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Full Length Research Paper

Exploring the antimicrobial modulatory potential of the sap from oil palm tree

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The sap from the oil palms (*Elaeis guineensis*), harbours complex microbiota and provides a rich source of therapeutic metabolites. This study investigated the antibacterial modulatory activity of sap from *Elaeis guineensis* on selected bacteria. To test how well the sap from the oil palm tree affects bacteria, the minimum inhibitory concentration (MIC) of some common antibiotics was found by mixing the sap from the oil palm tree with broth and measuring the results. The MIC of chloramphenicol, ampicillin, amoxicillin /clavulanic acid, and cefixime combined with the sap from the oil palm tree against the test organisms were in the range of 1.25 - 2.5, <0.0024 - 2.5, <0.0024 - 0.625, and 0.3125 - 2.5 mg/ml, respectively. There was a 4-fold and 16-fold reduction in the MIC of chloramphenicol against *Staphylococcus aureus* and *Pseudomonas aeruginosa* respectively, and an 8-fold reduction of the MIC of chloramphenicol in 64% of the in vitro modulatory tests. A 2 - >2083-fold increment in the MIC of the antibiotics was observed against the test pathogenic bacteria. Metabolite profiling of the sap from the oil palm tree showed the presence of simple sugars such as cellobiose, maltose, sucrose and glucose. The sap from the *E. guineensis* exerted a modulatory effect on the antibacterial activity of chloramphenicol, ampicillin /clavulanic acid and cefixime.

Key words: Elaeis guineensis, antibacterial modulation, antimicrobial resistance.

INTRODUCTION

The fresh sap from oil palm tree is very sweet and refreshing because of the presence of sucrose, but within 24 h the concentration of sucrose falls to less than 50% of the initial amounts. Microorganisms contaminate the palm sap and convert it into palm wine through a fermentation process. This fermented drink is traditionally appreciated and consumed by several people throughout the world. Fermentation virtually ends when the Ph falls

to 4.0; this whole process lasts about 48 h (Oluwole et al., 2023; Djeni et al., 2020; SatyaLakshmi et al., 2018). It is available to varied cultures worldwide as a locally manufactured drink with documented therapeutic benefits (Mbuagbaw and Noorduyn, 2012). In parts of Africa, the consumption of this fermented sap forms part of many ceremonies, including weddings, funerals, and birth celebrations. This fermented sap may be served in varied

*Corresponding author. E-mail: <u>cdodoo@uhas.edu.gh</u>.

Author(s) agree that this article remain permanently open access under the terms of the <u>Creative Commons Attribution</u> License 4.0 International License flavours which may be unfermented (sweet), fermented (sour), or vinegary (Chung and Yousef, 2003; Eze et al., 2019). Fewer stigmas is associated with the drinking of this fermented sap in all age groups as compared to other distilled derivatives which welcomes its use in many societies in Africa by children, adolescents, and the elderly. This fermented sap is often traditionally used in some African communities to extract bioactive metabolites from medicinal herbs (leaves, stems, barks) as a treatment for a wide variety of bacterial, parasitic, and viral infections including chicken pox, measles, malaria, and yellow fever (Nwaiwu et al., 2020; Akinrotoye, 2014; Sosa et al., 2009).

The increased evolution of antimicrobial resistance in pathogenic species of microorganisms, coupled with challenges in the discovery of new antimicrobial agents necessitates the search for varied agents that may synergistically enhance the activity of antimicrobials (Ali et al., 2021; Almuhayawi, 2020; Cheesman et al., 2017; Adusei et al., 2019). Foods and nutraceuticals may be able to modify the effects of commercial antimicrobials in a way that reverses the mechanism of resistance that resistant strains of microorganisms have developed (Sibanda and Okoh, 2007). Routine consumption of the sap either alone or with meals in many societies may gradually influence the use of this sap in orally administering medicinal formulations, including antibiotics (Endo et al., 2014). Folklorically, there is a belief that taking the sap with anti-infectives increases the activity of antimicrobials against pathogenic bacteria. Some community pharmacists have observed this belief in Ghana whereby clients request antibacterial agents, intending to take them with the sap from oil palm trees. This laboratory-based study, therefore, sought to ascertain this claim and also determine whether the sap from an oil palm tree has any potential antibacterial modulating activity using selected antibiotics against common pathogenic bacteria.

MATERIALS AND METHODS

Sample collection

Freshly tapped sap from oil palm (*Elaeis guineensis*) was collected from a farm at Sokode Gborgame in the Volta Region, Ghana. It was directly aliquoted into sterile bottles and frozen at -20°C.

Test microorganisms and antibiotics

The test organisms employed in determining the antimicrobial and resistance-modulating activity of the sap from oil palm were *Staphylococcus aureus* (ATCC 27853), *Proteus mirabilis* (ATCC 49565), *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922) and *Klebsiella pneumoniae* (ATCC 33495), *Salmonella paratyphi A* (clinical isolates) and *Salmonella paratyphi B* (clinical isolates). All the typed strained organisms were obtained as frozen stock cultures from the Centre for Plant Medicine Research, Mampong, Akuapem, Ghana while the clinical strains were obtained from the Microbiology Laboratory of Central

University, Ghana. The organisms were revived by inoculating two loopfuls of the frozen culture into peptone broth (Oxoid, UK, CM0009B) and incubating at 37°C for 24 h. The cells were then suspended in Mueller Hinton broth (Oxoid, UK, CM0405B) and incubated at 37°C for 24 h. A microbial count of 0.5 McFarland standard (approximately 1.0×10^8 CFU/mL) was used for the experiment. This was obtained by diluting the cultures with a sterile solution of 0.9% saline. The test antibiotics used in the study were pure powders of chloramphenicol, amoxicillin /clavulanic acid (co-amoxiclav), ampicillin, and cefixime obtained from Ernest Chemist Limited, Tema, Ghana.

Preliminary investigations and LC-MS Based Metabolomics Analysis of freshly tapped sap from oil palm

Benedict's test was conducted to confirm the presence of reducing sugars (Simoni et al., 2002) while ascorbic acid and alcohol content were quantified by iodometric and back titration methods respectively (Ikewuchi and Ikewuchi, 2011). Liquid chromatographymass spectrometry (LC–MS) was also conducted on the sap from the oil palm sample as follows. 30 ml of the sample was centrifuged at 12,000 × g. The supernatant was used for metabolomics analyses while the pellets were washed twice with sterile saline water and frozen at -80° C for later culturing and microbial diversity analyses. 1 ml of the sap from the oil palm sample supernatant was diluted in 1 ml of acetonitrile. The mixture was centrifuged at 18,000 × g for 10 min at 4°C and filtered through 0.2 µm PTFE filter into a 2 ml septum vial and used for LC-MS analysis.

