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Co-Prevalence of Quinolone Resistance and Extended-Spectrum Beta-Lactamases among Clinical *Enterobacteriaceae* Isolates from a Tertiary Hospital in Katsina, Nigeria

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Abstract

Antimicrobial resistance (AMR) poses a major hazard to global public health. It reduces the effectiveness of many antibiotics, making infections harder to cure and raising the likelihood of disease transmission and death. Globally, beta-lactam and quinolone antibiotics are among the commonly prescribed medications. Yet, a multitude of bacteria have evolved distinct multidrug resistance (MDR) characteristics, rendering many of these important drugs worthless. This study aimed to investigate the magnitude of the simultaneous occurrence of Extended-Spectrum Beta-Lactamases (ESBLs) and Quinolone-resistance (co-existence) among clinical Enterobacteriaceae isolates. A total of 95 Enterobacteriaceae pathogens isolated from different human samples were obtained from a Tertiary Hospital in Katsina. Then, the VITEK-2 Compact automated identification system was employed for the identification and antimicrobial susceptibility testing (AST) and the ESBL screening of isolates. This study showed that out of the total 95 isolates, 67 (70.5%) were quinolone-resistant, while 53 (55.8%) were ESBL-positive. Most of the quinolone-resistant (QRE) Enterobacteriaceae were ESBL-positive, 50 (74.6%), and conversely, most of the ESBL-positive Enterobacteriaceae were quinolone-resistant (50, 94.3%). Co-resistance (quinolone-resistance and ESBL-positive) was recorded in 50 (52.63%) of the isolates, all belonging to the Escherichia coli (42, 84.0%) and Klebsiella pneumoniae (8, 16.0%). Almost all the co-resistant isolates were resistant to the tested quinolones [Ciprofloxacin (49, 98.0%) and Levofloxacin (50, 100.0%). The lowest resistance was recorded to Ertapenem (6.0%), Meropenem (6.0%), and Amikacin (2.0%) and the highest to Ampicillin, Piperacillin and Levofloxacin (100.0% each). Almost all the co-resistant isolates were multidrug-resistant (MDR), 49 (98.0%), while 33 (66.0%) were extensively drug-resistant (XDR). According to the collected samples' demographic data, the highest prevalences were recorded among males (60.0%, based on gender), adults (50.0%, based on age), and urine (48.0%, based on sample). Continuous surveillance and stewardship are essential to achieve good health and well-being (Sustainable Development Goal 3).

Keywords: Antibiotic resistance, Enterobacteriaceae, ESBLs, multidrug resistance, quinolone resistance.

INTRODUCTION

Among the major concerns for global public health has been the evolution and spread of antibiotic resistance among *Enterobacteriaceae* and other microbial groupings. It becomes more complicated when multiple resistance characters, such as the Extended-Spectrum Beta-Lactamases (ESBLs) and quinolone resistance, co-occur among such bacterial groups, thus resulting in the ensuing multidrug resistance. The overall implications include limiting treatment options, leading to increased morbidity, mortality, and healthcare costs (Ahmed *et al.*, 2024; Okeke *et al.*, 2024).

A class of enzymes known as Extended-spectrum ß-lactamases (ESBLs) confers resistance to a variety of beta-lactam antibiotics, such as aztreonam and third-generation cephalosporins. They are produced by some Gram-negative bacterial groups, principally the *Enterobacteriaceae* family; examples include *Escherichia coli* and *Klebsiella pneumoniae* (Kimera *et al.*, 2021; Éric *et al.*, 2024; Tetteh *et al.*, 2024). These ESBL-producing bacteria often exhibit a multidrug-resistant character, where they tend to resist other important classes of antibacterials such as the cephalosporins, carbapenems, aminoglycosides, and quinolones (Egbule and Ejechi, 2021; Kimera *et al.*, 2021; Éric and Papy, 2024).

