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Original Article

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Multidrug and colistin resistance in *Enterobacter* species isolated from water, human, and animal faecal samples in selected rural communities in Akwa Ibom State, Nigeria

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Abstract:

Background: Infection caused by antibiotic resistant *Enterobacter* spp. is a growing public health challenge as this significantly contributes to disease burden and high mortality in resource-limited settings. This study aimed to determine multidrug and colistin resistance patterns of *Enterobacter* isolates from water, human and animal samples in six rural communities in Akwa Ibom State, Nigeria.

Methodology: This was a laboratory-based study of 124 non-duplicate *Enterobacter* species isolated from water (n=43), human (n=46), goat (n=22) and dog (n=13) faecal samples in six local government areas (LGAs) of Akwa Ibom State. *Enterobacter* species were isolated from the samples following aerobic culture on Violet Red Bile Glucose agar after preliminary incubation in Enterobacteriaceae Enrichment broth at 37°C for 18 hours. Identification of *Enterobacter* isolates to species level was done using VITEK®2 compact system. Antibiotic susceptibility testing (AST) of isolates to selected antibiotics was performed using the Kirby-Bauer disc diffusion method, while colistin susceptibility testing (CST) was performed using disk elution MIC method. Multidrug resistance (MDR) was defined as resistance of an isolate to antibiotics in three or more classes. Multiple antibiotic resistance (MAR) index was determined as the number of antibiotics to which an isolate was resistant to, divided by the number of antibiotics to which the isolate was tested.

Results: Of the 124 non-duplicate *Enterobacter* isolates, 8 species were identified; *E. cloacae* (n=42), *E. aerogenes* (n=41), *E. cloacae* subsp *dissolvens* (n=17), *E. gergoviae* (n=11), *E. quasiroggenkampii* (n=4), *E. mori* (n=3), *E. hormaechei* (n=3), and *E. bugandensis* (n=3). *Enterobacter* spp from water samples were 95.3% and 90.7% sensitive to ciprofloxacin and ceftazidime respectively; those from humans were 95.7% sensitive to amoxicillin-clavulanate, those from goats were 86.4% sensitive to ceftazidime while those from dogs were 92.3% sensitive to amoxicillin-clavulanate and 84.6% sensitive to doxycycline and ceftazidime. The isolates exhibited varying resistance to imipenem, ceftazidime, and streptomycin. *Enterobacter* isolates from water, human, goat and dog samples had MARI of > 2 in 34.9%, 60.9%, 27.3% and 46.2% respectively, with resistance to 2-6 antibiotics. The MDR rate among *Enterobacter* isolates was 34.7% (n=43), with 30.2%, 41.3%, 27.3% and 38.5% in isolates from water, human, goat and dog samples respectively. Colistin-resistant rates in *Enterobacter* isolates from water, human, goat and dog samples were 25.6%, 28.3%, 27.3% and 38.5%, respectively, with *E. cloacae*, *E. aerogenes* and *E. dissolvens* being the most colistin-resistant isolates. *Mcr-1* gene was detected in colistin-resistant isolates from samples in two of the six rural communities (Ikot Abasi and Uruan) in the State.

Conclusion: The findings of this study underscore the need for continuous surveillance to monitor resistance patterns and implementation of antibiotic stewardship and infection control policies to prevent the emergence and spread of resistant strains in the community.

Keywords: Colistin resistance, *Enterobacter* spp., Multidrug-resistance, water, faecal, samples

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Résistance multidrogue et colistine chez les espèces d'*Enterobacter* isolées à partir d'échantillons d'eau, de matières fécales humaines et animales dans certaines communautés rurales de l'État d'Akwa Ibom, Nigeria

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Résumé:

Contexte: Infection causée par *Enterobacter* spp. Il s'agit d'un défi de santé publique croissant dans la mesure où cela contribue de manière significative à la charge de morbidité et à une mortalité élevée dans les contextes aux ressources limitées. Cette étude visait à déterminer les profils de résistance aux médicaments et à la colistine des isolats d'*Enterobacter* provenant d'échantillons d'eau, d'humains et d'animaux dans six communautés rurales de l'État d'Akwa Ibom, au Nigeria.

Méthodologie: Il s'agissait d'une étude en laboratoire portant sur 124 espèces d'*Enterobacter* non dupliquées isolées d'échantillons fécaux d'eau (n=43), d'humains (n=46), de chèvres (n=22) et de chiens (n=13) dans six zones de gouvernement local (LGA) de l'État d'Akwa Ibom. Les espèces d'*Enterobacter* ont été isolées des échantillons après culture aérobie sur gélose Violet Red Bile Glucose après incubation préliminaire dans un bouillon d'enrichissement Enterobacteriaceae à 37°C pendant 18 heures. L'identification des isolats d'*Enterobacter* au niveau de l'espèce a été réalisée à l'aide du système compact VITEK®2. Les tests de sensibilité aux antibiotiques (AST) des isolats à des antibiotiques sélectionnés ont été réalisés à l'aide de la méthode de diffusion sur disque de Kirby-Bauer, tandis que les tests de sensibilité à la colistine (CST) ont été réalisés à l'aide de la méthode CMI par élution sur disque. La multirésistance aux antibiotiques (MDR) a été définie comme la résistance d'un isolat à des antibiotiques appartenant à trois classes ou plus. L'indice de résistance multiple aux antibiotiques (MAR) a été déterminé comme le nombre d'antibiotiques auxquels un isolat était résistant, divisé par le nombre d'antibiotiques auxquels l'isolat a été testé.

Résultats: Parmi les 124 isolats d'*Enterobacter* non dupliqués, 8 espèces ont été identifiées; *E. cloacae* (n=42), *E. aerogenes* (n=41), *E. cloacae* subsp *dissolvens* (n=17), *E. gergoviae* (n=11), *E. quasirogerkampii* (n=4), *E. mori* (n=3), *E. hormaechei* (n=3) et *E. bugandensis* (n=3). Les espèces d'*Enterobacter* provenant des échantillons d'eau étaient respectivement sensibles à 95,3% et 90,7% à la ciprofloxacine et à la ceftazidime; ceux provenant d'humains étaient sensibles à 95,7% à l'amoxicilline-clavulanate, ceux provenant de chèvres étaient sensibles à 86,4% à la ceftazidime tandis que ceux provenant de chiens étaient sensibles à 92,3% à l'amoxicilline-clavulanate et à 84,6% à la doxycycline et à la ceftazidime. Les isolats présentaient une résistance variable à l'imipénème, à la céfoxitine et à la streptomycine. Les isolats d'*Enterobacter* provenant d'échantillons d'eau, d'humains, de chèvres et de chiens présentaient un MARI > 2 dans 34,9%, 60,9%, 27,3% et 46,2% respectivement, avec une résistance à 2 à 6 antibiotiques. Le taux de MDR parmi les isolats d'*Enterobacter* était de 34,7% (n=43), avec 30,2%, 41,3%, 27,3% et 38,5% dans les isolats provenant d'échantillons d'eau, d'humains, de chèvres et de chiens, respectivement. Les taux de résistance à la colistine dans les isolats d'*Enterobacter* provenant d'échantillons d'eau, d'humains, de chèvres et de chiens étaient respectivement de 25,6%, 28,3%, 27,3% et 38,5%, *E. cloacae*, *E. aerogenes* et *E. dissolvens* étant les isolats les plus résistants à la colistine. Le gène *mcr-1* a été détecté dans des isolats résistants à la colistine provenant d'échantillons provenant de deux des six communautés rurales (Ikot Abasi et Uruan) de l'État.

Conclusion: Les résultats de cette étude soulignent la nécessité d'une surveillance continue pour surveiller les profils de résistance et la mise en œuvre de politiques de gestion des antibiotiques et de contrôle des infections afin de prévenir l'émergence et la propagation de souches résistantes dans la communauté.

Mots-clés: Résistance à la colistine, *Enterobacter* spp, multirésistance aux antibiotiques, eau, matières fécales, échantillons

Introduction:

Antimicrobial resistance (AMR) is a growing global public health threat. It is particularly worrisome among *Enterobacter* spp and other Gram-negative bacteria (GNB) as they contribute significantly to disease burden and mortality (1). In 2019, it was reported that AMR directly caused an estimated 1.27 million deaths, and an additional 5 million deaths were associated with *Enterobacter* spp (2). A major concern is the rise of drug-resistant infections, especially those caused by antibiotic-resistant bacteria acquired in hospitals, which are becoming more common in developing countries, including Nigeria (3).

