Klebsiella pneumoniae Resistance Pattern and Patient Outcomes at Kenyatta National Hospital Intensive Care Unit from September 2013 to August 2017

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Dedication

This work is dedicated to my family for their unconditional support.

Acknowledgment

First and foremost, I thank God for having brought me this far. I’m grateful to my supervisors Dr. Mureithi and Dr. Masika for their unrelenting support and guidance. I'm grateful to my family, and friends for their unquestioning support throughout the entire process. I’m also grateful to Kenyatta National Hospital Laboratory Medicine, Kenyatta National Hospital Health Information Department and Kenyatta National Hospital Research Department staff for guidance and Support.

List of Abbreviations and Acronyms

AMR	Antimicrobial Resistance
AST	Antimicrobial Sensitivity testing
BACKLINK	A conversion software for AMR data
CCU	Critical Care Unit
CVA	Cerebral Vascular Accident
ESBLs	Extended Spectrum Beta-lactamases
GDP	Gross Domestic Product
HDU	High Dependency Unit
ICU	Intensive Care Unit
KNH	Kenyatta National Hospital
KPC	Carbapenemase Producing *Klebsiella pneumoniae*
KPN	*Klebsiella pneumoniae*
MDR	Multi-drug Resistant
MIC	Minimum Inhibitory Concentration
RR	Relative Risk
USD	United States Dollar
VITEK 2	Automated Instrument for Microbial Identification/AST Testing
WHO	World Health Organization
WHONET	A Windows Based Software for Management of Microbiology Laboratory Data and AST Analysis

Operational Definitions

Antibiotic prescribing: - The comparison between the expected and what was prescribed for a given diagnosis.

Correlates: - The direction of relationship whether mutual or reciprocal between predictors of and antimicrobial resistance.

Definitive: - Antibiotic therapy guided by etiologic and AST results

Discharge: - Discharge summary available.

Empiric: - Initial antibiotic therapy guided by clinical presentation

Mortality: - Documented death in the ICU

Pan-drug resistance: - The Resistance to All Classes of Antibiotics

Patient outcomes: - Duration of stay and state at discharge

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Abstract

Background: Antimicrobial resistance is a growing concern globally. Antimicrobial resistance by gram-negative bacteria is of special concern in intensive care settings. At Kenyatta National Hospital, *Klebsiella pneumoniae* is a significant cause of nosocomial infections. Despite this, there is a lack of up to date data on *K. pneumoniae* antimicrobial susceptibility pattern at Kenyatta National Hospital Intensive Care Unit.

Objective: To describe antimicrobial susceptibility patterns and outcomes in patients with drug-resistant *K. pneumoniae* at Kenyatta National Hospital ICU, from September 2013-August 2017.

Methodology: This was a retrospective study. Data on antimicrobial resistant *K. pneumoniae* was extracted from the VITEK-2 system and patients' medical records. Data was analyzed using WHONET and IBM-SPSS statistical software. F-test was used to evaluate the equality of variances and relative risk (RR) to establish mortality risk.

Results and Outcomes: There was a progressive decline in susceptibility to antibiotics in *K. pneumoniae* from the 214 study participants. Susceptibility to gentamicin by all specimen isolates declined from 24.5% to 16.7%, while susceptibility to meropenem declined from 60.6% to 36.7% (P=0.043). Isolates from urine had marginally higher resistance when compared to all the isolates. Susceptibility to ciprofloxacin in urine isolates of *K. pneumoniae* was 25.6% versus 15.6% (P=0.009) for all isolates. The relative risk of death among those who received inadequate antibiotic treatment was 1.5 (CI: 0.85, 2.7) times the risk of death among those who received adequate antibiotic treatment.

Conclusion: There was an increase in the resistance in *K. pneumoniae* at KNH ICU over the study period. Despite this, the use of an inadequate antibiotic treatment, which is the use of an antibiotic to which an isolate is resistant, in the management drug-resistant *K. pneumoniae* is commonplace.

1. Introduction

Whilst antimicrobial resistance is a global problem, resource-poor nations, particularly those found within the sub-Saharan region lack the capacity and surveillance networks to monitor changing patterns of antimicrobial resistance (Vernet *et al.*, 2014). Decades of poor antibiotic stewardship coupled with increased access have helped fuel the rapid proliferation of antimicrobial resistance. As a result, antimicrobial resistance is ubiquitous in every region of the world (Kirika, 2009). This resistance ranges from monoresistance, multi-drug resistance, and extensive drug resistance to pan-drug resistance. As a result, there is a rising threat of infections that cannot be treated with antibiotics (Karaiskos *et al.*, 2014). This is also true for *Klebsiella pneumoniae* as there is evidence to support the evolution of this pathogen into highly virulent and multidrug-resistant strains (Bialek-davenet *et al.*, 2014). Strains of *K. pneumoniae* that are highly virulent and those that are multidrug-resistant have largely evolved separately until now when the hypervirulent strains have gained multi-drug resistance capacity.

In Intensive Care Units (ICUs), antimicrobial resistance organisms are prevalent, with gram-negative bacteria being problematic since they are associated with increased mortality (Karam *et al.*, 2016). A Vietnamese study of ventilator-associated pneumonia patients reported the most frequently isolated organisms as *K. pneumoniae*, *Pseudomonas aureginosa,* and *Acinetobacter baumannii* which contributed to 87.2% of all infections (Tran *et al.*, 2017). In Kenya, a study conducted at Aga Khan University Hospital Nairobi, reported that *K. pneumoniae (17%), E.coli (12%)* and *Enterococcus spp*. (11%) were responsible for bloodstream infections with a hospital-onset (Maina *et al.*, 2016). Nosocomial outbreaks of *K. pneumoniae* have been reported in intensive healthcare settings and neonatal units (WHO, 2014) with resistance strains being reported in all the WHO regions.

From a study in a Western Kenya tertiary teaching hospital, *K. pneumoniae* contributed 23% of all isolates recovered. Highest resistance was registered to beta-lactam antibiotics at 80%, while carbapenems had the lowest resistance at 23.2% (Apondi *et al.*, 2016). At Kenyatta National Hospital, *K. pneumoniae* was the second most isolated organism post admission, after *Pseudomonas aureginosa* with 26% of the patients receiving appropriate antibiotic treatment (Ngumi, 2006). It was further established that Intensive Care Unit stay was a risk factor for acquiring these infections. Likewise, from a study on nosocomial urinary tract infections at Kenyatta National Hospital ICU, the frequency of isolated organisms was 27%, 18% and 13.6% for *E. coli*, *K. pneumoniae,* and *P.aureginosa* respectively (Inyama *et al.*, 2011).

Outbreaks of *K. pneumoniae* resistant to antimicrobial agents are a growing concern due to diminishing options of treatment and central to this problem is antibiotic prescribing. A positive correlation exists between prescription rates of some antimicrobial agents and resistance rates exhibited by gram-negative organisms including Enterobacteriaceae. For instance, the correlation coefficient (R^2) of ceftriaxone use and emergence of ceftriaxone-resistant *Klebsiellae isolates* in a Singaporean surveillance study was 0.838 thus showing a strong positive correlation between the use of ceftriaxone and resistance (Hsu *et al.*, 2010). A Korean study found that prescription of ceftazidime and piperacillin-tazobactam to treat *K. pneumoniae* infections was correlated with increased resistance with correlation coefficients of R^2=0.66 ($P<0.02$) and R^2=0.54 ($P<0.01$) respectively (Ryu, Klein and Chun, 2018). The rising incidence of carbapenemase-producing *K. pneumoniae* was particularly a phenomenon of concern in Intensive care units (Gupta *et al.*, 2011).

As mentioned before, *K. pneumoniae* is a major contributor of nosocomial infections at Kenyatta National Hospital (Ngumi, 2006; Inyama *et al.*, 2011); further studies pertaining to antimicrobial resistance patterns and the consequent clinical outcomes need to be done in this setting. The findings herein will assist in defining the magnitude of the problem while also informing antibiotic stewardship efforts.

2. Literature Review

2.1 Background

Multidrug-resistant pathogens place a heavy toll on the health care system. It is projected that antimicrobial resistant organisms will result in ten million deaths each year by 2050 (O'neil, 2014). The economic impact of these deaths will be a decline in the global GDP by 2% - 3.5% and the cumulative economic cost will USD 100 trillion by 2050. In a systematic review to estimate patient mortality burden, 48% of the studies established that AMR was a significant contributor to mortality. Despite this, burden estimates vary widely (Naylor *et al.*, 2018).

K. pneumoniae is a significant multidrug-resistant pathogen with reports of resistance to almost all available antibiotics. *Klebsiellae* isolates revealed a resistance profile of 100%, 87.5%, 84%, 82.5%, and 80.4% for cephradin, cefaclor, tobramycin, cefotaxime, and norfloxacin respectively. Sensitivity to meropenem, amoxicillin/clavulanic acid, gatifloxacin, moxifloxacin, and chloramphenicol was 92.5%, 87.5%, 85%, 75%, and 62.8% respectively (Woldu, 2015).

In Africa, a systematic review of drug-resistant pathogens revealed a lack of data from 42.6 % of the countries. From the review, there was significant resistance by both gram-negative and gram-positive bacteria. There was less resistance to carbapenems by Enterobacteriaceae than by *Acinetobacter baumannii* and *Pseudomonas aureginosa*. A major issue for the region was poor quality data (Tadesse *et al.*, 2017).

Closer home, an Eastern Africa review of studies reported resistance to commonly prescribed antibiotics. Resistance to ampicillin, gentamicin, and ceftriaxone ranged between 50%-100%, 20%-47%, and 46%-69% respectively. *E. coli* and *K. pneumoniae* were the main contributors to the resistance (Blondeau and Vaughan, 2015).

According to a report by the World Health Organization, carbapenem-resistant bacterial infections are majorly caused by *K. pneumoniae* (WHO, 2014). This renders most of the choice antibiotics for managing these infections ineffective. Additionally, from the aforementioned report, there is evidence of resistance to the standard approach of managing *K. pneumoniae* infections, mainly the cephalosporins of the 3rd and 4th-generations. Further, the report asserts that antimicrobial resistance information in Kenya is incomplete with only a few publications on the matter. Kenya together with countries such as India and Russia are categorized as nations that have an action plan against AMR that is patterned after the global objectives (WHO, 2018).

2.2 Drivers of antimicrobial resistance

At the dawn of the antibiotic era, Alexander Fleming raised the issue of antibiotic resistance through overuse (Flemming, 1945). Antimicrobial resistance is largely a product of the use and misuse of existing antibiotic agents. This permeates in both human and veterinary medicine a (Karam *et al.*, 2016). It's agreed that antibiotic overuse fans antibiotic resistance (Davies and Shallcross, 2014). This health challenge is compounded by the slow or nonexistent development of new antibiotic classes (Harbarth *et al.*, 2015).

Another case in point is a study which demonstrated that exposure to imipinem among ICU patients even for a short duration of time resulted in the increased carriage of bacteria that are resistant to imipinem (Zhang and Singh, 2015). Similarly, a retrospective cohort study found out that subjects who had more antibiotics prescribed before the isolation of the *E. coli* had isolates with higher resistance (Catry *et al.*, 2018). It was proof of an association between antimicrobial resistance and the use of the antibiotics.

Similarly, a study demonstrated that exposure to antibiotics 30 days prior to infection with *Klebsiellae* species is associated with having ESBL-producing *Klebsiellae* infections. The

study found that the other predictors of similar infections included female gender and corticosteroid use thirty days prior to infection (Coffin et al., 2005).

Further proof of a correlation between use antibiotics and the density of resistance is from a study in Western China. The correlation coefficient's of the development of resistance in *K. pneumoniae* and use of quinolones was R^2=0.60 (P=0.004), beta-lactam-beta-lactamase inhibitors R^2=0.63 (P=0.03), and carbapenems R^2=0.76 (P=0.0004) (Wushouer *et al.*, 2018).

