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**Detection of Extended Spectrum Beta-  
Lactamase Producing Enterobacteriaceae Isolates from Children with  
Gastrointestinal infection in Ilorin, Kwara state**

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**ABSTRACT**

The emergence of antimicrobial resistance (AMR) is considered one of the most significant public health challenges of the 21<sup>st</sup> century, posing serious risks to the effective treatment of infections, and threatening to undo decades of medical progress. This study aims to investigate the phenotypic patterns of extended spectrum beta- lactamases (ESBL) producing Enterobacteriaceae in isolates obtained from two hospitals in Ilorin. A total of eighty- four non-duplicate stool samples were collected from children who had gastroenteritis. Bacterial isolation was carried out following standard laboratory procedures, and presumptive Gram-negative bacilli were stored on nutrient agar slants at 4°C until needed. Forty (40) presumptive gram- negative bacterial isolates were sub-cultured, purified, and identified using Microbact 12E identification kit. Isolates were screened for antibiotic susceptibility using the Kirby-Bauer disc diffusion method and thereafter screened for the production of ESBLs. Identified isolates include: *Klebsiella* spp. (16), *Acinetobacter* spp. (3), *Enterobacter* spp. (9), *Citrobacter* spp. (2), *Morganella* spp. (1), *Providencia* spp. (1), *Yersinia* spp. (1), *Serratia* spp. (6), and *Proteus* spp. (1). Imipenem showed the highest activity against the Enterobacteriaceae isolates by 92.5% followed by gentamicin, ciprofloxacin, ceftazidime, then sulphamethoxazole/ trimethoprim, amoxicillin clavulanate, tetracycline and amoxicillin had the least activity against the isolates by 17.5%. Twenty-one (21/40) multi-drug resistant Enterobacteriaceae isolates showing resistance to  $\geq 3$  antibiotics were identified, and 15 (71.43%) were phenotypically confirmed as ESBL producing Enterobacteriaceae with 10/15 (66.67%) being from *Klebsiella* spp, 26.67% belonging to the *Enterobacter* specie and 6.67% belonging to *Serratia* specie. A moderately high rate (37.50%) of ESBL producers were identified among the Enterobacteriaceae isolates screened. This study has revealed that there is a rising antibiotic resistance and increasing prevalence of ESBLs among the Enterobacteriaceae family, which is of public health concern. There is therefore the need for control strategies to be implemented in our hospital and community settings.

**Keywords:** Antimicrobial resistance, Enterobacteriaceae, ESBL producers, Children, stool.

**1.0 INTRODUCTION**

Antimicrobial resistance remains a rapidly evolving problem that faces the health sector (Prestinaci et al., 2015). According to World Health Organization (WHO), drug resistant infections are estimated to cause 700,000 deaths annually, and this could rise to 10million by 2050, if the current trends continue (WHO, 2019). Antimicrobial resistance compromises the efficacy of antibiotics, leading to longer illnesses, higher medical costs and increased mortality (WHO, 2023). A series of mechanisms for antimicrobial resistance has been identified with the most prevalent mechanism as the production of inactivating enzymes (Devi et al., 2024). Extended-spectrum  $\beta$  lactamases (ESBLs), are enzymes who have the ability to hydrolyze various types of the

newer  $\beta$ -lactam antibiotics, including the extended-spectrum or third-generation cephalosporins (e.g., cefotaxime, ceftriaxone, ceftazidime), and monobactams (e.g., aztreonam) but not the cephamycins (e.g., cefoxitin and cefotetan) and carbapenems (e.g. Imipenem, meropenem, and ertapenem) (Akpaka et al., 2021; CDC 2024). Extended-Spectrum Beta-Lactamase (ESBL)-producing Enterobacteriaceae pose a major public health threat and challenge due to their high resistance to beta-lactam antibiotics, ability to spread resistance genes, and limited treatment options leading to morbidity and mortality (Husna et al.,2023). The most common organisms capable of producing these enzymes are *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* (CDC, 2024; PHE, 2014; Woerther et al., 2013)

. Other Enterobacteriaceae documented as ESBL producers include; *Acinetobacter baumannii*, *Proteus mirabilis*, *Salmonella typhimurium*, *Enterobacter* spp. and *Pseudomonas aeruginosa* (Saleh et al., 2024; Shaikh et al., 2015; CDC, 2024).