Antibacterial assay of reference antibiotics

The MICs of the reference antibiotics (chloramphenicol, coamoxiclav, ampicillin, and cefixime) were determined against *S. aureus*, *P. mirabilis*, *S. paratyphi A*, *S. paratyphi B*, *P. aeruginosa*, *E. coli*, *K. pneumoniae* using the broth microdilution method (Wiegand et al., 2008). The reference antibiotics at concentrations of 0.0024 mg/ml to 5 mg/mL were prepared in 96-well plates and the volumes were adjusted to 190 µL. A volume of 10 µL of test organism suspension containing 5 x10⁵ CFU/mL was added to make it 200 µL per well. They were incubated at 35°C for 24 h (Andrews, 2001). The MIC was recorded as the least concentration that showed no visible bacterial growth which was detected by the absence of a purple colour after the addition of 10 µL of 0.1% w/v 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to each well followed by incubation at 37°C for 30 min.

Determination of the antibiotic resistance modifying activities of sap from oil palm

The MICs of the reference antibiotics were determined against the study organisms in the presence of a sub-inhibitory concentration of the sap from the oil palm. The sap from oil palm (alcohol content 0.7% v/v) was used as a vehicle to dissolve the antibiotics. The required volume of the antibiotic solution was added to 100 μ L of double-strength Mueller Hinton broth. The broth was adjusted to 190 μ L with sterile distilled water, and 10 μ L of test organism was added to produce 200 μ L. The plates were then incubated at 37°C for 24 h. The MIC was recorded as the least concentration that showed no visible bacterial growth which was detected by the absence of purple colour after the addition of a few drops of 0.1% MTT to each well followed by incubation at 37°C for 30 min. The experiment was done in triplicate. Modulation factor (MF), calculated as (MIC of antibiotic alone) / (MIC of antibiotic + sap from oil palm), was used to express the antibiotic-potentiating effects of

Table 1. Modulatory effect of freshly tapped sap from oil palm on the antibacterial activity of selected antibiotics.

Test organisms-S. aureus P. mirabilis S. paratyphi A		Chloramphenicol		Ampicillin					
	MIC of antibiotic only (mg/mL)	MIC of antibiotic + sap from oil palm (mg/mL)	MF	Δ	MIC of antibiotic only (mg/mL)	MIC of antibiotic + sap from oil palm (mg/mL)	MF	Δ	
S. aureus	1.25	0.3125	4	4+	0.1563	1.25	0.12504	8-	
P. mirabilis	1.25	2.5	0.5	2-	0.625	5	0.125	8-	
S. paratyphi A	1.25	1.25	1	-	<0.0024	5	<0.00048	>2083-	
S. paratyphi B	1.25	0.625	2	2+	0.0391	2.5	0.01564	64-	
P. aeruginosa	2.5	0.1563	15.99	15.99+	0.0391	1.25	0.03128	32-	
E. coli	1.25	0.625	2	2+	2.5	1.25	2	2+	
K. pneumonia	1.25	0.625	2	2+	0.3125	5	0.0625	16-	

Test organisms		Amoxicillin /clavulanic acid	d	Cefixime					
	MIC of antibiotic only (mg/mL)	MIC of antibiotic + sap from oil palm (mg/mL)	MF	Δ	MIC of antibiotic only (mg/mL)	MIC of antibiotic + sap from oil palm (mg/mL)	MF	Δ	
S. aureus	0.1563	1.25	0.12504	8-	2.5	0.3125	8	8+	
P. mirabilis	0.0098	5	0.00196	510-	0.625	2.5	0.25	4-	
S. paratyphi A	0.0781	2.5	0.03124	32-	2.5	5	0.5	2-	
S. paratyphi B	0.1563	5	0.03126	32-	0.3125	5	0.0625	16-	
P. aeruginosa	0.625	2.5	0.25	4-	2.5	2.5	1	-	
E. coli	<0.0024	2.5	<0.00096	>1042-	0.3125	2.5	0.125	8-	
K. pneumonia	0.1563	2.5	0.06252	16-	1.25	1.25	1	-	

MIC2: MIC of antibiotic + palm wine (mg/mL), (+): reduction in MIC (increased activity), (-): increase in MIC (decreased activity), Δ : Fold increase or decrease in the MIC, Amoxi/clav: amoxicillin/clavulanic acid, MF: modulatory factor.

the sap from oil palm.

RESULTS

Effect of freshly tapped sap from oil palm on the antibacterial activity of chloramphenicol, ampicillin, amoxicillin /clavulanic acid, and cefixime

The MIC of chloramphenicol, ampicillin, amoxicillin /clavulanic acid, and cefixime with sap from oil

palm against all the test organisms were in the range of 1.25 - 2.5, <0.0024 - 2.5, <0.0024 -0.625, and 0.3125 - 2.5 mg/ml respectively (Table 1). There was a resistance modifying effect of fresh sap from oil palm on the activity of chloramphenicol against all the test microorganisms except S. paratyphi A. A reduction in the MIC of chloramphenicol was observed against S. aureus (4-fold), S. paratyphi B (2-fold), P. aeruginosa (16-fold), E. coli (2-fold) and K. pneumoniae (2- fold). There was no change in the MIC of chloramphenicol against S. paratyphi A. The freshly tapped sap from oil palm enhanced the activity of ampicillin through a 2-fold reduction in the MIC against *Escherichia coli*. There was an increase in the MIC of ampicillin against *S. aureus* (8-fold), *P. mirabilis* (8-fold), *S. paratyphi A* (>2083-fold), *S. paratyphi B* (64-fold), *P. aeruginosa* (32-fold) and *K. pneumoniae* (16-fold). The antibacterial activity of amoxicillin /clavulanic acid against all the test organisms was reduced (increase in MIC) in the presence of the freshly tapped sap from oil palm. The MIC of coamoxiclav increased against *S. aureus* (8-fold),

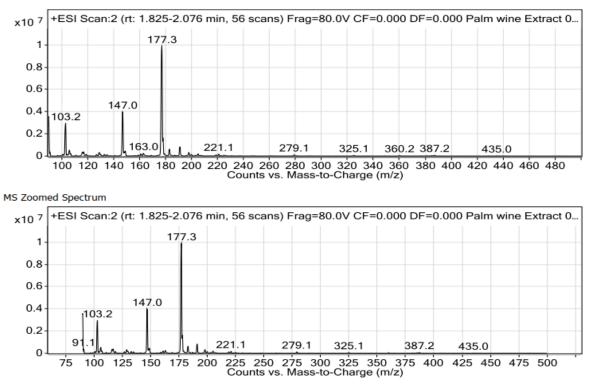


Figure 1. Chromatogram from LC-MS Based Metabolomics Analysis of sap from oil palm (Compound 5, RT: 1.905).

