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DOI: 10.46903/gjms/20.02.1127

ORIGINAL ARTICLE

PREVALENCE OF PHENOTYPIC CARBAPENEM-RESISTANT *ENTEROBACTERALES* ISOLATES AND THEIR DISTRIBUTION BY SEX, AGE GROUPS, STATE AND SPECIES IN SOUTH-EAST NIGERIA

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ABSTRACT

Background: Carbapenems were introduced in response to emergence of ESBL-producing gram-negative bacteria. The objective of this study was to determine prevalence of phenotypic carbapenem-resistant *Enterobacterales* isolates and their distribution by sex, age groups, state and species in South-East Nigeria.

Materials &Methods: This cross-sectional study was done in Department of Microbiology, Alex Ekwueme Federal University, Ndufu-Alike Abakaliki, Nigeria from 30th March 2019 to 12th January, 2021.All *Enterobacterales* isolates from various body specimens were eligible. Carbapenem-resistance was detected with ertapenem, meropenem, imipenem, and doripenem. Presence of carbapenem-resistance (yes/no) was single research variable. Sex, age group, state and species were grouping variables, all on nominal scale. All variables were analyzed by count and percentage with 95% confidence interval.

Results: Out of 400 *Enterobacterales* isolates, 192 were from men and 208 from women. Prevalence of carbapenem-resistance was 117 (29.25%). The prevalence was higher 65 (16.25%) in women than 52 (13%) men. It was highest in age group 20-39 years 54 (13.50%), followed by ≥ 60 years age group 26 (6.50%). It was highest 39 (9.75%) in Enugu state, followed by 30 (7.50%) in Ebonyi state. Prevalence was highest in *Escherichia coli* 9.50%, followed by *Klebsiella pneumonia* 6.50%.

Conclusion: In our population, prevalence of carbapenem-resistance to *Enterobacterales* isolates was higher (29.5%) than many studies. It was higher in women than men. It was highest in age group 20-39 years, followed by ≥60 years. It was highest in Enugu state, followed by Ebonyi state. Prevalence was highest in *Escherichia coli,* followed by *Klebsiella pneumonia*.

KEY WORDS: *Enterobacterales*; *Escherichia coli; KlebsiellaPneumonia; Klebsiella Oxytoca;* Bacteria; Antibiotics; Carbapenems; Prevalence; Sex; Age Groups.

Cite as: Ugah UI, Udeani TK. Prevalence of phenotypic carbapenem-resistant *enterobacterales* isolates and their distribution by sex, age groups, state and species in South-East Nigeria. Gomal J Med Sci 2022 Apr-Jun; 20(2):89-96. https://doi.org/1046903/gjms/20.02.1127

1. INTRODUCTION

1.1 Background: The carbapenems are a group of broad-spectrum beta-lactamase enzymes that possess hydrolytic activities against all cephalosporins, penicillins and carbapenems.[1] However, in the early 1990s the first carbapenem resistant bacterium was isolated in Japan.[2] Since then, there have been reports of emergence of carbapenem-resistant organisms in different healthcare settings worldwide.[3] The CDC recognized the public health threat and declared that carbapenem resistant organisms require aggressive action. The CDC also reported that up to half of all bloodstream infections caused by carbapenem-resistant *Enterobacterales* results in death.[4]

With increasing global prevalence of ESBL producing organisms, there has been increased dependence

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Date Submitted: 04-01-2022
Date Revised: 23-04-2022
Date Accepted: 30-04-2022

on carbapenems to effectively treat these infections. However, the development of carbapenem resistance has become a public health malady. They produce difficult to treat infections of all types with associated increase in morbidity, prolonged hospital stay, increased cost of treatment and a mortality rate that is greatly increased to about 50%.[5,6]

Different mechanisms for carbapenem resistance in *Enterobacterales* have been reported. They include; reduced outer membrane permeability due to loss of porins, over-expression efflux pumps and production of carbapenemase enzymes.[7] The carbapenemases are grouped as per Ambler classification as A, B and D.[8]