Multidrug-resistant (MDR) *Enterobacter* isolates have emerged and spread worldwide due to widespread use of antibiotics (4). These organisms seem to have innate resistance to older antimicrobial agents and have the propensity to rapidly develop resistance to newer antimicrobial agents (1). Treatment of infections with *Enterobacter* spp is difficult because of resistance to third generation cephalosporins, penicillin and quinolones (5). As reported by Davin-Regli et al., (6), *Enterobacter* spp naturally carries genes encoding AmpC β -lactamases, leading to intrinsic resistance to ampicillin, amoxicillin, first-generation cephalosporins and cefoxitin. These pathogens can adapt to the environment and acquire various mobile gene-

tic elements (MGEs) coding for resistance, making them multidrug-resistant (6). The emerging resistance of *Enterobacter* to β -lactams and carbapenem antibiotics makes treatment more challenging, especially in resource limiting countries (1).

To curtail the rising incidence of infections caused by MDR *Enterobacter* spp, health-care systems have increasingly turned to colistin, which is regarded as a last-line therapeutic option for the treatment of severe infections caused by MDR Gram-negative bacteria (GNB), including *Enterobacter* spp (1). Colistin is a polycationic antibiotic with broad-spectrum bactericidal activity. It targets the lipopolysaccharides in the bacterial cell walls, disrupting their outer membrane and causing the bacteria to break apart and die (7). Colistin was initially restricted to veterinary medicine due to its nephrotoxicity and neurotoxicity (8). However, the rise of MDR and carbapenem-resistant *Enterobacter* has led to its renewed use in humans (9).

Unfortunately, the increasing resistance to this critical antibiotic is becoming a global challenge, as it is becoming less effective in treating resistant infections, making patient care even more difficult (10). Understanding the patterns of antibiotic resistance and monitoring colistin-resistant *Enterobacter* isolates are essential for developing effective treatment and intervention strategies to prevent their spread in various environments, including hospitals and community settings. However, there is paucity of comprehensive data on multidrug and colistin resistance in environmental, human and animal isolates of *Enterobacter* spp. in Akwa Ibom State. Therefore, this study was carried out to determine the antibiotic susceptibility, multidrug resistance profiles and colistin resistance rates in *Enterobacter* spp isolated from water, human and animal samples in selected rural communities of Akwa Ibom State, Nigeria.

Materials and method:

Study design and settings:

This was a laboratory-based study of *Enterobacter* spp isolated from water, human and animal in rural communities of Akwa Ibom State, Nigeria. The State covers a total land area of 7,249 square kilometer and has a population of 5,451,277 (11). Akwa Ibom lies between latitude 4°32" and 5°33" North and longitude 7°35" and 8°25" East. The State is bordered on the East by Rivers State, on the West by Cross River State, on the North by Abia State and on the South by the Gulf of

Guinea.

The people of Akwa Ibom State are culturally homogeneous with a common identity and are reputed to be the first settlers in the present-day southeastern Nigeria. The three major dialects are the Ibibio, Anang and Oron. Other subgroups include Eket, Ibeno, Itu Mbuso and the Andonis. The six rural communities selected for study using random sampling technique included Ikot Ntuen in Ikono Local Government Area (LGA), Ikot obong in Ibiono Ibom LGA, Nto Edino in Obot Akara LGA, Issiet Ekim in Uruan LGA, Isong Inyang in Mbo LGA and Ikot Atan in Ikot Abasi LGA.

Ethical consideration:

Ethical approval was requested and obtained from Research Ethics Committee of Akwa Ibom State Ministry of Health Research Ethics Committee (AKSMHREC) with HREC assigned (AKHREC/20/04/23/145). Since the study also involved direct collection of specimens from human and animal subjects, written informed consent was obtained from the participants and animal owners prior to their inclusion and sample collection.

Collection and transportation of samples:

Samples collected for analysis include water, human faecal, goat faecal and dog faecal samples. Water samples were collected at targeted stream points directly into 500ml sterilized polypropylene bottles. At the sampling point, the bottles were opened aseptically and rinsed with the stream water and held at a right angle and submerged to a depth of about 20cm with the mouth of the bottle facing upwards directly opposite the current of the flowing stream and filled to the brim. The bottles were stored in ice packed coolers. In-situ physicochemical analyses were carried out using water scooper to transfer the water into a clean bucket where the actual measurement was taken, some part of the water was also taken in another 500ml container and labeled for further biochemical and physicochemical analysis.

Human faecal samples were collected from willing volunteers at the nearby primary healthcare centers within the community. Prior to sample collection, they were educated on how to collect their faecal samples using sterile widemouth, screw cap leak proof sample containers. Animal faecal samples from goats and dogs were collected within the six communities using sterile swab-sticks. Faecal samples were stored in ice-coolers and transported to Microbiology Laboratory, University of Uyo, Nigeria for processing.

Isolation and identification of *Enterobacter* from samples

For the isolation of *Enterobacter* spp. from water, animal and human faecal samples. One ml (1ml) of water sample and one gram (1g) of each faecal samples from human, goat and dog was aseptically inoculated into sterile peptone water and then inoculated into 9 mL of Enterobacteriaceae Enrichment (EEE) broth (Himedia, India). The enrichment cultures were incubated at 37°C for 18 hours, after which 1 ml of each pre-enriched culture was inoculated onto Violet Red Bile Glucose Agar (VRBGA, Himedia, India) by pour plating and incubated at 37°C for 24 hours. Colonies appearing as red or purple with a surrounding halo on VRBGA were presumptively identified as *Enterobacter* spp (12). All presumptive isolates were confirmed by VITEK®2 identification compact system (BioMérieux, Marcy-L'Étoile, France).

Antibiotic susceptibility testing:

The antibiotic susceptibility testing was performed by the Kirby-Bauer disk diffusion method on Mueller Hinton Agar (MHA, Oxoid™ Thermo scientific™ UK) plates. A loopful of the pure isolate was prepared and adjusted to 0.5 McFarland standard (equivalent to 10⁸ CFU/ml) and spread on the surface of the agar using a sterile hockey stick. Nine selected antibiotic disks (Bioanalyse^(R) Venimahalle Ankara/Turkey) were used and this included imipenem (IPM, 10µg), meropenem (MEM, 10µg), doxycycline (DOX, 30µg), ceftazidime (CAZ, 30µg), ciprofloxacin (CIP, 5µg), amoxicillin-clavulanate (AMC, 30µg), cefoxitin (FOX, 30µg), Streptomycin (S, 10µg) and trimethoprim/sulfamethoxazole (SXT, 23.75µg/1.25µg). The disks were gently placed on the agar plates, and incubated at 37°C for 24 hours. The diameters of the zones of inhibition (in mm) were measured with a meter ruler and interpreted as resistant, intermediate or sensitive in accordance with the 2024 CLSI guidelines and interpretative criteria (13). Multidrug resistance was defined as resistance of an isolate to antibiotics in three or more classes (14).

Colistin susceptibility testing by broth disk elution MIC method:

Colistin was tested by colistin broth disk elution (CBDE) test on cation-adjusted Mueller Hinton Broth (CA-MHB; Himedia laboratories, Mumbai, India) according to the CLSI 2024 guidelines (13,15). For each isolate, 0, 1, 2 and 4 10-µg colistin disc was added to four tubes containing 10 ml each of CA-MHB to achieve final concentrations of 0 (control growth), 1, 2, and 4 µg/ml in the CA-MHB tubes. The tubes were vortexed and left at room tem-

perature for 30 mins to allow the colistin to adequately elute from the discs.

To produce a standardized inoculum, 3-5 colonies from 24 hours agar plate were suspended in 4-5 ml of sterile saline. The turbidity was adjusted to match that of a McFarland 0.5 standard. To achieve a final inoculum concentration of 7.5x10⁵ CFU/ml, 50µL aliquot of the standardized inoculum was added to each tube. MIC values were read as the lowest concentration that completely inhibits growth of the isolate after 16-20 hours incubation at 35°C. Interpretation of result was done using the CLSI breakpoints of ≤2µg/mL as intermediate and ≥4µg/mL as resistant (13).

Determination of multiple antibiotics resistant index (MARI) and multidrug-resistant (MDR) profile of *Enterobacter* spp.:

Multiple antibiotic resistance (MAR) index was determined using the formula $MAR = x/y$, where 'x' was the number of antibiotics to which the test isolate displayed resistance and 'y' was the total number of antibiotics to which the test isolates were evaluated for sensitivity. MARI >2 indicates that the isolates are from an environment where antibiotics are widely used (16). Multiple antibiotic resistance was also described by determining multidrug-resistance (MDR) profiles of the isolates as defined by Magiorakos et al., (14).

Amplification of colistin resistance gene:

The *mcr-1* gene of the isolates were amplified using the *mcr-1F*: 5'-GTCGGTATGCTC GTTGCTTAG-3 and *Mcr1R*: 5'-CATAGGCATTGC TGTGCGTCTG-3' primers on a ABI 9700 Applied Biosystems thermal cycler at a final volume of 40µl for 35 cycles. The PCR mix included the X2 Dream Taq Master mix (Inqaba Biotec, South Africa), Taq polymerase, DNTPs, MgCl₂, primers at a concentration of 0.5µM and the extracted DNA as template.