Conversely, resistance to quinolone (such as Ciprofloxacin and Levofloxacin) reduces the efficacy and effectiveness of the fluoroquinolone antibiotics (Kariuki *et al.*, 2023; Shrestha *et al.*, 2023). The plasmid-mediated quinolone resistance (PMQR) genes, such as qnrA, qnrB, and qnrS, have been detected in ESBL-producing *Enterobacteriaceae* isolates as well (Kariuki *et al.*, 2023; Shrestha *et al.*, 2023). Although the PMQR genes confer low-level resistance to quinolones, they often facilitate the selection of additional chromosomal mutations, leading to high-level resistance (Kariuki *et al.*, 2023). Thus, the co-existence of such resistance traits (chromosomal mutations) and plasmids, being a mobile genetic element, indicates higher concerns for antimicrobial resistance spread (Nair *et al.*, 2024).

Several studies have reported the co-prevalence of ESBLs and quinolone resistance in different bacterial isolates recovered from various clinical and environmental samples around the globe (Pakzad *et al.*, 2011; Farajzadeh *et al.*, 2019; Xiong *et al.*, 2021; Furmanek-Blaszk *et al.*, 2023; Kariuki *et al.*, 2023; Abdelrahim *et al.*, 2024), however, studies/data in Nigeria, and more specifically in the Katsina State of Nigeria, are limited. Thus, to provide valuable insights into the local resistance epidemiology and guide empirical antibiotic therapy, this study aimed to investigate the co-occurrence of ESBLs and quinolone resistance among clinical *Enterobacteriaceae* isolates in a Tertiary Hospital in Katsina, Katsina, Nigeria.

MATERIALS AND METHODS

Ethical Approval and Sample Collection

Ethical approval (with reference number FMCNHRED. REG.N003/08/2012) was obtained from the Federal Teaching Hospital Katsina. A total of 95 suspected and non-duplicate clinical isolates of *Enterobacteriaceae* isolates recovered from different clinical samples (blood, catheter, high vaginal swabs, sputum, stool, throat, urine and wound) were obtained from the Microbiology laboratory of Federal Medical Centre, Katsina (from September 2020 – August 2021). Isolates were subcultured onto a Nutrient agar and stored accordingly. The biodata of the patients from which these isolates were recovered were also obtained.

Identification of the Clinical *Enterobacteriaceae* Isolates, Antimicrobial Susceptibility Profile, and Extended-Spectrum Beta Lactamases (ESBLs) Screening

The VITEK-2® compact automated identification system was employed to identify the *Enterobacteriaceae* isolates and carry out the antimicrobial susceptibility testing and the Extended-Spectrum Beta Lactamases (ESBLs) screening.

The collected isolates were subcultured on Nutrient agar (NA) to ensure pure cultures were obtained; MacConkey Agar (MAC) and Cystein-Lactose-Electrolyte-Deficient (CLED) Agar were used for the cultural identifications. Isolates were further subjected to Gram-stain procedures and then microscopically identified to confirm the isolates' Gram status and other microscopic features (shapes and arrangements).

As instructed by the manufacturer, the Identification (ID) Card suspensions were prepared using overnight purely grown MacConkey Agar colonies. A 0.5 McFarland standard was prepared while using the machine's DensiCHEK™ to confirm the optical densities. All tubes and cards were then appropriately set into their cassettes, and all other parameters were set accordingly.

The antimicrobial susceptibility/ESBL test card suspension preparation was prepared using overnight grown cultures on the MacConkey Agar plates, which were then transferred into the suspension tubes. All cards were filled and loaded into the automated system, and all parameters were set according to the manufacturer's instructions. The system was allowed to run until completion. Finally, the outcome of the identification, antimicrobial susceptibility, and ESBL status was read, recorded, and automatedly interpreted by the machine using the Clinical and Laboratory Standards Institute (CLSI) recommendations (CLSI, 2020).