Other mechanisms for carbapenem resistance include; production of AmpC enzymes and production of extended spectrum beta-lactamases.[9,10]

Gram-negative organisms are responsible for most clinical infections; therefore the emergence of carbapenem resistance among them is of public health significance.[11] Also, there is limited treatment option as approved drugs used against them (colistin and tigecycline) are fraught with high toxicities[12] and they can be easily disseminated.[13]

1.2 Research Objectives (RO)

RO 1: To determine the prevalence of phenotypic carbapenem-resistant *Enterobacterales* isolates in South-East Nigeria.

RO 2-5: To determine the distribution of phenotypic carbapenem-resistant *Enterobacterales* isolates by sex, age groups, state and species in South-East Nigeria.

1.3 Significance: There is limited data on the epidemiology of carbapenem resistance among *Enterobacterales* especially in most sub-Saharan African countries.[14] This study aimed at providing data on the current status of carbapenem-resistant *Enterobacterales* isolates in five states of South-East Nigeria.

2. MATERIALS AND METHODS

2.1 Design, setting, duration and ethical consideration: This cross-sectional study was carried out in the Department of Microbiology, Faculty of Biological Sciences, Alex Ekwueme Federal University Ndufu-Alike Abakaliki, Ebonyi State, Nigeria from 30th March 2019 to 12th January, 2021. The project was ethically approved by health ministries of five concerned states. Written informed consent was sought from subjects/ their parents (guardians) in case of children.

2.2 Population & sampling: The South-East Nigerian region has five states with approximate population of 16,395,555 as per census 2006. A sample of 400 specimens was collected from five out of 11 tertiary hospitals of the region by consecutive non-probability technique; Federal Medical Centre Umuahia, Abia State (77), Alex Ekwueme Federal University Teaching Hospital, Abakaliki (103), Enugu State University Teaching Hospital, Parklane, Enugu State (116), Imo State University Teaching Hospital, Imo State (52) and Chukwuemeka Odumegwu Ojukwu University Teaching Hospital, Anambra State (52).

All patients confirmed with *Enterobacterales* isolates from their specimens were eligible. Those on combined antibiotic therapy in the last two weeks were not eligible.

2.3 Specimen Collection and Identification: *Enterobacterales* isolates were obtained from different body specimens; urine, sputum, CSF, stool, blood, etc. Their identification was done through various microbiological methods as described by Cheesbrough15 and Forbes, et al.,16 including gram reaction and routine biochemical tests; indole, methyl red, Voges-Proskauer, citrate utilization, oxidase, urease, triple sugar iron, and sugar fermentation.

2.4 Carbapenem susceptibility and phenotypic screening for resistance: Phenotypic detection of carbapenem resistance was done using Kirby-Bauer disc diffusion method using discs with 10μg each for Ertapenem, Imipenem, Meropenem and Doripenem. The bacterial isolates were suspended in sterile normal saline to match 0.5 McFarland standard. A sterile swab stick was used to inoculate the surface of the Mueller-Hinton agar which was prepared as per guidelines of manufacturer and then autoclaved at 1210C for 15 minutes.

The antimicrobial discs were put when the surface of the media was dry. Then these plates were incubated at 370C for 18 hours. The inhibition zone diameters were measured and the results were interpreted as per European Committee on Antimicrobial Susceptibility Testing V.10.17 Isolates were recorded as carbapenem–resistant if they showed simultaneous resistance to ertapenem, doripenem, meropenem and imipenem.

2.5 Data collection and analysis plans: Presence of carbapenem-resistant *Enterobacterales* isolates (yes/ no) was a single research variable. Sex, age group, state and species were demographic/ grouping variables, all on nominal scale. All variables were analyzed by count and percentage with 95% confidence interval for proportion to represent population, using Wilson score interval method by an online calculator "Statistics Kingdom".

