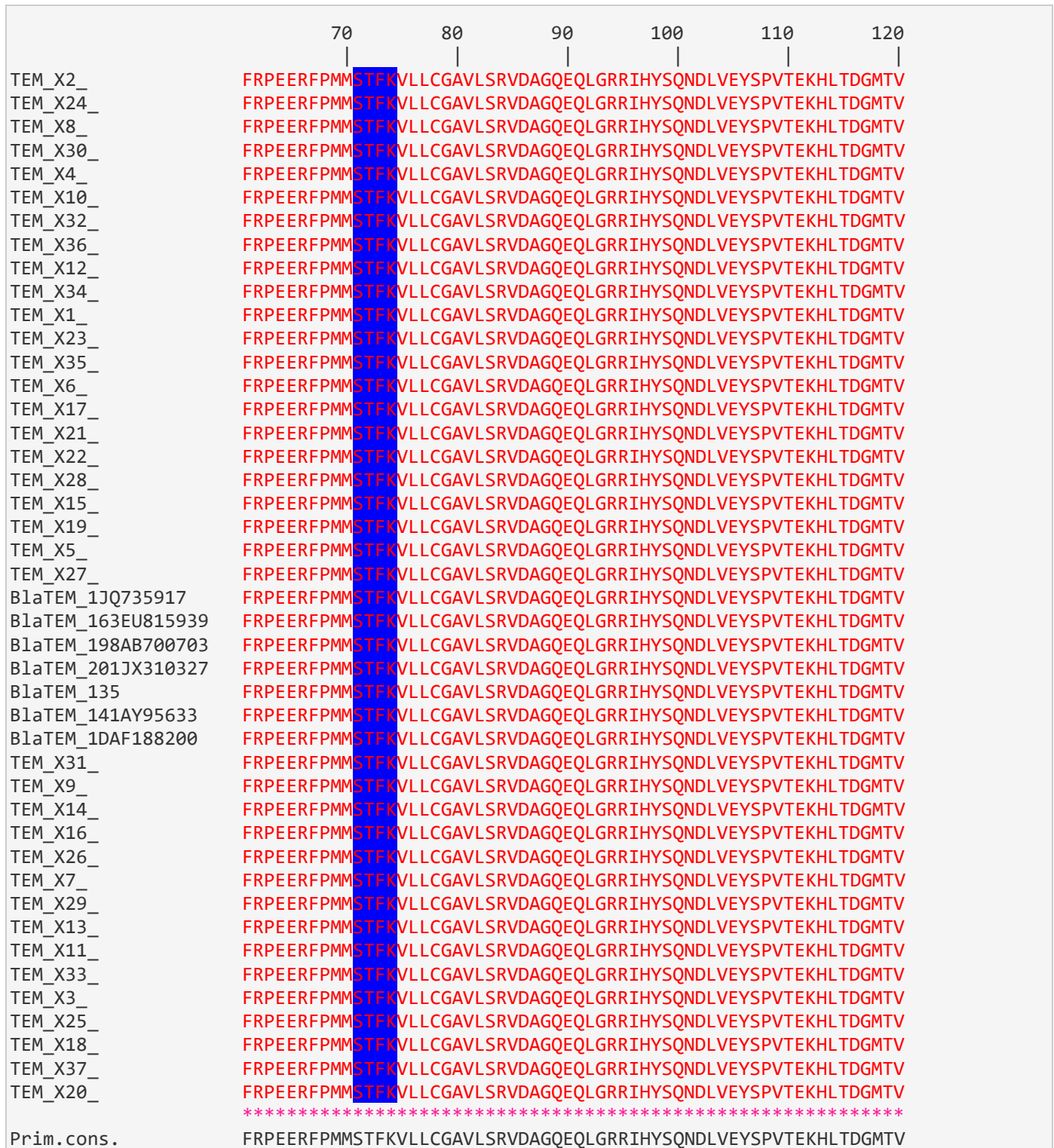


Fig. 4: Multiple alignment of the protein sequences of the blaTEM gene of Enterobacteriaceae strains and their homologues followed by presentation of their active site.