Table 2. Metabolites identified from the sap from oil palm samples.

S/N	Retention time (min)					Molecular formula	Identification	References
1	1.487	177.2 (M+H)	176.12	C ₁₄ H ₁₄ O ₉	Ascorbic acid	Doddipalla et al. (2022) and Ezeagu et al. (2010)		
2	1.487	365.2 (M+Na);	342.30	C12H22O11	Cellobiose	Ezeagu et al. (2010)		
3	1.487	365.2 (M+Na)	342.30	C12H22O11	Maltose	Ezeagu et al. (2010)		
4	1.487	381.1 (M+K)	342.30	C12H22O11	Sucrose	Ezeagu et al. (2010)		
5	1.905	198.1 (M+NH4)	180.16	C6H12O6	Glucose	Doddipalla et al. (2022) and Ezeagu et al. (2010)		

P. mirabilis (510-fold), *S. paratyphi* A (32-fold), *S. paratyphi* B (32-fold), *P. aeruginosa* (4-fold), *E. coli* (>1041-fold) and *K. pneumoniae* (16-fold). There was no change in the MIC of cefixime against *P. aeruginosa* and *K. pneumoniae*. A reduction in the MIC of cefixime was obtained against *S. aureus* (8-fold). However, an increase in MIC was observed in the in vitro modulatory assay of cefixime and fresh sap from oil palm against *P. mirabilis* (4-fold), *S. paratyphi* A (2-fold), *S. paratyphi* B (16-fold) and *E. coli* (8-fold).

Chemical constituents in sap from oil palm as determined from LC-MS Analysis

LC-MS screening of the fresh sap from oil palm

principally showed the presence of monosaccharides (like glucose), disaccharides (including cellobiose, maltose, and sucrose), and ascorbic acid (Figure 1 and Table 2). The presence of these compounds has been previously reported in the sap of oil palm tree (Doddipalla et al., 2022; Ezeagu et al., 2010). The sweet taste of the product could thus be attributed to the presence of the free sugars. Ascorbic acid, on the other hand, could be thought to contribute to the observed antimicrobial effects of the product.

DISCUSSION

The modulatory effect of sap from oil palm on selected antibiotics was assessed by determining the MIC of the

antibiotics with sap from oil palm against some reference organisms. A decrease in MIC of the antibacterial agent with sap from oil palm implied potentiation of the antibacterial activity by the sap from oil palm. An increase in MIC, however, suggested a decrease in the activity of the antibacterial agent against the test organism (Adusei et al., 2019).

The addition of sap from oil palm to the antibiotics did not have any resistance-modifying effect on chloramphenicol against S. paratyphi A. Also, there was no change in the MIC of ampicillin against P. aeruginosa and K. pneumoniae. In general, the test antibiotics' MIC (the amount they needed to kill bacteria) went down in 25% of the in vitro modulatory assays that were done. Considerable among these is the 4-fold and 16-fold reduction in the MIC of chloramphenicol against S. aureus and P. aeruginosa respectively, and the 8-fold reduction of the MIC of cefixime against S. aureus. The metabolites from fresh sap from oil palm have been reported to possess antimicrobial effects against S. aureus, E. coli, S. typhi, S. dysentariae, and some viruses (Oluwole et al., 2023; Akinrotoye, 2014).

This finding suggests that there may be some bioactive present in sap from oil palm worth exploring that could produce a potentiating effect on the activity of some antibiotics. The modulatory effect of the fresh sap from oil palm on the selected antibiotics increased the MIC (reduction in antibacterial activity) of the antibiotics in 64% of the in vitro modulatory assays conducted. No modulation occurred in 10% of the tests conducted. This finding suggests that the effect of sap from oil palm on the antibacterial activity of some antibiotics is not always synergistic. Several studies conducted have established that sap from oil palm has a complex microbial diversity (Djeni et al., 2022; Astudillo-Melgar et al., 2019). Predominant among them are yeast and bacteria cells as S. cerevisiae. responsible for such alcohol fermentation and characteristic odour of sap from oil palm, lactic acid bacteria (Lactobacillus spp, known for their probiotic potential), and acetic acid bacteria (Djeni et al., 2022; Djeni et al., 2020). These are responsible for the pH reduction through the production of organic acids, which give a sour taste to the sap from oil palm, and are also, associated with the aroma, consistency, and colour of sap from oil palm by the production of polysaccharides (Santiago-Urbina and Ruíz-Terán, 2014).

Metabolite profiling of sap from oil palm by Liquid chromatography-mass spectrometry analysis has shown sap from oil palm to be a chemically rich substrate of polyphenols, vitamins, and amino acids including free sugars, organic acids, sugar alcohols, sugar acids, ketones, terpenes, and several unknown compounds (Djeni et al., 2020; Oluwole et al., 2023). These metabolites could have interfered with the activity of the antibiotics by interacting with bioactive chemically unstable structural groups causing a reduction or potentiation in antibacterial activity (Martinez-Lopez et al., 2014; Erukainure et al., 2018). In the current study, LC-MS screening of the fresh sap from the oil palm showed the presence of ascorbic acid which may contribute to its antimicrobial activity. Ascorbic acid has been reported to exert an antibacterial effect against *Listeria monocytogenes* and *S. aureus* (Bayan, 2013). Additionally, the combination of ascorbic acid and lactic acid was also shown to be effective against *E. coli* 0157:H7 (Tajkarimi and Ibrahim, 2011). The presence of other organic acids, as reported in other studies has also been shown to possess significant antimicrobial effects. Thus, the cumulative presence of these compounds in the fresh sap from oil palm could be said to contribute to the observed enhanced antimicrobial effects of the antibiotics tested.

