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Description of carbapenemase variants type OXA-181 and NDM-5 in clinical isolates of Enterobacteria in Senegal

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Antibiotic resistance is a global scourge. Carbapenems are one remedy for treating infections caused by extended-spectrum beta-lactamases (ESBL)-producing enterobacterales. Unfortunately, carbapenemase-producing enterobacterales (EPC) are emerging. In Senegal, the epidemiology of carbapenem resistance genes needs to be updated. From January 2019 to July 2022, 240 enterobacteria were selected from Fann Hospital (Dakar) and Paix Hospital in Ziguinchor (southern Senegal). Identification was performed by MALDI-TOF mass spectrometry, and susceptibility testing by agar diffusion. Carbapenem resistance genes were identified by RT-PCR and standard PCR, and sequenced using the Sanger method. The *bla*$_{OXA-48}$ and *bla*$_{NDM}$ genes were found in 25 isolates (13 strains with *bla*$_{OXA-48}$ and 14 strains with *bla*$_{NDM}$), including two isolates (*K. pneumoniae* and *E. cloacae*) in which both genes coexisted. Sequence analysis shows a predominance of *bla*$_{OXA-181}$ (36%) and *bla*$_{NDM-5}$ (32%) variants. a new epidemiological aspect of resistance in enterobacterial isolates was noted. This involves the "discovery" of NDM-type carbapenemases with the *bla*$_{NDM-5}$ variant, and the "persistence" of OXA-48 and its *bla*$_{OXA-181}$ variant. A surveillance system is urgently needed to prevent the spread of EPCs.

Key words: Enterobacterales, carbapenemases, variants, *bla*$_{NDM-5}$, *bla*$_{OXA-181}$, Senegal.

INTRODUCTION

Antibiotic resistance in bacteria, and particularly in enterobacteria to betalactam antibiotics, continues to emerge worldwide (Robin et al., 2012). The problem of this resistance is currently worrying, as it affects carbapenems (Nordmann et al., 2012). These are molecules of last resort for treating infections caused by

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ESBL-producing Enterobacteriaceae. The treatment of Carbapenemase-Producing Enterobacteriaceae (CPE) infections is sometimes difficult, due to associated resistance to other antibiotics (aminoglycosides, fluoroquinolones, etc.), leading to a therapeutic impasse (Nordmann et al., 2012, 2011). In Senegal, the introduction of imipenem in 2008 was followed shortly afterwards by the description of the first carbapenemase genes (Moquet et al., 2011; Diene et al., 2013; Seynabou et al., 2018). However, epidemiological studies are few and far between and need to be strengthened and updated (Moquet et al., 2011; Diene et al., 2013; Seynabou et al., 2018). The main mechanism of carbapenem resistance in enterobacterales is enzymatic inactivation by carbapenemases; encoded by plasmids that are transferable from one bacterial species to another; at the origin of the emergence of resistance (Harbottle et al., 2006; Paterson and Bonomo, 2005). The carbapenemase genes and variants described in enterobacteria are essentially KPC, metallo-betalactamases and OXA-48 type oxacillinases (Nordmann et al., 2012, 2011; Schwaber and Carmeli, 2008). The *bla*$_{OXA-48}$ gene is the most common carbapenemase gene found in Enterobacteriaceae, and has emerged worldwide (Nordmann, 2014; Carrër et al., 2008). This gene was the first described in Senegal in 2008 in enterobacteria and the bacterial species *Acinetobacter baumannii* (Moquet et al., 2011; Diene et al., 2013; Seynabou et al., 2018). In West and East Africa, published clinical studies on EPC epidemiology have identified carbapenemase genes in Cameroon (*bla*$_{NDM-4}$), Kenya (*bla*$_{NDM-1}$), Sierra Leone (*bla*$_{VIM}$ and *bla*$_{DIM-1}$), Senegal (*bla*$_{OXA-48}$) and Tanzania (*bla*$_{KPC}$, *bla*$_{IMP}$, *bla*$_{OXA-48}$, *bla*$_{VIM}$ and *bla*$_{NDM}$) (Manenzhe et al., 2015). The emergence of NDM-type carbapenemases in Senegal and Africa has recently been reported in *A. baumannii* strains (Manenzhe et al., 2015; Camara et al., 2022).

