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GENOTYPIC RESISTANCE PROFILE OF *ESCHERICHIA COLI* PRODUCING EXTENDED-SPECTRUM BÊTA-LACTAMASE (ESBL) ISOLATED FROM PIGLETS IN ABIDJAN (CÔTE D'IVOIRE)

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Abstract – ESBL-producing bacteria are a major concern in animal and human health. In livestock, these bacteria have emerged because of the overuse of antibiotics. This study aims to evaluatethe genotypic resistance profile of *Escherichia coli* ESBL-producing isolated from weaned piglets stools in Abidjan. *Escherichia coli* were isolated on Mac Conkey medium from 40 stools samples obtained from a farm in Adiopodoumé locality. Then, antibiotic susceptibility test was performed using disk diffusion methodon Müller-Hinton agar to screen ESBL-producing *Escherichia coli*. In order to spot β-lactamase genes (bla_{TEM}, bla_{SHV}, and bla_{CTX-M}), polymerase chain reaction was conducted. Antibiotic susceptibility test reveals that 58 of 330 strains isolatedare ESBL-producing (17.5%). All of these strains were resistant to tetracycline, amoxicillin and piperacillin and all were sensitive to imipenem and colistin. *Escherichia coli* producing-ESBL also showed relatively high levels of resistance to nalidixic acid (58.7%), sulfamethoxazole-trimethoprim (56.9%) and ciprofloxacin (41.4%). The findings obtained from simplex PCR assay showed that out of collected strains of ESBL-producing *Escherichia coli*, had 70.7% bla_{TEM}, 20.7% bla_{CTX-M} and 48.3% bla_{SHV} genes. TEM prevalence was high among other types of ESBLs. *Escherichia coli* ESBL-producing of swine origin could be released into environment and cause public health concerns. It is therefore necessary to set up surveillance plan of ESBL in pig farm.

INTRODUCTION

Infectious digestive diseases in weaning piglets are responsible for high mortality rates in pig farms and antibiotic therapy seems to be the only way to fight these diseases (Biagui, 2002). Antibiotics are therefore necessary and effective tools to control swine bacterial diseases (Klopfenstein, 2004). In farms, various treatment modalities are encountered, namely use as curative, metaphylactic, prophylactic and growth promoters (Schwarz and Chaslus-Dancla, 2001). In Côte d'Ivoire,in Bingerville city, 98.8% of pig breeding use antibiotics either for prevention (64.7% of farms) or for the treatment of bacterial diseases (36.3% of farms), sometimes without prescription (Kili, 2016). However, the use of these molecules creates a selection pressure that promotes the survival of resistant bacteria in animal's intestinal microbiota. These bacteria are likely to exchange many resistance genes with each other, sometimes leading to appearance of other multi-resistant bacteria (Sorum and Sunde, 2001; Schwarz and Chaslus-Dancla, 2001; Campagnolo *et al.*, 2002). Antibiotic-resistant bacteria of animal origin can be transmitted to human through ingestion of

contaminated food, direct contact with animals or their environment (Barton, 2000). This antibiotic resistance is a major issue not only for animal health but also for human health. Indeed, human and animal sharing the same environment and antibiotics, human health and animal health are interconnected with the health of ecosystems in which they coexist under "One Health" approach (Chardon and Brugère, 2014). Then, many pathogenic bacteria are common to both humans and animals, and the same families of antibiotics are therefore used in both veterinary and human medicine (Sanders, 2005). Among multi-resistant bacteria, Extended-Spectrum Beta-Lactamase-producing *Enterobacteriaceae* (ESBL) infections are a major public health concern due to therapeutic impasses (Rodriguez *et al.*, 2006). ESBL are enzymes capable of hydrolysing the β-lactam nucleus of β-lactam antibiotics with exception of carbapenems and cephamycins (Bradford, 2001). There are distributed in Enterobacteriaceae, particularly in *Escherichia coli*, and the rapid emergence and spread of ESBL-producing *Escherichia coli* have been reported in food animals globally (Smet *et al.*, 2010). Plasmid transmission of resistance between bacterial species is responsible for its dissemination (Fouquet, 2012; Madec, 2012; Teuber, 2001). Resistance genes from these ESBL-producing bacteria have ability to spread very rapidly between bacteria and be transferred to commensal or pathogenic bacteria (Leclercq, 2010; Madec *et al.*, 2012). The majority of ESBLs are bla_{TEM}, bla_{SHV}, and $bla_{CTX\text{-}M}$types (Bush and Jacoby, 2010) and the production of ESBLs is mainly plasmid mediated, and such plasmids often carry genes that encode resistance to other classes of antimicrobials, such as fluoroquinolones and amino-glycosides (Pitout and Lauplant, 2008). The objective of this study is to determine the prevalence of bla_{TEM}, bla_{SHV}, and $bla_{CTX\text{-}M}$ genes from ESBL-producing strains of *Escherichia coli* isolated from piglet faeces.