The PCR conditions were as follows; initial denaturation at 95°C for 5 mins, denaturation at 95°C for 30 seconds, annealing at 54°C for 30 seconds, extension at 72°C for 30 seconds for 35 cycles, and final extension at 72 °C for 5 mins. The product was resolved on a 1% agarose gel at 130V for 30 mins and visualized on a blue light transilluminator.

Statistical analysis:

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, PASW-Predictive Analytics Software, version 25.0). Antimicrobial resistance patterns of *Enterobacter* spp, multiple antibiotic resistance (MAR) indices, multi-drug resistance, and colistin resistance were determined using descrip-

tive statistics. Associations between categorical variables were evaluated using the Chi-square (χ^2) test, and differences were considered statistically significant at $p < 0.05$.

Results:

***Enterobacter* species isolated from samples:**

A total of 124 non-duplicate *Enterobacter* spp were isolated from water (n=43), human (n=46), goat (n=22) and dog (n=13) faecal samples. A total of 8 species of *Enterobacter* were identified; *E. cloacae* (n=42), *E. aerogenes* (n=41), *E. cloaca* subsp *dissolvens* (n=17), *E. gergoviae* (n=11), *E. quasiroggenkampii* (n=4), *E. mori* (n=3), *E. hormaechei* (n=3), and *E. bugandensis* (n=3).

Antibiotic susceptibility of *Enterobacter* isolates:

Enterobacter cloacae isolated from water samples were highly sensitive to amoxicillin/clavulanate (86.7%) and ceftazidime (86.7%), and 66.7% were sensitive to ciprofloxacin, but 53.3% of the isolates were resistant to cefoxitin and streptomycin. *Enterobacter aerogenes* were sensitive to amoxicillin/clavulanate (92.3%), ceftazidime (84.6%) and trimethoprim/sulfamethoxazole (84.6%). However, 46.1% of the isolates were resistant to cefoxitin and streptomycin. All *E. mori* were highly sensitive to ceftazidime, ciprofloxacin, amoxicillin/clavulanate and trimethoprim/sulfamethoxazole. About 90.7% of the *Enterobacter* spp from water samples were sensitive to ceftazidime and 74.4% to amoxicillin/clavulanate while they were resistant to streptomycin (37.2%), imipenem (25.6%) and meropenems (27.9%) (Table 1).

The antibiotic susceptibility profile of *Enterobacter* spp isolated from human faecal samples result indicates that *E. aerogenes* were

sensitive to amoxicillin/clavulanate (88.9%), but 50.0% of the isolates were resistant to streptomycin. *Enterobacter gergoviae* was sensitive to amoxicillin/clavulanate (100.0%), ceftazidime (66.7%) and trimethoprim/sulfamethoxazole (66.7%), and resistant to cefoxitin and streptomycin (50.0%). Overall, *Enterobacter* spp from human faecal samples were sensitive to amoxicillin/clavulanate (95.7%) and trimethoprim/sulfamethoxazole (76.1%) while 39.1% of the isolates were resistant to doxycycline and (34.8%) to streptomycin (Table 2).

All *E. cloacae* from dogs were sensitive to amoxicillin/clavulanate and trimethoprim/sulfamethoxazole but 50.0% of the isolates were resistant to imipenem and meropenem. All *E. hormaechei* were sensitive to meropenem, doxycycline and ceftazidime but were resistant to all other antibiotics. All *E. quasiroggenkampii* were sensitive to doxycycline, ceftazidime, ciprofloxacin and amoxicillin/clavulanate. Overall, *Enterobacter* spp from dog samples were sensitive to amoxicillin/clavulanate (92.3%), doxycycline and ceftazidime (84.6%) (Table 3).

Enterobacter aerogenes from goat samples were highly sensitive to all the antibiotic used except ciprofloxacin. About 66.7% of *E. cloacae* subsp *dissolvens* were resistant to meropenem, cefoxitin and streptomycin. *E. bugandensis* was sensitive to doxycycline, ceftazidime, ciprofloxacin, amoxicillin/clavulanate and trimethoprim/sulfamethoxazole. All *E. hormaechei* from goat samples were sensitive to ceftazidime, but resistant to amoxicillin/clavulanate. Overall, *Enterobacter* spp from goat faecal samples were sensitive to ceftazidime (86.4%) and trimethoprim/sulfamethoxazole (81.8%) but resistant to imipenem (27.3%) and meropenem (31.8%) (Table 4).

Table 1: Antibiotic susceptibility profile of *Enterobacter* spp isolated from streams in some rural areas in Akwa Ibom State, Nigeria

<i>Enterobacter</i> spp	No of isolate susceptibility to selected antibiotics (%)									
	Status	IPM	MEM	DOX	CAZ	CIP	AMC	FOX	S	SXT
<i>E. cloacae</i> (n=15)	S	7 (43.8)	6 (40.0)	7 (43.8)	13 (86.7)	10 (66.7)	13 (86.7)	3 (20.0)	5 (33.3)	9 (60.0)
	I	3 (20.0)	5 (33.3)	2 (13.3)	0	5 (33.2)	2 (13.3)	4 (26.7)	2 (13.3)	2 (13.3)
	R	5 (33.3)	4 (26.7)	6 (40.0)	2 (13.3)	0	0	8 (53.3)	8 (53.3)	4 (26.7)
<i>E. aerogenes</i> (n=13)	S	7 (53.8)	8 (61.5)	10 (76.9)	11 (84.6)	7 (53.8)	12 (92.3)	5 (38.5)	7 (53.8)	11 (84.6)
	I	2 (15.4)	0	0	0	4 (30.7)	0	2 (15.4)	0	0
	R	4 (30.7)	5 (38.5)	3 (23.1)	2 (15.4)	2 (15.4)	1 (7.7)	6 (46.1)	6 (46.1)	2 (15.4)
<i>E. gergoviae</i> (n=5)	S	3 (60.0)	2 (40.0)	3 (60.0)	5 (100.0)	3 (60.0)	4 (80.0)	5 (100.0)	4 (80.0)	4 (80.0)
	I	1 (20.0)	1 (20.0)	0	0	2 (40.0)	1 (20.0)	0	0	0
	R	1 (20.0)	2 (40.0)	2 (40.0)	0	0	0	0	1 (20.0)	1 (20.0)
<i>E. cloacae</i> subsp <i>dissolvens</i> (n=7)	S	6 (85.7)	6 (85.7)	5 (71.4)	7 (100.0)	4 (57.1)	5 (71.4)	3 (42.9)	4 (57.1)	4 (57.1)
	I	0	0	0	0	3 (42.9)	0	3 (42.9)	0	0
	R	1 (14.3)	1 (14.3)	2 (28.6)	0	0	2 (28.6)	1 (14.3)	3 (42.9)	3 (42.9)
<i>E. mori</i> (n=3)	S	0	0	2 (66.7)	3 (100.0)	3 (100.0)	3 (100.0)	2 (66.7)	2 (66.7)	3 (100.0)
	I	3 (100.0)	3 (100.0)	1 (33.3)	0	0	0	0	0	0
	R	0	0	0	0	0	0	1 (33.3)	1 (33.3)	0
Total (n=43)	S	23 (53.5)	22 (51.2)	27 (62.8)	39 (90.7)	27 (62.8)	32 (74.4)	18 (41.9)	22 (51.2)	31 (72.1)
	I	9 (20.9)	9 (20.9)	3 (7.0)	0	14 (32.6)	3 (7.0)	9 (20.9)	2 (4.7)	2 (4.7)
	R	11 (25.6)	12 (27.9)	13 (30.2)	4 (9.3)	2 (4.7)	3 (7.0)	16 (44.2)	19 (37.2)	10 (23.3)

S: Sensitive; I: Intermediate; R: Resistant; IPM: Imipenem; MEM: Meropenem; DOX: Doxycycline; CAZ: Ceftazidime; CIP: Ciprofloxacin; AMC: Amoxicillin/Clavulanate; FOX: Cefoxitin; S: Streptomycin; SXT: Trimethoprim/Sulfamethoxazole; %: Percentage of the total isolates of each species of *Enterobacter* tested

Table 2: Antibiotic susceptibility profile of *Enterobacter* spp isolated from human faecal samples in some rural areas in Akwa Ibom State, Nigeria