The aim of this study was to review the epidemiology of carbapenemase genes in enterobacteria and to describe their variants.

MATERIALS AND METHODS

Selection, identification and antibiotic susceptibility

This is a retrospective study which took place between January 2019 and July 2022. 240 enterobacteria were selected at Fann Hospital in Dakar (western Senegal) and Paix Hospital in Ziguinchor (Southern Senegal). These were resistant or dose-dependent (intermediate) to C3G (ceftriaxone, ceftazidime) and/or imipenem at the time of the first antibiotic susceptibility test. A new identification was made by Matrix Assisted Laser Desorption Ionisation/Time Of Flight (MALDI/TOF), Bruker Daltonik, Bremen, Germany (Seng et al., 2009). An antibiogram was again performed using the agar diffusion method in accordance with the EUCAST 2022 recommendations (EUCAST, 2022). The minimum inhibitory concentration (MICs) of imipenem- and ertapenem-resistant strains were determined using the E-test method (BioMérieux, Marcy l'Etoile, France). The ß-CARBA test (Biorad, Hercules, CA, USA) was used to identify strains with carbapenemase activity. Isolates were obtained from hospitalized patients or from patients who had undergone a bacteriological check-up. At Fann hospital, the samples came from the neurology, neurosurgery, infectious diseases and otorhinolaryngology departments, while at Paix hospital in Ziguinchor, the originating departments were urology, infectious diseases, otorhinolaryngology and pediatrics.

Detection of carbapenemase genes

Bacterial DNA was extracted by heat shock (Dashti et al., 2009). Real-time Polymerase Chain Reaction (RT-PCR) and standard PCR were performed to detect carbapenemase genes (*bla*$_{OXA-23}$, *bla*$_{OXA-24}$, *bla*$_{OXA-48}$, *bla*$_{OXA-58}$, *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{VIM}$ and *bla*$_{IMP}$) (Poirel et al., 2004; Hou and Yang, 2015; Cicek et al., 2014). RT-PCR conditions were as follows: 50°C for 2 min; 95°C for 15 min; 95°C for 1 s; 60°C for 30 s ×35 cycles; 45°C for 30 s. Standard PCR was performed only for the *bla*$_{IMP}$ gene under the following conditions: 50°C for 2 min; 96°C for 15 min; 94°C for 1 min; 55°C for 50 s; 72°C for 2 min ×35 cycles; 72°C for 7 min; 15°C.

Sequencing

PCR products were purified and BigDye PCR was performed using the same primers. For each sample, the primers (Forward and Reverse) were used differently in two reactions. The reaction medium for BigDye PCR consisted of 3.5 µl BigDye buffer, 3 µl BigDye, 0.5 µl for each primer, 3 µl DNA and 10 µl DNase-free water for a final volume of 20 µl. The BigDye PCR protocol comprises the following steps: 96°C for 1 min; 96°C for 10 s; 50°C for 5 s; 60°C for 3 min ×35 cycles; 15°C. Sephadex powder + 300 µl of H_2O is added to the sequencing plate, which is then incubated for 3 h at room temperature. Big-Dye PCR products are placed in the sequencing plate + 10 µl of H_2O and centrifuged for 2 min at 2150 rpm. The plate is then covered. The BigDye PCR product is then filtered on sephadex and subjected to Sanger sequencing on ABI 3130 (PE Applied Biosystems, Foster City, CA, USA) using BigDye terminator chemistry. Sequenced genes were analyzed using ChromasPro-Amar software and compared with the BlastN database.

Data analysis

The results found were grouped together and analysed using Excel software.

