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Research Article

Antimicrobial Resistant Pattern of *Klebsiella pneumoniae* Isolated from the Stool of Healthy Volunteers of Niger Delta University, Wilberforce Island, Amassoma, Bayelsa State

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ABSTRACT

Background: *Klebsiella pneumoniae* bacteria is a normal flora of the human intestinal tract where they do not cause disease in normal circumstances but can also act as a human opportunistic pathogenic infection when it proliferates in increased amounts, where it may cause a host of health complaints and symptoms ranging from mild to serious infections (pneumonia, septicemia, Urinary tract infections). The virulence factors like capsule, lipopolysaccharide, and type 1 or type 3 fimbriae are responsible for *K. pneumoniae* to form biofilm. *Klebsiella pneumonia* responsible for serious outbreaks of multi-drug resistant diseases may be due to uncontrolled usage of antibiotics. **Method:** The samples were isolated and identified using standard microbiological methods. The isolates were screened for possible virulence traits using the Blood agar test and Congo-Red test. Antibiotic susceptibility screening was carried out for the isolates. **Results:** In this study (25.3%) *Klebsiella pneumoniae* isolates were recovered from the 300 stool samples of the healthy student volunteers, of which 29(38.2%) were from males and 47(61.8%) from females. The 76 *Klebsiella pneumoniae* isolates screened are biofilm producers while none produced hemolysin. The antimicrobial susceptibility pattern for the 76 *Klebsiella pneumoniae* isolates in this study revealed (Co-trimoxazole 3.9%, Ciprofloxacin 11.8%, Cefotaxime 9.2%, Ceftazidime 6.6% and Gentamicin 9.2%, Imipenem 17.1% and Ertapenem 40.8% and Nitrofurantoin (89.5%). In this study (17.1%) *Klebsiella pneumoniae* isolates exhibited multi-drug resistance. **Conclusion**: Drug resistance surveillance has revealed that asymptomatic carriers in the community are often colonized with resistant bacteria

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that subsequently lead to infections.

INTRODUCTION

A naturally occurring member of the *Enterobacteriaceae* family, *Klebsiella pneumoniae* can be found in the gastrointestinal tract microbiome of healthy humans and animals (Martin et al., 2018). It is a widespread pathogen that causes infections of the digestive system, surgical wounds, and community-onset infections, which can lead to nosocomial infection outbreaks (Qin et al., 2017). It also has a variety of pathways for antibiotic resistance. The prevalence of *K. pneumoniae* medication resistance has increased to 70% worldwide, and infection-related death rates have risen to 40%–70% (Li et al., 2022). Multiple-drug-resistant *Klebsiella pneumoniae* (MDR *K. pneumoniae*) and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) have become significant global public health issues in recent years (Iredell et al., 2016). Gastrointestinal carriage of *K. pneumoniae* as a reservoir for healthcare-associated *K. pneumoniae* infections was established in the early 1970s (Selden et al., 1971). Recent genomic studies show that gastrointestinal carriage is a risk factor for subsequent extraintestinal infections, and ~50% of *K. pneumoniae* bloodstream infections are caused by the patient's own gut isolates (Gorrie et al., 2017, Martin et al., 2016). Moreover, the relative abundance of *K. pneumoniae* in the gastrointestinal tract (Figure 1), is associated with an increased risk of *K. pneumoniae* bacteremia (Shimasaki et al., 2019). In a recent cross-sectional study of 911 pregnant women in low-income countries, Huynh *et al*. identified various country-specific environmental exposure factors linked to *K. pneumoniae* gastrointestinal carriage and a diverse *K. pneumoniae* population structure (Huynh *et al*., 2020).