<i>Enterobacter</i> spp	No of isolate susceptibility to selected antibiotics (%)									
	Status	IPM	MEM	DOX	CAZ	CIP	AMC	FOX	S	SXT
<i>E. aerogenes</i> (n=18)	S	9 (50.0)	9 (50.0)	10 (55.6)	10 (55.6)	9 (50.0)	16 (88.9)	8 (44.4)	9 (50.0)	12 (66.7)
	I	7 (38.9)	4 (32.2)	1 (5.6)	0	8 (44.4)	0	3 (16.7)	0	0
	R	2 (11.1)	5 (27.8)	7 (38.9)	8 (44.4)	1 (5.6)	2 (11.1)	7 (38.9)	9 (50.0)	6 (33.3)
<i>E. cloacae</i> (n=15)	S	7 (46.7)	8 (53.3)	8 (53.3)	12 (80.0)	12 (80.0)	15 (100.0)	7 (46.7)	11 (73.3)	12 (80.0)
	I	4 (26.7)	1 (6.7)	1 (6.7)	0	3 (20.0)	0	2 (13.3)	1 (6.7)	0
	R	4 (26.7)	6 (40.0)	6 (40.0)	3 (20.0)	0	0	6 (40.0)	3 (20.0)	3 (20.0)
<i>E. gergoviae</i> (n=6)	S	2 (33.3)	1 (16.7)	2 (33.3)	4 (66.7)	3 (50.0)	6 (100.0)	3 (50.0)	3 (50.0)	4 (66.7)
	I	3 (50.0)	4 (66.7)	0	0	2 (33.3)	0	0	0	0
	R	1 (16.7)	1 (16.7)	4 (66.7)	2 (33.2)	1 (16.7)	0	3 (50.0)	3 (50.0)	2 (33.3)
<i>E. cloacae sub dissolvens</i> (n=7)	S	3 (42.9)	4 (57.1)	4 (57.1)	6 (85.7)	3 (42.9)	7 (100.0)	5 (71.4)	5 (71.4)	7 (100.0)
	I	2 (28.6)	1 (14.3)	2 (28.6)	0	0	0	1 (14.3)	1 (14.3)	0
	R	2 (28.6)	2 (28.6)	1 (14.3)	1 (14.3)	4 (57.1)	0	1 (14.3)	1 (14.3)	0
Total (n=46)	S	21 (45.7)	22 (47.8)	24 (52.2)	32 (69.0)	27 (58.7)	44 (95.7)	23 (50.0)	28 (60.9)	35 (76.1)
	I	16 (34.8)	10 (21.7)	4 (8.7)	0 (14 (30.4)	13 (28.3)	0	6 (13.0)	2 (4.3)	0
	R	9 (19.6)	14 (30.4)	18 (39.1)	18 (39.1)	6 (13.0)	2 (4.3)	17 (37.0)	16 (34.8)	11 (23.9)

S: Sensitive; I: Intermediate; R: Resistant; IPM: Imipenem; MEM: Meropenem; DOX: Doxycycline; CAZ: Ceftazidime; CIP: Ciprofloxacin; AMC: Amoxicillin/Clavulanate; FOX: Cefoxitin; S: Streptomycin; SXT: Trimethoprim/Sulfamethoxazole; %: Percentage of the total isolates of each species of *Enterobacter* tested

Table 3: Antibiotic susceptibility profile of *Enterobacter* spp isolated from dog faecal samples in some rural areas in Akwa Ibom State, Nigeria

<i>Enterobacter</i> spp	No of isolate susceptibility to selected antibiotics (%)									
	Status	IPM	MEM	DOX	CAZ	CIP	AMC	FOX	S	SXT
<i>E. cloacae</i> (n=4)	S	2 (50.0)	2 (50.0)	3 (75.0)	3 (75.0)	3 (75.0)	4 (100.0)	1 (25.0)	1 (25.0)	4 (100)
	I	0	0	1 (25.0)	0	0	0	2 (50.0)	1 (25.0)	0
	R	2 (50.0)	2 (50.0)	0	1 (25.0)	1 (25.0)	0	1 (25.0)	2 (50.0)	0
<i>E. aerogenes</i> (n=6)	S	2 (33.3)	3 (50.0)	5 (83.3)	6 (100.0)	3 (50.0)	6 (100.0)	4 (66.7)	3 (50.0)	4 (66.7)
	I	3 (50.0)	3 (50.0)	1 (16.7)	0	3 (50.0)	0	1 (16.7)	0	0
	R	1 (16.7)	0	0	0	0	0	1 (16.7)	3 (50.0)	2 (33.3)
<i>E. hormaechei</i> (n=1)	S	0	1 (100)	1 (100)	1 (100.0)	0	0	0	0	1 (100.0)
	I	0	0	0	0	1 (100.0)	0	0	0	0
	R	1 (100)	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	0
<i>E. quasiroggenkampii</i> (n=2)	S	0	0	2 (100.0)	1 (100.0)	1 (100.0)	2 (100.0)	0	0	1 (50.0)
	I	1 (50.0)	1 (50.0)	0	0	0	0	1 (50.0)	0 2 (100)	0
	R	1 (50.0)	1 (50.0)	0	1 (100.0)	1 (100.0)	0	1 (50.0)		1 (50.0)
Total (n=13)	S	4 (30.8)	6 (46.2)	11 (84.6)	11 (84.6)	7 (53.8)	12 (92.3)	5 (38.5)	4 (30.8)	10 (76.9)
	I	4 (30.8)	4 (30.8)	2 (15.4)	0	4 (30.8)	0	4 (30.80)	1 (7.7)	0
	R	5 (38.5)	3 (23.1)	0	2 (15.4)	2 (15.4)	1 (7.7)	4 (30.8)	8 (61.5)	3 (23.1)

S: Sensitive; I: Intermediate; R; Resistant; IPM: Imipenem; MEM: Meropenem; DOX: Doxycycline; CAZ: Ceftazidime; CIP: Ciprofloxacin; AMC: Amoxicillin/Clavulanate; FOX: Cefoxitin; S: Streptomycin; SXT: Trimethoprim/Sulfamethoxazole; %: Percentage of the total isolates of each species of *Enterobacter* tested

Table 4: Antibiotic susceptibility of *Enterobacter* spp isolated from goat faecal samples in some rural areas in Akwa Ibom State, Nigeria

<i>Enterobacter</i> spp	No of isolate susceptibility to selected antibiotics (%)									
	Status	IPM	MEM	DOX	CAZ	CIP	AMC	FOX	S	SXT
<i>E. cloacae</i> (n=5)	S	3 (60.0)	3 (60.0)	3 (60.0)	4 (80.0)	2 (40.0)	4 (80.0)	1 (20.0)	2 (40.0)	5 (100)
	I	1 (20.0)	1 (20.0)	1 (20.0)	0	3 (60.0)	0	2 (40.0)	2 (40.0)	0
	R	1 (20.0)	1 (20.0)	1 (20.0)	1 (20.0)	0	1 (20.0)	2 (40.0)	1 (20.0)	0
<i>E. aerogenes</i> (n=7)	S	5 (71.4)	6 (85.7)	6 (85.7)	6 (85.7)	2 (28.6)	7 (100.0)	6 (85.7)	5 (71.4)	5 (71.4)
	I	2 (28.6)	1 (14.3)	0	0	5 (71.4)	0	0	0	0
	R	0	0	1 (14.3)	1 (14.3)	0	0	1 (14.3)	2 (28.6)	2 (28.6)
<i>E. cloacae</i> subsp <i>dissolvens</i> (n=3)	S	2 (66.7)	1 (33.3)	3 (100.0)	3 (100.0)	2 (66.7)	3 (100.0)	1 (33.3)	0	2 (66.7)
	I	0	0	0	0	1 (33.3)	0	0	1 (33.3)	1 (33.3)
	R	1 (33.3)	2 (66.7)	0	0	0	0	2 (66.7)	2 (66.7)	0
<i>E. quasiroggenkampii</i> (n=2)	S	0	0	1 (50.0)	1 (50.0)	1 (50.0)	2 (100.0)	0	1 (50.0)	2 (100.0)
	I	0	0	0	0	1 (50.0)	0	0 2 (100)	0	0
	R	2 (100.0)	2 (100)	1 (50.0)	1 (50.0)	0	0	0	1 (50.0)	0
<i>E. bugandensis</i> (n=3)	S	0	0	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	0	2 (66.7)	3 (100.0)
	I	1 (33.3)	2 (66.7)	0	0	0	0	2 (66.7)	0	0
	R	2 (66.7)	1 (33.3)	0	0	0	0	1 (33.3)	1 (33.3)	0
<i>E. hormaechei</i> (n=2)	S	0	0	1 (50.0)	2 (100.0)	1 (50.0)	0	1 (50.0)	1 (50.0)	1 (50.0)
	I	2 (100.0)	1 (50.0)	0	0	1 (50.0)	0	0	0	0
	R	0	1 (50.0)	1 (50.0)	0	0	2 (100.0)	1 (50.0)	1 (50.0)	1 (50.0)
Total (n=22)	S	10 (45.5)	10 (45.5)	17 (77.3)	19 (86.4)	11 (50.0)	19 (66.4)	9 (40.9)	11 (50.0)	18 (81.8)
	I	6 (27.3)	5 (22.7)	1 (4.5)	0	11 (50.0)	0	4 (18.2)	3 (13.6)	1 (4.5)
	R	6 (27.3)	7 (31.8)	4 (18.2)	3 (13.6)	0	3 (13.6)	9 (40.9)	8 (36.4)	3 (13.6)