Sample collection

A total of 40 samples of faeces from recently weaned piglets were collected from a semi-intensivefarm in the locality of Adiopodoumé in Côte d'Ivoire.

Isolation and identification of *Escherichia coli* from feaces

Five (5) g of each faeces sample from piglets were collected, emulsified in 45 mL of buffered peptone water and the mixture was homogenized with a vortex. Series of decimal dilutions were performed, then 100 µL of each sample dilutions were smeared on Mac Conkey agar (Bio-Rad, Marne la Coquette, France). The petri dishes were incubated at 37 °C for 24 hours. Presumptive colonies of *Escherichia coli* that appeared were transplanted into rapid *E. coli* 2 (REC2) medium and confirmed from morphological and biochemical characteristics.

Antibiotic susceptibility test of *Escherichia coli*

Antibiotic susceptibility test was carried out on *Escherichia coli* strains by Müller-Hinton agar diffusion method according to Antibiogram Committee of French Society of Microbiology (CA-SFM veterinary, 2017). Antibiotics discs tested were: Amoxicillin (25 µg), Amoxicillin + clavulanic acid (20/10 µg), Cefotaxime (30 µg), Ceftazidime (30g), Ciprofloxacin (5 µg), Aztreonam (30 µg), Nalidixic Acid (30 µg), Piperacillin, Tetracycline (30 µg), Trimethoprim/sulfamethoxazole (1.25 / 23.75 µg), Chloramphenicol (30 µg), Imipenem, Colistin (50 µg). The reference strain *Escherichia coli* ATCC 25922 was used as control.

ESBL-production

ESBL phenotypic *Escherichia coli* strains detected after antibiotic susceptibility test were confirmed by double disc synergy test using Cefotaxime (30g), Ceftazidime (30g) and Aztreonam (30 µg) placed at 30 mm distances with Amoxicillin / Clavulanic Acid (20/10 µg) placed in the center. ESBL production was detected when synergy was observed between cephalosporin inhibition zone and amoxicillin / clavulanic acid.

Detection of resistance genes encoding ESBL production from *Escherichia coli*

Escherichia coli producing broad spectrum bêta-lactamases were selected for the genotypic study.

The detection of bla_{TEM}, $bla_{CTX\text{-}M}$, bla_{SHV} resistance genes using PCR method was performed after extraction of total DNA by thermal shock technique. Genetic profiles of *Escherichia coli* resistance and positive control strains (Table 1) was done using simplex PCR method. The final volume of the reaction mixture was 50 µL and the composition was distributed as follows: 5µL of coloured buffer (5X Green GoTaq®), 5µL of uncoloured buffer (5X Colorless GoTaq®), 30.3 µL of ultrapure water (Nuclease-Free Water, Promega, USA), 3µL of MgCl2 (25 mM), 0.5 µL of DNTP (10 mM), 0.5 µL of the forward primer (20 mM), 0.5 µL of the reverse

Table 1. Control strains used for PCR Validation

Bacteria	Number	Positive control	Origin
Salmonella spp	U2A1446	*Bla* $_{TEM}$ and *Bla* $_{SHV}$	Institut Pasteur Paris
E. coli	U2A1790	*Bla* $_{CTX-M}$	

primer (20mM) (Table 2), 0.2 µL of Taq polymerase (GoTaq®, Promega) and 5 µL of the DNA to be amplified. Reactions without DNA were considered as negative controls.