Grouping of ESBL-Positive and Quinolone-Resistant *Enterobacteriaceae* isolates into specific Multidrug Resistance Classes

The result of the antibiotic susceptibility testing (AST) was used to group the organisms into specific resistance classes as recommended by the World Health Organization (Magiorakoss *et al.*, 2012). They are multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR). MDR = non-susceptible to ≥1 agent in ≥3 antimicrobial categories; XDR = non-susceptible to ≥1 agent in all but ≤2 categories; and PDR = non-susceptible to all antimicrobial agents.

RESULTS

A total of thirteen (13) bacteria species were identified (n = 95); *Escherichia coli* was the most frequent (58, 61.05%), followed by *Klebsiella pneumoniae* (15, 15.79%), *Morganella morganii*, (5, 5.26%), *Enterobacter aerogenes* and *Enterobacter cloacae dissolvens* (4, 4.21% each), *Proteus mirabilis* (2, 4.21% each), *Citrobacter freundii, Enterobacter georgoviae, Klebsiella oxytoca, Salmonella typhi, Serratia fonticola, Serratia mercescens,* and *Vibrio cholerae* (1, 1.05% each) (Table 1).

Extended-Spectrum Beta Lactamases (ESBLs) Screening among Clinical *Enterobacteriaceae* Isolates

Among all the thirteen (13) *Enterobacteriaceae* groups screened for ESBL, the ESBL-positive isolates accounted for 53 (55.8%), and the ESBL-negative isolates accounted for 42 (44.2%). Only *Escherichia coli* and *Klebsiella pneumoniae* were found to be the ESBL-positive species (Table 1).

Table 1: Prevalence of Extended-Spectrum Beta Lactamases (ESBLs) among Clinical *Enterobacteriaceae* Isolates

S/N	Organism	ESBL		Total
		Negative	Positive	
1.	*Citrobacter freundii*	1	0	1
2.	*Enterobacter aerogenes*	4	0	4
3.	*Enterobacter cloacae dissolvens*	4	0	4
4.	*Enterobacter georgoviae*	1	0	1
5.	*Escherichia coli*	14	44	58
6.	*Klebsiella oxytoca*	1	0	1
7.	*Klebsiella pneumoniae*	6	9	15
8.	*Morganella morganii*	5	0	5
9.	*Proteus mirabilis*	2	0	2
10.	*Salmonella typhi*	1	0	1
11.	*Serratia fonticola*	1	0	1
12.	*Serratia mercescens*	1	0	1
13.	*Vibrio cholerae*	1	0	1
	Total	**42 (44.2%)**	**53 (55.8%)**	**95 (100.0%)**

Antimicrobial Susceptibility Profile and ESBLs Screening of Clinical *Enterobacteriaceae* Isolates

Based on antibiotic susceptibility testing (Table 2; Figure 1), the highest resistance (non-susceptibility) was recorded to Ampicillin, Piperacillin and Levofloxacin (100.0% each), while the lowest was to Ertapenem and Meropenem (6.0% each), and Amikacin (2.0%). Almost all the co-resistant *Enterobacteriaceae* were resistant to all the tested quinolones [Ciprofloxacin (49/50, 98.0%) and Levofloxacin (50/50, 100.0%).

Of the *Enterobacteriaceae* isolates, 67/95 (70.5%) were resistant to at least one member of the tested quinolone antibiotics (Table 3). A high frequency of ESBLs among the Quinolone-resistant *Enterobacteriaceae* (50/67, 74.6%) was recorded; *Escherichia coli* (42/67, 62.7%) and *Klebsiella pneumoniae* (8/67, 11.9%) being the only ESBL-positives, as the other seven (7) species were ESBL-negative (17/67, 25.4%) (Table 3). Conversely, out of the 53 ESBL-positive isolates, 50 (94.3%) were resistant to at least one member of the quinolones, as only 3 (5.7%) were susceptible (Table 4).

