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Original Article **Open Access**

Prevalence of New Delhi Metallo-β-lactamase gene and antibiotic susceptibility of clinical *Klebsiella pneumoniae* isolates from selected hospitals in Calabar, Nigeria

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Abstract:

Background: The global spread of extended spectrum beta-lactamases (ESBL) and carbapenemase-producing strains of *Klebsiella pneumoniae,* is considered a major public health threat to humans. Antimicrobial resistance mediated by New Delhi Metallo-β-lactamase (NDM) enzyme has become a major threat to treatment outcome. This study is aimed at investigating the carriage rate of bla_{NDM} gene among multidrug resistant (MDR) clinical *K. pneumoniae* isolates from four selected health facilities in Calabar, Nigeria.
Methodology: This was a laboratory-based study of 70 confirmed *K. pneumoniae* isolates recovered from various clinical sources at the University of Calabar Teaching Hospital (UCTH), General Hospital Calabar (GHC), Faith Foundation Specialist Clinic (FFSC) and Bakor Medical Centre Calabar (BMCC) using the Vitek® 2 Compact system, with antibiotic susceptibility testing performed by the Kirby-Bauer disc diffusion method. Molecular detection of bla_{NDM} gene in 15 selected MDR isolates was carried out by conventional PCR assay and agarose gel electrophoresis detection of the gene amplicon.
Results: The distribution of the confirmed isolates according to healthcare facilities showed that the highest frequency of *K. pneumoniae* isolates was obtained from UCTH (52.9%, n=37), followed by GHC (17.1%, n=12), BMCC (15.7%, n=11) and FFSC (14.3%, n=10). Urine sample accounted for the highest frequency of the isolates (40.0%, n=28), followed by sputum (31.4%, n=22), wound swabs (8.6%, n=6), and blood (5.7%, n=4) while the frequency of isolates was higher among inpatients (57.1%, n=40) than outpatients (42.9%, n=30). The susceptibility of the isolates to meropenem, ertapenem, piperacillin/tazobactam, amoxicillin/clavulanate, ciprofloxacin, gentamicin and ceftazidime was 57.1% (n=40), 54.3% (n=38), 51.4% (n=36), 50.0% (n=35), 48.6% (n=34), 47.1% (n=33) and 17.1% (n=12) respectively. Eighteen (25.7%) isolates were MDR *K. pneumoniae* strains while bla_{NDM} gene was detected in 9 (60.0%) of 15 MDR isolates tested.
Conclusion: The high prevalence of the resistance gene in this study setting underscores the urgent need for an informed and discrete use of antimicrobial drugs, particularly β-lactam antibiotics, for management of bacterial infections to prevent further spread of drug-resistant *K. pneumoniae* strains.

Keywords: *Klebsiella pneumoniae*, Multidrug Resistance, Multiple antibiotic resistance index, NDM gene

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Prévalence du gène de la métallo-β-lactamase de New Delhi et sensibilité aux antibiotiques des isolats cliniques de *Klebsiella pneumoniae* provenant d'hôpitaux sélectionnés de Calabar, au Nigéria

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Résumé:

Contexte: La propagation mondiale des souches de *Klebsiella pneumoniae* productrices de bêta-lactamases à spectre étendu (BLSE) et de carbapénémases constitue une menace majeure pour la santé publique. La résistance aux antimicrobiens médiée par l'enzyme New Delhi Métallo-β-lactamase (NDM) représente un obstacle majeur à l'efficacité des traitements. Cette étude vise à déterminer la fréquence de portage du gène *bla*$_{NDM}$ parmi les isolats cliniques de *K. pneumoniae* multirésistants (MDR) provenant de quatre établissements de santé sélectionnés à Calabar, au Nigéria.
Méthodologie: Cette étude en laboratoire a porté sur 70 isolats confirmés de *K. pneumoniae* provenant de différents établissements cliniques du Centre Hospitalier Universitaire de Calabar (UCTH), de l'Hôpital Général de Calabar (GHC), de la Clinique Spécialisée de la Fondation Faith (FFSC) et du Centre Médical Bakor de Calabar (BMCC). Les prélèvements ont été effectués à l'aide du système Vitek® 2 Compact, et la sensibilité aux antibiotiques a été testée par la méthode de diffusion sur disque de Kirby-Bauer. La détection moléculaire du gène *bla*$_{NDM}$ dans 15 isolats multirésistants sélectionnés a été réalisée par PCR conventionnelle et électrophorèse sur gel d'agarose pour la détection de l'amplicon du gène.
Résultats: La répartition des isolats confirmés selon les établissements de santé a montré que la fréquence la plus élevée d'isolats de *K. pneumoniae* provenait de l'UCTH (52,9%, n=37), suivie du GHC (17,1%, n=12), du BMCC (15,7%, n=11) et du FFSC (14,3%, n=10). L'échantillon d'urine représentait la fréquence la plus élevée des isolats (40,0%, n=28), suivi par les expectorations (31,4%, n=22), les écouvillons de plaies (8,6%, n=6) et le sang (5,7%, n=4), tandis que la fréquence des isolats était plus élevée chez les patients hospitalisés (57,1%, n=40) que chez les patients ambulatoires (42,9%, n=30). La sensibilité des isolats au méropénem, à l'ertapénem, à la pipéracilline/tazobactam, à l'amoxicilline/acide clavulanique, à la ciprofloxacine, à la gentamicine et à la ceftazidime était respectivement de 57,1% (n=40), 54,3% (n=38), 51,4% (n=36), 50,0% (n=35), 48,6% (n=34), 47,1% (n=33) et 17,1% (n=12). Dix-huit isolats (25,7%) étaient des souches de *K. pneumoniae* multirésistantes, tandis que le gène *bla*$_{NDM}$ a été détecté chez 9 des 15 isolats multirésistants testés (60,0%).
Conclusion: La forte prévalence du gène de résistance observée dans cette étude souligne l'urgence d'un usage raisonné et ciblé des antibiotiques, notamment des bêta-lactamines, dans la prise en charge des infections bactériennes afin de prévenir la propagation des souches de *K. pneumoniae* résistantes aux médicaments.

Mots-clés: *Klebsiella pneumoniae*, multirésistance, indice de résistance aux antibiotiques multiples, gène NDM

Introduction:

Klebsiella pneumoniae is one of several bacteria that have expressed dramatic increase in antibiotic resistance in the past decades. Several mechanisms of antibiotic resistance are found in *K. pneumoniae*, with resistance to β-lactams having the greatest impact on effective treatment. Colonization with antibiotic-resistant *K. pneumoniae* has been associated with subsequent infection in hospitalized patients. Although the progression from colonization to infection is not completely understood, the accessory genome is central to antibiotic resistance in *K. pneumoniae*, with plasmid-based resistance genes rapidly reducing the armamentarium of effective antibiotics against this pathogen.

Extended-spectrum β-lactamases (EsβLs) are plasmid-borne resistance mechanisms that are part of the accessory genome. ESβL-producing *K. pneumoniae* were first identified in Europe in 1983 (1) and in the United States in 1989 (2). ESβLs are able to hydrolyze oxyimino-cephalosporins such as third-generation cephalosporins and aztreonam but are inhibited by clavulanic acid (3). Frequently, plasmids encoding β-lactamases also possess resistance genes to other antibiotics as well as heavy metals (4). Therefore, ESβLs are tightly linked to other accessory genes that could improve fitness of the strain harboring it, and plasmid-based resistance mechanisms are associated with certain lineages that may have a characteristic accessory genome.

Carbapenems have typically been the drug of choice to treat severe infections caused by ESβL-producing bacteria, however, carbapenem resistance in *K. pneumoniae* has emerged causing substantial clinical problems and further complicating treatment (5) The New Delhi metallo-β-lactamase-1 (NDM-1) in *K. pneumoniae* have been reported in Europe, Middle East, North Africa, Asia and North America, mostly from patients who have a history of hospitalization in the Indian subcontinent (6-7). OXA-48 in *K. pneumoniae* was first isolated from Turkey in 2004 and is now endemic in Turkey and countries around the Mediterranean and rapidly spreading into other countries in Europe (8).

Of the three main carbapenemases reported in *K. pneumoniae*, KPC producers are still mostly identified in nosocomial isolates while the NDM and OXA-48 are extensively identified in both nosocomial and community-acquired strains. Genetic analyses have indicated that the gene encoding OXA-48 has the propensity to spread among the Enterobacterial species at a much higher rate than the KPC and NDM genes (9).

After 30 years since the emergence of ESβLs, the occurrence of ESβL-producing *K. pneumoniae* is increasing worldwide, reaching an epidemic proportion in many countries (10). Although the prevalence and ESβL gene

carriage varies between different geographical regions, according to the World Health Organization (WHO), the occurrence of ESβL-producing *K. pneumoniae* has reached an endemic rate of up to 50% in many parts of the world and up to 30% resistant rate in the community, demonstrating the widespread nature of this resistance (11). This study was thus aimed at investigating the extent of spread of specific carbapenemase encoded by the NDM gene, which confers resistance to commonly used antimicrobial drugs in this study setting.