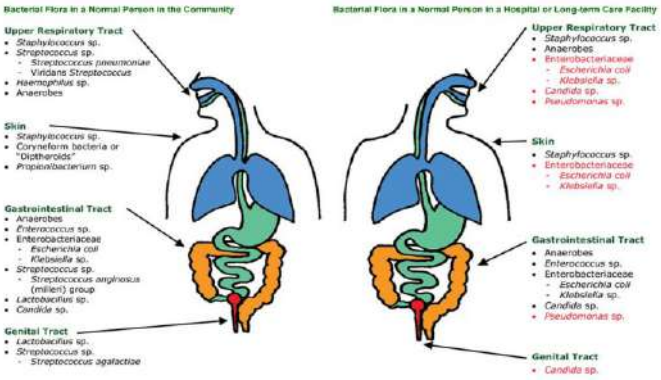

Figure 1. Human gastrointestinal tract (Garner, 2013)

Cross-sectional studies have shown that *Klebsiella pneumoniae* gastrointestinal carriage prevalence varies from 6% to 88% depending on geographical locations, detection methods, and the populations investigated (Gorrie et al., 2017, Martin et al., 2016, Chung et al., 2012, Lin et al., 2012, Huynh et al., 2020). However, we have a sparse understanding of risk factors for *Klebsiella pneumoniae* gastrointestinal carriage and the population structure of *Klebsiella pneumoniae* in the general human population (Raffelsberger et al., 2021).

Although the majority of *K. pneumoniae* HA infections are not ESBL or CP infections, there is little information available on the prevalence and clinical importance of *K. pneumoniae* colonization in general (Mathai et al., 2001, Weinstein et al., 2005). Although few researches directly address this, it is known that *Klebsiella pneumoniae* can asymptomatically invade the skin, and oral, respiratory, and GI tracts. *K. pneumoniae* was found using culture-free techniques in 3.8% of stool samples and 10% of samples from the mouth, nares, and skin collected for the Human Microbiome Project (Gorrie et al., 2017). Here, we use gastro-intestinal *Klebsiella pneumoniae* isolates collected from the stool of 300 healthy students of Niger Delta University, Wilberforce Island, Amassoma, Bayelsa State to determine the antimicrobial resistant pattern. Additionally, we investigated the biofilm and virulent

characteristics of the *Klebsiella pneumoniae* isolates from the study.

METHODS

Study design

A cross-sectional study was carried out among 300 healthy undergraduate students of Niger Delta University, Amassoma, Bayelsa State. The objective of the study was to assess the level of prevalence of *Klebsiella pneumoniae* in these healthy individuals, detect the production of hemolysin, detect the production of biofilm, and determine the antimicrobial susceptibility pattern of the *Klebsiella pneumoniae* isolates from stool samples of healthy students of Niger Delta University, Wilberforce Island, Amassoma, Bayelsa State. The volunteers gave informed consent. A study questionnaire was used to recruit those who claimed they had not been on any antibiotic for at least one month at the time of sampling nor had been admitted into any hospitals in the last year before the study and to obtain their basic demographic data.

Study Population/Sample collection

Stool samples were collected from three hundred (300) healthy students, comprising males and females, of different ages, from various departments in Niger Delta University, Wilberforce Island, Amassoma, Bayelsa state in South-South Nigeria. The willingness of the subjects to participate in the study was a strong criterion. The stool samples were collected with labeled sterile swab sticks and were taken to the laboratory within 1hr of collection for inoculation on selective media. The study was carried out from September 2018 to November 2018.