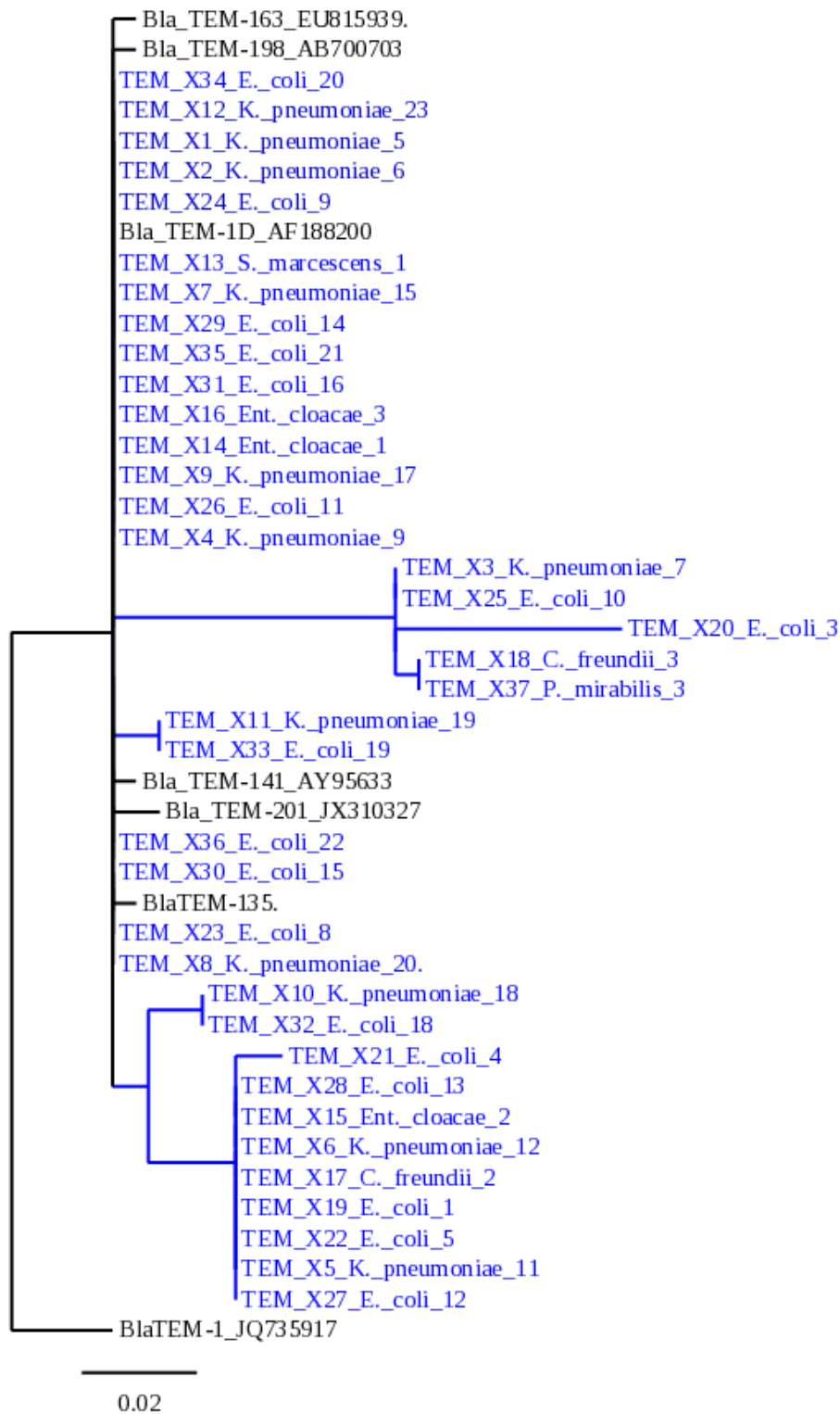


Fig 5: Phylogenetic tree of the *bla*TEM gene

They are then involved in infectious pathologies, in particular in hospitalized individuals (pediatric, psychiatric or intensive care units), immunosuppressed, probed, paraplegic or having urinary tract abnormalities.