Table 2: Antimicrobial Susceptibility Result of the ESBL-Positive Quinolone-Resistant (Co-resistant) *Enterobacteriaceae*

Bacteria	Pattern	Antibiotics (%)																	
		Ampicillin	Ampicillin-sulbactam	Piperacillin	Cefazolin	Cefoxitin	Ceftazidime	Ceftriaxone	Cefepime	Ertapenem	Meropenem	Amikacin	Gentamicin	Tobramycin	Ciprofloxacin	Levofloxacin	Nitrofurantoin	Trimethoprim - sulphamethoxazole
E. coli	S	0.0	7.1	0.0	2.6	54.8	2.4	2.5	2.4	93.0	93.0	97.6	41.5	25.6	2.4	0.0	75.0	7.5
(n = 42)	I	0.0	7.1	0.0	0.0	11.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11.6	0.0	0.0	15.0	0.0
	R	100	85.7	100	97.4	33.3	97.6	97.5	97.6	7.0	7.0	2.4	58.5	62.8	97.6	100	10.0	92.5
K. pneumoniae	S	0.0	0.0	0.0	0.0	75	0.0	0.0	0.0	87.5	87.5	100	25	0.0	0.0	0.0	62.5	0.0
	I	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12.5	0.0	0.0	12.5	0.0
(n = 8)	R	100	100	100	100	25	100	100	100	12.5	12.5	0.0	75	87.5	100	100	25	100

Key: S- Susceptible; I- Intermediate; R- Resistant; n- Number of isolates (count)