Amplification was performed in thermocycler (GeneAmp PCR System 9700, Applied Biosystems). The following amplification protocol was use for bla_{SHV} *and* bla_{CTX-M} : initial denaturation 94°C for 1 min, Cyclic denaturation 94 °C for 1 min, Annealing 60 °C for 1 min, Cyclic elongation 72 °C for 1 min, Final elongation 72 °C for 7 min and 30 cycles. Then, protocol used for bla_{TEM} was : initial denaturation 94 °C for 1 min, Cyclic denaturation 94 °C for 1 min, Annealing 50 °C for 1 min, Cyclic elongation 72 °C for 1 min, Final elongation 72 °C for 7 min and 30 cycles (Guessennd *et al.,* 2008).

PCR conditions for the detection of bla_{TEM}, bla_{CTX-M}, bla_{SHV} gene were carried out in a thermalcycler and the revelation of amplification products was performed by electrophoresis with 1.5% agarose gel. Once migration completed, the gel has been placed in a computer machine with Gel Doc EZ Imager (BioRad) for viewing the bands. The presence of bands corresponding to the amplified fragment was compared with molecular marker size and that of the positive controls. The lack of tape was considered as negative result.

RESULTS

Detection of ESBL-producing *Escherichia coli*

A total of 58 strains of *Escherichia coli* were detected producing Extended Spectrum Beta Lactamase (ESBL) out of 330 strains isolated from porcine digestive microbiota with a prevalence of 17.5%.

Cross resistance of ESBL producing strains with other antibiotics

Cross resistance rates of ESBL-producing strains are shown in Table 3. All *Escherichia coli* ESBL-producing were sensitive to imipenem and colistin. However, they were resistant to tetracycline with proportions of 100%. It should be noted that these strains had relatively high resistance rates to fluoroquinolones such as nalidixic acid and ciprofloxacin with resistance rates of 58.7% and 41.4% respectively.

Electrophoretic profile of beta-lactam resistance genes

The electrophoretic profile of amplification products of bla_{CTX-M} gene is shown in Figure 1 with positive bands (863 base pairs).

The electrophoretic profile of amplification products of bla_{SHV} gene is shown in Figure 2 with positive (bands 392 base pairs).

The electrophoretic profile of amplification products of bla_{TEM} gene is shown in Figure 3 with positive (bands 465 base pairs).

Frequency of detection of genes encoding ESBL-Production

The frequencies of resistance genes were 70.7%, 20.7% and 48.3% respectively for bla_{TEM}, bla_{CTX-M} and bla_{SHV} genes.

DISCUSSION

The occurrence of ESBL-producing *Escherichia coli* in food animals has been increasing around the world (Seiffert *et al.,* 2013). The results of this study show that 17.5% of *Escherichia coli* strains isolated from

Table 2. List of specific primers used

Gène	Amorce[a]	Séquence (5'->3')	Taille du produit PCR (pb)	Références
bla_{TEM}	TEM-F	TTGGGTGCACGAGTGGGTTA	465	Bajpai *et al.,* 2017
	TEM-R	TAATTGTTGCCGGGAAGCTA		
bla_{SHV}	SHV-F	AGGATTGACTGCCTTTTTG	392	Bajpai *et al.,* 2017
	SHV-R	ATTTGCTGATTTCGCTCG		
bla_{CTX-M}	CTX-M1-F	GGTTAAAAAATCACTGCGTC	863	Alouache *et al.,* 2012
	CTX-M1-R	TTGGTGACGATTTTAGCCGC		

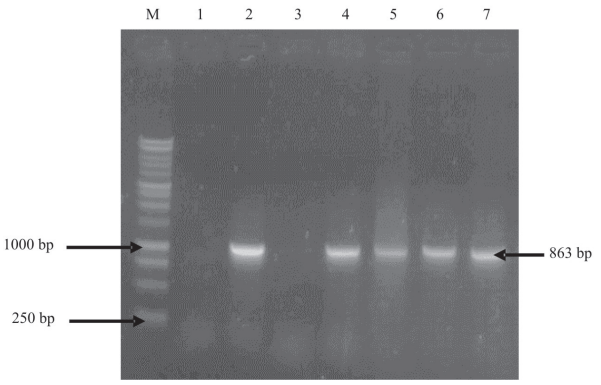

Fig. 1. Electrophoretic profile of bla_{CTX-M}(863 bp) gene amplification product
Lane M : Molecular weight marker (Invitrogen, 250 bp DNA Ladder); Lane 1 : Negative control ; Lane 2 : Positive control bla_{CTX-M}(863bp); Lane 4, 5, 6 and 7: Reference of strains analyzed harboring bla_{CTX-M}genes.