S: Sensitive; I: Intermediate; R: Resistant; IPM: Imipenem; MEM: Meropenem; DOX: Doxycycline; CAZ: Ceftazidime; CIP: Ciprofloxacin; AMC: Amoxicillin/Clavulanate; FOX: Cefoxitin; S: Streptomycin; SXT: Trimethoprim/Sulfamethoxazole; %: Percentage of the total isolates of each species of *Enterobacter* tested

Antibiotic susceptibility of *Enterobacter* spp to colistin

The minimum inhibitory concentration (MIC) of colistin for *Enterobacter* spp from water samples shows that 4 of 15 (26.7%) *E. cloacae* and 5 of the 13 (38.5%) *E. aerogenes* isolates were resistant to colistin. However, all 3 (100.0%) *E. mori* isolates were sensitive to colistin. Overall, 11 (25.6%) of the 43 *Enterobacter* spp from water samples were resistant to colistin (Table 5).

The MIC of colistin for *Enterobacter* spp from human faecal samples shows that 7 of 18 (38.9%) *E. aerogenes*, 4 of 15 (26.7%) *E. cloacae* and 2 of 6 (33.3%) *E. gergoviae*, were resistant to colistin, while all the 7 (100%) *E. dissolvens* were sensitive to colistin. Overall, 28.3% of the 46 *Enterobacter* spp from human samples were resistant to colistin (Table 6).

From goat samples, 20.0% (n=1/5) of *E. cloacae*, 14.3% (n=1/7) of *E. aerogenes*, 33.3% (n=1/3) of *E. cloacae* subsp *dissolvens*, 50.0% (n=1/2) *E. hormaechei*, and 100.0% of *E. quasiroggenkampii* were resistant to colistin, while all 3 (100.0%) *E. bugandensis* isolates were sensitive to colistin. Overall, 27.3% (n=6/22) *Enterobacter* isolates from goat samples were resistant to colistin (Table 7).

Of the 13 *Enterobacter* spp isolated from dog faecal samples, 25.0% (n=1/4) *E. cloacae*, 16.7% (n=1/6) *E. aerogenes*, 100.0% (n=1/1) *E. hormaechei* and 100.0% (n=2/2) *E. quasiroggenkampii* isolates were resistant to colistin. Overall, 38.5% (n=5/13) *Enterobacter* isolates from dog samples were resistant to colistin (Table 8).

In summary, colistin resistance rate among all the *Enterobacter* isolates was 28.2% (n=35/124). The resistance rate among *Enterobacter* isolates from water samples (25.6%) was not significantly different from 28.3% from human, 27.3% from goat, and 38.5% from dog samples ($\chi^2=0.8306$, $p=0.8421$).

Multiple antibiotic resistance indices of *Enterobacter* spp

The MAR indices of *Enterobacter* spp. isolated from water samples showed that some *E. cloacae*, *E. aerogenes*, *E.*

aerogenes and *E. cloacae* subsp *dissolvens* were resistant to similar antibiotic combinations such as cefoxitin and streptomycin, and imipenem, meropenem, streptomycin and trimethoprim/sulfamethoxazole. The MARI of all the 43 isolates from water samples ranged from 0.2 to 0.7, with resistance profiles ranging from 2 to 6 antibiotics (Table 9).

The MAR indices of *Enterobacter* spp. isolated for human faecal samples showed that *E. aerogenes*, *E. gergoviae*, and *E. cloacae* subsp *dissolvens* had MAR index of 0.2, while *E. cloacae* had MAR index of 0.4 and *E. gergoviae* MAR index of 0.7 (Table 10).

For goat faecal samples, MAR indices of *Enterobacter* spp showed that *E. cloacae* subsp *dissolvens*, *E. bugandensis* and *E. hormaechei* had MAR index of 0.2, *E. aerogenes* had MAR index of 0.3, and *E. cloacae* had MAR index of 0.7 (Table 11).

The MAR indices of *Enterobacter* spp for dog faecal samples showed that *E. aerogenes* MARI index of 0.2, *E. quasiroggenkampii* and *E. aerogenes* MAR index of 0.3, and *E. quasiroggenkampii* had MAR index of 0.6 (Table 12).

Multidrug resistance profiles of *Enterobacter* spp

Of the total 124 *Enterobacter* isolates, 43 (34.7%) were MDR. As shown in Tables 9-12, 13 of 43 (30.2%) *Enterobacter* isolates from water samples are MDR, 19 of 46 (41.3%) from human samples were MDR, 6 of 22 (27.3%) from goat samples are MDR, and 5 of 13 (38.5%) from dog samples are MDR isolates. The difference in MDR rate with respect to sample source is not statistically significant ($\chi^2=1.882$, $p=0.5974$).

Mcr-1 gene carriage among colistin resistant *Enterobacter* spp

The result of the colistin resistance gene amplification showed that one *Enterobacter* spp from Ikot Abasi LGA and one *Enterobacter* spp from Uruan LGA, both from human faecal samples, carried the mobile colistin resistance (*mcr-1*) gene, while *Enterobacter* spp from Mbo LGA isolated from goat faecal sample did not carry *mcr-1* colistin gene (Fig 1).

Table 5: Minimum inhibitory concentration (MIC) of Colistin for *Enterobacter* spp. isolated from water sample

<i>Enterobacter</i> isolate	No of isolate	Colistin MIC	
		I ≤2µg/ml (%)	R ≥4µg/ml (%)
<i>E. cloacae</i>	15	11 (73.3)	4 (26.7)
<i>E. aerogenes</i>	13	8 (61.5)	5 (38.5)
<i>E. gergoviae</i>	5	4 (80.0)	1 (20.0)
<i>E. dissolvens</i>	7	6 (85.7)	1 (14.3)
<i>E. mori</i>	3	3 (100.0)	0
	43	32 (74.4)	11 (25.6)

I: Intermediate ≤2; R: Resistance ≥4; %: percent of the number of isolates for each species of *Enterobacter* testedTable 6: Minimum inhibitory concentration (MIC) of colistin for *Enterobacter* spp. isolated from human faecal samples

<i>Enterobacter</i> isolate	No of isolate	Colistin MIC	
		I (<2µg/ml) %	R (≥4µg/ml) %
<i>E. aerogenes</i>	18	11 (61.1)	7 (38.9)
<i>E. cloacae</i>	15	11 (73.3)	4 (26.7)
<i>E. gergoviae</i>	6	4 (66.7)	2 (33.3)
<i>E. dissolvens</i>	7	7 (100.0)	0
	46	33 (71.3)	13 (28.3)

I: Intermediate ≤2; R: Resistance ≥4; %: percent of the number of isolates for each species of *Enterobacter* testedTable 7: Minimum inhibitory concentration (MIC) of colistin for *Enterobacter* spp isolated from goat faecal samples

<i>Enterobacter</i> isolate	No of isolate	Colistin MIC	
		I (<2µg/ml) %	R (≥4µg/ml) %
<i>E. cloacae</i>	5	4 (80.0)	1 (20.0)
<i>E. aerogenes</i>	7	6 (85.7)	1 (14.3)
<i>E. dissolvens</i>	3	2 (66.7)	1 (33.3)
<i>E. quasiroggenkampii</i>	2	0	2 (100.0)
<i>E. hormaechei</i>	2	1 (50.0)	1 (50.0)
<i>E. bugandensis</i>	3	3 (100.0)	0
	22	16 (72.7)	6 (27.3)

I: Intermediate ≤2; R: Resistance ≥4; %: percent of the number of isolates for each species of *Enterobacter* testedTable 8: Minimum inhibitory concentration (MIC) of colistin for *Enterobacter* spp. isolated from dog faecal samples

<i>Enterobacter</i> isolate	No of isolate	Colistin MIC	
		I (<2µg/ml) (%)	R (≥4µg/ml)
<i>E. cloacae</i>	4	3 (75.0)	1 (25.0)
<i>E. aerogenes</i>	6	5 (83.3)	1 (16.7)
<i>E. hormaechei</i>	1	0	1 (100.0)
<i>E. quasiroggenkampii</i>	2	0	2 (100.0)
	13	8 (61.5)	5 (38.5)

I: Intermediate ≤2; R: Resistance ≥4; %: percent of the number of isolates for each species of *Enterobacter* Tested