3. RESULTS

3.1 Prevalence of carbapenem-resistant *Enterobacterales* isolates: Out of 400 *Enterobacterales* isolates, 117 (29.25%) were carbapenem-resistant. (Table 3.1)

3.2 Distribution of carbapenem-resistant *Enterobacterales* isolates by sex: Out of 400 *Enterobacterales* isolates, 192 were from men and 208 from women. The prevalence of resistance was higher in women 16.25% than men 13.00%. (Table 3.2)

3.3 Distribution of carbapenem-resistant *Enterobacterales* isolates by age groups: The highest resistance was observed among the age group 20-39 years (13.50%), followed by ≥ 60 years age group (6.50%). (Table 3.3)

Table 3.1: Prevalence of carbapenem-resistant *Enterobacterales* isolates in South-East Nigeria

S. No.	Isolates	Sample statistics		95%CI for proportion	
		Count	Percentage	Lower	Upper
1	Resistant isolates	117	117*100/400=29.25%	25.00	33.88
2	Sensitive isolates	283	283*100/400=70.75%	66.11	74.99
Total isolates		400	100%	Population parameters	

Table 3.2: Distribution of carbapenem-resistant *Enterobacterales* isolates by sex in South-East Nigeria

S. No.	Sex	Sample size	Sample statistics		95%CI for proportion	
			Count	Percentage	Lower	Upper
1	Men	192	52	52*100/400= 13.00%	10.05	16.65
2	Women	208	65	65*100/400 = 16.25%	12.95	20.18
Total resistant isolates			117	117*100/400=29.25%	25.00	33.88
Total sensitive isolates			283	283*100/400=70.75%	66.11	74.99
Total isolates/ sample		400	400	100%	Population parameters	

Table 3.3: Distribution of carbapenem-resistant *Enterobacterales* isolates by age groups in South-East Nigeria

S. No.	Age groups	Sample size	Positive isolates		95%CI for proportion	
			Count	Percentage	Lower	Upper
1	<20 years	71	21	21*100/400=5.25	03.06	07.43
2	20-39 years	170	54	54*100/400=13.50	10.15	16.84
3	40-59 years	63	16	16*100/400=4.00	02.07	05.92
4	≥ 60 years	96	26	26*100/400=6.50	04.08	08.91
Total resistant isolates			117	117*100/400=29.25%	25.00	33.88
Total sensitive isolates			283	283*100/400=70.75%	66.11	74.99
Total isolates/ sample		400	400	100%	Population parameters	

3.4 Distribution of carbapenem-resistant *Enterobacterales* isolates by state: The highest resistance was observed in Enugu state (9.75%), followed by Ebonyi state (7.50%). (Table 3.4)

3.5 Distribution of carbapenem-resistant *Enterobacterales* isolates by species: The prevalence of resistance is given in descending order. Among these, the highest resistance was observed among *Escherichia coli* 9.50%, followed by *Klebsiella pneumonia* 6.50%. *Proteus vulgaris* and *Y. enterocolytica* were fully susceptible to the carbapenems. (Table 3.5)

Table 3.4: Distribution of carbapenem-resistant *Enterobacterales* isolates by age groups in South-East Nigeria

S. No.	States	Sample size	Positive isolates		95%CI for proportion	
			Count	Percentage	Lower	Upper
1	Abia	77	19	19*100/400=4.75	02.66	06.83
2	Ebonyi	103	30	30*100/400=7.50	04.91	10.08
3	Enugu	116	39	39*100/400=9.75	06.84	12.65
4	Imo	52	15	15*100/400=3.75	01.88	05.61
5	Anambra	52	14	14*100/400=3.50	01.69	05.30
Total resistant isolates			117	117*100/400=29.25%	25.00	33.88
Total sensitive isolates			283	283*100/400=70.75%	66.11	74.99
Total isolates/ sample		400	400	100%	Population parameters	

Table 3.5: Distribution of carbapenem-resistant *Enterobacterales* isolates by species in South-East Nigeria