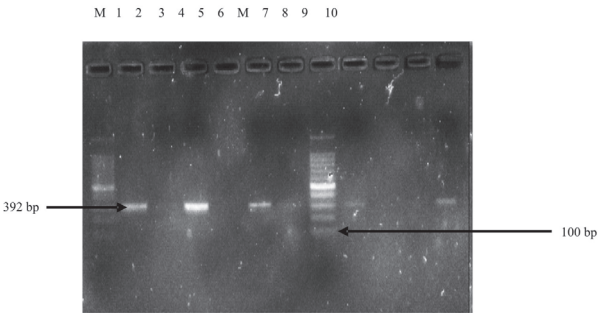

Fig. 2. Electrophoretic profile of bla_{SHV}(392 bp) gene amplification product
Lane M : Molecular weight marker (Invitrogen, 100 bp DNA Ladder);
Lane 2 : Negative control; Lane 1 : Positive control bla_{SHV} (392 bp);
Lane 3, 5, 7 and 10 : Reference of strains analyzed harboring bla_{SHV} genes.

Table 3. Cross resistance rates of *Escherichia coli* ESBL-producing

Antibiotics	Number of ESBL producing strains	Prevalence (%)
Tetracycline	58	100
Piperacillin	58	100
Amoxicillin	58	100
Nalidixic acid	34	58.7
Trimethoprim/ sulfamethoxazole	33	56.9
Ciprofloxacine	24	41.4
Chloramphenicol	2	3.4
Colistine	0	0
Imipenem	0	0

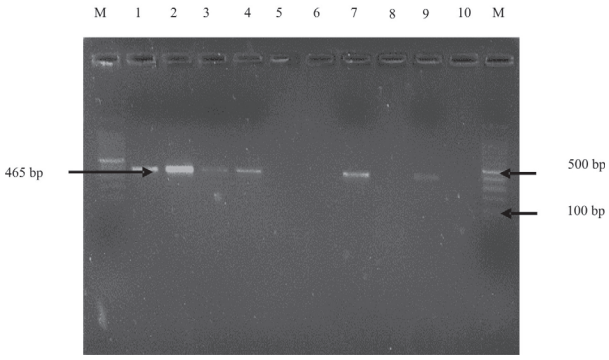

Fig. 3. Electrophoretic profile of bla_{TEM} (465 bp) gene amplification product
Lane M : Molecular weight marker (Invitrogen, 100 bp DNA Ladder);
Lane 10: Negative control ; Lane 9 : Positive control bla_{TEM} (465 bp);
Lane 1, 2, 3, 4 and 7: Reference of strains analyzed harboring bla_{TEM} genes

healthy, recently weaned piglets were ESBL-producing. This relatively high rate in these healthy animalscould be explained by their contamination with faecal flora bacteria of their mother. Antibiotic resistant bacteria could be excreted by sow via faeces, leading to contamination piglets environment before weaning. The presence of ESBL-producing *Escherichia coli* in the fecal flora of food-producing animals is worrisome. Indeed, transmission between livestock is plausible, as animals are usually housed together in groups where frequent contact with other group members, as well as with the shared environment (e.g. faecal matter) occurs. In addition, these multi-resistant bacteria are likely to be transmitted to humans through the consumption of contaminated food such as meat, meat products and vegetables. This results are similar to those observed by in Taiwan by Lee and Yeh (2017). The study conducted by their authors showed 19.7% of ESBL–producing *Escherichia coli* in diarrheal piglets. However, a study conducted by Koudio *et al.* (2017) in Côte d'Ivoire showed hight prevalence (35%) of ESBL-producing *Escherichia coli* in recently weaned piglets administered with Amoxicillin. This relatively high rate of ESBL-producing strains in the work of these authors could be explained by the administration of Amoxicillin to these piglets for 5 days to these healthy piglets. Note that the misuse of antibiotics is the most important risk factor in bacterial resistance development according to Rubin and Samore (2002). Then more than 40% of the ESBL-producing

Escherichia coli were detected from piglets with post-weaning diarrhea in Heilongjiang Province, China (Xu *et al.,* 2015).