Table 9: Multiple antibiotic resistance (MAR) index and resistance profiles of *Enterobacter* spp. from water sample in rural communities in Akwa Ibom State

MARI	No of antibiotics	Resistance profiles	No of isolates	<i>Enterobacter</i> species/codes
0.2	2	DOX, S	1	<i>E. cloacae</i> -wIK/03
0.2	2	S, FOX	4	<i>E. cloacae</i> -wI/04, <i>E. aerogenes</i> -wIK/06, <i>E. aerogenes</i> -wI/09, <i>E. dissolvens</i> -wU/12
0.2	2	FOX, CIP	1	<i>E. aerogenes</i> -wI/14
0.2	2	IMP, MEM	1	<i>E. gergoviae</i> -wM/07
0.2	2	DOX, SXT	1	<i>E. dissolvens</i> -wO/12
0.2	2	FOX, DOX	1	<i>E. cloacae</i> -wM/24
0.3	3	MEM, S, SXT*	1	<i>E. dissolvens</i> -wM/20
0.3	3	IPM, MEM, CAZ	2	<i>E. cloacae</i> -wU/18, <i>E. aerogenes</i> -wIK/04
0.3	3	MEM, CAZ, SXT*	1	<i>E. aerogenes</i> -wU/08
0.3	3	DOX, AMC, SXT*	1	<i>E. dissolvens</i> -wI/01
0.3	3	MEM, SXT, DOX*	1	<i>E. cloacae</i> -wU/03
0.4	4	IPM, MEM, S, SXT*	3	<i>E. cloacae</i> -wU/02, <i>E. aerogenes</i> -wM/10, <i>E. dissolvens</i> -wIK/21
0.4	4	IPM, DOX, S, FOX*	3	<i>E. cloacae</i> -wU/24, <i>E. cloacae</i> -wI/02, <i>E. cloacae</i> -wO/10
0.6	5	MEM, CAZ, FOX, S, SXT*	1	<i>E. cloacae</i> -wO/06
0.6	5	IPM, MEM, DOX, S, FOX*	1	<i>E. cloacae</i> -wU/04
0.7	6	IPM, MEM, DOX, S, CIP, FOX*	1	<i>E. aerogenes</i> -wU/20

MAR index in this study was defined as the ratio of the number of antibiotics resisted by an isolate to the total number of antibiotics the isolate was exposed to (12b), while MDR in this study was defined as resistance of an isolate to at least one to three classes of antimicrobial agent tested (14). IPM: Imipenem; MEM: Meropenem; DOX: Doxycycline; CAZ: Ceftazidime; CIP: Ciprofloxacin; AMC: Amoxicillin/Clavulanate; FOX: Cefoxitin; S: Streptomycin; SXT: Trimethoprim/Sulfamethoxazole (MAR INDEX= 34.9%) ; *E. Enterobacter*, w- water, I-Ikono, , O-Obot Akara, M- Mbo, U-Uruan, IK - Ikot Abasi; * = Multidrug Resistant (MDR)

Table 10: Multiple antibiotic resistance (MAR) index of *Enterobacter* spp. from human faecal samples in rural communities in Akwa Ibom State, Nigeria

MAR index	Number of antibiotics	Resistance profiles	No of isolates	<i>Enterobacter</i> species/codes
0.2	2	DOX, S	1	<i>E. aerogenes</i> -hM/07
0.2	2	CAZ, FOX	2	<i>E. aerogenes</i> -hM/26, <i>E. gergoviae</i> -hM/20
0.2	2	DOX, SXT	2	<i>E. cloacae</i> -hI/31, <i>E. gergoviae</i> -hU/06
0.2	2	IPM, MEM	3	<i>E. cloacae</i> -hM/30, <i>E. dissolvens</i> -hIb/10, <i>E. dissolvens</i> -hM/35
0.3	3	DOX, S, FOX*	3	<i>E. aerogenes</i> -hIk/11, <i>E. gergoviae</i> -hIk/26, <i>E. cloacae</i> -hM/28
0.3	3	DOX, S, SXT*	1	<i>E. cloacae</i> -hI/30
0.3	3	CAZ, AMC, FOX*	1	<i>E. aerogenes</i> -hu/33
0.3	3	IPM, MEM, DOX	1	<i>E. cloacae</i> -hO/09
0.3	3	MEM, DOX, FOX*	1	<i>E. cloacae</i> -hI/06
0.4	4	MEM, CAZ, S, FOX*	1	<i>E. cloacae</i> -hU/05
0.4	4	MEM, CAZ, S, SXT*	1	<i>E. aerogenes</i> -hO/14
0.4	4	DOX, CAZ, S, FOX*	1	<i>E. gergoviae</i> -hIK/26
0.4	4	MEM, DOX, S, FOX*	1	<i>E. aerogenes</i> -hU/17
0.4	4	MEM, CAZ, FOX, SXT*	1	<i>E. aerogenes</i> -hO/28
0.4	4	MEM, IPM, DOX, SXT*	1	<i>E. cloacae</i> -hU/19
0.5	5	DOX, CAZ, GP, FOX, Z*	1	<i>E. aerogenes</i> -hIk/03
0.5	5	IPM, MEM, CAZ, S, SXT*	1	<i>E. aerogenes</i> -hIb/01
0.5	5	DOX, CAZ, FOX, S, SXT*	2	<i>E. aerogenes</i> -hIb/36, <i>E. aerogenes</i> -hO/34
0.5	5	IPM, MEM, DOX, S, SXT*	1	<i>E. aerogenes</i> hI /13
0.5	5	IPM, MEM, DOX, S, FOX*	1	<i>E. cloacae</i> -hU/31
0.7	6	IPM, MEM, DOX, CIP, S, SXT*	1	<i>E. gergoviae</i> -hI/26

MAR index in this study was defined as the ratio of the number of antibiotics resisted by an isolate to the total number of antibiotics the isolate was exposed to (14), while MDR in this study was defined as resistance of an isolate to at least one to three classes of antimicrobial agent tested (16). IPM: Imipenem; MEM: Meropenem; DOX: Doxycycline; CAZ: Ceftazidime; CIP: Ciprofloxacin; AMC: Amoxicillin/Clavulanate; FOX: Cefoxitin; S: Streptomycin; SXT: Trimethoprim/Sulfamethoxazole (MARI = 60.9%) ; *E-Enterobacter*, h-human, I-Ikono, Ib-Ibiono, O-Obot Akara, M- Mbo, U-Uruan, IK - Ikot Abasi; * = Multidrug Resistant (MDR)

Table 11: Multiple antibiotic resistance (MAR) index of *Enterobacter* spp. from goat faecal sample in rural communities in Akwa Ibom State

MAR index	No of antibiotics	Resistance profiles	No of isolates	Antibiotic class	Resistance categories	<i>Enterobacter</i> species /codes
0.2	2	FOX, S	1	2	-	<i>E. dissolvens</i> -gI/02
0.2	2	IPM, MEM	1	1	-	<i>E. bugandensis</i> -gM /22
0.2	2	DOX, FOX	1	2	-	<i>E. cloacae</i> -gIb/33
0.2	2	DOX, AMC	1	2	-	<i>E. bugandensis</i> -gIk/26
0.3	3	DOX, FOX, SXT*	1	3	MDR	<i>E. aerogenes</i> -gIb/29
0.4	4	IPM, MEM, S, FOX*	2	3	MDR	<i>E. dissolvens</i> -gO/21, <i>E. gergoviae</i> -gM/03
0.6	5	MEM, AMC, FOX, S, SXT*	1	5	MDR	<i>E. bugandensis</i> -gIk/06
0.6	5	IPM, MEM, DOX, CAZ, FOX*	1	4	MDR	<i>E. gergoviae</i> -gM/15
0.7	6	IPM, MEM, CAZ, AMC, S, FOX*	1	4	MDR	<i>E. cloacae</i> -gU/27

MDR in this study was defined as resistance of an isolate to at least one to three classes of antimicrobial agent tested (14), while MAR index in this study was defined as the ratio of the number of antibiotics resisted by an isolate to the total number of antibiotics the isolate was exposed to (16). IPM: Imipenem; MEM: Meropenem; DOX: Doxycycline; CAZ: Ceftazidime; CIP: Ciprofloxacin; AMC: Amoxicillin/Clavulanate; FOX: Cefoxitin; S: Streptomycin; SXT: Trimethoprim/Sulfamethoxazole (MAR=27.3%); E- *Enterobacter*, g-goat, I-ikono, Ib-Ibiono, O-Obot Akara, M- Mbo, U-Uruan, Ik - Ikot Abasi; * = Multidrug Resistant

Table 12: Multiple antibiotic resistance (MAR) index of *Enterobacter* spp from dog faecal samples in rural communities in Akwa Ibom State