S.No.	Bacterial Isolates	Sample size	Positive isolates		95%CI for proportion	
			Count	Percentage	Lower	Upper
1	*Escherichia coli*	123	38	38*100/400=9.50	06.62	12.37
2	*Klebsiella pneumoniae*	77	26	26*100/400=6.50	04.08	08.91
3	*Klebsiella oxytoca*	28	10	10*100/400=2.50	00.97	04.03
4	*Morganella morganii*	27	9	9*100/400=2.25	00.79	03.70
5	*Citrobacter freundii*	41	6	6*100/400=1.50	00.30	02.69
6	*Serratia marcescens*	22	6	6*100/400=1.50	00.30	02.69
7	*Proteus mirabilis*	19	6	6*100/400=1.50	00.97	04.03
8	*Enterobacter cloacae*	18	6	6*100/400=1.50	00.30	02.69
9	*Shigella dysenteriae*	17	5	5*100/400=1.25	0.1612	02.33
10	*Salmonella enterica*	14	5	5*100/400=1.25	0.1612	02.33
11	*Proteus vulgaris*	13	0			
12	*Yersinia enterocolytica*	1	0			
Total resistant isolates			117	117*100/400=29.25%	25.00	33.88
Total sensitive isolates			283	283*100/400=70.75%	66.11	74.99
Total isolates/ sample		400	400	100%	Population parameters	

4. DISCUSSION

4.1 Prevalence of carbapenem-resistant *Enterobacterales* isolates: There have been consistently increasing reports of high occurrence of antimicrobial resistant isolates in various developing and developed countries. This study reports the occurrence of carbapenem-resistant *Enterobacterales* among population in South-Eastern Nigeria. We used strict criteria by recording an isolate as carbapenem-resistant if the isolate was simultaneously resistant to doripenem, meropenem, imipenem and ertapenem. A study which compared phenotypic screening methods for carbapenem resistance determined that 10μg of ertapenem and imipenem discs had 100% sensitivity, while meropenem disc had 95.7% sensitivity when compared with the E-test and Modified Hodge Test methods.[18] This is comparable to the Kirby-Bauer method for phenotypic detection of carbapenem resistance which was used by this study.

In our population 29.25% (95%CI 25-33.88) (117 out of 400) *Enterobacterales* isolates were carbapenem-resistant. (Table 3.1)

Similar to our study, Olowo-Okere, et al.[1] reported 28.18% (31*100/110) carbapenem resistance in Gram-negative bacterial isolates from Sokoto, Nigeria in 2018 and 28.20% (22*100/78) by Oli, et al.[9] from Anambra State, South-East Nigeria in 2017.

Lower prevalence 22.03% (39*100/177) of carbapenem-resistance among *Enterobacteriaceae* was reported by Adesanya, et al.[19] from Ibadan, South-west Nigeria from Jan. to June 2018, Aminu, et al.[21] 10.52% using ertapenem disc (8 out of 76 isolates of *Enterobacteriaceae*) in Kano, North-eastern Nigeria, Muhammad, et al.[22] 10.22% in year 2014 from Maiduguri, Borno State, North-eastern Nigeria, Oduyebo, et al.[23] from Idi-Araba, Lagos State, South-West Nigeria 15.25% (27*100/177), Ngbede, et al.[24] 18.87% (110*100/583) from Nigeria, Badmasti, et al.[25] from Isfahan, Iran 22.70% (96*100/423) in year 2021 and Barbadoro, et al.[26] from Ancona, Marche Region, Italy from Feb. to Sep. 2018 in rectal swabs as 1.93% (48*100/2478).

Ajuba, et al.[20] from Anambra State, South-eastern Nigeria showed that out of 187 *E. coli* isolates, 41 (21.92%) were confirmed to be carbapenem-resistant, while 21 (11.23%) of these were proven as carbapenemase producers. Carbapenem resistant *Enterobacterales* are major pathogens that have been reported to have an 8% mortality rate in the United States annually.[27]

4.2 Distribution of carbapenem-resistant *Enterobacterales* isolates by sex: In our population, the prevalence of resistance was higher in women 16.25% (95%CI 12.95-20.18) than men 13% (95%CI 10.05-16.65). (Table 3.2)

Similar to our study, Olowo-Okere, et al.[1] reported higher prevalence of resistance in women 15.45% (17*100/110) than men 12.73% (14*100/110) from Sokoto, Nigeria in 2018.