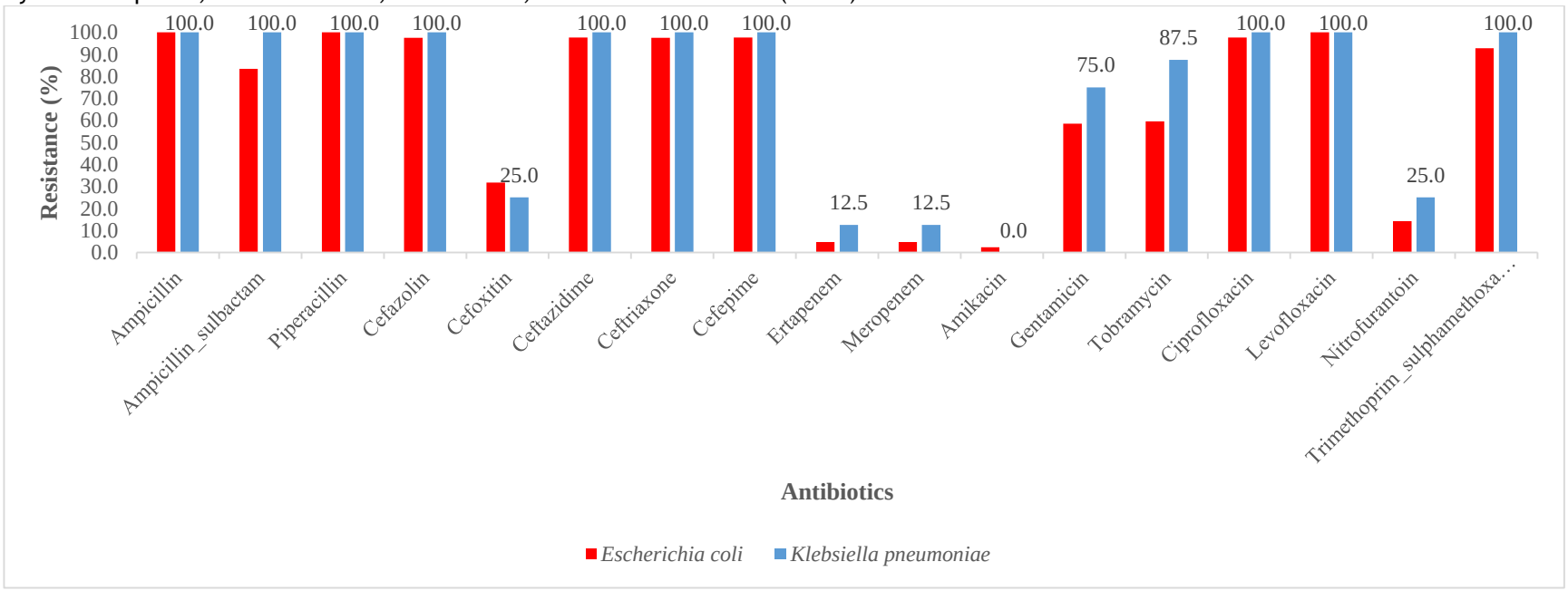

Figure 1: ESBL-Positive Quinolone-Resistant *Enterobacteriaceae* Resistance Profile

Table 3: Extended-Spectrum Beta Lactamases (ESBLs) Screening among Quinolone-resistant *Enterobacteriaceae* (QRE) Isolates

S/N	Organism	ESBL		Total
		Negative	Positive	
1.	*Citrobacter freundii*	1	0	1
2.	*Enterobacter cloacae dissolvens*	1	0	1
3.	*Escherichia coli*	6	42	48
4.	*Klebsiella pneumoniae*	1	8	9
5.	*Morganella morganii*	3	0	3
6.	*Proteus mirabilis*	2	0	2
7.	*Serratia fonticola*	1	0	1
8.	*Serratia mercescens*	1	0	1
9.	*Vibrio cholerae*	1	0	1
	Total	**17**	**50**	**67**

Table 4: Prevalence of Quinolone-Resistance among ESBL-Positive *Enterobacteriaceae* Isolates

S/N	Specie	Quinolones		Total
		Susceptible	Resistant	
1.	*Escherichia coli*	2	42	44
2.	*Klebsiella pneumoniae*	1	8	9
	Total	**3 (5.7%)**	**50 (94.3%)**	**53 (100%)**

Co-prevalence of Quinolone Resistance and Extended-Spectrum Beta Lactamases among Clinical *Enterobacteriaceae* Isolates

Overall, quinolone-resistance and ESBL (co-resistance) were recorded in 50/95 (52.7%), of which *E. coli* accounted for 42 (84.0%), while *K. pneumoniae* accounted for 8 (16.0%). No co-resistance was recorded in other bacterial species, 45 (47.4%) (Table 5).

Table 5: Co-prevalence of Quinolone Resistance and Extended-Spectrum Beta Lactamases (ESBLs) among Clinical *Enterobacteriaceae* Isolates

	Escherichia coli	*Klebsiella pneumoniae*	Total
Co-resistance	42	8	50

Grouping of ESBL-Positive Quinolone-Resistant *Enterobacteriaceae* Isolates according to Multidrug Resistance Classes

Out of the 50 ESBL-Positive Quinolone-Resistant *Enterobacteriaceae*, 49/50 (98.0%) were Multidrug-resistant (MDR), 33/50 (66.0%) were Extensively drug-resistant (XDR) and 1/50 was Not MDR. Among the *K. pneumoniae* and *E. coli* species, the result showed the presence of MDR (8 and 41), XDR (7 and 28) and Not MDR (0 and 1), respectively. No Pandrug-resistant (PDR) bacteria were recorded throughout the study (Figure 2).