Materials and method:

Study area and design:

This descriptive laboratory-based study was carried out in four health facilities in Calabar metropolis including University of Calabar Teaching Hospital (UCTH), General Hospital Calabar (GHC), Faith Foundation Specialist Clinic (FFSC) and Bakor Medical Centre Calabar (BMCC) within the Calabar metropolis, Nigeria.

Ethical consideration:

Ethical approval for the research work was fully granted by the University of Calabar Teaching Hospital Health Research Ethics Committee (UCTH NHREC NO: NHREC/07/10/2012) and Cross River State Health Research Ethics Committee (REG. NO: CRSMOH/HRP/REC/2023/401).

Phenotypic identification of *K. pneumoniae* isolates:

A total of 78 suspected *K. pneumoniae* isolated from urine, sputum, wound swab and blood samples of patients in the routine microbiology laboratories of the healthcare facilities were initially cultured on MacConkey agar media. A total of 70 isolates were confirmed as *K. pneumoniae* by the Vitek® 2 Compact system (BioMérieux; Marcy L'Étoile, France). The confirmed isolates were sub-cultured on nutrient agar slant for antibiotic susceptibility testing.

Antibiotic susceptibility testing (AST):

Antibiotic susceptibility of the 70 confirmed *K. pneumoniae* isolates was performed against 6 classes of antibiotics including gentamicin (CN-10µg), ciprofloxacin (CIP-5µg), ertapenem (ETP-10µg), meropenem (MEM-10µg) amoxicillin/clavulanate (AUG-30µg), piperacillin/tazobactam (TZP-30µg) and ceftazidime (CAZ-30µg), using the Kirby-Bauer disc diffusion technique. Sterile swabs were used to inoculate sterile Mueller Hinton (MH) agar plates with inoculum of the isolates that was prepared in tryptone soy broth and standardized to 0.5 McFarland turbidity standard. Antibiotic discs were applied to the inoculated MH agar plates and incubated aerobically at 37^0C for 24 hours. The zone diameters of inhibition were measured with a ruler and results were recorded for each isolate as sensitive, intermediate or resistant using the interpretative criteria of the Clinical and Laboratory Standards Institute (12).

Multi-drug resistance (MDR)

Multidrug resistance was defined as resistance of *K. pneumoniae* isolate to three or more classes of antibiotics tested against the isolate (13).

Multiple antibiotic resistance (MAR) index:

The MAR index was determined for *K. pneumoniae* isolate by dividing the number of antibiotics to which the isolate was resistant to, by the total number of antibiotics tested against it (14).

Molecular detection of NDM genes by conventional PCR:

Genomic DNA extraction using boiling method:

Five ml of an overnight broth culture of the bacterial isolate in Luria Bertani (LB) was spun at 12,000rpm for 3min. The cells were re-suspended in 500µl of normal saline and heated at 95^0C for 15min. The heated bacterial suspension was cooled on ice for 10 min and spun for 3min at 12000rpm, 200µl of the supernatant containing the DNA was transferred to a 1.5ml microcentrifuge tube and stored at -20°C for other downstream tests.

DNA quantification:

The extracted genomic DNA was quantified using the Nanodrop 1000 spectrophotometer. The software of the equipment was lunched by double clicking on the Nanodrop icon. The equipment was initialized with 2µl of sterile distilled water and blanked using normal saline. About 2µl of the extracted DNA was loaded onto the lower pedestal, the upper pedestal was brought down to contact the extracted DNA on the lower pedestal. The DNA concentration was measured by clicking on the "measure" button.

PCR amplification of NDM genes:

The NDM genes from 15 selected MDR isolates were amplified by conventional PCR assay using the NDM F: 5-GGTTTGGCGATCTG GTTTTC-3' and NDM R: 5'-CGGAATGGCTCATC ACGATC-3' primers on ABI 9700 Applied Biosystems thermal cycler at a final volume of 30 µl for 35 cycles. The PCR mix included X2 Dream Taq Master mix supplied by Inqaba, South Africa (Taq polymerase, dNTPs, $MgCl_2$), primers at a concentration of 0.4M and 50ng of the extracted DNA as template.