Levels of bacterial resistance vary from country to country and from year to year. Also, knowledge of the local situation and its evolution is necessary for the choice of first-line antibiotic therapy (Paterson and Bonomo, 2005). Indeed, our results show a considerable resistance rate to most of the antibiotics tested. Enterobacteriaceae resistant to 3rd generation cephalosporins (C3G) occupy an important place in nosocomial infections, particularly in intensive care settings. These bacteria are becoming increasingly resistant to antibiotics and are beginning to cross hospital boundaries to emerge into the community. The dissemination of these bacteria presents a serious threat that calls into question the validity of the currently available antibiotic arsenal, especially since no new class of antibiotic is expected in the coming years (Mkaouar et al., 2008). The study of the sensitivity of Enterobacteriaceae to C3G, showed average rates of acquired resistance in hospital.

The resistance levels are considered lower than those observed at the Tlemcen University Hospital (Mkaouar et al., 2008).

However, our results are, on the other hand, higher than those reported in Algeria (Amazian et al., 2006), and in some Asian countries (India and China) (Hirakata et al., 2005)

For more than 20 years, the resistance of enterobacteria to cephalosporins 3rd generation (C3G) continues to strengthen, particularly through the acquisition of extended-spectrum beta-lactamases (ESBL) (Belmonte et al., 2010). Thus 56.92% of the studied strains are producers of extended-spectrum beta-lactamases (ESBL). This value is clearly lower than that found in Tlemcen (Souana, 2011) and in Egypt (38.5%) but very much higher than that reported in France (+5.2%), Germany (2.6%) and Holland (2%) (Bouchillon et al., 2004). Also, the coexistence of different beta-lactamases in the same bacterium can pose a problem of diagnosis and therapy. These associations lead to a co-selection of resistance genes and a pandemic scenario in the hospital and in the community (Meradi et al., 2011).

However, we note that the number of ESBL-producing strains is greater in *Enterobacter cloacae* at 75% which is in disagreement with the results obtained by Sekhsokh (2008) and by Edelstein et al. (2003) Edelstein, 2003).

Escherichia coli comes in second with 62.06%. This rate is higher than that reported (43.33%) and much higher than that of Souana (2011).

We should also note an ESBL production rate of 52.17% for strains of *Klebsiella pneumoniae* which is higher compared to the results obtained in Algeria (30%).

The rate of production of plasmid cephalosporinase was 5.40%. Our results agree with those of Souana (2011) (4.3%). Note also an ESBL production rate of 18.5% for the *Proteus spp.* higher compared to the results obtained in Italy (8.8 to 10%) (Pagani et al., 2003) and in France (10.2%) (Mahamat et al., 2006). The results reveal a low frequency of the ESBL phenotype in *Escherichia coli* (15.4%) unlike several studies carried out by Leotard and Negrin (2010). The rate of high-level acquired penicillinase production is 25%, of which nearly 11.4% was not recovered by tazobactam and the wild-type phenotype concerned 33.6% of the isolates.

The isolation rate of strains with the ESBL phenotype is higher in metabolic diseases (60%) than in surgery (55.55%), or other reported services. This is certainly linked to the excessive or even massive use of antibiotics in this department thanks to recurrent infections in diabetics. Thus, the wide use of 3rd generation cephalosporins (C3G) has resulted in the development of resistant enterobacteria by the production of extended-spectrum beta-lactamases (ESBL), the production of such an enzyme allows the bacteria to resist all beta-lactams except cephamycins and imipenem (Souana, 2011).