The rise in resistance is not helped by the fact that antimicrobial consumption is increasing globally. In a global study, antibiotic consumption of 76 countries increased by 39% from 2000-2015 (Klein *et al.*, 2018). Resource-poor nations registered the largest increases. With no interventions, antibiotic consumption in 2030 is projected to be 200% greater than that of 2015.

In contrast, among the Masaai of Kenya who predominantly practice traditional medicine, antibiotic resistance was lower than other areas of the country where traditional medicine didn't have a dominant role (Kimang'a, 2012).

2.3 Patterns and Profiles of *K. pneumoniae* Resistance in ICUs

Resistance rates of *K. pneumoniae* in resource-poor nations such as Kenya and India are relatively higher than those of developed nations such as Australia and the United Kingdom as shown in figure 1 below (Center for Disease Dynamics, Economics & Policy, 2017).

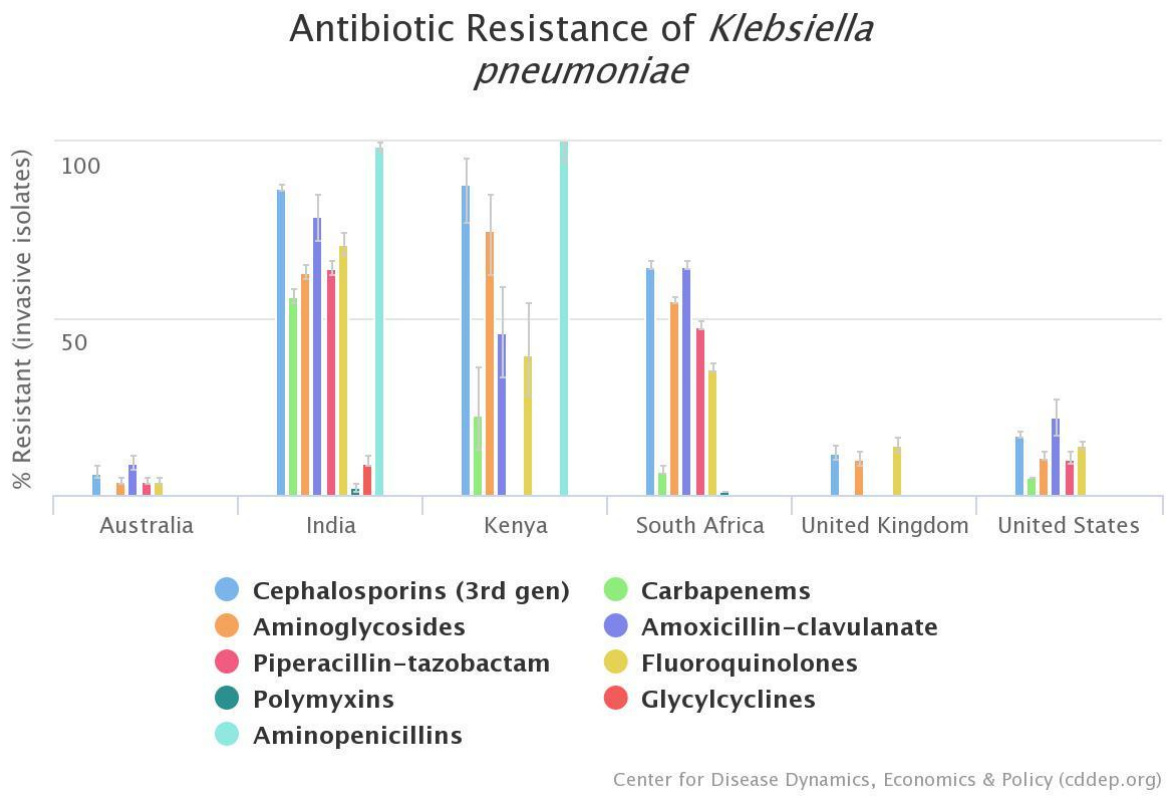


Figure 1: A Chart on global distribution of invasive K. pneumoniae isolates (Center for Disease Dynamics, Economics & Policy, 2017)***.*** *Kenya, India and South Africa have higher resistant proportions than Australia, the United Kingdom, and the United States.*

In a retrospective Intensive Care Unit hospital study conducted in Southern Italy from 2008-2013, *Klebsiella pneumoniae* incidence density rate rose from 22.3/1000 patient days as of 2010 to 55.9/100 patient days as of 2013. Isolates of *Klebsiellae* that were resistant to 3rd generation cephalosporin's rose from 41.9% in 2010 to 87% in 2012. Whereas resistance to carbapenem rose from 0% in 2008 to 59.2% in 2013 (Agodi *et al.*, 2015)**.**

A similar case demonstrating the rise in the incidence of drug-resistant *K. pneumoniae* was reported in New York. From 1999 to 2006 multidrug-resistant *K. pneumoniae* increased from 1% to 59.1% in Brooklyn, New York. Of the isolates, 25% demonstrated resistance to carbapenems. It was concluded that *K. pneumoniae* had become the predominant multi-drug resistant bacteria (Landman *et al.*, 2007). Therefore, it is evident that the general trend points towards increasing levels of antimicrobial resistance.

Besides, an antimicrobial resistance study in Germany's Intensive Care units demonstrated a rise in the level of resistance by *K. pneumoniae* between 2001 and 2008, with resistance to third generation cephalosporin's rising from 3.8% in 2001 to 25.5% in 2008. Resistance to Imipinem increased from 0.4% to 1.1% over the same period (Meyer *et al.*, 2010).

It is also evident that the antimicrobial resistant *K. pneumoniae* has a worldwide distribution, a global study on antimicrobial resistance revealed that of the tested isolates, 25.7% were multi-drug resistant with a distribution all over the world (Hackel *et al.*, 2016). From this study, the ceftazidime-avibactam combination proved to be the most active antibiotic against multi-drug resistant *Klebsiellae,* with avibactam protecting beta-lactams from beta-lactamases and carbapenemases.

A systematic review of studies conducted in thirteen African countries sought to determine the proportion of Enterobacteriaceae exhibiting extended-spectrum beta-lactamases. The proportions ranged from 1.5% to 22.8% among the countries studied; an intensive unit study in Egypt reported that 75% of Enterobacteriaceae isolates were positive for ESBL (Tansarli *et al.*, 2014).

Furthermore, as per a sentinel surveillance conducted in South Africa, *K. pneumoniae* had established resistance to cephalosporins without sparing the 3rd and 4th generation of this antibiotic group. The proportion of ESBLs-producing *K. pneumoniae* resistant to ciprofloxacin and piperacillin-tazobactam was at 70%, 39%, and 48%, respectively (Perovic, Chetty and Iyaloo, 2014). Additionally, an antimicrobial resistance study in Karachi hospitals demonstrated resistance by *K. pneumoniae* to cefuroxime and cefazolin to be 64.3% and 71.4% respectively (Arsalan *et al.*, 2003).

In Kenya, several studies have been conducted on antimicrobial resistant *K. pneumoniae*. One study on neonates and infants born out of the hospital reported the increasing incidence of drug-resistant Klebsiellae isolates. In this population, there was a 23% increase between 2007 and 2009 (Talbert *et al.*, 2012). At Kilifi County Referral Hospital, an increase in drug-resistant isolates of *K. pneumoniae* over a 10 year period was observed (Henson *et al.*, 2017). Resistance to gentamicin rose from 43% (2001) to 83% (2011). Of the isolates evaluated during the study period, 79% were multi-drug resistant.

2.5 Predictors of Outcomes of *K. pneumoniae* Resistance

Several factors can predict mortality in patients with systemic carbapenemase producing *K. pneumoniae*. Mono-drug therapy was associated with a higher mortality rate than combined-drug therapy at 54.3% of the former and 34.1% for the latter according to a study conducted in three Italian hospitals. Treatment with a combination of tigecycline and colistin was associated with a lower mortality rate with OR of 0.11 and 95% CI: .02–.69; while inadequate antibiotic therapy mortality risk had an OR of 4.17 and 95% CI: 1.61–10.76 (Tumbarello *et al.*, 2012).

Similarly, a study conducted in Greece revealed that patients infected with carbapenemase-producing strains of *K. pneumoniae* when put on combination therapy had zero mortality as opposed to 46.7% for those on monotherapy. Sensitivity tests revealed that 89.9% of the isolates were sensitive to tigecycline, 75.5% to colistin, 96.2% to meropenem and 21% to gentamicin. Mortality among patients admitted in the ICU was 28.9% versus 46.7% among those not admitted to the ICU. Mortality with inappropriate antibiotic therapy was 61.1% versus 20% for those who received appropriate antibiotic therapy (Zarkotou *et al.*, 2011)

A retrospective cohort study of two medical facilities in New York also established the superiority of combined therapy over monotherapy in the treatment of carbapenemase-

producing *K. pneumoniae*. Crude mortality at the 28th day was 57.8% for monotherapy group and 13.3% among the combined therapy group. As such, definitive therapy with a combination of effective antimicrobial agents is superior to monotherapy in reducing mortality (Qureshi *et al.*, 2012).

The nature of *K. pneumoniae* resistance is strongly correlated to the mortality rate. One study reported mortality rates of 17%, 22% and 48% for susceptible, ESBL, and carbapenem-resistant *K. pneumoniae* infections respectively. In addition, the last category of patients had greater previous exposure to antimicrobials, higher utilization of therapeutic invasive devices and concurrent nosocomial infections (Kordevani *et al.*, 2011).

.A study on carbapenemase-producing *K. pneumoniae* at a teaching hospital in Brazil revealed that 4 out of 9 patients with *Klebsiellae* isolates that had the *bla*KPC gene (codes for carbapenemase) died. (Seibert *et al.*, 2014). This shows that antimicrobial resistant *K. pneumoniae* is a significant contributor to mortality among the infected.

2.5 Research Gap

Antimicrobial resistance is a global problem more so in intensive care environments. It results in higher mortality and increased healthcare costs. Lack of recent data on *K. pneumoniae* susceptibility pattern at Kenyatta National Hospital ICU coupled evidence of nosocomial infections made this study necessary.

2.6 Research Questions

1. What is the antimicrobial susceptibility pattern of *Klebsiella pneumoniae* isolated at KNH ICU between September 2013 and September 2017?
2. What were the clinical outcomes of KNH ICU patients with drug-resistant *Klebsiella pneumoniae* isolates?
3. What is the proportion of antibiotics prescribed before and after antimicrobial sensitivity testing among the study subjects?

2.7 Justification

Antimicrobial resistance poses a significant threat to the prevention and treatment of common infections, bacterial and otherwise (WHO, 2014). A recent report by the World Health Organization categorizes *K. pneumoniae* as a critical priority pathogen together with other organisms in the Enterobacteriaceae family (WHO, 2017). Additionally, there is evidence to support the rising incidence of antimicrobial resistance in intensive care settings (Gupta *et al.*, 2011). This emphasizes the gravity of the problem associated with Enterobacteriaceae. *Klebsiella pneumoniae* is a significant contributor to nosocomial infections at Kenyatta National Hospital (Inyama *et al.*, 2011; Ngumi, 2006) and Kilifi County Referral Hospital (Henson *et al.*, 2017). The above studies agree that antimicrobial resistance to *K. pneumoniae* is a problem. WHO lists Kenya among countries with incomplete information on antimicrobial resistance (WHO, 2014). It is part of this gap that this study seeks to address.

2.8 Objectives

Main objective

To describe antimicrobial susceptibility patterns and outcomes in patients with drug-resistant *K. pneumoniae* Kenyatta National Hospital ICU, September 2013- August 2017.