MAR index	Number of antibiotics	Resistance profiles	No of Isolates	Antibiotic class	Resistance categories	<i>Enterobacter</i> species /codes
0.2	2	IPM, SXT	1	2	-	<i>E. aerogenes</i> -dI/22
0.3	3	CIP, S, SXT*	1	3	MDR	<i>E. quasiroggenkampii</i> -dM/10
0.3	3	FOX, S, SXT*	1	3	MDR	<i>E. aerogenes</i> -dIb/34
0.3	3	IPM, MEM, CAZ	1	2	-	<i>E. cloacae</i> -dIk/01
0.4	4	IPM, MEM, S, FOX*	1	3	MDR	<i>E. cloacae</i> -dU/04
0.4	4	IPM, AMC, S, FOX*	1	4	MDR	<i>E. hormaechei</i> -dIk/29
0.6	5	IPM, MEM, CAZ, S, FOX*	1	4	MDR	<i>E. quasiroggenkampii</i> -dM/25

MDR in this study was defined as resistance of an isolate to at least one to three classes of antimicrobial agent tested (14), while MAR index in this study was defined as the ratio of the number of antibiotics resisted by an isolate to the total number of antibiotics the isolate was exposed to (16). IPM: Imipenem; MEM: Meropenem; DOX: Doxycycline; CAZ: Ceftazidime; CIP: Ciprofloxacin; AMC: Amoxicillin/Clavulanate; FOX: Cefoxitin; S: Streptomycin; SXT: Trimethoprim/Sulfamethoxazole (MAR=46.2%); E- *Enterobacter*, d- dog, I-ikono, Ib-Ibiono, M- Mbo, U-Uruan, IK - Ikot Abasi; * = Multidrug Resistant

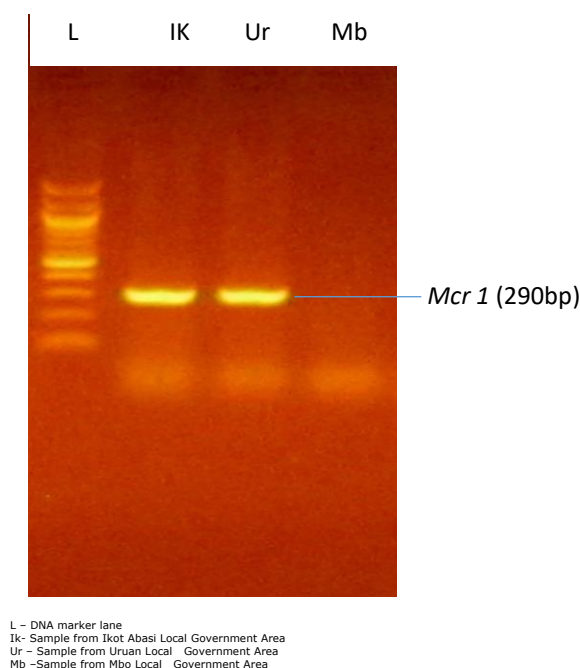


Fig 1: Agarose gel electrophoresis picture of *mcr-1* amplicon

Discussion:

Antibiotic resistance arises when bacteria mutate and reduce the efficiency of the antibiotics used to treat infections caused by them. This constitutes one of the most critical challenges affecting public health in the 21st century. Human-animal-environment interactions are critical for antimicrobial containment, according to the One Health concept (17,18). Antibiotic use in medical, veterinary care, and agriculture has contributed significantly to the evolution of bacterial resistance (18). This is true for Akwa Ibom State, Nigeria, where antibiotic resistance occurs across the study locations in water, humans, and animals.

The isolation of antibiotic-resistant *Enterobacter* species in water, human and animal sources is of public and clinical significance, as over-use of antibiotics may lead to treatment failure, extra length of hospital stays, increased mortality and economic losses (19). In this study, the antibiotic susceptibility profile of *Enterobacter* isolates from water, human, goat and dog samples analyzed showed varying outcomes. Most of the *Enterobacter* isolates from water were resistant to cefoxitin and streptomycin, which may be due to the wide availability of these antibiotics because they are cheap and therefore consistently used even by rural dwellers. This finding is consistent with the study of Tula et al., (20), which reported that majority of *Enterobacter* isolates were resistant to streptomycin. Previous studies in

Abakaliki, Nigeria (21) and Cape Town, Ghana (22), have reported similar resistance rates.

Among the *Enterobacter* isolates, *E. cloacae* subsp *dissolvens* was resistant to trimethoprim/sulfamethoxazole. This may be due to the acquisition of resistant genes from the parent genus *E. cloacae*. *Enterobacter aerogenes* and *E. cloacae* exhibited the highest rate of resistance to doxycycline, cefoxitin, streptomycin, and colistin, probably due to the frequent use of these antibiotics for treatment of related infections. High resistance to these antibiotics, especially colistin, by enteric pathogens including *Enterobacter* species in water sources has been previously reported (23).

The high prevalence of resistance by *Enterobacter* isolates to most of the commonly used antibiotics in this study constitutes a public health risk because these antibiotics may not be effective in treating infections that may occur in individuals who utilize the water sources for drinking or other domestic purposes. This study also recorded resistance to imipenem, meropenem, and ciprofloxacin among the *Enterobacter* isolates. This is reasonably expected since these antibiotics, particularly the carbapenems, are now commonly abused as they are available over-the-counter and dispensed without medical authorization. However, the resistance observed among the isolates might suggest the occurrence of cross-resistance, which occurs when an organism is resistant to an antibiotic to which it has not been exposed, probably because of acquisition of resistance markers to related antibiotics (24). Freshwater is a favorable environment for growth of many microorganisms such as the family Enterobacteriaceae (24), as a result of which they may serve not only as a vehicle for the spread of antibiotic-resistant organisms among humans and animals, but also as a means of resistance gene transfer in the natural bacterial ecosystems (25).

The antibiotic susceptibility profile of the *Enterobacter* isolates from human faeces indicates low resistance to trimethoprim/sulfamethoxazole due to infrequent use by members of the community and high resistance to imipenem due to over-the-counter availability, which is worrisome because carbapenems are regarded as antibiotics of last resort for treating Gram-negative bacterial infections (1,20). The clinical influence of carbapenemase producers has emerged worldwide due to their regular use in farm animal treatment (26). Medically valuable carbapenem-res-

istant *Enterobacter* species are a threat due to their resistance profile, accelerated emergence, and rapid transmission. Additionally, it can spread to other genera of Gram-negative organisms through genetic elements such as plasmids, insertion sequences, and transposons (27).

The emergence of antibiotic-resistant bacteria in animal populations may have important human public health consequences if isolates are transmitted to humans from their pets or via faecal contamination of water bodies (28). Understanding the prevalence of antibiotic resistance among *Enterobacter* isolates is thus important both from veterinary medicine and public health perspectives. Multidrug resistance is the most important challenge encountered in treating microbial infections, and there is an exponential increase in MDR over the last decade (28). The emergence of MDR *Enterobacter* spp has a negative impact on the clinical outcomes of infected patients with concomitant increase in morbidity and mortality (29).

This study found that *Enterobacter* spp. from goat faecal samples were sensitive to imipenem, ceftazidime and amoxicillin/clavulanate acid with very low resistance to trimethoprim/ sulfamethoxazole, probably due to lack of exposure to these antibiotics, as there are no veterinary services in the rural communities studied. This observation may be partly supported by the fact that *Enterobacter* isolates from human samples had the highest MDR rate (41.3%), compared to water and animal samples, although the difference in rates was not statistically significant ($\chi^2=1.882$, $p=0.5974$). However, overuse of antibiotics for treatment of infections in humans can create 'selection pressure' for emergence of MDR strains.

Enterobacter isolates from dog faecal samples in this study were 100% sensitive to amoxicillin/clavulanic acid, and 84.6% sensitive to doxycycline and ceftazidime. This high sensitivity rate may be due to lack of exposure to these antibiotics in the rural setting. However, there was a high rate of resistance to streptomycin, which may be due to overuse of streptomycin as Penstrep (penicillin and streptomycin) combination to treat bacterial infections in veterinary medicine (30), which they may acquire through transfer of resistance genes from the waste food that they eat while scavenging dump sites, as they are free-roaming animals in rural areas. Studies conducted by Mezzatesta *et al.* (31) reported that almost all *Enterobacter* isolates from faecal samples of goats and dogs exhibited resistance to amoxicillin/clavulanic acid, ceftazidime and ampicillin, possibly due to AmpC β -lacta-

mase production, which strongly suggests dissemination of resistant isolates among the animals via direct spread from animal to animal, or indirect transmission from sources in the environment.