This study aims to investigate the prevalence and antibiogram patterns of Extended-Spectrum Beta-Lactamase (ESBL)-producing Enterobacteriaceae in stools of children with gastroenteritis from the Civil Service Hospital and General Hospital, Ilorin. This research will contribute to raising awareness about the emergence of these resistant strains, enhancing our understanding of the epidemiology and evolution of ESBLs in the Ilorin region and providing valuable data to assist clinicians in developing effective and efficient therapeutic strategies.

## 2.0 MATERIALS AND METHOD

### 2.1 Study Area, Design and Population

The study was conducted in the Civil Service clinic and General Hospital in Ilorin, the capital city of Kwara state, Nigeria, over a period of 3 months (April to June, 2019). The research took the form of a descriptive cross-sectional study, in which children with suspected gastroenteritis who were present at the hospitals were recruited. A total of 40 children with age range between 2 and 12 years were consecutively recruited over the period of the study. The inclusion criteria included children with gastroenteritis at the study area and those who gave consent to participate in the study. Children and care givers who could not give informed consent, and those who had taken antibiotics within the last 2 weeks, at the same time of collection were excluded.

### 2.2 Ethical consideration:

Ethical approval was obtained from the Ethical Review Committee of the Ministry of Health, Ilorin, with identification number MOH/KS/777/284 and written informed consent was obtained from the participants before inclusion in the study.

### 2.3 Data and Sample collection:

A pretested structured questionnaire was used to interview the patients. Information sought on the questionnaire included: age of the patient, history of suggestive infection and ingestion of antibiotics in the preceding two weeks.

After seeking and obtaining consent, appropriately labelled sterile disposable universal bottles were given to each participant for collection of clean stool specimen following explanation of the procedure for such

collection. The samples were immediately transported to the department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, University of Ilorin for analysis.

### 2.4 Sample Culturing and Isolation

A total of forty (40) samples were collected and cultured in previously sterilized nutrient broth, incubated for 18-24 hours at 37°C. Overnight cultured inoculum was then transferred to different media using standard procedures as described by Cheesebrough (2006). Isolates which were presumptively identified as gram-negative bacilli were stored on nutrient agar slants in the Pharmaceutical Microbiology and Biotechnology laboratory, Faculty of Pharmaceutical Sciences, University of Ilorin.

#### 2.4.1 Identification Tests

The oxidase test was first carried out using Oxidase strip (Oxoid Ltd, England). Identification of the oxidase negative isolates was done using the Microbact 12E Gram – negative bacilli identification kit. The kit contained reaction wells for Glucose, Mannitol, Hydrogen Sulphide, lysine, Ornithine, Xylose, Indole, Urease, Voges-proskauer, Citrate and Tryptophan Deaminase. The tests were carried out according to the manufacturer's specifications. The colour changes were read and octal codes generated for the interpretation using the interpretative charts from the protocol.

### 2.5 Antibiotic Susceptibility Testing

The antibiotic susceptibility of the identified *Enterobacteriaceae* isolates using eight (8) antibiotics were determined using the Kirby-Bauer disc diffusion method as described by the Clinical and Laboratory Standard Institute (CLSI), 2020.

#### 2.5.1 Phenotypic determination of Extended Spectrum Beta-Lactamase production

Overnight cultures of the multi-drug-resistant isolates on Mueller-Hinton agar were subjected to further testing using the Kirby- Bauer disc diffusion method in which 3<sup>rd</sup> generation cephalosporins (Ceftriaxone, Cefpodoxime, Cefotaxime and Ceftazidime) and a monobactam (Aztreonam) were used to determine if the isolates were ESBL producers. Interpretation of the diameters of zones of inhibition was carried out using CLSI 2020.