Specific objectives

2.2.1 To describe the antimicrobial susceptibility pattern of *Klebsiellae* isolates at Kenyatta National Hospital ICU from September 2013- August 2017.

2.2.2 To determine clinical outcomes of patients with drug-resistant *K. pneumoniae* isolates.

2.2.3 To determine the proportion of antibiotics prescribed before and after antibiotic sensitivity testing in the study population.

3 Methodology

3.2 Study design

This was a retrospective study using patients medical and laboratory records.

3.3 Study area

Kenyatta National Hospital, which is the largest tertiary hospital in Eastern and Central Africa, with a bed capacity of 1800. Areas of interest were the Medical Microbiology laboratory's electronic database and the Health Information department for the retrieval of information. The critical care units with a total bed capacity of 20 are multidisciplinary with an average monthly admission of 100 patients in the proposed research time frame. Assaults and road traffic accidents are the leading causes of ICU (main) admission with an average mortality rate standing at 40% (ICU and HDU Admission records, accessed August 2017). Antibiotic prescription in the facility is guided by the national standards and guidelines.

3.4 Study population

All patients admitted to the ICU who tested positive for *K. pneumoniae* from September 2013 – August 2017.

3.5 Inclusion criteria /Exclusion criteria

The availability of antimicrobial susceptibility results for *K. pneumoniae* for the patients admitted to the ICU. Records between September 2013 and August 2017 were used. All patients still admitted to the unit were excluded from the study.

3.6 Sample size estimation

The prevalence of *K. pneumoniae* resistant isolates among critical care units' patients in Kenya is unknown. The assumed prevalence was 50%.

$N=Z^2PQ/d^2$ (Fisher 1991)

Where

N= minimum sample size

Z= 1.96 (95% confidence interval)

P= population proportion with the characteristic of interest (0.5)

Q= 1-P (0.5)

d= acceptable margin of error (0.05)

$N= (1.96)^2*0.5*(1-0.5) = 384$

The minimum sample size is 384 subjects

3.7 Study variables

a. Independent variables: age, gender,
b. Dependent variables: Prior exposure to steroids, prior antibiotic history, prior admission to the intensive care units, invasive procedures, time from admission till discharge or death.

3.8 Data Collection Procedures and management

3.8.1 Sampling technique

Only 239 electronic records fit the inclusion criteria and were all included in the study.

3.8.2 Susceptibility trends of *K. pneumoniae* to antibiotics

Data was retrieved from the electronic database and imported to WHONET using BACKLINK. The corresponding data was retrieved from patient files using a prescribed data abstraction form then entered into IBM SPSS. This data was analyzed using WHONET/IBM SPSS & MS Excel. Data has been presented using graphs, pie charts, and tables. Isolates were classified as susceptible, or intermediate or resistant according to the Clinical and Laboratory Standards Institute and guidelines 2016, using WHONET software.

3.8.3 Discharge and mortality proportions and antibiotic prescribing

Patient data abstraction

Parameters that were reviewed include demographics (age and gender), duration of hospitalization, working diagnosis, comorbidities, invasive procedures, current infection antimicrobial therapy, clinical characteristics, previous admission in an intensive care unit, outcomes, prior steroid use within the last 30 days of the infection, and other non-antimicrobial interventions as indicated in the data extraction tool in the appendix. Information on clinical outcomes and associated risk factors was obtained from the patient's file. Data cleaning was carried out for data retrieved from the patients' medical records.

The files were retrieved by the registry personnel at the central registry. The researcher and two nurses abstracted the data from the files. The projected retrieval rate was 7 files per data collector per day. It took 21 working days to retrieve and abstract all the data from the subject's medical records. In terms of completeness of the information in the files, the available documentation for each study subject was documented to include physicians' notes, nursing records, medical administration record, lab results, and discharge summary/mortality notes.

This information has been captured in the data extraction tool. Additionally, a daily audit of the collected data was undertaken to check for completeness.

3.8.4 Statistical Analysis

Data was analyzed using WHONET and IBM-SPSS statistical software. Relative Risk (RR) was used to estimate the risk of mortality between groups. F-test was employed to test for equality of variances. A *p* value of <0.05 was considered significant.

3.9 Ethical issues

Ethical approval was obtained from and Kenyatta National Hospital-University of Nairobi Ethical Review Committee on 5th Feb, 2017. The ethical approval number of this study is P630/11/2017. No physiological risks were experienced from this study since it involved the retrieval of archived data. Any personal and clinical information obtained in connection with the research is held in confidence and will not be published. Permission from KNH-UoN ERC, departments of Laboratory Medicine, and Health Information was granted for retrieval of archived patient data from the records office and the laboratory's electronic database. The data obtained is stored in a secure database (Google drive) which is password protected to prevent unauthorized access. Only the study investigators, including the statistician, have an access to the data. Given the nature of the study, there was no direct contact with the study subjects. As such informed consent was not applicable. A waiver of consent to the proposal was granted by KNH-UoN ERC.

3.10 Quality Assurance

For quality assurance purposes, data cleaning of the extracted data was conducted to detect any errors in data retrieval. Daily audit of the retrieved data was carried out by a nurse to ensure data accuracy. Two separate entries of the retrieved data into excel spreadsheets were conducted to check for errors prior to analysis. A laboratory technologist familiar with the Clinical Laboratory Standard Institute 2016 was consulted for the proper interpretation of antibiogram results.

4. Findings

4.1 Demographics

The electronic database yielded 239 records that met the study inclusion criteria. Of these, a total of 25 study participants were excluded due to data incompleteness with regards to laboratory results, demographic data, prescription information and patient medical records that could not be retrieved (see figure 2).

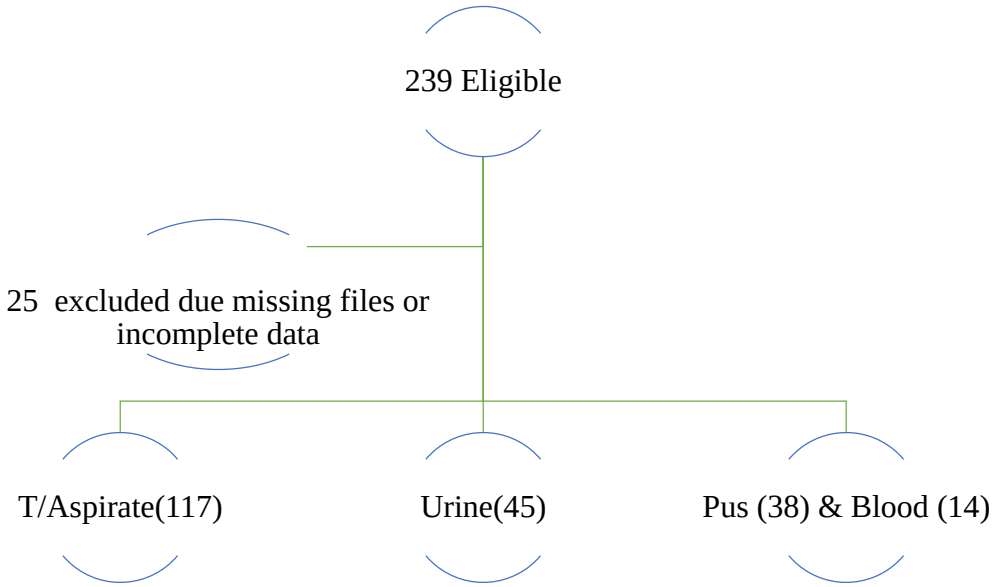


Figure 2: Flowchart depicting subject selection

The age of the study participants ranged from 9 to 92 years with a mean age of 38.7 (SD 18.67) years. The median age of the patients was 36 (Interquartile Range (IQR = 27); 50% of the participants were aged below 36 years. More than half, 121 (56.5%) of the patients were males.

Subject Distribution by Year of Isolate analysis

The subject distribution by year of isolate analysis was 11% (24/214), 36% (77/214), 33% (71/214), 20% (42/214) for September 2013- August 2014, September 2014 - August 2015, August 2015-September 2016 and September 2016-August 2017 respectively (see figure 3).

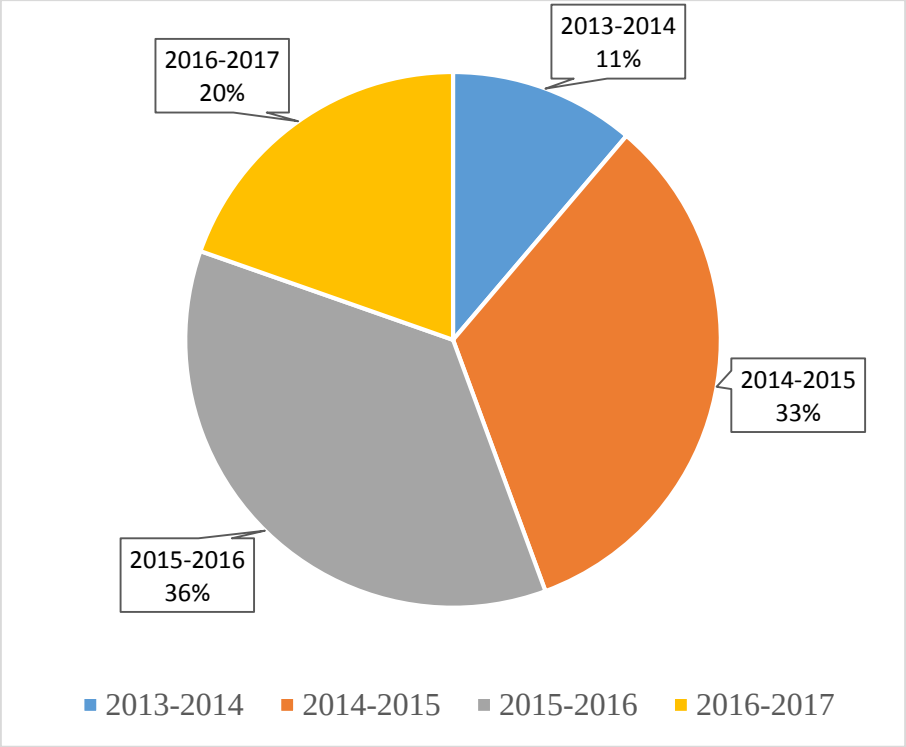


Figure 3: Subject Distribution by year. *Years in this study run from September of one year to August of the next year.*

Age Distribution of the Subjects (n=214)

The majority of the patients were from the 31 to 40 years age category representing 24% of the study population. Those age 21-30 years represented 19% of the study population. This is shown in figure 4 below.