The PCR conditions were as follows; initial denaturation at 95ºC for 5min, denaturation at 95ºC for 30 sec, annealing at 56ºC for 45 sec, extension at 72ºC for 45 sec for 35 cycles, and final extension at 72ºC for 5 min. The product was resolved on a 1% agarose gel

at 200V for 15 minutes and visualized on blue light imaging system for a 380bp product size.

Statistical analyses:

Data generated in the study were analyzed using SPSS statistical software, version 20.0 (IBM Corporation, Armonk, New York, USA) for test of significance. Proportions were presented as frequency and percentages. Pearson's Chi square test was used to measure dependence between study variables, while *p*-value ≤0.05 was considered statistically significant.

Results:

The highest frequency of *K. pneumoniae* isolates (52.9%, n=37) was obtained from UCTH, followed by GHC (15.3%, n=12), BMCC (15.7%, n=11) and FFSC (14.3%, n= 10). The distribution of *K. pneumoniae* isolates by clinical source showed that 42.9% (n=30) were isolated from urine samples, followed by sputum samples (35.7%, n=25) while 14.3% (n=10) and 7.1% (n=5) were isolated from wound swab and blood samples respectively. A total of 40 (57.1%) *K. pneumoniae* isolates were recovered from inpatients compared to 30 (42.9%) from outpatients (Table 2).

Table 1: Distribution of *Klebsiella pneumoniae* according to health facility

Hospital	Isolates	Percentage
UCTH	37	52.9
GHC	12	17.1
FFSC	10	14.3
BMCC	11	15.7
Total	**70**	**100.0**

UCTH=University of Calabar Teaching Hospital; GHC=General Hospital Calabar; FFSC=Faith Foundation Specialist Clinic; BMCC=Bakor Medical Centre Calabar

The result of the antibiotic sensitivity testing of *K. pneumoniae* isolates in Table 3 showed that the isolates were susceptible to meropenem (n=40, 57.1%) at inhibition zone size (IZ) of 28-40mm and mean value of 34 mm, closely followed by ertapenem (n=38, 54.3%), piperacillin/tazobactam (n=36, 51. 4%; IZ: 24-30; mean: 27), amoxicillin/clavulanate (n=35, 50.0%; IZ: 18-20; mean: 19), ciprofloxacin (n=34, 48.6%; IZ: 16-22; mean: 29) and gentamicin (n=33, 47.1%; IZ: 16-22; mean: 19) while the isolates were least susceptible (highly resistant) to ceftazidime (n= 12, 17.1%; IZ: 24-34; mean: 29).

Table 2: Distribution of *Klebsiella pneumoniae* isolates by clinical source

Source	Isolates (%)	Inpatients (%)	Outpatients (%)
Urine	30 (42.9)	19 (27.1)	11 (15.7)
Sputum	25 (35.7)	12 (17.1)	13 (18.6)
Wound swab	10 (14.3)	6 (8.6)	4 (5.7)
Blood	5 (7.1)	3 (4.3)	2 (2.9)
Total	**70 (100.0)**	**40 (57.1)**	**30 (42.9)**

$p = 0.1967$

Of the 70 *K. pneumoniae* isolates, 16 (22.9%) isolates were resistant to 4 antibiotics with MAR index of 0.6, followed by 14 (20. 9%) isolates to 3 antibiotics with MAR index of 0.4, 13 (18.6%) to 5 antibiotics with MARI of 0.7, 11 (15.7%) isolates to 2 antibiotics with MARI of 0.3, 6 (8.6%) isolates with MARI of 0.9, 5 (7.1%) isolates with MARI of 0.1 and 5 (7.1%) isolates with MARI of 1.0 (Table 4).

Eighteen (25.7%) isolates were multidrug resistant, out of which 11 (15.7%) were from UCTH, followed by BMCC with 3 (4.3%) while only 2 (2.9%) were obtained each from GHC and FFSC. Majority of the MDR isolates were resistant to three classes of antibiotics (n=8, 44.4%), followed by four classes of antibiotics (n=4, 22.2%) and five classes of antibiotics (n=3, 16.7%) (Table 5). Of 15 MDR isolates subjected to PCR and agarose gel electrophoresis, NDM gene was detected in 9 (60.0%).