Also, some of the metabolites could enhance the overexpression of antibiotic resistance determinants (plasmids, integrons, transposons, and antibiotic resistance genes) in the study bacteria causing a change in their susceptibility profile to the tested antibiotics (Kung et al., 2010; Bockstael and Aerschot, 2009). A study by Doddipalla and colleagues using nuclear magnetic resonance and liquid chromatography - high resolution mass spectrometry also confirmed the presence of organic acids and sugars, however, they reported that the amounts of these metabolites were significantly altered upon storage (Doddipalla et al., 2022). This, therefore, has the potential to alter any resistance modulatory activity that could be observed from the sap of oil palm tree.

Conclusion

The findings from this research indicate that sap from oil palm obtained from *Elaeis guineensis* can modulate the antimicrobial activity of some antibiotics. This modulatory activity in some instances potentiates antimicrobial effects while in others it attenuates this effect *in vitro*. Further work will now be conducted to elucidate which bioactives in the sap from the oil palm are responsible for the modulatory effects observed.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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Full Length Research Paper

Resistance profile of urine isolate enterobacteral strains at Donka University teaching hospital in Conakry, Guinea

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The objective of this study was to describe the resistance profile of enterobacterals isolated from urine samples at the laboratory of Donka National Hospital. Urine samples were collected from both outpatients and hospitalized patients. Cultures were performed using standard techniques, strains were identified using the API 20E kit, and antibiotic susceptibility testing was carried out using the ATB TM UR EU (08) kit. The results were interpreted according to the recommendations of the Antibiogram Committee of the French Society of Microbiology (CASFM v1 2023). Out of a total of 520 urine samples analyzed, 111 were positive for enterobacteral strains. Among them, 75 (67.57%) were of community origin. *Escherichia coli* was the most represented species (n=61, 55%), followed by *Klebsiella pneumoniae* (n=24, 22%). The resistance of *E. coli* strains to third generation cephalosporins (TGC) varied from 5.41% (n=6) to 25.23% (n=28) in the community and from 13 to 38% in the hospital. The profile for carbapenems was categorized as "susceptible to high dosage (SHP)," accounting for 16.22% (n=18). This study provided insight into the resistance profile to antibiotics used in urinary tract infections. The increasing resistance to carbapenems poses a threat to the management of strains producing extended-spectrum beta-lactamases (ESBL). It would be important to strengthen resistance surveillance in this context.

Key words: Enterobacteral, urinary tract infection, resistance, community, hospital, Guinea.

INTRODUCTION

Enterobacterals constitute a group of Gram-negative bacteria divided into seven groups (groups 0 to 6). They

constitute most of the commensal flora in the intestine (Jenkins et al., 2017; Machado et al., 2013). They have

natural resistance to certain antibiotics based on their group membership due to the presence of ß-lactamase capable of hydrolyzing penicillins. enzvmes carboxypenicillins, and first-generation cephalosporins (FGC) (Carattoli, 2009; Paterson, 2006; Philippon and Arlet, 2006). Secondary resistances can occur and spread within the groups through genetic supports (plasmids, integrons) (Carattoli, 2009; Machado et al., 2013). This phenomenon can lead to a therapeutic deadlock due to the acquisition of multidrug resistance, making enterobacterals redoubtable among the causative agents of urinary tract infections (Carattoli, 2009; Paterson, 2006; Philippon and Arlet, 2006). Among uropathogenic enterobacterals, Escherichia coli is the most frequent, followed by Klebsiella species (Matalka et al., 2021; Moges et al., 2021).

Multidrug resistance poses a challenge to the selection of antibiotics, impacting all prescribed classes of antibiotics. Various studies conducted in different locations highlight the extent of this phenomenon (Lee et al., 2018; Pasom et al., 2013; Sbiti et al., 2017) and its consequences, both at the individual and public health levels.

Thus, high proportions of multidrug resistance have been reported in various studies conducted in Africa, and these proportions vary from one region to another (Djim-Adjim-Ngana et al., 2023; Moges et al., 2021). The prevalence of multidrug-resistant bacteria can reach up to 85% (Moges et al., 2021). A review on the emergence and spread of resistance in West Africa described a particularly concerning situation regarding the production of extended-spectrum ß-lactamases (ESBLs) among Enterobacterales. The same trend has been observed for carbapenem resistance (Ouedraogo et al., 2017).

Guinea is not spared from the phenomenon of resistance. The prevalence of urinary tract infections accounts for between 16 and 60.2% of healthcareassociated infections, according to studies (Diallo et al., 2022; Keita et al., 2016). E. coli and Klebsiella pneumoniae are the most isolated pathogens. Resistance characterized by high-level in Enterobacteral is cephalosporinases (56%), extended-spectrum ßlactamases (20%), and carbapenems (12%). Resistance to quinolones is reported at 36%, and 20% for aminoglycosides (Diallo et al., 2022). However, antibiotic susceptibility data are not always accessible, and treatments are often empirical. This study aimed to describe the resistance profile of Enterobacterales isolated from urine samples at the National Hospital of Donka laboratory.

MATERIALS AND METHODS

Study design, sites and samples collection

This is a cross-sectional study conducted at Laboratoire de Biologie médicale du Centre Hospitalier Universitaire de Donka (CHU Donka) over a period of 15 months (September 2022-December 2023). It is one of the level I hospital structures that reopened its doors after a renovation period. The laboratory service of the CHU consists of 7 technical units (Immunology, Biochemistry, Bacteriology, Parasitology, Haematology, Blood Transfusion, and the emergency laboratory) and a sample collection room. The assays were performed in the bacteriology unit.

Urine samples were collected from both outpatients and hospitalized patients at the University Teaching Hospital of Donka (Emergency Department and other services). Urine samples were collected in sterile containers and transported to the laboratory within 2 h of collection.