In contrast to our findings, the prevalence was similar 14.10% (11*100/78) for both the men and women as reported by Oli, et al.[9] from Nigeria and Aminu, et al.[21] as 5.26% (4*100/76) for both the men and women from Kano, North-eastern Nigeria.

In contrast to our findings, the prevalence was higher for men 14.12% (25*100/177) than women 7.91% (14*100/177) as reported by Adesanya, et al.[19] from Nigeria, Badmasti, et al.[25] from Isfahan, Iran as 13.24% (56*100/423) men versus 9.46% (40*100/423) women and Barbadoro, et al.[26] from Italy as 1.29% (32*100/2478) men versus 0.64% (16*100/2478) women.

4.3 Distribution of carbapenem-resistant *Enterobacterales* isolates by age groups: Our population showed highest resistance 13.50% (95%CI 10.15-16.84) among the age group 20-39 years, followed by 6.50% (95%CI 4.08-8.91) among ≥60 years, 5.25% in <20 years and 4% in 40-59 years. (Table 3.3)

Oli, et al.[9] reported highest prevalence of resistance 10.25% (8*100/78) in age group 21-40 years, followed by 7.69% (6*100/78) in 41-60 years and then equal prevalence of 5.13% (4*100/78) in 1-20 years and 61-80 years from Nigeria. Olowo-Okere, et al.[1] reported somewhat opposite findings with highest prevalence of resistance 11.82% (13*100/110) in age group 18-50 years, followed by equal prevalence of 8.18% (9*100/110) in 0-17 years and 51+ years from Sokoto, Nigeria in 2018.

Adesanya, et al.[19] from Nigeria reported highest prevalence of resistance 7.91% (14*100/177) in age group 40-54 years, followed by 5.65% (10*100/177) in 25-39 years and then equal prevalence of 2.82% (5*100/177) in 55-69 years and ≥70 years. Aminu, et al.[21] reported higher prevalence of 7.89% (6*100/76) in adults (≥18 years) than 2.63% (2*100/76) in pediatrics (0-17 years).

Badmasti, et al.[25] reported highest resistance 35.42% (34*100/96) in age group ≥60 years, followed by 34.37% (33*100/96) in 16-30 years, 19.79% (19*100/96) in 46-60 years, 6.25% (6*100/96) in 31-45 years and 4.17% (4*100/96) in 0-15 years. Barbadoro, et al.[26] from Italy reported highest resistance 1.09% (27*100/2478) in age group >65 years, followed by 0.68% (17*100/2478) in 45-64 years and 0.16% (4*100/2478) in <44 years.

4.4 Distribution of carbapenem-resistant *Enterobacterales* isolates by State: In our population, highest resistance was observed in Enugu State 9.75% (95%CI 6.84-12.65) followed by Ebonyi State (7.50%). (Table 3.4)

No study showing distribution by these States was available online.

4.5 Distribution of carbapenem-resistant *Enterobacterales* isolates by species: Our population showed highest prevalence of resistance among *Escherichia coli* 9.50% (95%CI 6.62-12.37) followed by *Klebsiella pneumonia* 6.50% (95%CI 4.08-8.91) and *Klebsiella oxytoca* 2.50% (95%CI 0.97-4.03). *Proteus vulgaris* and *Y. enterocolytica* were fully susceptible to the carbapenems. (Table 3.5)

Oli, et al.[9] reported opposite to our findings with highest prevalence of resistance 11.54% (9*100/78) in *Klebsiella oxytoca*, followed by 8.97% (7*100/78) in *Klebsiella pneumoniae* and 7.69% (6*100/78) in *Escherichia coli* from Nigeria. Adesanya, et al.[19] has opposite to our findings with highest prevalence of resistance 7.91% (14*100/177) in *Klebsiella pneumoniae*, followed by 6.78% (12*100/177) in *Pseudomonas aeruginosa,* 3.39% (6*100/177) in *Klebsiella oxytoca* and 1.13% (2*100/177) in *Escherichia coli* from Nigeria.