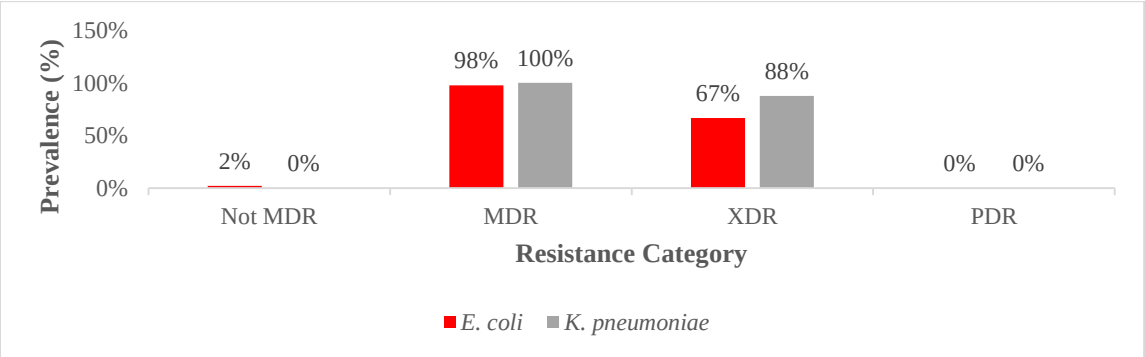

Figure 2: Grouping of ESBL-Positive Quinolone-Resistant *Enterobacteriaceae*Isolates according to Multidrug Resistance Classes

Key: MDR (Multidrug-resistant)- non-susceptible to ≥1 agent in ≥3 antimicrobial categories; **XDR** (Extensively drug-resistant)- non-susceptible to ≥1 agent in all but ≤2 categories; **PDR** (Pandrug-resistant)- non-susceptible to all antimicrobial agents.

Distribution of ESBL-Positive Quinolone-Resistant *Enterobacteriaceae* among Clinical Samples

Figure 3 presents the distribution of the ESBL-Positive Quinolone-Resistant *Enterobacteriaceae* isolates among various clinical samples; the highest number of the isolates were recovered from Urine, 24 (48.0%) and Wound, 15 (30.0%) and the least from Sputum, 1 (2.0%).