Isolation and identification

Upon receiving the samples, the conformity of the container was checked. The samples were macroscopically assessed for color and turbidity upon receipt. Microscopy using a Malassez cell allowed for the evaluation of the presence of leukocytes, red blood cells, crystals, and other elements. Culture media, Uriselect, and CLED (cystine lactose electrolyte deficient) were inoculated and incubated for 24 to 48 h at 37°C in aerobic conditions. Enumeration was performed with a threshold of 103 CFU/mL for E. coli and 104 CFU/mL for other Enterobacteral strains. Identification was conducted using the 23 biochemical tests (O-nitrophenyl-β-Dgalactosidase, arginine dihydrolase, lysine and ornithine decarboxylase, citrate utilization, hydrogen sulfide, urease, tryptophan deaminase, indole, Voges-Proskauer, gelatin liquefaction, fermentation of glucose, mannitol, inositol, sorbitol, rhamnose, sucrose, melibiose, amygdalin and arabinose, nitrate reduction, and nitrogen gas production, and catalase production) available on the API 20E gallery (BioMérieux SA, Marcy-l'Étoile, France).

Antibiotics susceptibility test and detection of extended spectrum beta-lactamase producers

The antibiotic susceptibility testing was conducted using ATBTM UR EU (08) (BioMérieux SA, Marcy-l'Étoile, France) following the manufacturer's recommendations (*Lustiner - Galerie ATBTM UR EU* [Antibiogramme/Norme NCCLS] Biomérieux®, n.d). The ATBTM UR EU (08) gallery is a standardized qualitative technique for determining the sensitivity of urinary Enterobacterales to antibiotics in a semi-solid medium under conditions very close to reference dilution techniques in agar or microdilution. It consists of 16 pairs of wells. The first pair, without antibiotics, serves as a positive growth control. The next 15 pairs contain antibiotics at one or two concentrations (c and C). The bacteria to be tested are suspended and then transferred to the culture medium, inoculated into the gallery. After incubation, the growth in the wells is visually assessed. The obtained result categorizes the strain as Susceptible,

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Variable	Overall, N = 520 ¹	Negative culture, n = 409 ¹	Positive culture, n = 111 ²	p-value
Age	43 (28, 60)	42 (27, 58)	44 (28, 63)	0.3
Age range (years)				0.7
<5	5 (1.0)	5 (1.2)	0 (0)	
5-15	26 (5.0)	22 (5.4)	4 (3.6)	
16-25	76 (15)	61 (15)	15 (14)	
26-45	180 (35)	140 (34)	40 (36)	
46-60	104 (20)	85 (21)	19 (17)	
>60	129 (25)	96 (23)	33 (30)	
Gender				<0.001
Feminine	269 (52)	188 (46)	81 (73)	
Masculine	251 (48)	221 (54)	30 (27)	
Origin of strains				<0.001
Community	465 (89)	390 (95)	75 (68)	
Hospital	55 (11)	19 (4.6)	36 (32)	

Table 1. Characteristics of patients.

¹Median (IQR); n (%) ²Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test.

Intermediate, or Resistant. Since 2020, the EUCAST committee introduced the concept of "Susceptible at standard dosage" for the Susceptible category and "Susceptible at high dosage" for the Intermediate category. The "Resistant" category remains unchanged.

The most commonly used antibiotics were tested: Beta-lactams (Penicillins: ampicillin, ticarcillin, piperacillin, amoxicillin+clavulanic piperacillin-tazobactam, Cephalosporins: Cephalexin, acid. Cefoxitin, Cefuroxime, Cefixime, Cefotaxime, Ceftazidime, Cefepime, Carbapenems: imipenem, ertapenem, meropenem µg), Aminoglycosides (amikacin, gentamicin, tobramycin), Quinolones (nalidixic acid, ciprofloxacin, ofloxacin, norfloxacin, levofloxacin), Tetracyclines (tigecycline, tetracycline), and other antibiotics (nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin). The results obtained were interpreted according to the recommendations of Comité de l'Antibiogramme de la Société Française de Microbiologie (CA-SFM 2023).

Statistical analysis

The data was extracted from the information system of CHU Donka, sent to Excel, and analysed using the R software. Chi-square test and Fisher's exact test were used for comparing proportions or estimating the association between variables when the conditions for use were met. Quantitative variables were compared using the Student's t-test.

Ethical consideration

The protocol was approved by the Research Committee of the University Gamal Abdel Nasser (Conakry, Guinea) and performed following the Declaration of Helsinki.

RESULTS

Table 1 describes the socio-demographic characteristics of the patients. Out of a total of 520 urine samples

received and analyzed in the laboratory over a period of 15 months (September 2022 to December 2023), 111 were positive for Enterobacteral after culture on ordinary media. The median age of the patients was 42 (IQR: 28-63). The female gender was predominant with a ratio of 0.4.

Among the isolated Enterobacteral strains, 75 (67.57%) were of community origin, and 36 (32.43%) were of hospital origin (Table 1). The species *E. coli* was the most represented, whether of community origin (n=40) or hospital origin (n=21), followed by the species *K. pneumoniae*, with n=14 (58%) community strains and n=10 (42%) hospital strains.

Among the antibiotics tested on the 111 strains of Enterobacteral (Table 2), resistance to penicillin varied between 15.31% (n=17) and 81.08% (n=90). The resistance by antibiotic was distributed as follows: 72.97% (n=81) were resistant to ampicillin, 81.08% (n=90) were resistant to ticarcillin, 49.55% (n=55) were resistant to piperacillin, 39.64% (n=44) were resistant to amoxicillin/clavulanic acid, and 15.32% (n=17) were resistant to the piperacillin/tazobactam combination. The resistance for E. coli strains was (n=44), distributed in the community setting (n=23) and the hospital setting (n=21) (Table 2). For K. pneumoniae strains (n=17), seven were in the community setting and ten were in the hospital setting, and for Klebsiella oxytoca strains (n=5), all were in the community setting. Resistance to amoxicillin/ clavulanic acid varied between 4.5 and 52%, with a predominance in E. coli strains (52%, n=23), which were community-acquired. Resistance to carboxypenicillins was predominantly found in E. coli, with n=53 for ticarcillin and n=32 for piperacillin. Resistance to piperacillin/tazobactam ranged from 6.30 to 63.00%, and

Species	Overall (N = 111) ¹	Community strain, n=75	Hospital strain (n=36)
Citrobacter freundii	7 (6.3)	6 (86)	1 (14)
Klebsiella aerogenes	1 (0.9)	0 (0)	1 (100)
Enterobacter cloacae	4 (3.6)	3 (75)	1 (25)
Escherichia coli	61 (55)	40 (66)	21 (34)
Klebsiella oxytoca	6 (5.4)	6 (100)	0 (0)
Klebsiella pneumoniae	24 (22)	14 (58)	10 (42)
Proteus mirabilis	4 (3.6)	4 (100)	0 (0)
Proteus spp.	1 (0.9)	0 (0)	1 (100)
Serratia marcescens	1 (0.9)	0 (0)	1 (100)
Serratia odorifera	2 (1.8)	2 (100)	0 (0)

 Table 2. Distribution of enterobacteral species by origin.