In addition, the problem associated with ESBLs is above all the frequent presence of co-resistances making the strains multi-resistant (Spanu et al., 2002). Indeed, ESBLs are generally carried by large plasmids which also carry genes for resistance to classes of non-beta-lactams antibiotics, such as aminoglycosides, quinolones, and trimethoprim/sulfamethoxazole. Also, the use of these antibiotics contributes to the selection of ESBL-producing strains (Paterson and Bonomo, 2005). The incidence of the emergence of resistance to aminoglycosides has increased in recent years, particularly in ESBL-producing strains (Spanu et al., 2002). The resistance levels of these strains in our study is more important. Amikacin remains the most effective molecule with 98.47% of sensitive strains as reported in several studies (Gangoue, 2007; Wu, 2007). Quinolones show moderate activity, with the overall sensitivity of the strains dropping considerably in the case of ESBL-producing strains. For the majority of strains, acquired resistance is the consequence of a mutation, which limits its spread (Larabi et al., 2003).

A very weak activity is detected for trimethoprim / sulfamethoxazole with 10.77% of susceptible strains. This trimethoprim / sulfamethoxazole resistance rate (89.23%) remains higher than that described in the literature by several studies (Ammari and Bellouni, 2001; Guneyssel, 2009)

As for colistin, it is one of the molecules keeping the highest sensitivity rates on naturally sensitive species (apart from *Proteus* and *Serratia*). This is probably linked to a lower use of this antibiotic in current practice (Souana, 2011).

Carbapenems are the treatments of choice for severe infections caused by ESBL-producing enterobacteria

(Ouédraogo et al., 2016). The resistance of Enterobacteria to these molecules is still a marginal phenomenon as evidenced by the epidemiological data obtained for many strains, with sensitivity percentages of 99-100% (Munoz-Price et al., 2013).

In our study, 6.15% of the strains showed resistance to ertapenem and 100% of the strains were susceptible to imipenem. This decrease in sensitivity for ertapenem observed in *Klebsiella pneumoniae* strains could be the result of a modification of porins, associated with the production of β -lactamases of the type OXA-48 or AmpC, thus reducing the permeability of the membrane external (Bonnet et al., 2000).

Of most concern is the production of carbapenems since the activity of carbapenems can be compromised by the emergence of these enzymes (Facult et al., 2017) (Pasteran et al., 2005).

In the January 2008 edition of the CLSI M100 document (Clinical and Laboratory Standards Institute, 2008), an article included an alert to laboratories to monitor and search for any production of carbapenemase in Enterobacteriaceae with MICs of 2 or 4 $\mu\text{g} / \text{ml}$ (Munoz-Price et al., 2013). Phenotypic methods, which can be combined, have the advantage of being easy to perform. They make it possible to demonstrate resistance to carbapenems without precisely identifying the mechanism. Confirmation of the presence of these genes can currently only be done using molecular tools (Cuzon, Naas, and Nordmann, 2010). The treatment of infections caused by enterobacteriaceae resistant to carbapenems is indeed difficult, the therapeutic choices against this type of germs are limited. To avoid these epidemics, strict monitoring of resistance and antibiotic consumption in hospitals should be carried out (Wu et al. 2007).

Conclusion

Enterobacteriaceae producing an ESBL are still a topical issue in healthcare structures, despite the measures to prevent their spread, which are now well codified in some countries. We rather observe an increase in their number with CTX-M type ESBLs while the “older” ESBLs of the TEM or VHS family seem to be decreasing.

Congo Brazzaville, like the rest of the world, faces a serious problem of emerging resistance to antibiotics. Several factors including the health status and the level of education of the populations, the level of training of prescribers, the infrastructures and the quality of the antibiotics dispensed favor their emergence and their spread.

Prevalence and genetic studies provide fundamental information for the epidemiology of BMR, an essential basis for understanding the fight and control of these resistant pathogenic organisms. This monitoring must be generalized and must be an integral part of the fight against multi-resistant bacteria in all the most important health centers in the Republic of Congo.

Conflict of Interest

The author hereby declares no conflict of interest.

Consent for publication

The author declares that the work has consent for publication.

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