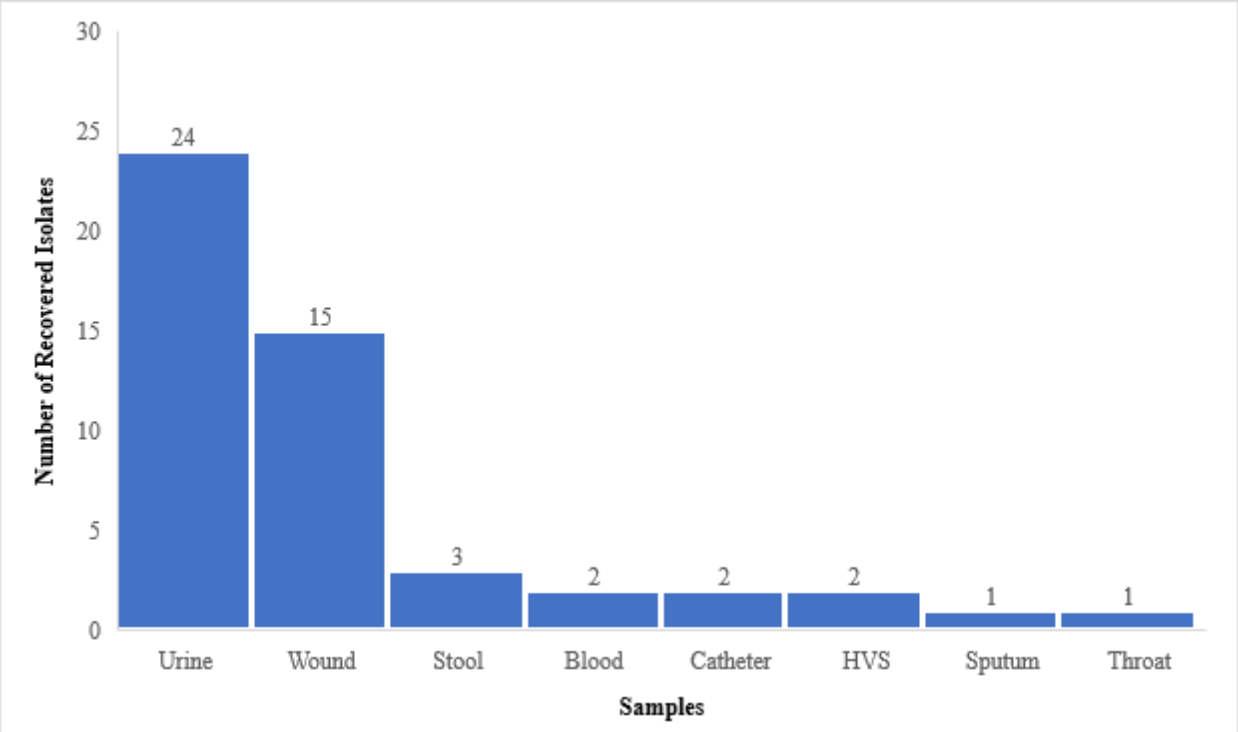

Figure 3: Distribution of ESBL-Positive Quinolone-Resistant *Enterobacteriaceae* according to Clinical Samples

Distribution of ESBL-Positive Quinolone-Resistant *Enterobacteriaceae* according to Genders

The ESBL-Positive Quinolone-Resistant *Enterobacteriaceae* isolates were more predominant among males, 30 (60.0%) gender than their female counterparts, 20 (40.0%).

Distribution of ESBL-Positive Quinolone-Resistant *Enterobacteriaceae* according to Ages

Subjects were classified into five (5) different age categories. They are Infants (less than 1 year), Children (1-11 years), Adolescents (12-18 years), Adults (19-59 years) and Senior Adults (60 years and above) (Nithyashiri and Kulanthaivel (2012). The highest positive isolates were recorded in the Adults group, 25 (50.0%), and the lowest in the Adolescents group, 1 (2.0%) (Figure 4)

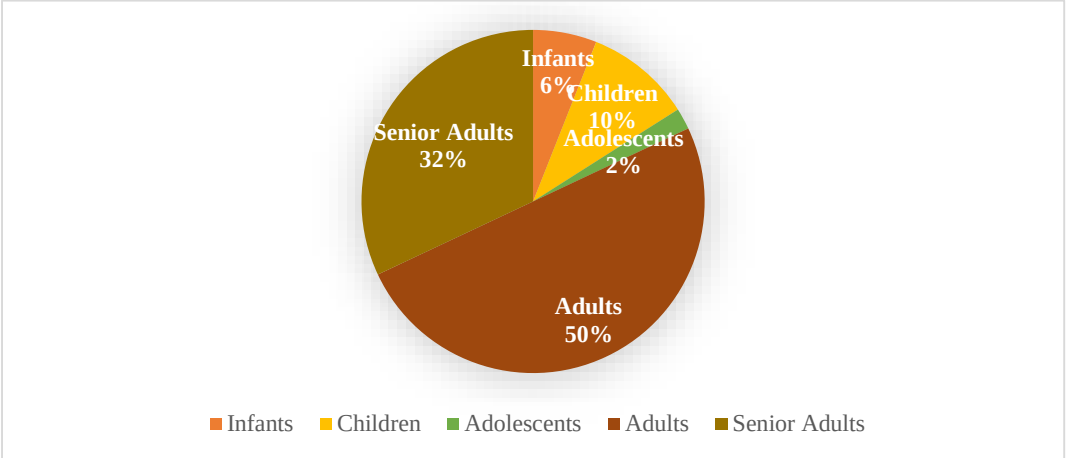

Figure 4: Distribution of ESBL-Positive Quinolone-Resistant *Enterobacteriaceae* According to Ages

DISCUSSION

Based on the ESBL screening performed in this study, only *Escherichia coli* and *Klebsiella pneumoniae* species were found to be ESBL-positive (55.8%) among the isolates and the Quinolone-resistant *Enterobacteriaceae* (QRE), (74.6%). Thus, this signifies that ESBL is majorly produced by *E. coli* and *K. pneumoniae* and even much higher among the Quinolone-resistant *Enterobacteriaceae* isolates, thereby agreeing with other reports (Kimera *et al.*, 2021; Éric *et al.*, 2024; Tetteh *et al.*, 2024).