#### 2.5.2 Extended Spectrum Beta-Lactamase production Confirmatory test

The isolates were subjected to Phenotypic confirmatory disc diffusion test using Cefpodoxime (10 µg) alone and

in combination with Clavulanic acid (10 µg) according to Derbyshire *et al.*, (2009). Cefotaxime (30 µg) alone and in combination with Clavulanate (10 µg) were also used as described by Lin *et al.*, 2010. Isolates that showed a difference of  $\geq 5$ mm in the zones of inhibitions of the

individual antibiotic discs when compared to their corresponding combinations were confirmed as ESBL producers (CLSI, 2020).

### 3.0 RESULTS

Plate 1 shows the colour changes observed for the biochemical reaction of selected isolates on Microbact plate. The Enterobacteriaceae isolates identified showed *Klebsiella* spp as the most prevalent organisms, followed by *Enterobacter* spp, then *Acinetobacter* spp followed by *Citrobacter* spp then *Serratia* spp and other organisms identified include *Morganella* spp., *Providencia* spp., *Yersinia* spp., and *Proteus* spp. as shown in figure 1. Imipenem was observed to show the highest activity against the isolates, followed by gentamicin, then ciprofloxacin and the least activity against the isolates was exhibited by Amoxicillin (Table 1). Table 2 shows fifteen multidrug resistant isolates with MARI range of between 0.5 – 0.88 which were observed to show eleven phenotypic resistance patterns. A total of 21 MDR isolates were phenotypically screened for the production of ESBLs and 16 (76.19%) of them were observed to show resistance to aztreonam and at least one of the cephalosporins used (Table 3). Then twenty out of the 21 MDR Enterobacteriaceae isolates were further taken for phenotypic disc diffusion test, and fifteen (15) of them were confirmed as ESBL producers giving us a rate of 71.43% (Plate 2 and Table 4).

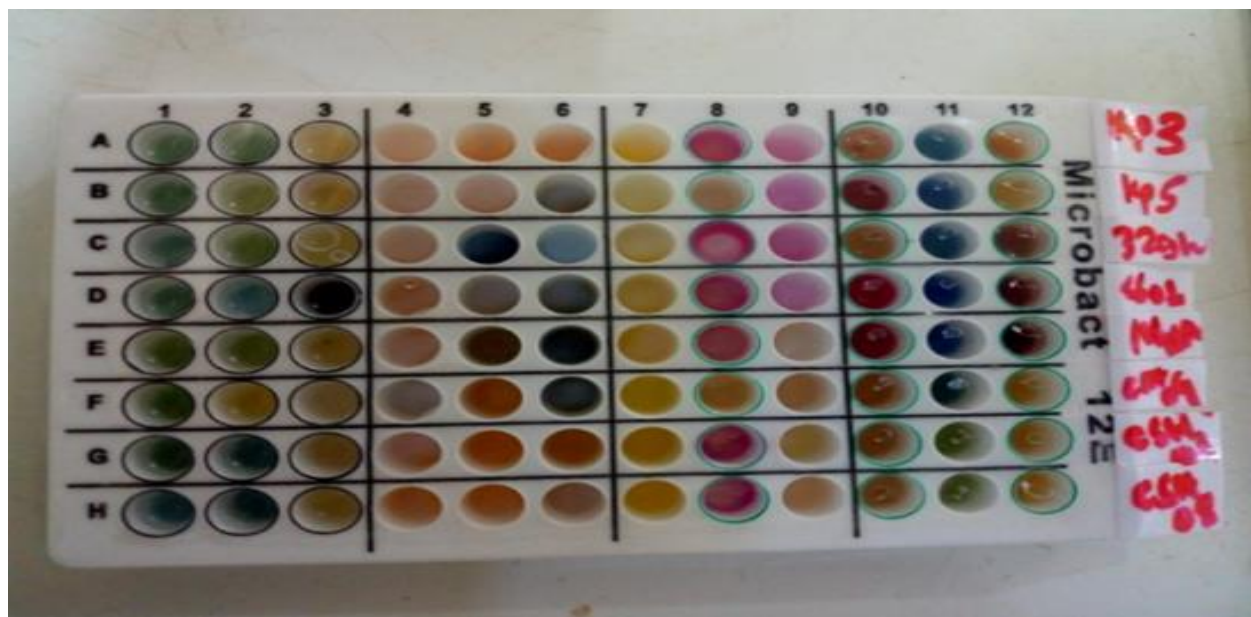
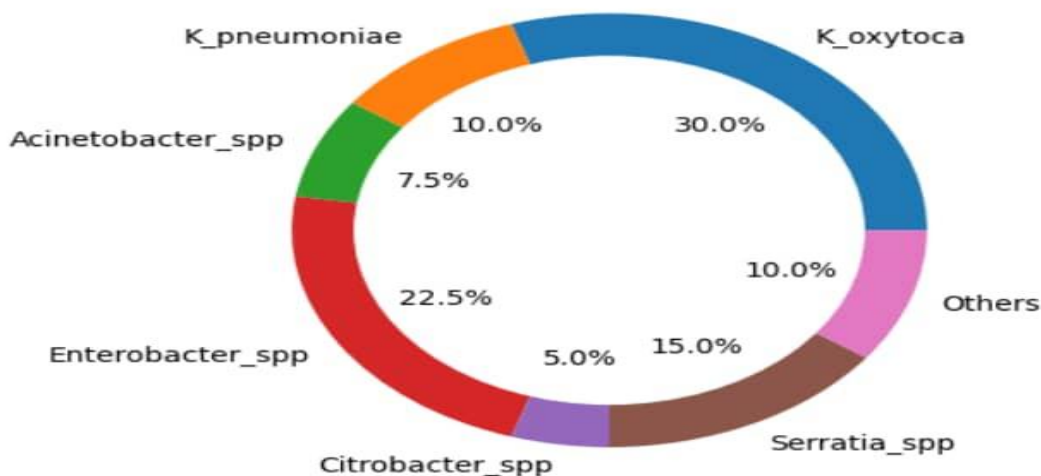