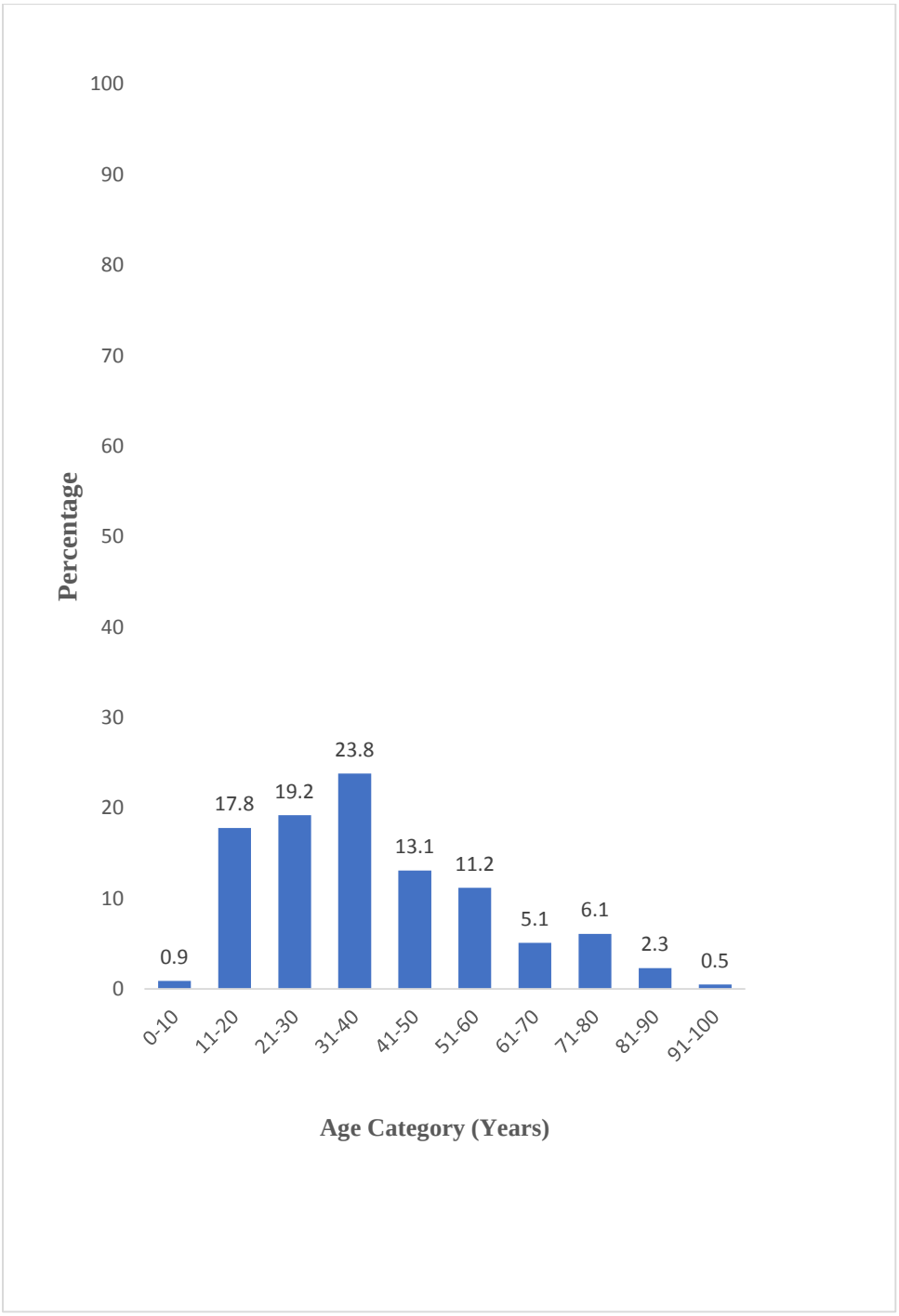


Figure 4: Age distribution of study participants.

Primary Diagnoses of Study Participants

Out of the 214 patients, 89 (42%) had a diagnosis of trauma, 16 (7.5%), cardiac diseases and 16 (7.5%). Cerebral Vascular Accident (CVA). This is depicted in figure 5 below.

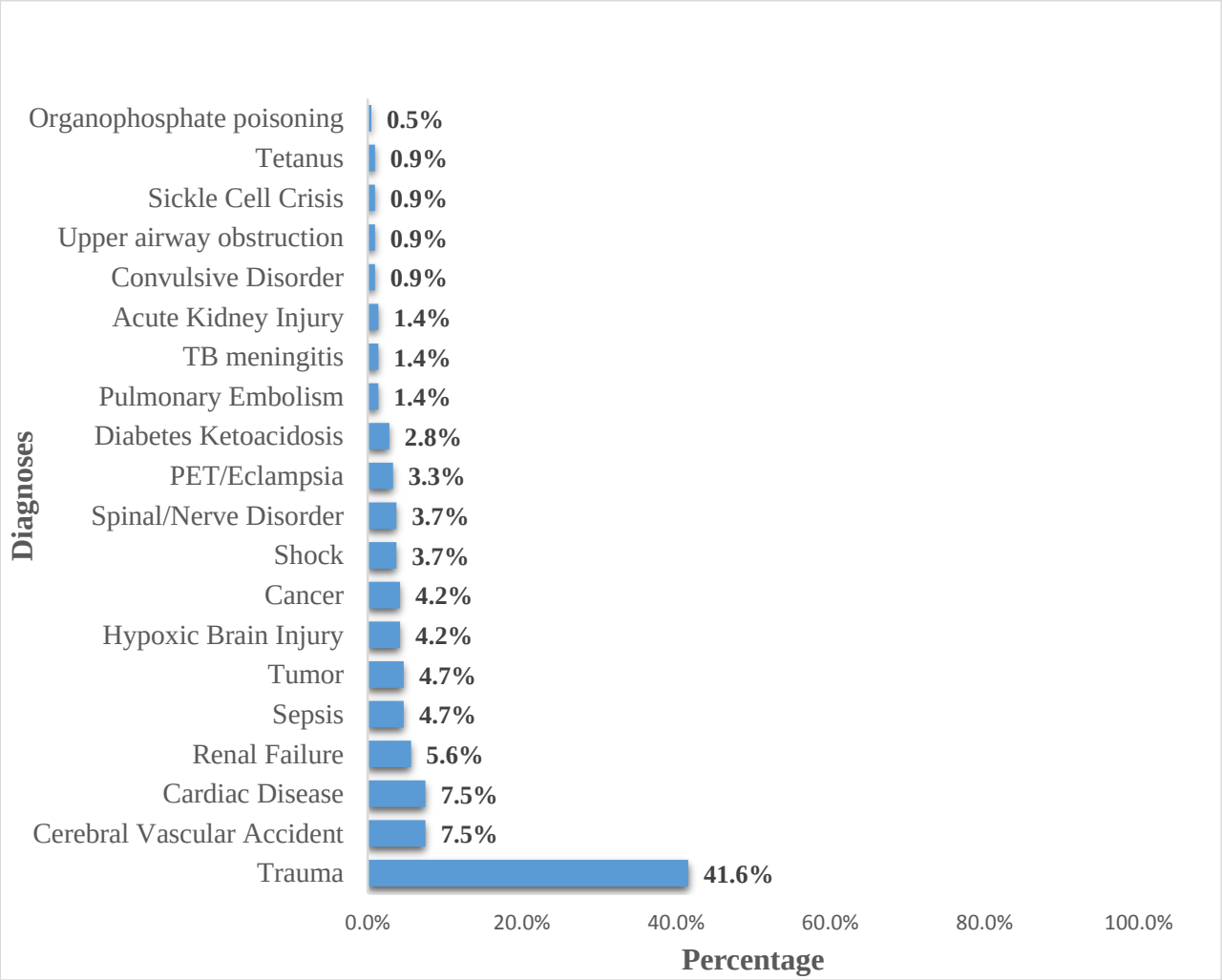


Figure 5: Primary diagnoses of study participants. *(X-axis in the proportion of the diagnoses among the study participants).*

Subject distribution by specimen type (n=214)

More than half 117 (55%) of samples were tracheal aspirates. This is summarized in figure 6 as shown.

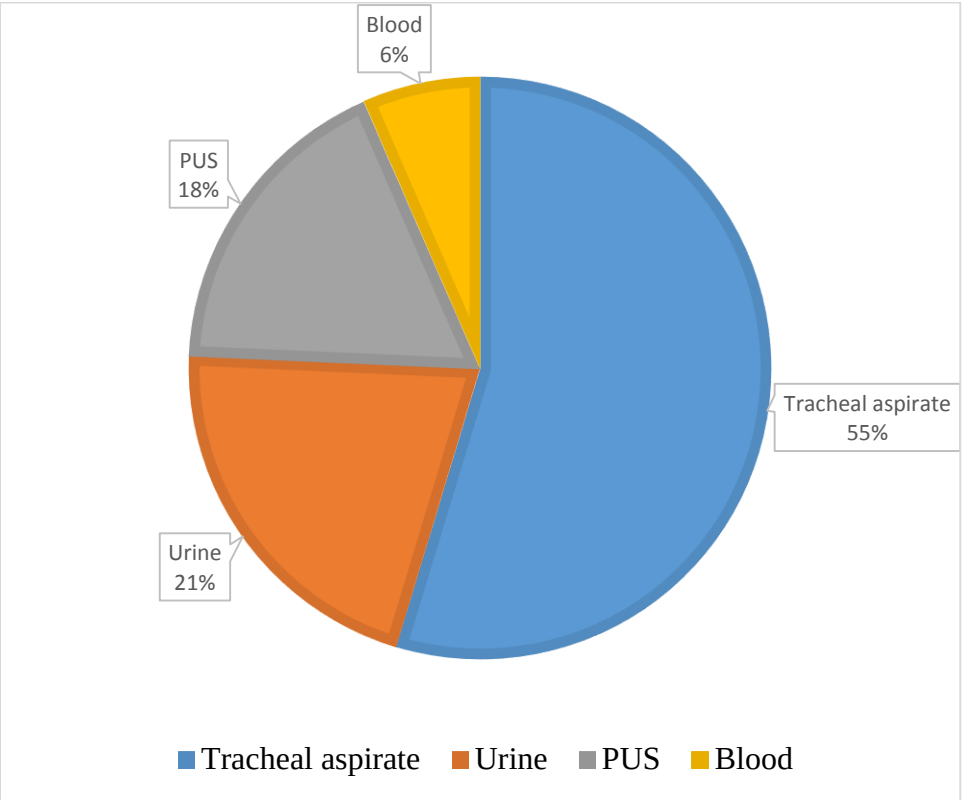


Figure 6: Sample distribution by specimen type.

Invasive procedures conducted on study subjects

As shown in table 1, in ICU, 95.3% of the subjects were intubated and all had an IV catheter.

Insertion of a central venous line was carried out on 88.7% of the study participants.

Table 1: Invasive Procedures on Study Subjects. *(A summary of the invasive procedures carried out on the study subjects).*

Invasive Procedure	Frequency	Percent
Central venous line	190	88.7
Intubation	204	95.3
Mechanical ventilation	204	95.3
Urinary catheterization	214	99.0
Intravenous catheter	214	100

4.2 Objective 1: Description of the antimicrobial susceptibility pattern of *Klebsiella pneumoniae* isolates at Kenyatta National Hospital ICU from September 2013- August 2017

Across all specimen types (Overall), the proportion of *K. pneumoniae* susceptible to cefoxitin, meropenem, and gentamicin was 50.9%, 45.8%, and 25.7 % respectively as shown in table 2.

Table 2: Susceptibility proportion of K. pneumoniae from 2013 September to 2017 August across all specimen types (n=214). *(The breakpoints and susceptibility proportions of K. pneumoniae isolates across all specimen types).*

Antibiotics	Breakpoints	S%
Cefoxitin	<=4 >32	50.90%
Amikacin	<=2 >32	49.10%
Meropenem	<=.25 >8	45.80%
Ciprofloxacin	<=.25 >2	25.70%
Gentamicin	<=1 >8	24.80%
Piperacillin/Tazobactam	<=4 >64	15.00%
Trimethoprim/Sulfamethoxazole	<=1 >8	10.30%
Cefepime	<=1 >32	10.30%
Cefazolin	<=4 >32	5.10%
Cefotaxime	<=1 >32	5.60%
Ceftazidime	<=1 >32	5.10%
Ceftriaxone	<=1 >32	5.10%
Amoxicillin/clavulanic acid	<=2 >16	4.70%
Cefuroxime	<=1 >32	4.20%
Cefuroxime axetil	<=1 >32	3.70%
Nitrofurantoin	<=16 >256	2.80%
Ampicillin	<=2 >16	0.50%

S%= Susceptible proportion

Drug sensitivity by specimen type

K. pneumoniae susceptibility to amikacin of urine, tracheal aspirate, and other isolates was 37.8%, 56.4%, and 42.3% correspondingly, while that of ciprofloxacin to urine, tracheal aspirate, and other isolates was 15.6%, 30.8%, and 23.1% respectively (see table 3).