Moreover, this study also showed an escalated resistance to all the two (2) quinolones tested against the ESBL-positive *Enterobacteriaceae* (Table 2; Figure 1). This proves that the majority of Quinolone-resistant *Enterobacteriaceae* are usually ESBL-positive (co-resistance) and thus a very important problem of concern.

This study also showed that most of the ESBL-positive QRE were resistant to almost all the 17 antibiotics tested, with 60.0 - 100% resistance recorded to 12 out of the 17 antibiotics and 2.0 - 16.0% resistance recorded to four (4/17) of the antibiotics. Therefore, proving that Ertapenem, Meropenem and Amikacin (with 6.0%, 6.0% and 2.0% resistance, respectively) would likely be the most effective treatment options against the ESBL-positive QRE. The highest and lowest resistance recorded in this study is similar to that of Tetteh *et al.* (2024), who reported the least resistance to Amikacin (36.0%) and Meropenem (0.0%) and highest to Ampicillin (96.0%) among ESBLs-producing *K. pneumoniae* and *E. coli* clinical isolates from a teaching hospital in Ghana. Moreover, this study's resistance pattern was relatively similar to the study of Egbule and Ejechi (2021), who reported a 100% resistance to ceftazidime, cefotaxime, and cefuroxime and a low resistance to nitrofurantoin- a study on clinical isolates of *K. pneumoniae* and *E. coli* recovered from hospitalized patients in the Delta State of Nigeria. Also, the study of Nwanko *et al.* (2015) reported a high-level resistance against quinolones and aminoglycosides among ESBL producers.

Furthermore, the outcome of this study is indeed worrisome and worth noting as almost all the ESBL-positive QRE in the study area were Multidrug-resistant (MDR, 98.0%), as 66.0% of the tested enteric bacteria were Extensively drug-resistant (XDR), and this is higher among the ESBL-positive QRE. This is valid as compared to other studies, such as the study of Tekele *et al.* (2021), who reported a prevalence of 68.6% MDR among *Enterobacteriaceae* (using an automated system for the AST)- even though this study reported a higher prevalence of the MDR isolates.

Based on the demographic (bio) data, the ESBL-positive QRE was most prevalent in Males (60.0%), Adults (50.0%), and Urine (48%) among gender, age, and clinical samples, respectively. This conforms with other studies that reported the highest frequencies of the *Enterobacteriaceae* in Adults than in neonates (Mujahid *et al.*, 2023; Tetteh *et al.*, 2024), Males and Urine (Tekele *et al.*, 2021; Mujahid *et al.*, 2023). Among the possible reasons for the high prevalence in males may be due to the urogenital anatomy and sociocultural factors; in adults, it may be due to increased antibiotics exposure; while in urine, it may be due to urinary catheterization and urinary tract being a common microbial colonization site.

Looking at the high co-prevalence of the ESBL and quinolone resistance, as well as multidrug resistance among the clinical *Enterobacteriaceae* isolates, further studies are therefore recommended to be carried out in the study area for a more efficient monitoring/surveillance and enactment of proper measures. Overall, this will go a long way in contributing to good health and well-being (Sustainable Development Goal, SDG 3).

CONCLUSION

Most of the screened *Enterobacteriaceae* isolates were ESBL-positive (55.8%) and resistant to the tested fluoroquinolones. Most of the ESBL-positive *Enterobacteriaceae* (94.3%) were quinolone-resistant, as most of the quinolone-resistant *Enterobacteriaceae* (QRE) (74.6%) were ESBL-positive. Co-resistance (quinolone-resistance and ESBL-positive) was recorded in 50/95 (52.63%) of the isolates, of which 84.0% were recorded in *E. coli* and 16.0% in *K. pneumoniae*. Almost all co-resistant isolates were multidrug-resistant (MDR, 98.0%), while 66.0% were extensively drug-resistant (XDR). For efficient surveillance and proper antibiotic stewardship, further studies on co-prevalence of the quinolone-resistance and ESBL-associated genes among *Enterobacteriaceae* in the study area are recommended.

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