Plate 1: A Microbact 20E identification plate showing colour changes for Different biochemical reactions for selected isolates.



Others: *Morganella* spp (2.5%); *Providencia* spp (2.5%); *Yersinia* spp (2.5%); *Proteus* spp (2.5%)

Figure 1: Distribution of Enterobacteriaceae isolates obtained from clinical samples from selected hospitals in Ilorin

Table 1: Antibiotic Susceptibility testing results for 40 clinical Enterobacteriaceae isolates against selected antibiotics

S/no.	Antibiotics (Potency of disc)	Number of isolates susceptible (n= 40)	Percentage susceptibility
1	Amoxicillin (20µg)	7	17.50%
2	Imipenem (10 µg)	37	92.50%
3	Gentamicin (10 µg)	33	82.50%
4	Ciprofloxacin (5 µg)	32	80.00%
5	Ceftazidime (30 µg)	30	75.00%
6	Amoxicillin/ Clavulanic acid (20 /10 µg)	22	55.00%
7	Tetracycline (30 µg)	21	52.50%
8	Sulfamethoxazole/ trimethoprim (23.75/ 1.25 µg)	24	60.00%

Table 2: Phenotypic Resistance Patterns of MDR- E isolates showing their multiple antibiotic resistance index

Code	Organism	Phenotypic resistance patterns
CSH001	<i>K. oxytoca</i>	AML, CAZ, CIP, AMC, TE, SXT
CSH007	<i>K. oxytoca</i>	AML, CIP, TE, SXT
CSH010	<i>K. oxytoca</i>	AML, AMC, TE, SXT
36GH	<i>K. pneumoniae</i>	AML, CAZ, AMC, TE
65GH	<i>S. marcescens</i>	AML, IPM, CN, AMC, SXT