In the present study, minimum inhibitory concentrations (MICs) of colistin were determined for all *Enterobacter* isolates from water, human, goat and dog faecal samples. The overall colistin resistance rate among the *Enterobacter* isolates was 28.2%, and this rate was higher for isolates from dog samples (38.5%) than humans (28.3%), goats (27.3%) and water (25.6%) samples, although the difference in rates between sample sources was not statistically significant ($\chi^2=0.8306$, $p=0.8421$). Among the 43 *Enterobacter* isolates from water samples, 11 (25.6%) were resistant to colistin, and this could be as a result of transfer of colistin resistance by plasmid between different Gram-negative bacilli in the water body, which could lead to antibiotic resistance, especially in a community with low exposure to colistin.

Also, the rate of colistin resistance of *Enterobacter* isolates in human faecal samples was 28.3% ($n=13$) with *E. cloacae*, *E. aerogenes*, *E. gergoviae* and *E. dissolvens* being the implicated isolates. Resistance to colistin in this study may be attributed to the gradual use of colistin in farm animals like poultry and pigs which are reared by some members of the communities and are eventually consumed by the people who ordinarily do not take the antibiotics themselves (32). The *Enterobacter* isolates from the goat faecal samples were resistant to colistin (27.3%, $n=6$). This relatively high resistance rate may have occurred from consumption of colistin resistant *Enterobacter*-contaminated water, from the only source of drinking water for both man and animals in the community (33). The level of resistance of *Enterobacter* spp from dog faecal samples to colistin was 38.5% ($n=5$). This resistance rate could be attributed to the dogs coming in contact with human faecal wastes within the environment and their exposure to the streams, which may harbor colistin-resistant *Enterobacter* spp (33).

Although colistin was considered a drug of last resort for treatment of infections caused by multidrug-resistant organisms (MDROs), resistance to it is developing in recent times, probably due to its increased use in humans and continuous unauthorized use in farm animals such as poultry and pigs reared by some members of the communities. Colistin-resistant isolates may spread through the water and food chain to reach the populace who had not previously been exposed to colistin

(32,33). It is important to note that most antimicrobial-resistant non-clinical *Enterobacter* isolates can enter the food chain undetected (34). Previous reports indicate that these MDR bacteria can transfer their resistant genes from animals to humans through the use of glycopeptides growth promoters such as avoparcin in feed animals (27).

According to Thenmozhi et al., (35), MARI of >0.2 indicate resistant isolates are from environment where antibiotics are frequently used, while MARI of ≤ 0.2 indicates infrequent antibiotic usage. The MAR indices of *Enterobacter* spp isolated from water samples in our study showed *E. cloacae*, *E. aerogenes*, and *E. cloacae* subsp *dissolvens* exhibited resistance to two drug combinations probably due to low or no exposure antibiotics in the environment. Some isolates from Issiet Ekim in Uruan LGA, Isong Inyang in Mbo LGA, and Ikot Atan in Ikot Abasi LGA were resistant to three or more antibiotics, which implies that these isolates may carry antibiotic resistance genes probably acquired from other bacilli within the water source, brought about through human activities, runoff from erosion downstream, or agricultural activities in the farmlands around the vicinity of the stream.

Three *Enterobacter* spp from human faecal samples exhibited resistance to two drugs and had the MAR index of 0.2, which may indicate low exposure from infrequent antibiotic use. However, *E. cloacae*, *E. aerogenes*, *E. cloacae* subsp *dissolvens* and *E. gergoviae* isolates from human faecal samples were resistant to at least three different antibiotics with MAR index ranging from 0.3 to 0.7, indicating indiscriminate or frequent antibiotic usage. This observation is supported by the fact that the population is predominantly rural dwellers who rely solely on drugs purchased from untrained drug vendors because of lack of access to physicians in the rural settings.

In goat faecal samples, the MAR index revealed that *E. cloacae* subsp *dissolvens* from Ikono, *Enterobacter bugandensis* from Mbo, and *Enterobacter hormaechei* from Ikot Abasi, were resistant to two antibiotics each with a MARI of 0.2, which implies low exposure to antibiotics. *Enterobacter aerogenes* from Ibiono were resistant to three antibiotics, and *E. gergoviae* from Uruan setting was resistant to six antibiotics, which may suggest that goats have been exposed to water containing antibiotic-resistant strains of *Enterobacter* species.

The MAR index of *Enterobacter* spp in dog faecal samples showed that *E. aerogenes* had an MAR index of 0.2, indi-

cating low or no antibiotic exposure in the dogs in Ikot Ntuen community of Ikono LGA. *Enterobacter quasiroggenkampii* in Mbo LGA were resistant to five antibiotics with MARI of 0.6, indicating that these *E. quasiroggenkampii* isolates in Isong Inyang, Mbo LGA may have possibly acquired resistance to many antibiotics through gene transfers within the environment or dogs feeding on faecal samples of humans harboring resistant bacteria. A previous study indicate that multidrug-resistant bacteria can transfer their resistant genes from animals to humans through glycopeptide growth promoters such as avoparcin (27).

The resistance profiles observed in human, water, and dog samples show a relatively close connection between some *Enterobacter* spp from these sources, which may indicate transmission from the environment (water) to human or animals. For instance, in Tables 9-12, one isolate (*E. cloacae* wU/04) from water sample had the same resistance profile (IPM/MEM/DOX/S/FOX) as one isolate (*E. cloacae* hU/31) from a human faecal sample. This may suggest transmission of the same *E. cloacae* to humans through contaminated water. Also, one isolate (*E. cloacae* wIK/03) from water sample had the same resistance profile (DOX/S) with one isolate (*E. aerogenes* hM/07) from human sample, while two isolates from goat samples (*E. dissolvens* gO/21 and *E. gergoviae* gM/03) had the same resistance profile (IPM/MEM/S/FOX) with one isolate (*E. cloacae* dU/04) from dog sample. Although these isolates shared the same resistance profile, they are different species of *Enterobacter*, which make them remotely unrelated, and therefore unlikely that there is transmission of these isolates from water to human or animal. Antibiotic resistance profile is known to be a poor discriminatory tool for epidemiological typing.

The high MAR indices obtained in this study, with resistance to many antibiotics including imipenem, meropenem, doxycycline, ciprofloxacin, ceftazidime, amoxicillin-clavulanic acid and colistin, is worrisome, as this may depict the existence of high-level antibiotic-resistant *Enterobacter* spp in the study area. The emergence of colistin resistance among *Enterobacter* isolates agrees with a previous study (36), due to increasing use for colistin in the treatment of carbapenem-resistant bacterial infections (36). Colistin has been regarded as the last-line therapeutic option against carbapenem-resistant Gram-negative bacteria (37). The detection of colistin-resistant (*mcr-1*) gene in some of the *Enterobacter* isolates in our study indicates a potential for exchange of genes at the human-animal-environment interface

among *Enterobacter* spp and other Gram-negative bacilli. Resistance to colistin may also be due to several mechanisms such as beta-lactamase production, efflux pumps, altered porin channels, and intrinsic low permeability of *Enterobacter* spp. These mechanisms may also contribute to the high level of resistance among the *Enterobacter* isolates, resulting in the high MDR phenotypes.

This study has some limitations. First, the study was conducted in only 6 selected rural communities in Akwa Ibom State, which make findings not generalizable to the entire population in the rural communities and urban areas of the State. However, based on the scientific method of sampling used to select the six communities, we believe there is a fair representation of the population in the State. Secondly, the study was limited by sample size variation across the sample sources; water (n=43), human (n=46), goat (n=22), and dog (n=13), however comparisons were made using unique denominators for each sample source, which allowed accurate comparisons of prevalence of MDR and colistin resistance between the sample sources. Lastly, the study was restricted to molecular testing of only the *mcr-1* gene in colistin-resistant isolates, while other resistance mechanisms were not investigated. This could explain the wide disparity between phenotypic colistin resistance and genetic basis of this resistance. There is need to investigate further other molecular mechanisms responsible for colistin resistance in the study area.

Conclusion:

The findings of this study indicate that most *Enterobacter* isolates in the rural setting were resistant to cefoxitin and streptomycin but susceptible to cef-tazidime, amoxicillin/clavulanic acid and trimethoprim/sulphamethoxazole. Multiple antibiotic resistance indices, multidrug resistance profiles and colistin resistance rates were generally high for the *Enterobacter* isolates from water, human, goat and dog faecal samples. An effective antimicrobial stewardship and surveillance system should be put in place to contain emergence and spread of multidrug and colistin-resistant *Enterobacter* spp in both human and animal populations in Akwa Ibom State, Nigeria.

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Contribution of authors:

AIT and UJU designed the study, performed laboratory analysis, wrote the original draft of the manuscript and reviewed the write-up. BM, UFZ and NEI were involved in sample collection and literature review. All authors critically reviewed the final manuscript.

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