Table 3: Susceptibility proportion of K. pneumoniae by specimen type. *Susceptible proportions of K. pneumoniae from tracheal aspirate, urine and other (pus and blood combined).*

Antibiotics	**Break Points**	**T/Aspirate (n=117)**	**Urine (n=45)**	**Other (n=52)**
Cefoxitin	<=4 >32	65.80%	26.70%	38.50%
Meropenem	<=2 >32	63.20%	20.00%	28.80%
Amikacin	<=.25 >8	56.40%	37.80%	42.30%
Ciprofloxacin	<=.25 >2	30.80%	15.60%	23.10%
Gentamicin	<=1 >8	18.80%	35.60%	28.80%
Piperacillin/Tazobactam	<=4 >64	13.70%	13.30%	19.20%
Trimethoprim/Sulfamethoxazole	<=1 >8	12.00%	11.10%	5.80%
Cefepime	<=1 >32	11.10%	4.40%	13.50%
Cefazolin	<=4 >32	5.10%	4.40%	5.80%
Cefotaxime	<=1 >32	5.10%	6.70%	5.80%
Ceftazidime	<=1 >32	5.10%	4.40%	5.80%
Ceftriaxone	<=1 >32	5.10%	4.40%	5.80%
Amoxicillin/clavulanic acid	<=2 >16	3.40%	6.70%	5.80%
Cefuroxime	<=1 >32	3.40%	6.70%	3.80%
Cefuroxime axetil	<=1 >32	3.40%	4.40%	3.80%
Nitrofurantoin	<=16 >256	0.90%	4.40%	5.80%
Ampicillin	<=2 >16	0.00%	6.70%	0.00%

Key: Other=Pus and Blood isolates T/aspirate= Tracheal aspirate

***K. pneumoniae* susceptibility comparison for the period between September 2013 to August 2015 and September 2015 to August 2017**

Susceptibility of *K. pneumoniae* to antibiotics declined over time as shown in figure 7. Susceptibility proportion to ciprofloxacin declined from 33.0% in 2013 September-2015 August period to 20.0% in 2015 September-2017 August time period while susceptibility to amikacin declined from 58.5% to 41.7% in the same time period (P=0.043).

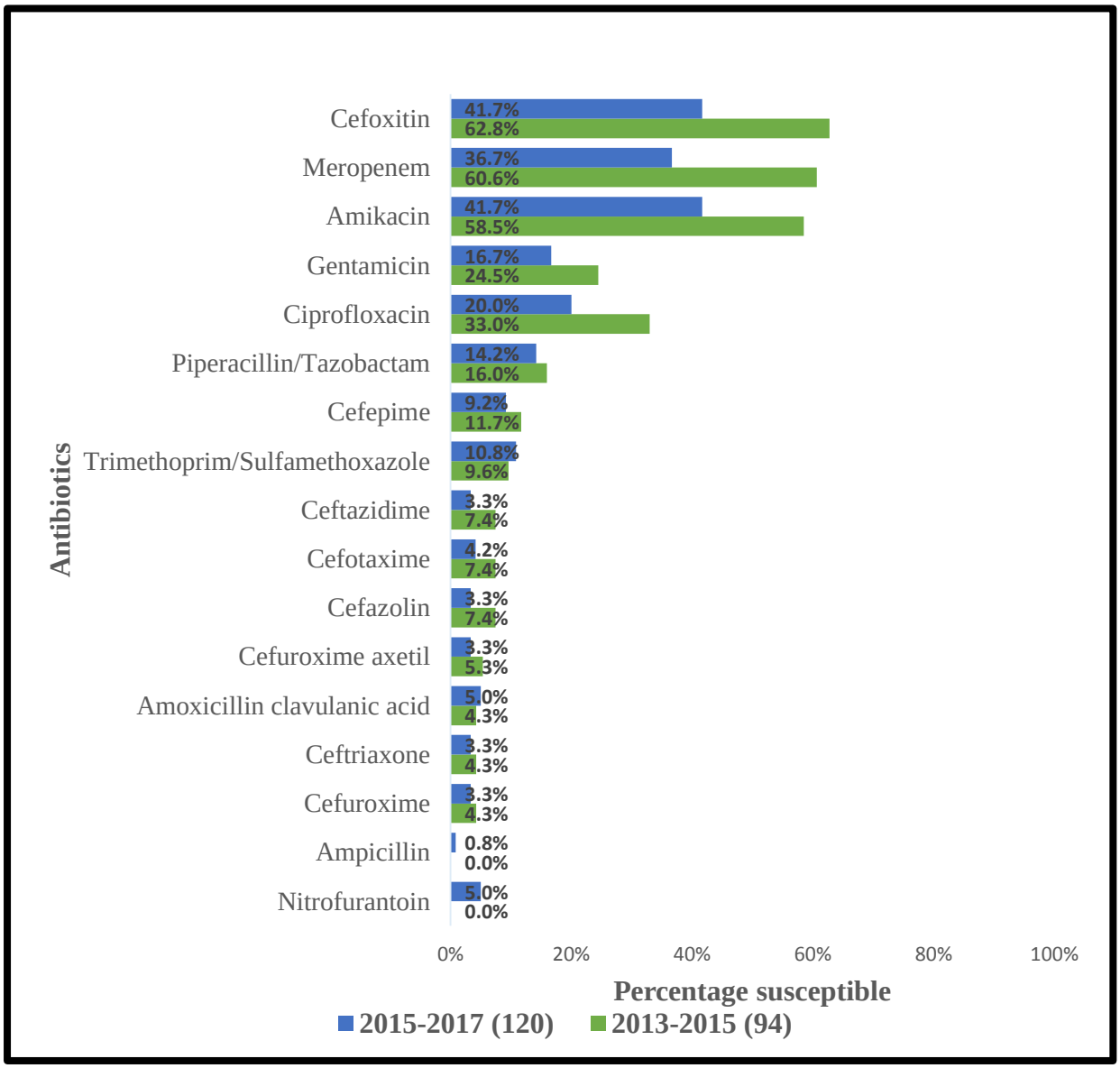
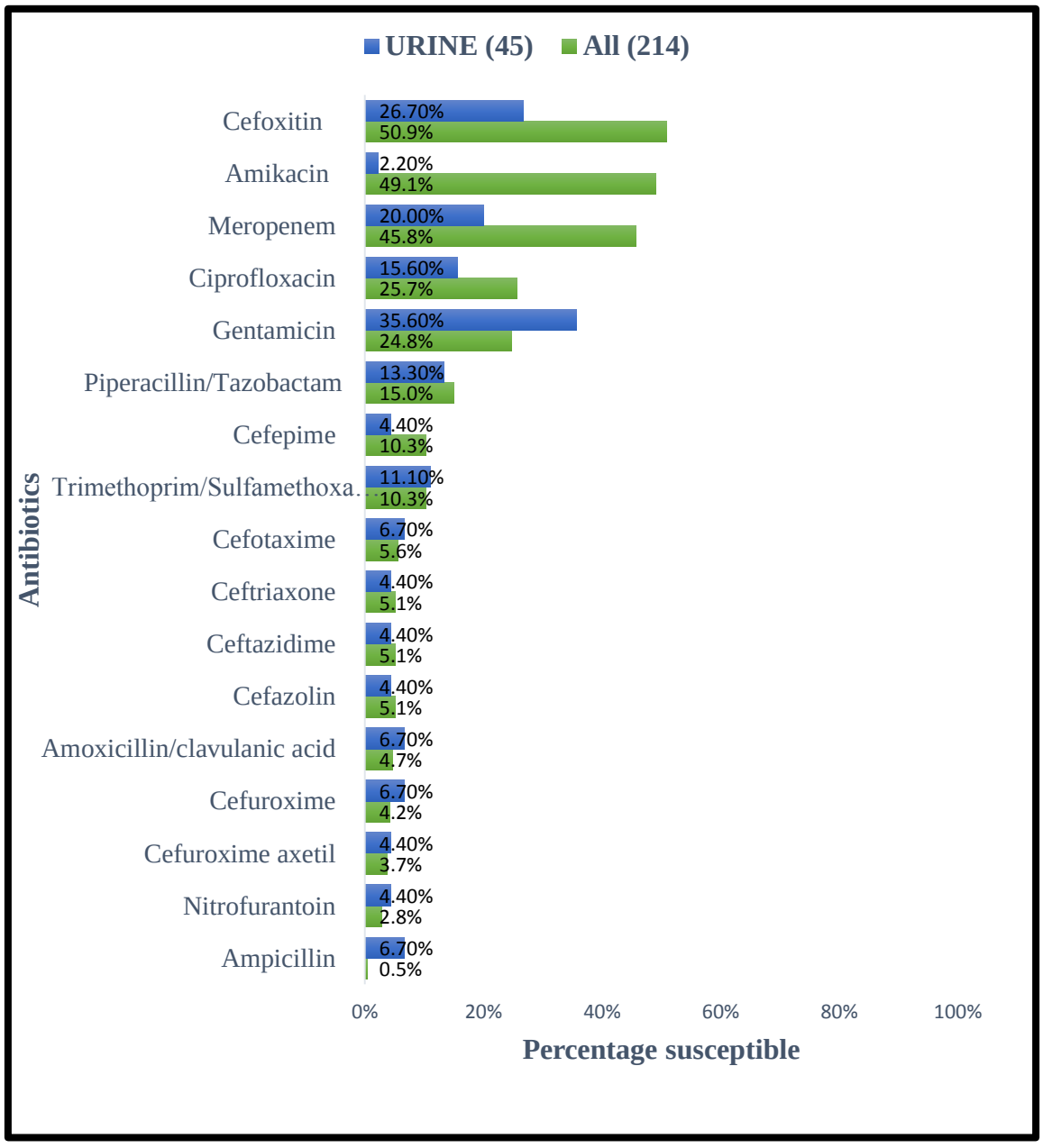


Figure 7: Susceptibility pattern of K. pneumoniae across all specimen types. (*X-axis is the proportion of susceptible isolates to a given antibiotic Y-axis).*

Comparison of Susceptibility of *K. pneumoniae* Isolates between Urine and All Specimen Types.

Isolates from urine had lower susceptibility when compared to the overall susceptibility proportion. Susceptibility of urine isolates to cefoxitin 26.7% versus 50.9% for all the isolates (P=0.009) as shown in figure 8.



Key: All Isolates= Isolates from Tracheal/aspirates, blood, urine and pus.

Figure 8: Susceptibility comparison of urine isolates versus all specimen isolates of K. pneumoniae. *(X-axis is the proportion susceptible to a given antibiotic Y-axis)*

Susceptibility pattern of tracheal aspirates *K. pneumoniae* isolates

According to figure 9, *K. pneumoniae* isolates from tracheal aspirates registered a decline in susceptibility over time. Susceptibility to cefuroxime axetil in September 2013- August 2015 time period was 5.3% while in September 2015 to August 2017 time period was 1.7% (P=0.09).