RESULTS

Distribution of isolated strains

In all, 25 enterobacteria isolated from various biological samples were collected, 9 from Ziguinchor and 16 from Dakar. The following bacterial species were identified: *E. coli* (40%), *E. cloacae* (32%), *K. pneumoniae* (24%) and *C. freundii* (4%) (Table 1). In the laboratory at Paix hospital, these enterobacteria were isolated from the following biological samples: Urine (77.8%) and pus (22.2%), whereas at Fann hospital, these enterobacteria came from the following biological samples: Urine (50%), pus (25%), blood culture (18.75%) and CSF (6.25%).

Table 1. Distribution of isolates per years.

Parameter		Years				Total
		2019	2020	2021	2022	
Bacterial species	*E. coli* (n=10)	4(16%)	0(0%)	6(24%)	0(0%)	10(40%)
	K. pneumoniae (n=6)	0(0%)	0(0%)	1(4%)	5(20%)	6(24%)
	E. cloacae (n=8)	1(4%)	2(8%)	3(12%)	2(8%)	8(32%)
	C. freundii (n=1)	0(0%)	0(0%)	0(0%)	1(4%)	1(4%)
Hospitals	Paix hospital (Ziguinchor)	0(0%)	0(0%)	8(32%)	1(4%)	9(36%)
	Fann hospital (Dakar)	5(20%)	2(8%)	2(8%)	7(28%)	16(64%)

Antibiotic resistance profile of isolated strains

For all enterobacteria tested, the antibiogram showed 100% resistance to amoxicillin, 100% to amoxicillin/ clavulanic acid, 92% to cefepime, 100% to piperacillin/ tazobactam, 96% to ceftriaxone, 72% to ertapenem and 24% to imipenem. In Ziguinchor, resistance tests showed 100% resistance to amoxicillin, 100% to amoxicillin/ clavulanic acid, 89% to cefepime, 100% to piperacillin/ tazobactam, 100% to ceftriaxone, 44% to ertapenem and 11% to imipenem (Figure 1a). In Dakar, the antibiogram showed 100% resistance to amoxicillin, 100% to amoxicillin/clavulanic acid, 94% to cefepime, 100% to piperacillin/tazobactam, 94% to ceftriaxone, 88% to ertapenem and 31% to imipenem (Figure 1b). It was found that two isolates (*E. cloacae* and *C. freundii*) were resistant to both imipenem (MIC > 4 mg/L) and ertapenem (MIC > 0.5 mg/L).

Carbapenem resistance genes

The carbapenemase genes *bla*$_{OXA-48}$ and *bla*$_{NDM}$ were found in all 25 isolates (13 strains with *bla*$_{OXA-48}$ and 14 strains with *bla*$_{NDM}$), including two strains (*K. pneumoniae* and *E. cloacae*) in which both genes coexist. Analysis of the sequences obtained shows a predominance of the *bla*$_{OXA-181}$ variant followed by *bla*$_{NDM-5}$. The ß-CARBA test was positive for all enterobacteria resistant to imipenem and/or ertapenem (Table 2).

DISCUSSION

Carbapenem resistance through carbapenemase production in Enterobacteriaceae is increasingly described worldwide and represents a serious public health problem (Potron et al., 2011a; Potron et al., 2011c; Queenan and Bush, 2007; Yigit et al., 2001). In Africa, this scourge is gradually spreading with the description of new carbapenemase genes (Manenzhe et al., 2015; Berrazeg et al., 2014). In Senegal, the epidemiology of carbapenem resistance genes and their variants in clinically isolated enterobacteria is poorly understood, with data that is often obsolete (Dia et al., 2016; Lo et al., 2018; Diakhaby et al., 2020). This study focused on the sequencing of carbapenemase genes in imipenem- and/or ertapenem-resistant Enterobacteriaceae. Resistance to imipenem and ertapenem was respectively 31 and 88% in Dakar and 11 and 44% in Ziguinchor among the isolates. Resistance to imipenem was found in 10, 33, 25 and 100% of *E. coli*, *K. pneumoniae*, *E. cloacae* and *C. freundii* strains, respectively.