Isolation and Characterization of *Klebsiella pneumonia*

All growth media were prepared under aseptic conditions according to the manufacturer's instructions and stored at appropriate conditions. The 300 stool samples collected using sterile swab sticks which were well labeled were transported immediately in iced packs to the laboratory where each of the samples was inoculated on Nutrient agar (Oxoid, UK) plates, then streaked and incubated at 37ºC for 24 hours. The single uncontaminated colonies were plated on Hicrome Mueller Hinton agar, then the cultured plates were incubated at 37°C for 24 hours and observed for color change (characteristic dark blue color for *Klebsiella pneumoniae*) indicating the presence of the *Klebsiella pneumoniae*. The colonies that gave a characteristic dark blue color were further confirmed by streaking on the surface of CLED (Oxoid, UK) solidified agar then the plates were incubated at 37°C for 24 hours. After incubation, they were observed for color change (mucoid yellow color for *Klebsiella pneumoniae*). These isolates were then stored on fresh slants of Nutrient agar (Oxoid, U.K) for antimicrobial susceptibility testing, virulent traits, and biofilm-forming characteristics. All procedures were carried out under aseptic conditions.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility of all *K. pneumoniae* strains was determined for Nitrofurantoin (F 300 µg), Ertapenem (ETP 10 µg), Co-trimoxazole (trimethoprim/sulfamethoxazole) (SXT 1.25/23.75 µg), Imipenem (IPM 10 µg), Gentamicin (CN 10 µg), Cefotaxime (CTX 30 µg), Ceftazidime (CAZ 30 µg) and Ciprofloxacin (CIP 5 µg) (Qxoids, UK) using the modified Kirby-Bauer disc diffusion technique in accordance with the Clinical and Laboratory Standard Institute guidelines (CLSI, 2014). The *K. pneumoniae* isolates that were resistant to at least one agent in three or more of the eight classes of antimicrobial agents used in this study were defined as having MDR (Magiorakos *et al*., 2012). If an antimicrobial activity was present on the plates, it was indicated by zones of inhibition. The diameter of the zones of inhibition were measured in millimetre at 24 hours using a scale and was

interpreted using the Clinical Laboratory Standard Institute (CLSI) chart.

Screening for Hemolysin Production in the *K. pneumoniae* Isolates

The hemolytic property of the *K. pneumoniae* isolates was determined by inoculating the isolates on freshly prepared sterile 5%v/v Blood Agar (consisting of 5 mL of human blood in 100 mL of Nutrient Agar) plates using a straight wire loop and incubated at 37°C for 24 hours. Thereafter, plates were observed for yellow coloration of the agar (partial lysis of red blood cells-alpha hemolysis) and clear zones (complete lysis of red blood cells-beta hemolysis) around inoculated organisms, indicating the production of hemolysin.

Screening for Biofilm Production in the *K. pneumoniae* Isolates

Biofilm production in *K. pneumoniae* isolates was performed using Congo Red Agar medium which was prepared using the combination of brain heart infusion agar 52 g/L, sucrose 50 g/L and Congo red indicator 8 g/L as described by (Mathur T *et al*., 2006). The Congo red was prepared as concentrated aqueous solution separately from other medium constituents and then sterilized in different containers before adding them together when the agar had cooled to 55°C before distributing to sterile plates to solidify. The plates were then inoculated with the test organisms and incubated at 37°C for 24 hours before examining for black colonies with a dry crystalline consistency indicating biofilm production.

RESULTS

Study population

A total of 300 stool samples were collected in this study from healthy student volunteers comprising 111(37%) males and 189 (63%) females of ages ranging from 18-33 years with an average age of 22.6 years as shown in Figure 2.

The healthy student volunteers were gotten from 34 Departments of the Niger Delta University, Wilberforce Island, Amassoma, Bayelsa State, Nigeria. The gender distribution across the various departments in this study is shown in Table 1 below.