Table 3: Antibiotic susceptibility of *Klebsiella pneumoniae* isolates to six selected antibiotics tested

Status	Number of *Klebsiella pneumoniae* isolates (%)						
	TZP	CIP	CAZ	CN	AUG	MEM	ETP
Sensitive	36 (51.4)	34 (48.6)	12 (17.1)	33 (47.1)	35 (50.0)	40 (57.1)	38 (54.3)
Intermediate	16 (22.9)	10 (14.3)	13 (18.6)	13 (18.6)	15 (21.4)	15 (21.4)	16 (22.9)
Resistant	18 (25.7)	26 (37.1)	45 (64.3)	24 (34.3)	20 (28.6)	15 (21.4)	16 (22.9)

TZP=Piperacillin/tazobactam; CIP=Ciprofloxacin; CAZ=Ceftazidime; CN=Gentamicin; AUG=Amoxicillin/clavulanate; MEM=Meropenem; ETP=Ertapenem

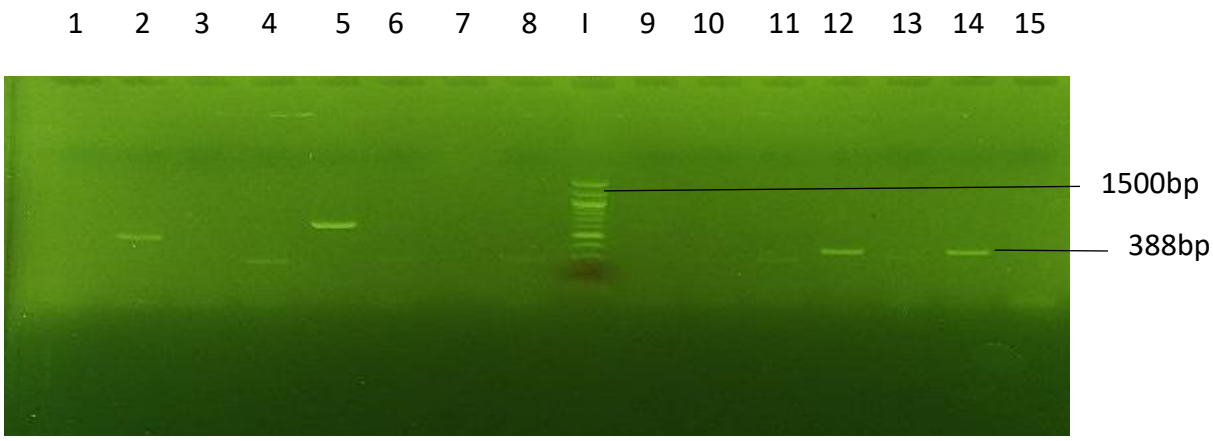
Table 4: Multiple antibiotic resistance index (MARI) of *Klebsiella pneumoniae* isolates

Number of antibiotics	Number of resistant isolates	MARI	MARI (%)
1	5 (7.1)	1/7	0.1
2	11 (15.7)	2/7	0.3
3	14 (20.0)	3/7	0.4
4	16 (22.9)	4/7	0.6
5	13 (18.6)	5/7	0.7
6	6 (8.6)	6/7	0.9
7	5 (7.1)	7/7	1.0

Table 5: Multidrug resistance pattern of *Klebsiella pneumoniae* isolates to the classes of antibiotics

Antibiotics	Number of resistant isolates	Drug resistance status
CAZ, CN, CIP, TZP, MEM	3 (16.7)	MDR
CAZ, AUG, CIP, TZP, ETP	3 (16.7)	MDR
CAZ, AUG, MEM, TZP	4 (22.2)	MDR
CAZ, CIP, ETP	8 (44.4)	MDR
Total	**18 (100.0)**	**MDR**

TZP=Piperacillin/tazobactam; CIP=Ciprofloxacin; CAZ=Ceftazidime; CN=Gentamicin; AUG=Amoxicillin/clavulanate; MEM=Meropenem; ETP=Ertapenem; MDR=Multi-drug resistance



Lanes I represent 100bp molecular ladder of 1500bp. Lanes 2,4,5,6,8,11,12,13 and 14 represent the NDM gene band (388bp).

Plate: Agarose gel electrophoresis of NDM gene of some *Klebsiella pneumoniae* strains

Discussion:

Klebsiella pneumoniae isolates were most frequently recovered from urine, followed by sputum sample, while wound swab and blood samples had the least number of *K. pneumoniae* isolates in the study. Although, similar result was obtained in other part of Nigeria, study in New York city by Parrott et al., (15) and the report of Palmeiro et al., (16) identified *K. pneumoniae* isolates as the major causal agent of blood and wound infections, while Sedighi et al., (17) identified throat, urine, and tracheal region as the major sites affected by this bacterium. This remarkable difference in incidence of *K. pneumoniae* according to sample types across the world underscores the significant impact of the immune status of individual and lifestyle to the epidemiology of the infection.