Aminu, et al.[21] reported highest prevalence of 3.95% (3*100/76) in *Escherichia coli,* followed by 2.64% (2*100/76) in *Klebsiella pneumonia* and 1.31% (1*100/76) in each of *Enterobacter ozaenae, Enterobacter cloacae* and *Serratia odorifera.* Oduyebo, et al.[23] reported highest prevalence of 4.52% (8*100/177) in *Klebsiella pneumonia,* followed by 2.83% (5*100/177) in *Escherichia coli,* 2.26% (4*100/177) each in *Klebsiella oxytoca* and *Enterobacter ozaenae,* 1.70% (3*100/177) in *Serratia rubidaea,* and 0.56% (1*100/177) each in *Enterobacter agglomerans, Morganella morganii* and *Citrobacter freundi.*

Badmasti, et al.[25] reported highest prevalence of 91.67% (88*100/96) in *Klebsiella pneumonia,* followed by 5.21% (5*100/96) in *Escherichia coli* and 3.12% (3*100/96) in *Proteus mirabilis.* Barbadoro, et al.[26] from Italy reported higher resistance of 1.81% (45*100/2,478) in *Klebsiella pneumonia,* followed by 0.12% (3*100/2,478) in *Escherichia coli*. Similar to our finding is reported by Olowo-Okere, et al.[1] who found *E. coli* as the most prevalent resistant isolates in North-West region of Nigeria.

The presence of carbapenem-resistant *Enterobacterales* signals an urgent call for the strengthening of antimicrobial resistance surveillance programs. Across Nigeria, there is almost a dearth of data on antimicrobial resistance among isolates from hospitals and almost an absent emergency reporting channel when multidrug resistant isolates are detected in clinical laboratories. There is an abundance of last resort antibiotics which are sold over the counter without control. Worst still is the practice of empirical therapy by clinicians as well as self-medication and abuse of antibiotics.

Together, the factors that trigger the development and spread of antimicrobial resistance genes are numerous and multifaceted. However, there can be effective control with necessary actions. The need for strict control of antibiotics cannot be over-emphasized. Also is the urgent need for the institution and implementation of infection-control policies and programs in secondary and tertiary healthcare facilities. The high prevalence of carbapenem-resistant isolates in the various centres studied and the reports from other geographic regions of Nigeria begs the question; are we entering the post-antibiotic era?

CONCLUSION

The significance of this finding is far reaching considering the dependence placed on this class of antibiotics by clinicians who use them as drugs of last resort for multidrug resistant *Enterobacterales* isolates.

In our population of South-East Nigeria, the prevalence of carbapenem-resistance to *Enterobacterales* isolates was higher (29.5%) than many studies. It was higher in women than men. It was highest in age group 20-39 years, followed by ≥ 60 years age group. It was highest in Enugu State, followed by Ebonyi State. The prevalence was highest in *Escherichia coli,* followed by *Klebsiella pneumonia*. The overall prevalence was high and this is a cause for concern and urgent need for emergency intervention to forestall widespread emergence of pandrug resistant infections.

Acknowledgement: We highly acknowledge the help of Dr. Muhammad Marwat (muhammadm@gmcdikhan.edu.pk) of Gomal Medical College, D.I.Khan, Pakistan in organizing of this document, its statistical analysis and write up.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
GRANT SUPPORT AND FINANCIAL DISCLOSURE
None declared.

AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	UIU, TKU
Acquisition, Analysis or Interpretation of Data:	UIU, TKU
Manuscript Writing & Approval:	UIU, TKU

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.