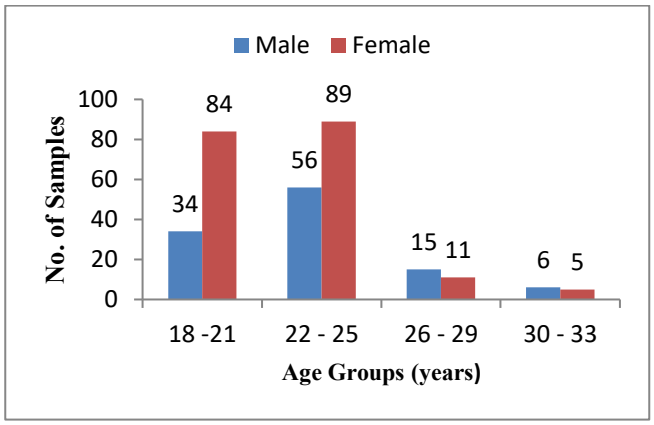

Figure 2: Age and gender distribution of the volunteers

Table 1 Sources of volunteers for the isolation of *Klebsiella pneumoniae*

Department	No. of samples	Male	Female
Accounting	2	1	1
Agricultural Economics	1	0	1
Agricultural Science	9	6	3
Animal Science	4	1	3
Banking and Finance	6	5	1
Banking and Insurance	1	0	1
Biochemistry	26	6	20
Biological Science	6	2	4
Business Administration	8	5	3
Civil Engineering	6	3	3
Computer Science	2	1	1
Crop/Soil Science	3	2	1
Education	2	1	1

Engineering	10	5	5
English And Literally Studies	5	2	3
Fine and Applied Art	9	6	3
Fisheries/Aquatic Studies	3	2	1
Geology	4	3	1
History and Diplomacy	5	3	2
Law	2	0	2
Mechanical Engineering	3	3	0
Medical Laboratory Science	24	3	21
Medicine	33	8	25
Microbiology	1	1	0
Nursing	29	3	26
Office Management	1	1	0
Petroleum Engineering	1	0	1
Pharmacy	54	17	37
Philosophy	15	7	8
Political Science	5	5	0
Pure and Applied Chemistry	4	2	2
Religious Studies	4	1	3
Theatre Art	11	6	5
Vocational Education	1	0	1
Total	**300**	**111**	**189**

Prevalence of *Klebsiella pneumoniae* isolates from the stool of healthy students

A total of 76 (25.3%) *Klebsiella pneumoniae* isolates were recovered from the 300 stool samples of the healthy student volunteers, of which 29(38.2%) were from males and 47(61.8%) from females as shown in Table 3.

Prevalence of virulent traits among the *Klebsiella pneumoniae* isolates.

All the 76 *Klebsiella pneumoniae* isolates screened are biofilm producers while none produced hemolysin.

Antibiotic susceptibility testing of *Klebsiella pneumoniae* isolates.

The antimicrobial susceptibility testing (zone diameters of inhibitions) of the 76 *Klebsiella pneumoniae* isolates in this study were interpreted using a CLSI interpretative chart. The *Klebsiella pneumoniae* isolates in this study revealed the least resistance to co-trimoxazole (3.9%) and exhibited the highest resistance to nitrofurantoin (89.5%) as shown in Table 4 below.

Prevalence of multi-drug resistant *Klebsiella pneumoniae*

Multi-drug resistance in this study is defined as the resistance of an isolate to at least three classes of antimicrobial agents. Thus, a total of 13(17.1%) *Klebsiella pneumoniae* isolates exhibited multi-drug resistance in this study (Table 5). However, 6(7.9%) of the isolates were completely susceptible to all agents tested as shown below in Table 4.

Table 2: Age and Gender distribution of *Klebsiella pneumoniae* isolates.

Age	No. of samples	No. (%) of *Klebsiella pneumoniae* isolates	
		Male	Female
18 – 21	118	8	19
22 – 25	145	13	23
26 – 29	26	7	3
30 – 33	11	1	2
Total	**300**	**29 (38.2%)**	**47 (61.8%)**

Table 3: Antibiotic-resistant patterns of *Klebsiella pneumoniae* isolates

Antibiotic agents	No. (%) of resistant *Klebsiella pneumonia*
Cefotaxime	7 (9.2)

Ceftazidime	5 (6.6)
Cotrimoxazole	3 (3.9)
Gentamicin	7 (9.2)
Nitrofurantoin	68 (89.5)
Ciprofloxacin	9 (11.8)
Imipenem	13 (17.1)
Ertapenem	31 (40.8)