The *bla*$_{OXA-48}$ and *bla*$_{NDM}$ genes were found in the isolates. The OXA-48 enzyme is part of Ambler's class D and remains the most widely described carbapenemase in Enterobacteriaceae and the most common to have emerged in countries around the Mediterranean and in Africa (Carrër et al., 2008; Nordmann et al., 2014). This is the first carbapenemase gene described in Senegal in 2011, but it probably appeared earlier. Indeed, imipenem has been in use since 2008, and few regular epidemiological studies have been carried out in Senegal (Moquet et al., 2011; Diene et al., 2013; Seynabou et al., 2018). The emergence of New Delhi metallo-β-lactamase (NDM|) carbapenemases in *A. baumannii* has recently been reported in Senegal and the rest of Africa (Manenzhe et al., 2015; Camara et al., 2022).

The *bla*$_{OXA-181}$ gene is the second most common variant of OXA-48. It differs from the latter by the substitution of 4 amino acids (Thr104Ala, Asn110Asp, Glu175Gln and Ser179Ala), with the same hydrolytic spectrum as OXA-48 (Mairi et al., 2018; Potron et al., 2011b). They are active on penicillins and weakly hydrolyze carbapenems, with limited activity against broad-spectrum cephalosporins and most betalactaminase inhibitors (Poirel et al., 2012; Evans et al., 2014). *K. pneumoniae* and *E. coli* are the enterobacteria in which *bla*$_{OXA-48}$ is mainly identified (Mairi et al., 2018). In this study, in addition to having been found in these two bacterial species, we also found it in *Citrobacter freundii* and *E. cloacae*. The *bla*$_{OXA-181}$ variant is found in 30% of *E. coli* strains, 33% of *K. pneumoniae* strains, 38% of *E. cloacae* strains and 100% of *C. freundii* strains. Previous studies carried out in two Senegalese hospitals reported the detection of the *bla*$_{OXA-48}$ gene in 11 isolates