Fisher's exact test; p-value= 0.11.

Table 3. Resistance profile to Penicillin of enterobacteral strain according to their origin.

Species	N_444	Ampicillin		Tica	rcillin	AMC	PipTaz		
Species	N=111	Com, n=45	Hosp, n=36	Com n=55	Hosp, n=35	Com n=44	Com n=1	Hosp, n=16	
Citrobacter freundii	7	4 (8.9)	1 (2.8)	4 (7.3)	1 (2.9)	4 (9.1)	0 (0)	0 (0)	
Klebsiella aerogenes	1	-	1 (2.8)	-	1 (2.9)	-	0 (0)	1 (6.3)	
Enterobacter cloacae	4	2 (4.4)	1 (2.8)	2 (3.6)	1 (2.9)	2 (4.5)	0 (0)	0 (0)	
Escherichia coli	61	23 (51)	21 (58)	31 (56)	21 (60)	23 (52)	0 (0)	10 (63)	
Klebsiella oxytoca	6	5 (11)	-	4 (7.3)	-	5 (11)	0 (0)	0 (0)	
Klebsiella pneumoniae.	24	7 (16)	10 (28)	10 (18)	10 (29)	6 (14)	1 (100)	5 (31)	
Proteus mirabilis	4	2 (4.4)	0 (0)	3 (5.5)	0 (0)	2 (4.5)	0 (0)	0 (0)	
Proteus ssp.	1	0 (0)	1 (2.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Serratia marcescens	1	-	1 (2.8)	0 (0)	1 (2.9)	-	0 (0)	0 (0)	
Serratia odorifera	2	2 (4.4)	-	1 (1.8)	0 (0)	2 (4.5)	0 (0)	0 (0)	

Com= Community, Hosp=hospital, AMC=amoxicillin + clavulanic acid, PipTaz=piperacillin+tazobactam.

this resistance was mostly encountered in hospitalacquired strains (14.41%, n=16).

Out of a total of 111 isolated Enterobacteral strains, resistance to cephalosporins (Table 3) varied between 7.21% (n=8) and 48.65% (n=54). Third generation cephalosporins (TGC) were affected, with proportions ranging from 36.94% (n=41) to 47.75% (n=53).

Resistance to fourth-generation cephalosporin (FGC) was around 7.2% (n=8). *E. coli* strains had resistance proportions to second and third generation cephalosporins ranging from 12.8 to 7.6%. Resistance to TGC (Table 4) ranged from 3.60% (n=4) to 23.42% (n=26) for hospital-acquired strains and from 42.34% (n=47) to 47.75% (n=53) for community-acquired strains. Resistance to FGC was 7.21% (n=8). The resistance of *E. coli* strains ranged from 5.41% (n=6) to 25.23% (n=28) in the community setting and from 13 to 38% in the hospital setting.

The profile for carbapenems (Table 5) was categorized as "Sensitive at High Dosage (SFP)," accounting for 16.22% (n=18). The SFP category varied from 8.5 to 100% depending on the Enterobacteral strains. The "Resistant (R)" category was 1.80% (n=2), involving resistance to Ertapenem, specifically 1.80% (n=2). The SFP category for *E. coli* strains was 8.5% (n=4.5).

Resistance to aminoglycosides varied from 6.31% (n=7) to 27.93% (n=31). This resistance fluctuated from 0.90% (n=1) to 18.01% (n=20) depending on the strains. Resistance based on the origin of Enterobacteral strains ranged from %(n=2) to %(n=6) for community-acquired strains and from 2.70% (n=3)

to 22.52% (n=25) for hospital-acquired strains.

Resistance to quinolones varied from 9.91% (n=11) to 53.15% (n=59). This resistance ranged from 36% (n=4) to 64% (n=18) for *E. coli* strains. Quinolone resistance according to the origin of the strain varied from 14.66% (n=11) to 37.33% (n=28) for community-acquired and from 72.22% (n=26) to 83% (n=30) for hospital-acquired strains.

Resistance to other tested antibiotics based on strains varied from 13 to 43% for nitrofurantoin, from 3.6 to 61% for trimethoprim-sulfamethoxazole, and from 13 to 75%

		1st gen	eration		2nd generation	า			3rd generatio	n		4th generation
Species	N=111	Cefa	lotin	Cefo	oxitin	Cefuroxim	Cefixim	Cefo	taxim	Cefta	azidim	Cefepim
		Com, n = 53	Hosp, n = 1	Com, n = 20	Hop, n = 14	Com, n = 47	Com, n=53	Com, n=47	Hosp, n=4	Com, n=15	Hosp, n=26	Com, n=8
Citrobacter freundii		4 (7.5)	0 (0)	1 (5.0)	1 (7.1)	3 (6.4)	3 (5.7)	3 (6.4)	0 (0)	0 (0)	1 (3.8)	0 (0)
Klebsiella aerogenes		-	-	0 (0)	1 (7.1)	-	-	-	-	0 (0)	1 (3.8)	-
Enterobacter cloacae		3 (5.7)	0 (0)	1 (5.0)	0 (0)	0 (0)	3 (5.7)	0 (0)	0 (0)	0 (0)	1 (3.8)	0 (0)
Escherichia coli		27 (51)	1 (100)	6 (30)	8 (57)	23 (49)	28 (53)	23 (49)	3 (75)	6 (40)	15 (58)	3 (38)
Klebsiella oxytoca		5 (9.4)	0 (0)	3 (15)	0 (0)	5 (11)	5 (9.4)	5 (11)	0 (0)	2 (13)	0 (0)	1 (13)
Klebsiella pneumoniae		8 (15)	0 (0)	5 (25)	3 (21)	10 (21)	8 (15)	11 (23)	1 (25)	5 (33)	8 (31)	2 (25)
Proteus mirabilis		4 (7.5)	0 (0)	2 (10)	0 (0)	4 (8.5)	4 (7.5)	3 (6.4)	0 (0)	1 (6.7)	0 (0)	2 (25)
Proteus ssp.		-	0 (0)	0 (0)	0 (0)	-	-	-	-	0 (0)	0 (0)	-
Serratia marcescens		-	0 (0)	0 (0)	1 (7.1)	-	-	-	-	0 (0)	0 (0)	-
Serratia odorifera		2 (3.8)	0 (0)	2 (10)	0 (0)	2 (4.3)	2 (3.8)	2 (4.3)	0 (0)	1 (6.7)	0 (0)	0 (0)

Table 4. Resistance profile to Cephalosporin of enterobacteral strain according to their origin.