The study identified only 12 (17.1%) *K. pneumoniae* from sputum samples of in-patients with probable hospital acquired pneumonia compared to 13 (18.6%) from out-patients with report from Chen et al., (18) showing increased prevalence of hospital-acquired pneumonia across the world, but there was no significant difference in the prevalence of *Kleb-*

siella infection between hospital and community settings (p=0.1967) in our study.

The antibiotic sensitivity of *K. pneumoniae* isolates showed higher sensitivity to meropenem (57.1%) and ertapenem (54.3%) than other antibiotics tested in the study. The susceptibility of these clinical isolates to carbapenems is higher compared to the study in Ebonyi State Nigeria, where Ejikeugwu et al., (19) reported about 43.0% meropenem-resistant *K. pneumoniae* strains. Surprisingly, *in vitro* sensitivity testing of carbapenems reported by Muller-Schulte et al., (20) showed that, all *K. pneumoniae* isolates tested were 100% sensitive to carbapenems in Central Cote d'Ivoire, a development which could be connected to some regulations on the use of carbapenems for treatment in the region. However, finding from Northern Province of China by Wang et al., (21) contrastingly reported highly resistant *K. pneumoniae* isolates to meropenem at 93.2%. The susceptibility to other commonly used antibiotics in the study, showed varying degrees of *in vitro* antimicrobial activity against *K. pneumoniae* isolates with piperacillin/tazobactam (51.4%), amoxicillin/clavulanate (50.0%), but sensitivity to ceftazidime was the least by the clinical isolates with only 17.1%.

Furthermore, 25.7% of the *K. pneumoniae* isolates were multidrug resistant strains, and higher number of these strains (61.1%) were recovered from patients on hospital admission compared to 38.9% from out-patients who visited the hospital for medical treatment. The prevalence MDR-*K. pneumoniae* strain in the study is relatively low compared to recent study from South-Eastern Asia by Salawudeen et al., (22) who reported higher prevalence of 55.0% for MDR-*K. pneumoniae* in the clinical setting. Generally, infections caused by MDR *K. pneumoniae* are associated with high mortality which is often linked to inadequate and inappropriate antimicrobial therapy.

The bla_{NDM} gene was detected in urine and sputum samples of 9 (60.0%) of the 15 patients with *K. pneumoniae* infections across the four selected healthcare facilities. Six of the bla_{NDM} gene were detected among those on hospital admission while 3 were detected among out-patients. Earlier report by Asuquo et al., (23) reported bla_{NDM} gene in two *K. pneumoniae* isolates in the same population, however, the presence of bla_{NDM} gene in nine *K. pneumoniae* strains in our study, suggest an increased spread of this resistant gene in Calabar, Nigeria. Ogbolu and Webber (24) also reported low prevalence (5.5%) of this carbapenemase-producing isolates in some Nigerian tertiary hospitals. Wailan and Peterson (6) had earlier linked NDM to medical tourism in India, however, some of the patients with *K. pneumoniae* that harbored this gene had no travel history outside of Nigeria, suggesting increased local spread of the resistant organisms in the study population.

A study in other part of Nigeria detected bla_{NDM} gene in patients with no history of travel to India (25). Initially, this bla_{NDM} gene in Africa was first identified in Kenya among seven clonally related *K. pneumoniae* isolates from urine and urethral pus of adult patients hospitalized in different wards of the Aga Khan University Hospital (26), and since then, has spread across various countries in the African continent, including South Africa, Benin, Angola and Algeria (27).

Conclusion:

In this study, the prevalence of MDR among *K. pneumoniae* isolates was 25.7%, with high resistance to ceftazidime. High carriage (60.0%) of NDM gene encoding carbapenemase production was detected among MDR strains. The high prevalence of the resistance gene in the study population underscores the urgent need for regulations on use of antibiotics especially the β-lactams for treatment of infections, to prevent further spread of difficult to-treat infections.

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Contributions of authors:

IIU and NOM were involved in the conceptualization, design and writing of the manuscript; IIU and SAB were involved in data collection and analysis of results; Ethical approval of the study was facilitated by SOI. NOM and OMO supervised the research work. JCU and BMW edited the manuscript. All authors read and approved the manuscript for publication.

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Conflict of interest:

No conflict of interest is declared.

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