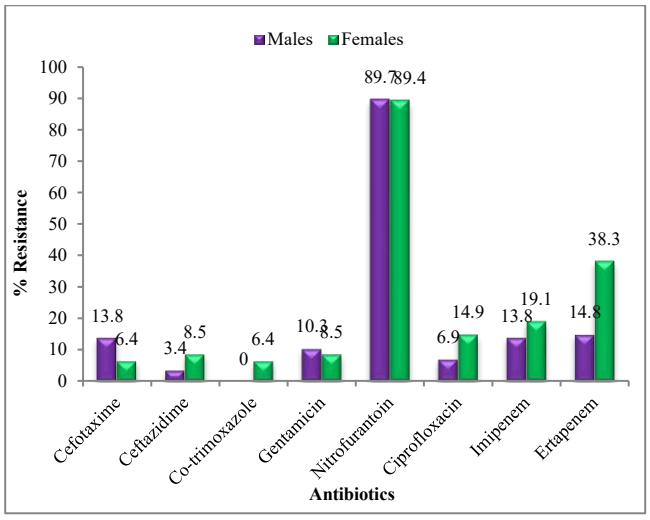

Figure 3: Gender comparison of the antibiotic-resistant pattern of *K. pneumoniae* isolates.

Table 4: Multi-drug resistant pattern

No. of classes with resistance	No. of resistant isolates
0	6
1	28
2	29
3	7
4	3
5	3
6	0
≥3	13 (17.1%)

DISCUSSION

Klebsiella pneumoniae bacteria is a normal flora of the human intestinal tract where they do not cause disease in normal circumstances but can also act as a human opportunistic pathogenic infection when it proliferates in increased amounts, where it may cause a host of health complaints and symptoms ranging from mild to serious infections (pneumoniae, septicaemia, Urinary tract infection). When the immune system is healthy, it maintains *Klebsiella pneumoniae* in healthy numbers which offers benefits such as the digestion of carbohydrates such as lactose, resistant starches, inulin, fructose, and mannose (Leang *et al*., 2003, Harris *et al*., 2015).

The intestinal carriage of *Klebsiella pneumoniae* in the stool of healthy volunteers in this study, including male and female (Figure 3) participants was 25.3%. This study supports the findings that the intestinal carriage of *Klebsiella pneumoniae* in the stool of healthy individuals ranges from 5-38% (Esposito *et al*., 2018). However, higher rates of colonization have been reported in those of Chinese ethnicity and those who experience chronic alcoholism. In hospitalized patients, the carrier rate for *K. pneumoniae* is much higher than that found in the community'' (Walter *et al*., 2018).

All the *Klebsiella pneumoniae* isolates screened for biofilm production using Congo-Red agar in this study were (100%) biofilm producers. The findings in this study agree with the studies of Cruz-Cordova *et al* which reported (100%) biofilm production in *Klebsiella pneumoniae* strains isolated from urine, blood, catheters, and cerebrospinal fluid samples from 34 patients hospitalized in (HIMFG) Mexico. This study's results are higher than the studies of Lathamani and Kotigadde showed (48.13%) biofilm production in *Klebsiella pneumoniae* strains isolated from urine, sputum, and stool from KVG Medical College and hospital Sullia, Karnataka. In agreement with this study are the recent observations by de Campos *et al.* (2016), who did not find a link between antimicrobial resistance and biofilm production in clinical isolates of *K. pneumoniae* and *A. baumannii* (de Campos *et al*., 2016). However, our results contrast with other previous studies in which a direct relationship between antimicrobial resistance and biofilm production has been shown. These authors base their argument on the fact that under antibiotic pressure, mostly with a sub-inhibitory