Com= Community, Hosp=hospital.

Table 5. Resistance profile to Carbapenem of enterobacteral strain according to their origin.

Species		Imipe	nem	Imipe	enem		Ertapenem		Meropenem
	N=111	Com S, n=53	Hosp, s=33	Com SFP, n=17	Hosp, SFP n=1	Hosp R, n=2	Com S, n=2	Hosp S, n=31	Com S, n=18
Citrobacter freundii		2 (3.8)	1 (3.0)	3 (18)	0 (0)	1 (50)	1 (50)	0 (0)	0 (0)
Klebsiella aerogenes		0 (0)	1 (3.0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.2)	0 (0)
Enterobacter cloacae		3 (5.7)	1 (3.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Escherichia coli		34 (64)	20 (61)	5 (29)	0 (0)	0 (0)	0 (0)	19 (61)	13 (72)
Klebsiella oxytoca		3 (5.7)	0 (0)	2 (12)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.6)
Klebsiella pneumoniae		7 (13)	10 (30)	5 (29)	0 (0)	1 (50)	1 (50)	9 (29)	2 (11)
Proteus mirabilis		3 (5.7)	0 (0)	1 (5.9)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11)
Proteus ssp.		0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (3.2)	0 (0)
Serratia marcescens		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.2)	0 (0)
Serratia odorifera		1 (1.9)	0 (0)	1 (5.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Com=Community, Hosp=Hospital, S=susceptible, SFP= susceptible to high posology. The strains categorized as SFP were 15.32% (n=17) at the community level and 0.90% (n=1) at the hospital level. Category R was 1.80% (n=2).

for fosfomycin.

Regarding the overall resistance profile (Figure

1), the most affected antibiotics were penicillins (aminopenicillin and carboxypenicillin),

cephalosporins, and quinolones. Carbapenems retained their activity against the strains, while

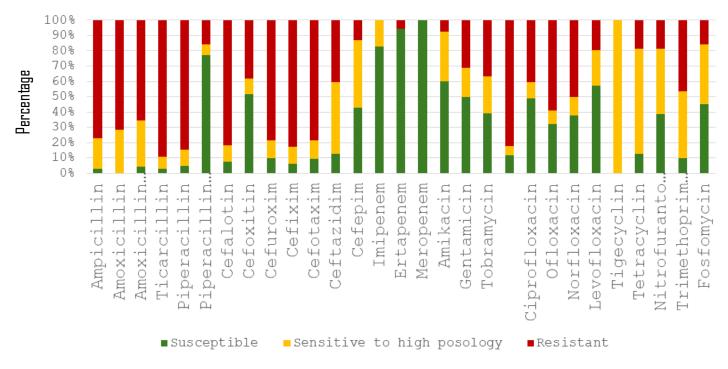


Figure 1. Overall resistance profile of enterobacteral to all antibiotics tested.

tetracyclines showed lower sensitivity.

DISCUSSION

A cross-sectional study was conducted over a period of 15 months (September 2022 to December 2023) with the aim of describina the resistance profile of Enterobacterales isolated from urine samples at the Laboratory of Medical Biology of CHU Donka. The limitation of this study was the duration and the size of the samples from the hospital setting This could be attributed, firstly, to the fact that the laboratory initially started receiving samples from outpatient consultations, and secondly, hospitalizations at CHU began only after 3 months of the facility's opening. However, this does not allow for generalization to the entire population. Nevertheless, the results obtained provide an idea of the current level of resistance and should help clinician for management of patient with urinary tract infection (UTI) and also to encourage the surveillance of antimicrobial resistance in hospital and community setting.

Out of a total of 520 urine samples received and analysed in the laboratory, 111 tested positive for Enterobacterales. This allowed us to outline a comprehensive resistance profile of Enterobacterales to various antibiotic classes commonly used in urinary infections. The antibiotics most affected by resistance were penicillins (amino-penicillins and carboxy-penicillins), cephalosporins, and quinolones (fluoroquinolones), accounting for more than half. It is important to note that with Enterobacterales, there is a risk of spreading these resistances within the group. They possess resistance carriers (plasmids, integrons) that can be shared among them, facilitating the spread of resistance (Partridge et al., 2018; Rozwandowicz et al., 2018).

The strains of *E. coli* were the most isolated, followed by K. pneumoniae. These species are considered the most commonly isolated around the world, both in community and hospital settings. Some studies conducted in Germany, Espana, Peruvia, Ethiopia, Tanzania, and Ghana highlighted the same constatation (Abubaker and Anwar, 2023; Alzahrani et al., 2022; Donkor et al., 2019; Moges et al., 2021; Rondon et al., 2023; Schmider et al., 2022; Stoltidis-Claus et al., 2023). However, this pattern may vary in certain areas, as seen in a study conducted in Sierra Leone, where samples from the community showed a predominance of Citrobacter freundii strains (Leski et al., 2016) and another study among elderly patients living in the community and in the nursing home showed that Proteus mirabilis was the second strains isolated after E. coli (Pulcini et al., 2019).

The resistance profile to penicillins was dominated by high resistance to amino-penicillins and carboxypenicillins. *E. coli* strains showed high resistance to these groups of penicillins, extending to the amoxicillinclavulanic acid combination. This resistance profile has been described in other studies with high prevalence, ranging from 51 to 97.2% for ampicillin and 20.5 to 77.3% for amoxicillin-clavulanic acid (Ahmed et al., 2019; Bernabé et al., 2017; Matalka et al., 2021; Moges et al., 2021; Schmider et al., 2022; Stoltidis-Claus et al., 2023). However, their sensitivity was restored by the combination of penicillin/beta-lactamase inhibitor (tazobactam), as described in other studies with sensitivity rates reaching between 94 and 96.12% (Matalka et al., 2021; Nkont et al., 2023; Schmider et al., 2022).