Escherichia coli strains ESBL-producing have associated other resistances and particularly resistance to fluoroquinolones (Ciprofloxacin 41.4%, and Nalidixic acid 58.7%) and Sulfamethoxazole-trimethoprim (56.9%). These results are similar to those of Ouattara *et al.* (2014) who observed prevalence rates of 55.3% and 44.7% respectively for nalidixic acid and ciprofloxacin in enterobacterial strains isolated from pigs stools. On the other hand, all strains were resistant to tetracycline, piperacillin and amoxicillin. The resistance levels of these strains are globally high compared to antibiotics widely used in swine production such as amoxicillin or tetracyclines (Gay *et al.,* 2010). In this study, imipenem and colistin maintained excellent antimicrobial activity against ESBL-producing *Escherichia coli*. These results are similar to those of Arsalane *et al.* (2010) who reported that all isolated ESBL strains during their study in a multipurpose intensive care unit of university hospital in Marrakech (Morocco) were all susceptible to colistin and carbapenems (imipenem, ertapenem). The problem related to ESBL is mainly frequent presence of co-resistance to aminoglycosides and quinolones, making the strains multi-resistant to several families of antibiotics (Nseir *et al.,* 2011). Indeed, resistance genes to different families of antibiotics are sometimes present on the same plasmid, thus representing a mode of effective diffusion of several simultaneously mechanisms of resistance.

In Enterobacteriaceae, ESBLs are generally encoded by plasmid-located genes. The most common ESBL-gene families are bla_{TEM}, bla_{SHV}, bla_{CTX-M}observed in this study in the proportions of 70.7%, 20.7% and 48.3% respectively. The bla_{CTX-M} genes constitute the majority of ESBLs in all regions of the world, to the extent that they are described as pandemic (Ruppé, 2010). A study carried out by Padamini *et al.* (2008) in southern India also reported that bla_{CTX-M} genes were the predominant ESBL genes. However, in our study, the predominantly isolated genes were $bla_{TEM.}$ The predominance of these genes over bla_{SHV} and bla_{CTX-M} genes in this study could be explained by the massive use of penicillins in pig farming in Côte d'Ivoire compared to cephalosporins. Similar results have been reported by Kouadio *et al.* (2017) in their study on genetic supports characterization for betalactamase resistance in *Escherichia coli* strains producing extended-spectrum bêta-lactamase (ESBL) in pig farming, in which they obtained a majority of bla_{TEM} genes (51%). According to these authors, the low prevalence of bla_{CTX-M} genes (31%) observed in their study could also be attributed to the low use of third-generation cephalosporins compared with other antibiotics in pig farms in Côte d'Ivoire. The prevalence of resistance phenotypes is most often a loyal reflection of antibiotic prescription habits (Bertrand *et al.,* 2003). The bla_{SHV} genes were detected with a relatively high frequency of 48.3%. These enzymes produced by *Escherichia coli* induce resistance to penicillins, cephalosporins and monobactams.

CONCLUSION

Antibiotic resistance is a global public health challenge with severe health and socio-economics repercussions that is significantly influenced by antibiotic use in food animals. This study revealed high prevalence of resistance of *Escherichia coli* strains producing ESBL, to tetracycline, penicillins and fluoroquinolones. Genotypic profiles responsible search for these resistances revealed the presence of bla_{TEM}, bla_{CTX-M} and bla_{SHV} with high prevalence for bla_{TEM}genes. These resistance genes sometimes present on plasmids are likely to be transferred to commensal or pathogenic bacteria from porcine microbiota or even to humans and lead to therapeutic deadlocks. To control the bacteria producing ESBL in pigs, hygiene measures and rules of good use of antibiotics are necessary to limit the selection of these multi-resistant bacteria and their dissemination.

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