concentration of antimicrobials such as cefotaxime, biofilm formation was enhanced (Vuotto *et al*., 2014, Rao *et al*., 2008, Lee *et al*., 2008). Biofilm formation protects bacteria from attacks by phagocytosis and toxic molecules (Mah and O'Toole, 2001). Bacteria-producing biofilms are accountable for many non-compliant infections and are difficult to destroy and treat because they restrict the penetration of antibiotics into the organism (Afreenish *et al*., 2011). All the *Klebsiella pneumoniae* isolates screened for haemolysin production were none haemolysin producers. This study finding is similar to the studies of Palanisamy that reported 1% haemolysin production in *Klebsiella pneumoniae* isolates from urine samples in South India (Palanisamy M, 2015). This none haemolysin production can be due to the fact that the *Klebsiella pneumoniae* isolates are normal flora of the gastrointestinal tract apparently from healthy individuals and they do not possess virulent traits to establish haemolysin production.

The antimicrobial susceptibility testing has shown variable levels of resistance to the tested antibiotics. The antimicrobial susceptibility pattern for the 76 *Klebsiella pneumoniae* isolates in this study revealed a low level of resistance to (Co-trimoxazole 3.9%, Ciprofloxacin 11.8%, Cefotaxime 9.2%, Ceftazidime 6.6% and Gentamicin 9.2%). The resistant pattern in this study is smaller than the study of Manikandan and Amsath which showed a resistance pattern of *Klebsiella pneumoniae* to (Cefotaxime 33.3%, Ceftazidime 45.8%, Ciprofloxacin 23.6%, Gentamicin 19.4% and Cotrimoxazole 70.8%) isolated from urine samples from Pattukkottai, India (Manikandan and Amsath, 2013), while moderate level of resistance of *Klebsiella pneumoniae* was observed in this study to (Imipenem 17.1% and Ertapenem 40.8%) which is similar to the study of Manikandan and Amsath which showed Imipenem (13.9%) isolated from urine samples from Pattukkottai, India (Manikandan and Amsath,2013). In this study high level of resistance was seen in Nitrofurantoin (89.5%) which is higher than the study of Masood that reported resistance of *Klebsiella pneumoniae* to Nitrofurantoin (67%) which was isolated from urine samples in Islamabad, Pakistan by (Masood *et al*., 2002). The *Klebsiella pneumoniae* isolates are generally susceptible to the tested antibiotics except Nitrofurantoin.

Multi-drug resistance in this study is defined as the resistance of an isolate to at least three classes of antimicrobial agents. Thus, a total of 13(17.1%) *Klebsiella pneumoniae* isolates exhibited multi-drug resistance. However, 6(7.9%) of the *Klebsiella pneumoniae* isolates were completely susceptible to all agents tested. The multi-drug resistance (17.1%) noted in this study is smaller than the study of Stanley *et al.* (2018) (82%) *Klebsiella pneumoniae* isolated from the stool of out-patients in Kasese district, Uganda (Stanley *et al*., 2018). The level of resistance can be a result of overuse or suboptimal use of broad-spectrum antibiotics both in hospitals and the community. Antimicrobial resistance is a major factor contributing to mortality and morbidity in settings with limited diagnostic facilities and treatment options. Resistance to antimicrobial agents has become important in clinical management and control of many diseases and deserves scientific intervention to bring about some control measures (Soyege *et al.*, 2014).

CONCLUSION

This study revealed a moderate prevalence level of MDR isolates with all isolates being biofilm producers and none being hemolysin producers among the healthy University students. This therefore calls for prompt implementation of proper personal hygiene strategies through regular daily hand washing in order to prevent the spread of these biofilm MDR strains and strict antibiotic

stewardship for the control of MDR in the community.

AUTHORS' CONTRIBUTIONS

GWP: field/laboratory work, data collection, and collation, manuscript initial draft; **SJB**: data analysis, manuscript critical review, and approval; **AAO**: design and conception, supervision, and manuscript critical review. All authors read and approved the final manuscript.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article. Other data may be requested through the corresponding author.

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DECLARATION OF INTERESTS

The authors declare no conflict or competing interests.

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