Resistance to penicillins was similar in both hospital and community settings, with a predominance of E. coli strains. This profile has been previously observed in other studies with variable prevalence rates depending on the regions (Nkont et al., 2023). Study conducted among rural patients in Karnataka (India) showed the high prevalence over than 45% (Mardourian et al., 2023). However, study performed in two French centres describe that Temocillin showed a high level of activity against Enterobacterales strains from community acquired urinary tract infection (UTI) (Alexandre et al., 2018). An increase in resistance to the combination of amoxicillin-clavulanic acid and ticarcillin was described for E. coli strains. Nevertheless, this resistance can be either natural or acquired for certain strains. It corresponds to a group resistance for the wild-type phenotype (Chagneau et al., 2024). The combination of piperacillin-tazobactam could be an alternative for managing infections caused by multidrug-resistant strains (Bader et al., 2017: Long and Kovfman, 2018).

Resistance profile to cephalosporins was impacted with high rates for TGC. E. coli strains showed high rates for TGC, as reported in Benin with 100% resistance of E. coli strains to cefixime and ceftriaxone (Assouma et al., 2023). However, the resistance rate to TCF was about 12.6% for E. coli, K. pneumoniae, and P. mirabilis UTI in Northern California (USA) (Mark et al., 2021) and 18.4% for E. coli, 30.7% for Klebsiella spp. in a systematic review conduction in some west African countries (Nigeria, Senegal, Ghana, Benin, Burkina Faso, and Cote d'Ivoire) (Bernabé et al., 2017). In addition, the activity of FGC remains maintained for all Enterobacterales isolated in our study. Nevertheless, low resistance proportions to FGC, particularly for *E. coli* strains, were noted. This calls for their rational use. Hospital strains showed high resistances as described in other areas, with rates ranging from 43.9 to 77% for E. coli and 49.2 to 72% for K. pneumoniae being resistant to TGC (Abubaker and Anwar, 2023; Rondon et al., 2023). A low level of resistance to FGC for community strains, unlike other studies that reported high rates around 50% (Abubaker and Anwar, 2023). FGC could be an alternative for managing multidrug-resistant strains in our context.

Carbapenems are antibiotics that are effective against Enterobacteral secreting penicillinase and cephalosporinase (Nkont et al., 2023). Strains categorized as "sensitive at high dosage (SHD)" or resistant to at

least one of the carbapenems can be considered suspicious of producing a carbapenemase. These strains are producers of significant resistance mechanisms, including carbapenemases (Comité de l'Antibiograme de la Société Française de Microbiologie, 2023). A low rate of resistance was observed to carbapenems and an increase in strains categorized as SHD. This profile has been described in other studies with prevalence rates of 0.9% for E. coli and 3.2% for K. pneumoniae to carbapenem (García-Castillo et al., 2018; Rondon et al., 2023). However, in a study on the confirmation of the carbapenem profile of Enterobacterales, only 8.9% were confirmed resistant (Steward et al., 2003). Another study conducted in Benin reported resistance rates ranging from 12.5 to 66.6% of Enterobacterales to imipenem (Assouma et al., 2023). This low resistance rate to carbapenems could make these antibiotics an option for managing multidrug-resistant bacteria in our context and Ceftazidime-avibactam could be used to manage UTI caused by carbapenemase producing Enterobacteral such as KPC and OXA-48 producers (García-Castillo et al., 2018). Nevertheless, the increase in strains categorized as SHD should alert and lead to the search for carbapenemases. Another study conducted over the 20-year period showed that except carbapenems, all the antibiotics tested showed increasing resistance rate (Milano et al., 2022).

The resistance to aminoglycosides was high, affecting a quarter of the strains. The main aminoglycosides affected were gentamicin and tobramycin. Twenty-five percent of hospital strains were affected by this resistance. Higher rates have been described in other studies. In Iran the resistance rate was 47.9% for tobramycin, 39.3% for kanamycin, and 27.8% for gentamicin (Yekani et al., 2018) and in India the rate was 31% for all aminoglycosides (Mardourian et al., 2023). In Nigeria, the study conducted among pediatric population found 96.9% of resistance to kanamycin (Oli et al., 2019). These molecules, often used in the management of urinary tract infections due to their good diffusion, could be limited by the emergence of resistance.

Resistance to guinolones was high, with an overall proportion of 53%. It involved nalidixic acid, which was higher in hospital strains, and fluoroquinolones with the same proportions in hospital and community strains. High rates have been described, ranging from 32 to 63.2% of E. coli strains resistant to fluoroquinolones (Lyonga et al., 2015; Mardourian et al., 2023; Moirongo et al., 2020; Rondon et al., 2023; Schmider et al., 2022). As described in some studies, the resistance to quinolones is mediated by plasmid and more examination should be conducted in case of strains exhibiting reduced susceptibility and intermediate phenotype (Pasom et al., 2013; Szabó et al., 2018). This increase in resistance for this group raises concerns about the rational use of these molecules, as they are used in the management of multidrug-resistant bacteria (MDR) (Bader et al., 2017).

All strains tested for tetracycline were categorized as sensitive to high dosage. A study conducted in four sub-Saharan African countries reported an overall prevalence of 17%, with rates varying from 7 to 23% depending on the countries (Moirongo et al., 2020). Concerning other antibiotics, resistance was high for fosfomycin and trimethoprim-sulfamethoxazole, with a predominance among K. pneumoniae strains in the community and E. coli strains in the hospital setting. In contrast to other reported widespread sensitivity authors who to fosfomycin and strong resistance to trimethoprimsulfamethoxazole (Schmider et al., 2022), a study conducted in sub-Saharan Africa reported prevalence ranging from 42 to 100% (Moirongo et al., 2020).

Conclusion

This study provided insight into the resistance profile of enterobacteral to antibiotics used in urinary tract infections. The observed resistance is substantial in both hospital and community environments. Additionally, the increasing resistance to carbapenems presents a challenge to the management of strains producing extended-spectrum beta-lactamases (ESBL). It would be important to strengthen resistance surveillance in this context.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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