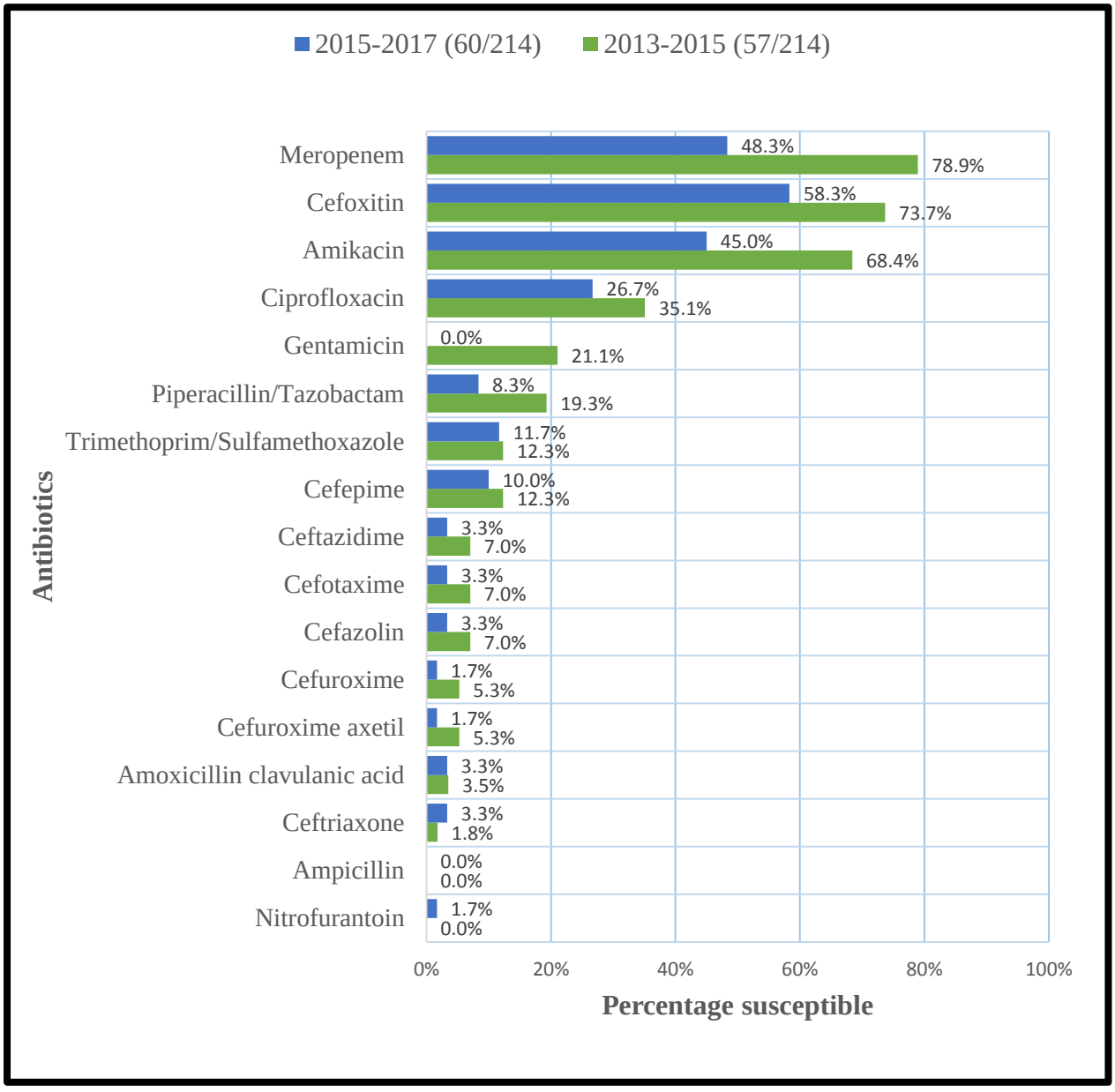


Figure 9*: *Susceptibility Pattern of K. pneumoniae Isolates from Tracheal Aspirates at KNH ICU 2013-2017.* (*The proportion refers to susceptibility X-axis to a given antibiotic Y-axis)

Susceptibility Pattern of Pus and Blood Isolates of *K. pneumoniae*

In figure 10, the susceptibility of *K. pneumoniae* isolates from pus and blood to antibiotics declined over time. From September 2013 -August 2015 time period to September 2015 to August 2017 time period, the susceptibility of *K. pneumoniae* to cefazolin declined from 10.0% to3.1% while susceptibility to meropenem declined from 40.0% to 21.9%. (P=0.22)

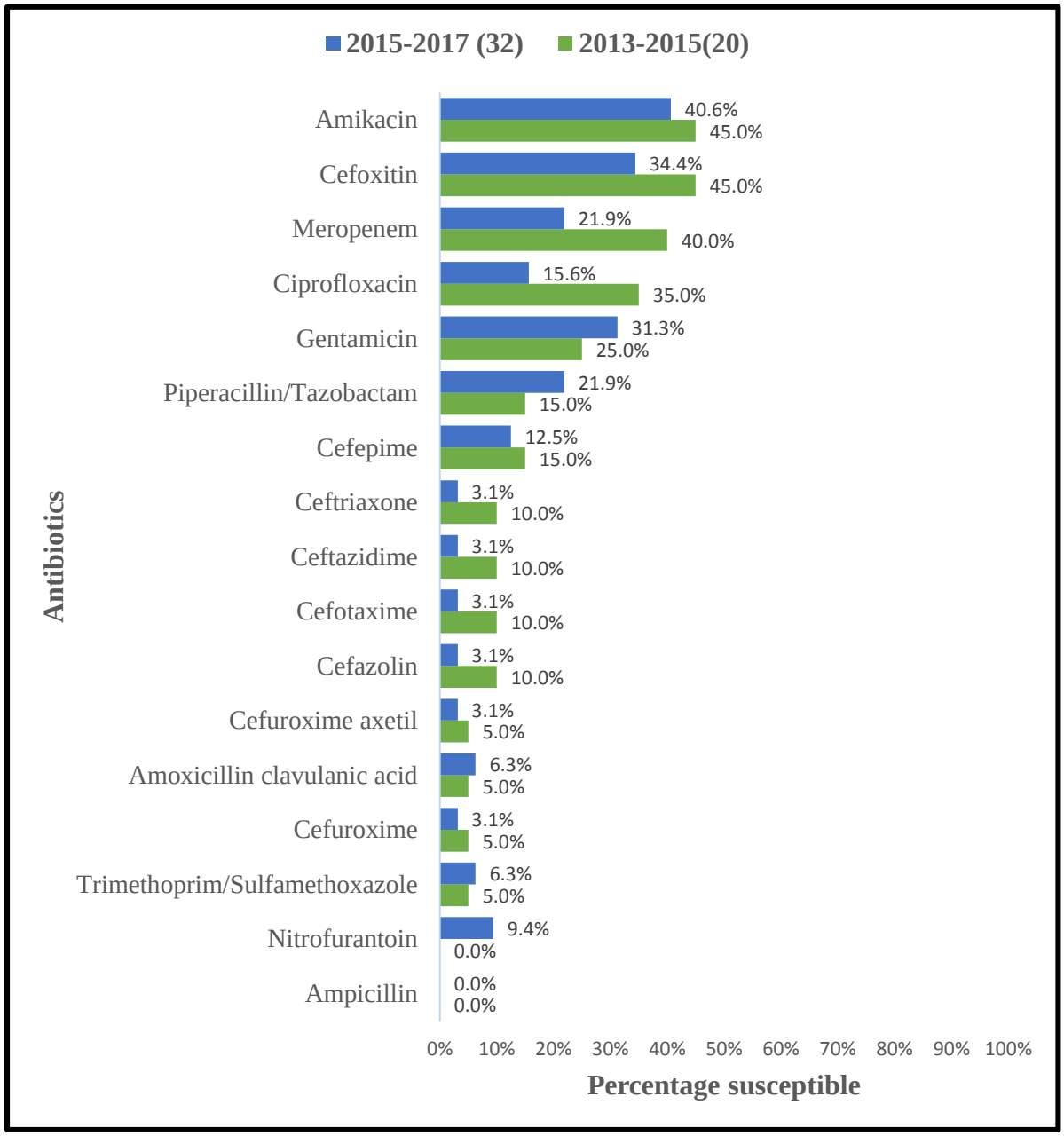


Figure 10*: *Susceptibility pattern of pus and blood isolates of K. pneumoniae at KNH ICU from September 2013-August 2017. *(X-axis is the proportion of isolates susceptible to a given antibiotic Y-axis)*

Susceptibility pattern of urine isolates of *K. pneumoniae in* KNH ICU from September 2013 to August 2017

Susceptibility to cefoxitin declined from 47.1% in 2013 September- August 2017 to 14.3% in the September 2015 to 2017 August time period. In the same time period, susceptibility to trimethoprim/sulfamethoxazole by *K. pneumoniae* increased from 5.9% to 17.9% (P=0.11). This is depicted in figure 11 below.

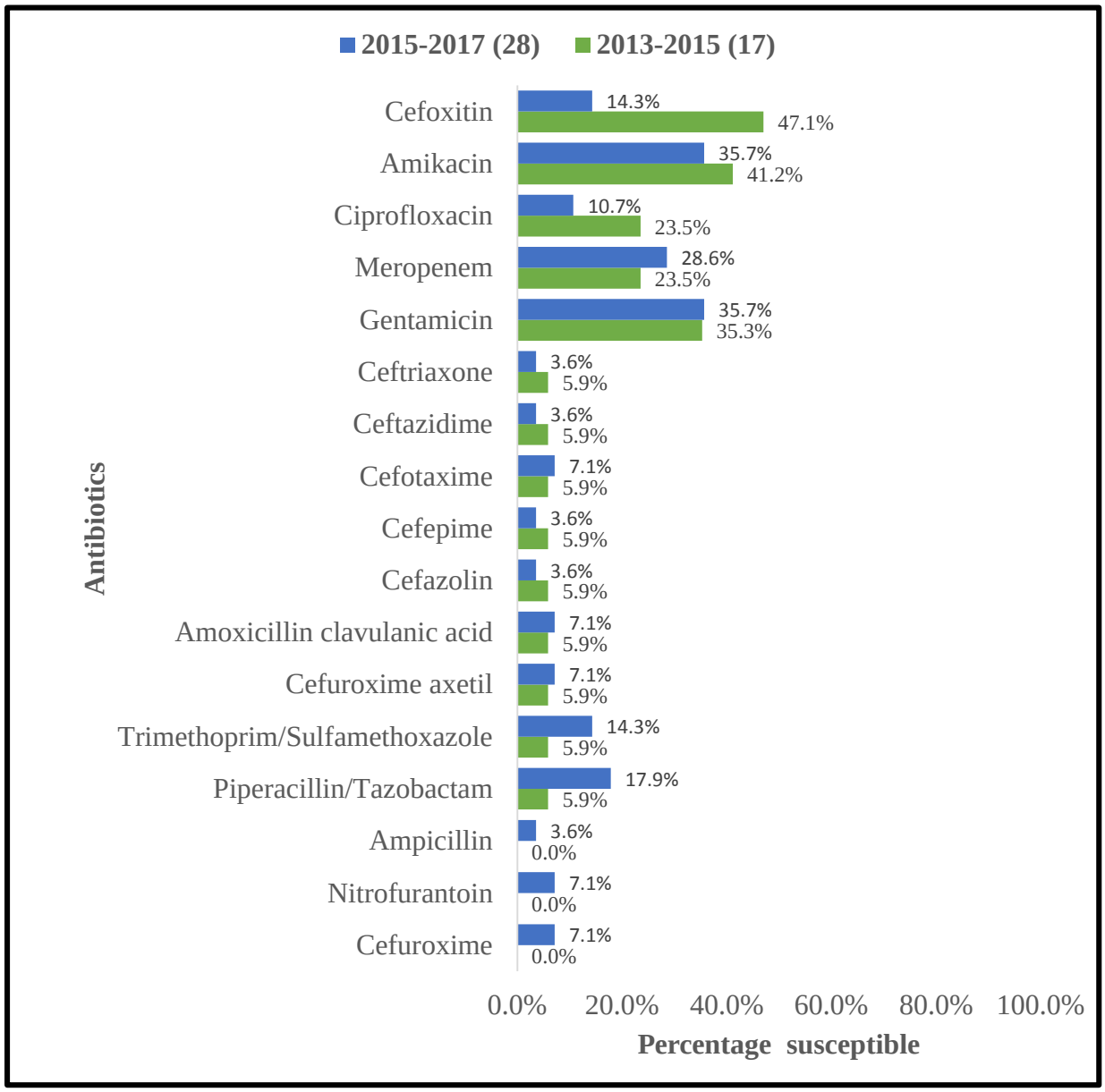


Figure 11: Susceptibility Pattern of Urine Isolates of K. pneumoniae. (*X-axis depicts proportion of isolates susceptible to a given antibiotic Y-axis)*

Carbapenem (meropenem) Susceptibility Pattern

As shown in figure 12, the overall susceptibility to meropenem declined from 60.6% to 36.7%.