44GH	<i>K. oxytoca</i>	AML, IPM, CN, AMC, SXT
	A.	
43GH	<i>haemolyticus</i>	AML, IPM, TE, SXT
	E.	
18A	<i>agglomerans</i>	AML, AMC, TE, SXT
54AH	<i>K. oxytoca</i>	AML, AMC, TE, SXT
10K	<i>C. freundii</i>	AML, AMC, TE, SXT
	E.	
63NA	<i>agglomerans</i>	AML, AMC, TE, SXT
KP4	<i>K. oxytoca</i>	AML, CAZ, CIP, CN, AMC, TE, SXT
	K.	
KP5	<i>pneumoniae</i>	AML, CAZ, CIP, CN, AMC, TE, SXT
	K.	
KP3	<i>pneumoniae</i>	AML, CIP, CAZ, CN, AMC, SXT
KP2	<i>K. oxytoca</i>	AML, CAZ, CIP, CN, TE, SXT

**KEY:**

AML=Amoxicillin, IPM= Imipenem, CAZ=Ceftazidime, CIP= Ciprofloxacin, CN= Gentamicin, TE=Tetracycline, AMC=Amoxiclav, SXT=Co-trimoxazole.

**Table 3: Phenotypic Patterns of multidrug resistant Enterobacteriaceae isolates subjected to ESBL Screening.**

Isolates	Phenotypic resistance pattern
KP5	CRD, CPD, ATM, CTX, CAZ
KP1	CRD, CPD, ATM, CTX, CAZ
43GH	-
KP2	CRD, CPD, ATM, CTX, CAZ
CSH001	ATM, CAZ
CSH009	CAZ
KP3	CRD, CPD, ATM, CTX, CAZ
10K	CRD, CPD, ATM, CTX
18A	ATM, CTX
54AH	CRD, ATM, CTX
65GH	CTX
63NA	ATM, CTX
CSH008	ATM, CTX
44GH	CRD, CPD, ATM, CTX
17GH	ATM, CTX
CSH010	CRD, ATM, CTX, CAZ
46GH	CRD, CPD, ATM, CTX, CAZ
36GH	CRD, ATM, CTX, CAZ
69NA	CTX, CAZ
KP4	CRD, CPD, ATM, CTX, CAZ
CSH007	CTX

**KEY:** CRD=ceftriaxone, CPD= Cefpodoxime, ATM= Aztreonam, CTX=Cefotaxime, CAZ=Ceftazidime.



**Plate 2: Zones of Inhibition observed during phenotypic ESBL Confirmatory test.  
(Larger zones observed around combination discs).**

**Table 4: Diameter of Zones of Inhibitions for ESBL Confirmatory Test**

Code	Identity	Diameter Of Zones of Inhibition (mm)				RESULT
		CPD	CD	CTX	CTX-CLA	
KP3	<i>K. pneumonia</i>	0.00	19.00	0.00	18.00	+
KP1	<i>K. pneumonia</i>	9.00	8.00	0.00	25.00	+
KP5	<i>K. pneumonia</i>	0.00	19.00	0.00	21.00	+
65GH	<i>S. marcescens</i>	20.00	8.00	27.00	30.00	-
44GH	<i>K. oxytoca</i>	0.00	19.00	0.00	0.00	-
CSH010	<i>K. oxytoca</i>	17.00	22.00	20.00	24.00	-
17GH	<i>E. sakazakii</i>	26.00	0.00	22.00	9.00	-
KP4	<i>K. oxytoca</i>	0.00	21.00	0.00	18.00	+
46GH	<i>E. agglomerans</i>	9.00	24.00	8.00	12.00	+
63NA	<i>E. agglomerans</i>	28.00	13.00	13.00	22.00	+
CSH009	<i>S. marcescens</i>	21.00	16.00	18.00	24.00	+
CSH001	<i>K. oxytoca</i>	20.00	27.00	26.00	31.00	+
10K	<i>C. freundii</i>	21.00	20.00	20.00	14.00	-
KP2	<i>K. oxytoca</i>	8.00	9.00	0.00	24.00	+
36GH	<i>K. pneumonia</i>	23.00	20.00	19.00	24.00	+
CSH008	<i>K. oxytoca</i>	21.00	24.00	25.00	31.00	+
54AH	<i>K. oxytoca</i>	8.00	8.00	8.00	14.00	+
CSH007	<i>K. oxytoca</i>	26.00	26.00	27.00	32.00	+