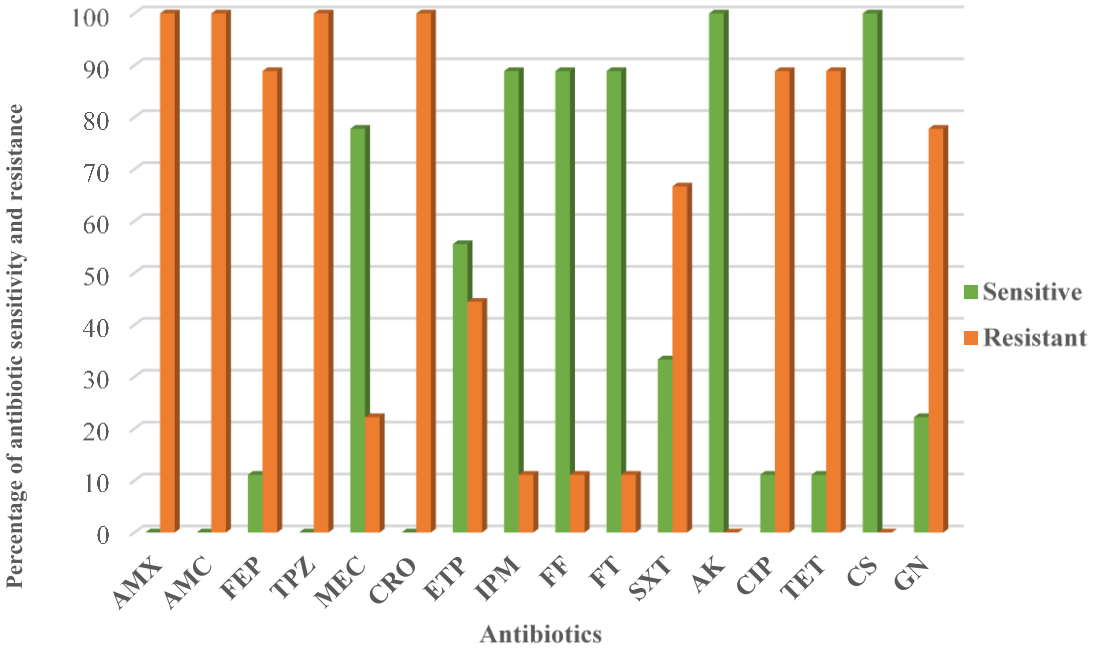

Figure 1a. Antibiotic resistance in strains of enterobacteria isolated in Ziguinchor.

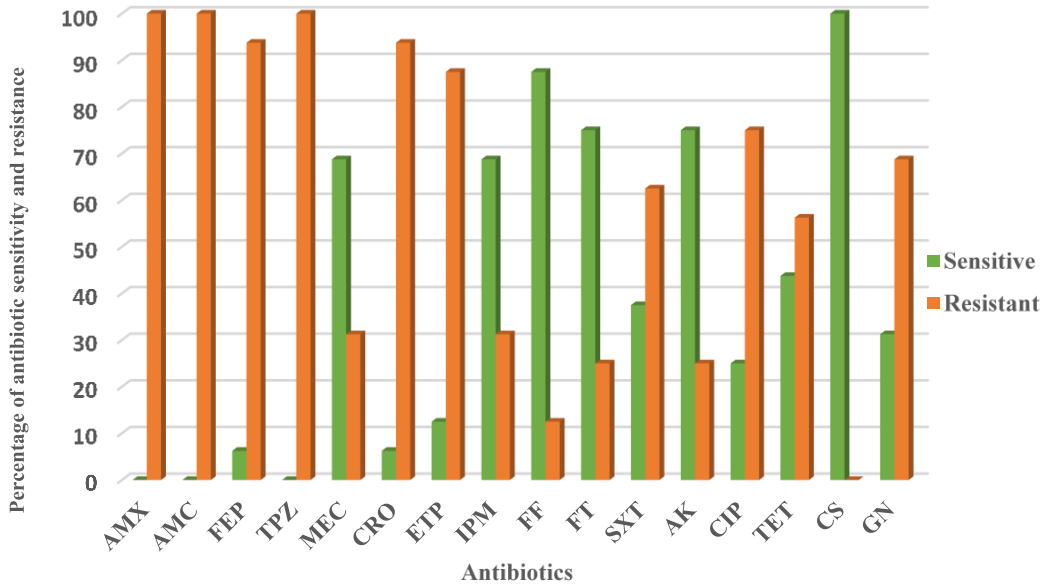

Figure 1b. Antibiotic resistance in strains of Enterobacteriaceae isolated in Dakar. AMX = Amoxicillin, AMC = Amoxicillin/Clavulanic Acid, FEP = Cefepime, TPZ = Piperacillin/Tazobactam, MEC = Mecillinam, CRO = Ceftriaxone, ETP = Ertapenem, IPM = Imipenem, FF = Fosfomycin, FT = Furan, SXT = Trimethoprim/Sulfamethoxazole, AK = Amikacin, CIP = Ciprofloxacin, TET = Tetracycline, CS = Colistin, GN = Gentamicin.

enterobacteria between 2008 and 2009 in Dakar. In Saint Louis, the *bla*$_{OXA-48}$ gene was detected in 49 *K. pneumoniae* isolates isolated from urine in 2016 (Moquet et al., 2011; Diene et al., 2013; Seynabou et al., 2018). The *bla*$_{OXA-48}$ gene and its variants have been described as the phantom threat due to its discrete phenotype in the absence of co-resistance mechanisms (Poirel et al., 2012; Lutgring et al., 2018). Elsewhere in Africa, carbapenemases are more frequently described in *Pseudomonas aeruginosa* and *A. baumannii*, with the

Table 2. Different carbapenemase gene variants.