Urine isolates registered an increase in susceptibility of 5.1% over the study period (P=0.12).

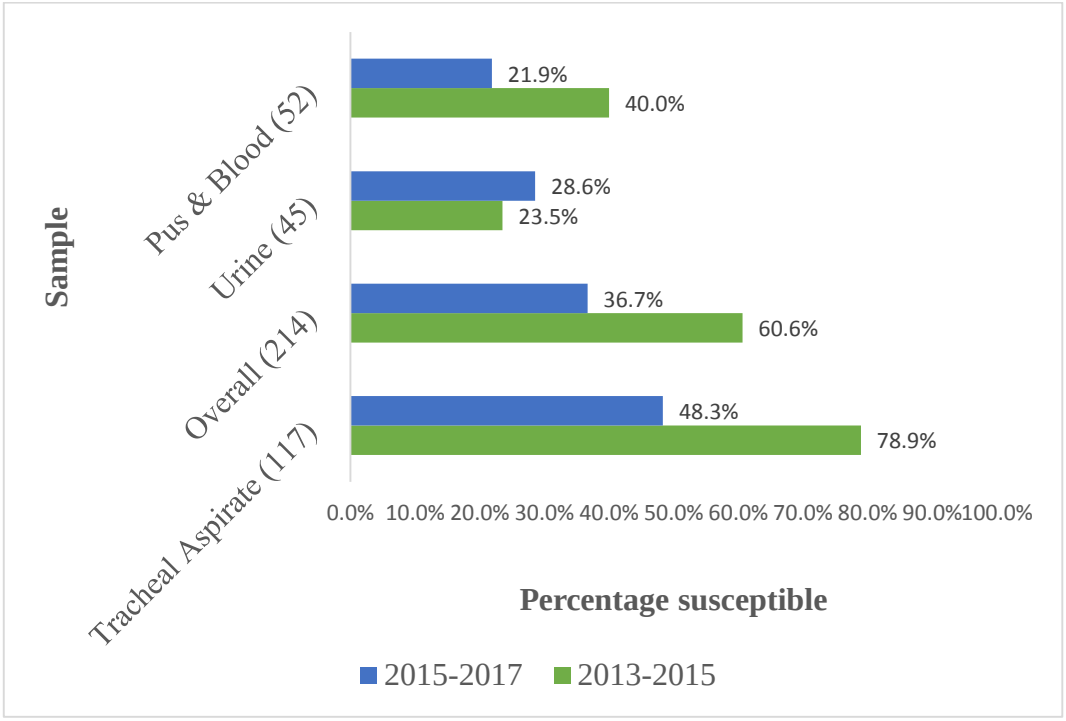


Figure 12: Susceptibility Pattern of K. pneumoniae to carbapenems for the entire study period. (*X-axis proportion of isolates susceptible to a given antibiotic Y-axis)*

4.3 Objective 2: The Clinical outcomes of KNH patients with drug-resistant Klebsiella pneumoniae isolates from September 2013 to August 2017?

Discharge and Mortality proportions

The overall mortality among study participants was 41.0%. The overall mortality for monotherapy and multi-drug therapy were 41.9% and 39.5% respectively. With a relative risk of 1.11 (CI: 0.62, 1.96), the risk of death among those who received one antibiotic was 1.1 times the risk of death among those who received two antibiotics as shown in table 4

Table 4: Number of definitive antibiotics used and outcome. (*The difference in outcome between those who received two definitive antibiotics versus those who got one wasn't statistically significant.)*

Antibiotics	Dead	Alive	Total
One	41.9%	58.1%	100.0%
Two	39.5%	60.5%	100.0%
Total	41.0%	59.0%	100.0%

As shown in table 5, mortality among those who received inadequate antibiotic regimen as per the antibiogram results was 47.8%, while the mortality for those who received adequate antibiotic therapy as guided by the antibiogram results was 37.8%. The relative risk of dying was 1.51 (CI: 0.8, 2.7) times for those who received inadequate antibiotic treatment than for those who received adequate antibiotic treatment.

Table 5: Association between treatment adequacy and outcome.

Treatment adequacy	Dead	Alive	Total
Inadequate	47.8%	52.2%	100.0%
Adequate	37.8%	62.2%	100.0%
Total	41.0%	59.0%	100.0%

4.4 Objective 3: Antibiotics prescribed prior to and after antimicrobial sensitivity testing

Antibiotic prescription

Ceftriaxone was the most commonly prescribed empiric antibiotic at 45.6%, followed by ceftriaxone and Metronidazole combination, amikacin then meropenem as shown in table 6 prior to antibiogram results**.** Meropenem was the most commonly prescribed definitive antibiotic which was determined by antibiotic in the patients file at least five days after receipt of antibiogram results at 24.8%. The preferred antibiotic combinations in ICU were meropenem and amikacin at 9.3% followed by meropenem and gentamicin at 7.5% (see table 7).

Table 6: Antibiotic therapy prior to antibiotic sensitivity testing. The proportion of prescribed antibiotics.

Antibiotic	Frequency	Percentage (%)
Ceftriaxone	98	45.6%
Ceftriaxone & Metronidazole	55	25.9%
Amoxicillin/Clavulanic acid	10	4.7%
Meropenem	9	4.1%
Amoxicillin/Clavulanic acid & Metronidazole	7	3.1%
Amikacin & Meropenem	7	3.1%
Flucloxacillin	6	2.6%
Cefuroxime	4	2.1%
Amikacin	3	1.6%
Ceftriaxone & Meropenem	3	1.6%
Flucloxacillin & Metronidazole	3	1.6%
Cefuroxime & Metronidazole	2	1.0%
None	1	0.5%
Amoxicillin/Clavulanic acid & Ciprofloxacin	1	0.5%
Ceftazidime & Metronidazole	1	0.5%
Ciprofloxacin & Ceftriaxone	1	0.5%
Ciprofloxacin & Meropenem	1	0.5%
Meropenem & Trimethoprim/sulfamethoxazole	1	0.5%

Table 7: Antibiotic therapy post antibiogram results. It depicts the proportion of antibiotic use among study participants after drug sensitivity testing.

Antibiotic	Frequency	Percentage (%)
Meropenem	53	24.8%
Ceftriaxone	30	14.0%
Meropenem & Amikacin	20	9.3%
Meropenem & Gentamicin	16	7.5%
Amikacin	13	6.1%
Piperacillin/Tazobactam	13	6.1%
Ceftazidime	12	5.6%
Cefuroxime	7	3.3%
Amikacin & Piperacillin/Tazobactam	7	3.3%
Ceftriaxone & Metronidazole	4	1.9%
Meropenem & Ciprofloxacin	4	1.9%
Meropenem & Ceftriaxone	4	1.9%
None	3	1.4%
Meropenem & Metronidazole	3	1.4%
Ciprofloxacin	2	0.9%
Nitrofurantoin	2	0.9%
Ceftazidime & Amikacin	2	0.9%
Meropenem & Piperacillin/Tazobactam	2	0.9%
Meropenem & Vancomycin	2	0.9%
Amoxicillin/Clavulanic acid	2	0.9%
Amoxicillin/Clavulanic acid & Metronidazole	1	0.5%
Amikacin & Ciprofloxacin	1	0.5%
Amikacin & Gentamicin	1	0.5%
Amikacin & Nitrofurantoin	1	0.5%
Ceftazidime& Metronidazole	1	0.5%
Ceftazidime & Meropenem	1	0.5%
Ciprofloxacin & Amoxicillin/Clavulanic acid	1	0.5%
Ceftriaxone & Amikacin	1	0.5%
Cefuroxime & Metronidazole	1	0.5%
Gentamicin & Ceftriaxone	1	0.5%
Gentamicin & Piperacillin/Tazobactam	1	0.5%
Meropenem & Cefuroxime	1	0.5%
Tigecycline & Amikacin	1	0.5%

Association between duration of stay and adequacy of the antibiotic treatment

The median duration of stay among those who received adequate antibiotic treatment was 47 with IQR of 30 days, while those who received inadequate treatment was 44 and an IQR of 49.5 days.

Table 6: Association between duration of stay and adequacy of the antibiotic treatment. *The median and interquartile range are shown.*

Treatment adequacy	**Median Hospital Stay (Days)**	**IQR**
Inadequate	44	30
Adequate	47	49.5

5. Discussion of Findings, Conclusions, and Recommendations

5.1 Discussion of Findings

The main objective of this study was to describe the antimicrobial resistance pattern and outcomes among patients with drug-resistant *K. pneumoniae* at KNH ICU. The study confirms that antibiotic-resistant *K. pneumoniae* is a significant challenge in intensive care settings. From this *K. pneumoniae* registered a decline in susceptibility to several antibiotics of over the study period. The relative risk of mortality among those who received inadequate antibiotic treatment was 1.5 times the mortality risk among those who received adequate antibiotic treatment.

These findings are in line with related studies that depict that antibiotic-resistant *K. pneumoniae* is a critical pathogen in the fight against antimicrobial resistance as evidenced by rapidly rising levels of resistance by this pathogen to antibiotics including 4th generation cephalosporins and carbapenems in these settings. A ten-year study of *Klebsiella pneumoniae* conducted at an Indian tertiary care facility revealed an increase in antibiotic resistance over the years by *K. pneumoniae* for piperacillin-tazobactam, cefotaxime, and carbapenems. (WHO, 2014). In this study, susceptibility to piperacillin-tazobactam, cefotaxime, and meropenem declined from 16.0% to 14.2%, 7.4% to 4.2% 60.6% to 36.7% respectively over the study period. This decline in susceptibility is statistically significant.

Mortality for monotherapy is generally higher than mortality for multi-drug therapy if guided by antibiogram results. Mortality proportion for multidrug therapy and mono-drug therapy is 34.1% and 53.4% respectively. Tigecycline, Colistin and Meropenem combination resulted in the lowest mortality of 12.5% other tigecycline combinations resulted in a mortality rate range of 30.4%% to 57% (Tumbarello *et al.*, 2018). This concurs with the findings of this study where mono-drug and multidrug therapy, mortality was 41.9% and 39.5% respectively for therapy

directed by antibiogram results. The relative risk of mortality among the monotherapy group was 1.1 times the risk of mortality among the combined antibiotic group.

One of the key determinants of antimicrobial resistance is prescription. A surveillance study conducted in Singapore from 2006 to 2008 established an association between antibiotic-resistant gram-negative bacteria, including *K. pneumoniae*, and prescription (Hsu *et al.*, 2010). The findings indicate that the greatest increase in resistance coincides with the most prescribed antibiotics.

The study findings validate the findings that resistance by *K. pneumoniae* to commonly prescribed third and fourth-generation cephalosporins is commonplace. Over the study period, susceptibility to commonly prescribed third-generation cephalosporins such as ceftazidime was 5.1%, while the susceptibility to a fourth generation cephalosporins such as cefepime was 10.3%. This increasing resistance to third and fourth generation cephalosporins was also observed by the World Health Organization(WHO, 2017). This is also in-line with a Swiss study that demonstrated an increase from 1.1% to 4.2% of an extended spectrum cephalosporin resistant *K. pneumoniae* (Kronenberg *et al.*, 2013).