69NA	<i>E. agglomerans</i>	28.00	28.00	30.00	35.00	+
18A	<i>E. agglomerans</i>	0.00	0.00	0.00	22.00	+

**KEY:** CPD=Cefpodoxime, CD=Cefpodoxime/clavulanate, CTX=Cefotaxime, CTX-CLA=Cefotaxime/Clavulanate, (+) = ESBL producer, (-) = Non - ESBL producer

#### 4.0 DISCUSSION

The Microbact 12E identification kit was used in this study because it is a standardized biochemical method for rapid and accurate identification for Enterobacteriaceae and other non-fastidious, Gram-negative rods, using 20 miniaturized biochemical tests and a database. Each isolate gave colour changes in each reaction wells and members of the Enterobacteriaceae family were differentiated. The most prevalent organism identified was *Klebsiella* specie with 40% prevalence, followed by *Enterobacter* specie (22.5%), *Serratia* spp (15%). *Acinetobacter* spp, *Citrobacter* spp, *Morganella* specie, *Providencia* spp, *Yersinia* spp and *Proteus* spp showed 7.5%, 5%, 2.5%, 2.5%, 2.5% and 2.5% prevalence respectively. This report correlates with work carried out in Ethiopia by Diriba et al 2021 who reported *Klebsiella pneumoniae* as the most predominant Enterobacteriaceae isolate. Teklu et al, 2019 and Saidou et al, 2023 in Ethiopia and Niger

republic respectively reported *Escherichia coli* as the most predominant Enterobacteriaceae isolates. These reports are in contrast to this study and the reason for this could be possibly due to sites of infection and/or origin of samples collected. The size of inoculum used could also be a major factor. Imipenem was observed to show the highest activity against the isolates with 92.5% sensitivity, followed by Gentamicin (82.5%), then Ciprofloxacin (80%), Ceftazidime (75%), Sulfamethoxazole/ trimethoprim (60%), Amoxicillin-clavulanic acid (55%), tetracycline (47.5%) and amoxicillin showed the least activity with 17.5% of the Enterobacteriaceae isolates showing sensitivity to the antibiotic. This report correlates with studies reported by Onyibe et al (2018) in North Central Nigeria who reported meropenem to have the highest activity and Saidou et al (2023) in Niger republic who reported amoxicillin to have shown the least activity in their study, but it is in contrast with the work carried out by Teklu producers indicating the possibility of a different mechanism of resistance from use of multidrug efflux pump for the non-ESBL producing bacteria. Carbapenems (imipenem, meropenem, ertapenem) are usually required as the last-resort treatment, resistance to carbapenems consequently leads to increasing risk of carbapenem-resistant Enterobacteriaceae (CRE) emergence (Paterson & Bonomo, 2005).

Results of the phenotypic antibiotic resistance patterns and multiple antibiotic resistance index from this study identifies multidrug resistant bacteria where we have resistance to  $\geq 3$  antibiotics and it also suggests the detection of Extended spectrum beta-lactamases. The misuse and overuse of antimicrobials in human, animals and plants are the main drivers in the development of drug-resistant pathogens (WHO, 2023). There is also the

et al (2019) in Addis Ababa, Ethiopia who reported Sulfamethoxazole/ trimethoprim to have shown the least activity. The observed resistance to amoxicillin in this study is possibly due to the fact that bacterial species produce beta-lactamases which are enzymes that hydrolyze and inactivate beta-lactam antibiotics like amoxicillin. Also, members of the family Enterobacteriaceae are known to use multidrug efflux pump to pump out amoxicillin and actively remove Sulfamethoxazole or trimethoprim from bacteria cells by reducing their efficacy. Resistance rate of 7.5% to Imipenem observed in this study which is in contrast to a 0.0% (no resistance) recorded by both Giwa *et al.*, (2018) in Zaria and by Fadeyi *et al.*, (2016) in Ilorin, shows that the bacteria in this environment are possibly beginning to harbour carbapenemase resistance genes. However, the isolates that showed resistance to Imipenem in this study were found to be both ESBL and non-ESBL

suggestion of the potential risk of contamination from a high-antibiotic-exposure environment like the hospital – acquired pathogens or wastewater.