Variable			Bacterial species				Total
			***E. coli* (n=10)**	***K. pneumoniae* (n=6)**	***E. cloacae* (n=8)**	***C. freundii* (n=1)**	
Variants carbapenemase genes	*bla*$_{OXA}$	*bla*$_{OXA-48}$	1(10%)	0(0%)	1(13%)	0(0%)	2(8%)
		bla$_{OXA-181}$	3(30%)	2(33%)	3(38%)	1(100%)	9(36%)
	bla$_{NDM}$	*bla*$_{NDM-5}$	5(50%)	0(0%)	3(38%)	0(0%)	8(32%)
		bla$_{NDM-1}$	1(10%)	3(50%)	0(0%)	0(0%)	4(16%)
	bla$_{NDM-5}$ + *bla*$_{OXA-48}$		0(0%)	1(17%)	0(0%)	0(0%)	1(4%)
	bla$_{NDM-5}$ + *bla*$_{OXA-181}$		0(0%)	0(0%)	1(13%)	0(0%)	1(4%)
ß-CARBA test +			2(20%)	4(67%)	5(63%)	1(100%)	12(48%)
Hospital	Paix hospital (Ziguinchor)		4(40%)	1(17%)	4(50%)	0(0%)	9(36%)
	Fann hospital (Dakar)		6(60%)	5(83%)	4(50%)	1(100%)	16(64%)

OXA-48 enzyme being more frequently observed than NDM (Manenzhe et al., 2015). In France, these same genes and their variants have been described in essentially the same strains in this study (Uzuriaga et al., 2022)

The *bla*$_{NDM-1}$ gene has been described since 2009 and codes for a metallo-beta-lactamase (Ambler class B) (Yong et al., 2009). The NDM-5 variant differs from NDM-1 by two amino acid substitutions (Val88Leu and Met154Leu). This difference results in increased carbapenemase hydrolytic activity (Hornsey et al., 2011). The *bla*$_{NDM-5}$ gene was found in 50 and 38% of the *E. coli* and *E. cloacae* isolates respectively. This variant was present in enterobacteria isolated in Dakar and Ziguinchor, showing a fairly homogeneous distribution of this variant between the west and south of the country. The few available studies on EPC epidemiology in West and East Africa report the identification of carbapenemases in Cameroon (NDM-4), Kenya (NDM 1), Sierra Leone (VIM and DIM-1), Senegal (OXA-48) and Tanzania (KPC, IMP, OXA-48, VIM and NDM) (Manenzhe et al., 2015). The emergence of EPCs is extremely worrying, with carbapenemase genes and their variants spreading worldwide (Antunovic and Andrasevic 2021). The coexistence of two carbapenemase variants was also noted in a strain of *K. pneumoniae* (*bla*$_{NDM-5}$ + *bla*$_{OXA-48}$) and a strain of *E. cloacae* (*bla*$_{NDM-5}$ + *bla*$_{OXA-181}$). Co-production of OXA-181 with NDM-5 has been reported in *K. pneumoniae* (Cho et al., 2015). In *E. coli*, this coexistence is worrying, as the worldwide spread of this enzyme would mirror that of NDM-1 (Poirel et al., 2012; Cho et al., 2015).

Conclusion

With the evolution of antimicrobial resistance (AMR), studies on the epidemiology of antibiotic resistance in Senegal need to be strengthened and updated. This study reveals a new epidemiological aspect of carbapenem-resistant Enterobacteriaceae isolates in the country. The "discovery" of NDM-type carbapenemase with its *bla*$_{NDM-5}$ variant, and the "persistence" of OXA-48 and its *bla*$_{OXA-181}$ variant in enterobacterial strains have been noted. In this context, it has become essential to set up a regular surveillance system to prevent the spread of antibiotic-resistant bacteria, particularly CPEs.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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