There was a high prevalence of ESBL producing Enterobacteriaceae observed in this study. This report does not correlate with studies carried out in Zaria, Anambra and Benin where 34.3%, 16% and 47.1% of the isolates were observed as ESBL producers respectively (Giwa *et al.*, 2018; Akujobi & Ewuru, 2010 and Ogefere *et al.*, 2015). However, the high prevalence rate observed in this study is similar to studies reported in India (52.5%), Ethiopia (57.7%), Kano (66.7%), India (79%), India (88.2%) and Bangladesh (94.67%), (Sharma *et al.*, 2013; Teklu *et al.*, 2019; Yusha'u *et al.*, 2010; Hawser *et al.*, 2009; Sarker *et al.*, 2019; Sarasu and Girija., 2021) respectively. ESBL resistance is caused by enzymes

produced by bacteria that break down certain antibiotics thereby making some infections difficult to treat (CDC, 2024). ESBL producing Enterobacteriaceae has become a major multidrug resistant pathogen in the last two decades, especially in the community settings (Doi et al., 2017). This could possibly be a reason for the observed result. Moreover, escalating antimicrobial resistance among enteric pathogens has been documented to pose a substantial public health challenge (Ribeiro *et al.*, 2024).

The genus *Klebsiella* (66.67%) was the most prevalent ESBL producing Enterobacteriaceae observed in this study, followed by Enterobacter species (26.6%) and lastly Serratia species (6.67%). This finding correlates

with the findings from Shanyanfar *et al.*, (2010) in Iran, Sharma et al., (2013) in India and Diriba et al., (2021) in Ethiopia who respectively reported 27%, 67.04% and 49% of *Klebsiella* species as the highest ESBL producing Enterobacteriaceae isolates. This finding is also similar to those obtained in Nigeria; Ilorin, 26.70% (Faari *et al.*, 2016) and Enugu, 26.00% (Ejikeugwu *et al.*, 2013), 36.60% obtained in Benin (Ozazuwa & Ozazuwa, 2013), 43.20% in Ibadan (Okesola & Oni, 2012) and 51.30% in Ile-Ife (Olowe *et al.*, 2012). England public health department in 2014, documented a report that the two main bacteria that produce ESBLs are *Escherichia coli* and *Klebsiella* species. Additionally, *Klebsiella* isolates have been indicated in most community acquired infections as well as nosocomial infections. This can therefore be used to explain the high dominance of the specie in these isolates. 26.6% of the genus Enterobacter species were observed to be ESBL producers. This finding is similar to previous reports by Akujobi & Ewuru, 2010 and Saleh *et al.*, 2024. This suggests that many bacteria are now harbouring ESBLs and that poses a serious threat to our wellbeing.

All the ESBL producing Enterobacteriaceae strains except one isolate (6.67%) were observed to be sensitive to imipenem in this study. This observation suggests that there could be a growing trend of resistance to carbapenems since ESBLs have been known not to hydrolyze carbapenems and therefore carbapenems are regarded as last resort in treatment of infections and as drugs of choice in treatment of infections caused by ESBL producing bacteria.

## 5.0 CONCLUSION

The results of this study showed a high isolation rate of 47.62% and a high rate (37.5%) of ESBL producing Enterobacteriaceae isolates recovered from children with

gastroenteritis in Civil service hospital and General Hospital in Ilorin, Kwara state. Imipenem showed the highest activity against the Enterobacteriaceae isolates, and *Klebsiella* species were the most prevalent genus identified in this study. Antibiotics resistance through ESBL production is continuously evolving and there is a great need for up-close monitoring as well as regular phenotypic testing to track evolving resistance.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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