5.2 Strength and Limitations of the Study

Some shortcomings related to retrospective study were expected, but the biggest challenge in this context was data completeness and accuracy. The researchers relied on others for accurate record keeping since they could control exposure or outcome assessment and as such a good portion of the files could not provide sufficient information. There was also limited information from the study participants such as prior antibiotic use. The findings are also subject to confounding variables which might have been present, but were not measured or recorded. This study design was chosen due to its ability to inform on changing patterns. The entire target population was selected to increase the strength of the study.

5.3 Conclusions

1. *K.pneumoniae* resistance to antibiotics increased during the study period.
2. Isolates of *K. pneumoniae* from urine samples demonstrate marginally higher resistance (statistically significant) than similar isolates from tracheal aspirates, pus, and blood.
3. Inadequate antibiotic treatment confers a higher mortality risk

5.4 Recommendations

1. This study calls for enhanced AMR surveillance to keep track of the changing trends
2. The resultant surveillance information needs to inform antibiotic stewardship efforts to help reduce selection pressure.
3. A prospective study unencumbered by the limitations such sequence of events and completeness of data of a retrospective study needs to be conducted.

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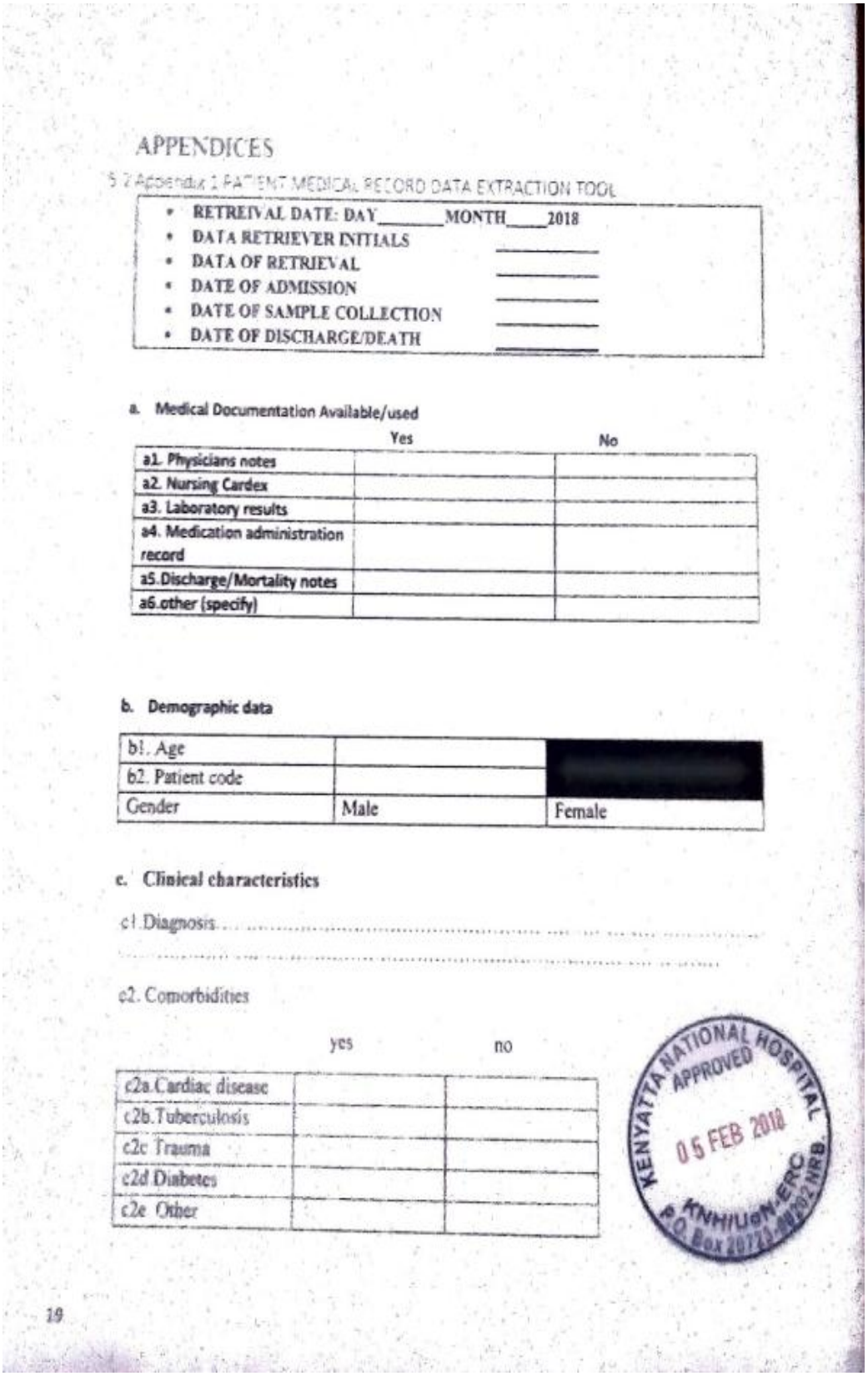
APPENDICES

Appendix 3 PATIENT MEDICAL RECORD DATA EXTRACTION TOOL



APPENDICES

5.7 Appendix 3 PATIENT MEDICAL RECORD DATA EXTRACTION TOOL

- RETREIVAL DATE: DAY_____MONTH____2018
- DATA RETRIEVER INITIALS _____
- DATA OF RETRIEVAL _____
- DATE OF ADMISSION _____
- DATE OF SAMPLE COLLECTION _____
- DATE OF DISCHARGE/DEATH _____

a. Medical Documentation Available/used

	Yes	No
a1. Physicians notes		
a2. Nursing Cardex		
a3. Laboratory results		
a4. Medication administration record		
a5.Discharge/Mortality notes		
a6.other (specify)		

b. Demographic data

b1. Age		[redacted]
b2. Patient code		
Gender	Male	Female

c. Clinical characteristics

c1.Diagnosis .....

.....

c2. Comorbidities

	yes	no
c2a.Cardiac disease		
c2b.Tuberculosis		
c2c Trauma		
c2d Diabetes		
c2e Other		

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d. Clinical Outcomes

d1. Duration of stay in the ICU ..... Days

d2. Status at discharge ..... Live ..... dead

e. Procedures and Interventions

e1 Cardiac catheterization		
e2 Central venous line		
e3 IV catheter		
e4 Urinary catheterization		
e5 Intubation		
e6 Mechanical ventilation		
e7 Other (specify)		

f. Antibiotic regimen given and duration

f1.Empirical (before lab results)

.....

.....

.....

f2.Definitive (after lab results)

.....

.....

.....

h. History

h1. Exposure to corticosteroid YES(1) ..... NO(0) .....

i. If yes, when.....

h2 Prior admission to the Intensive Care Unit YES(1) ..... NO(0) .....

i. If yes, when.....

h3. Antibiotic use 30 days prior to the current admission YES (1) ..... NO(0) .....

i. If yes, specify.....

i. State at closure of file

a. Discharged/Alive YES ..... No .....

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j. Other relevant information

.....

.....

.....

.....

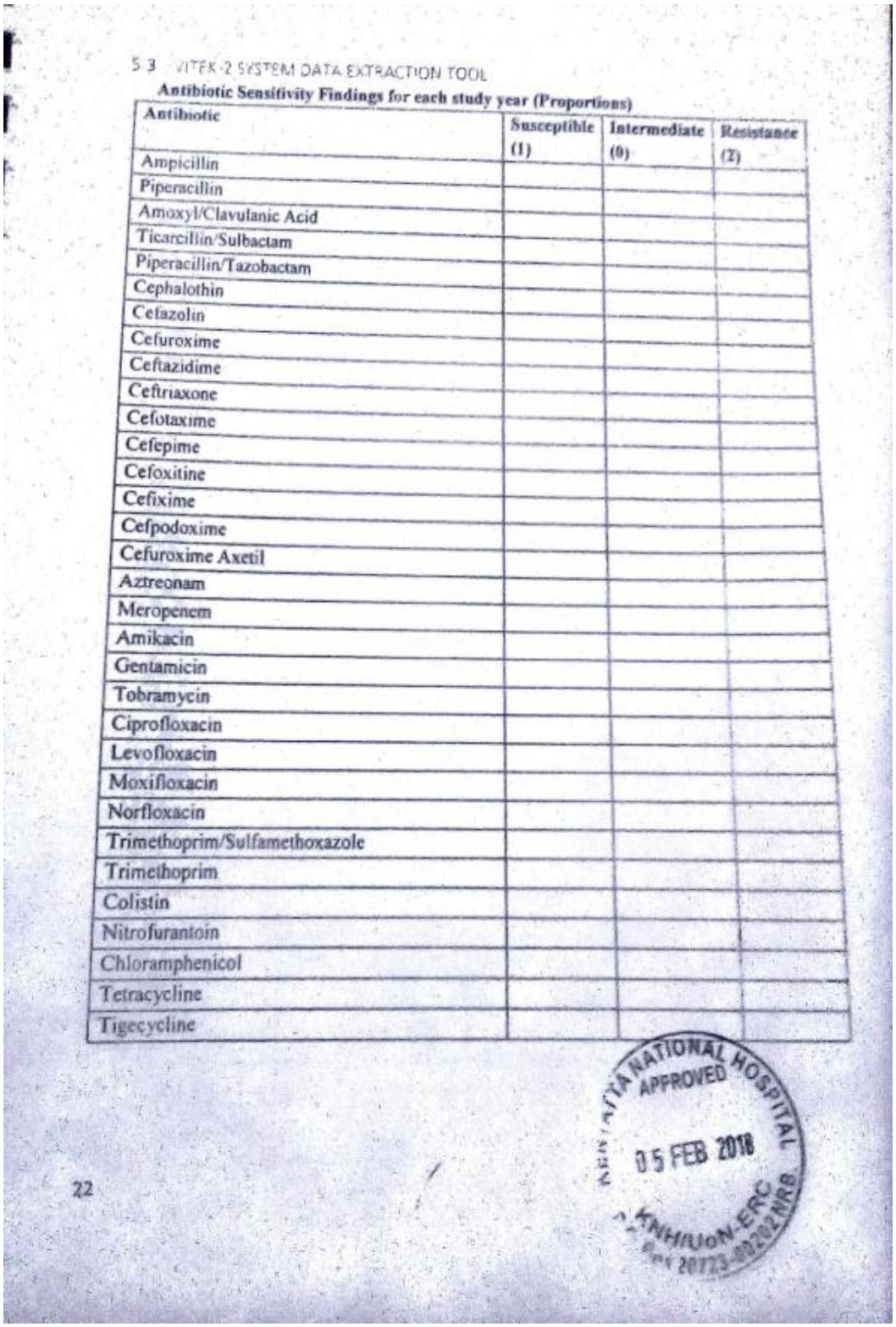
.....

.....

.....

Vitek-2 System Data Extraction Tool

Antibiotic Sensitivity Findings



5.3 VITEK-2 SYSTEM DATA EXTRACTION TOOL

Antibiotic Sensitivity Findings for each study year (Proportions)

Antibiotic	Susceptible (1)	Intermediate (0)	Resistance (2)
Ampicillin			
Piperacillin			
Amoxyl/Clavulanic Acid			
Ticarcillin/Sulbactam			
Piperacillin/Tazobactam			
Cephalothin			
Cefazolin			
Cefuroxime			
Ceftazidime			
Ceftriaxone			
Cefotaxime			
Cefepime			
Cefoxitine			
Cefixime			
Cefpodoxime			
Cefuroxime Axetil			
Aztreonam			
Meropenem			
Amikacin			
Gentamicin			
Tobramycin			
Ciprofloxacin			
Levofloxacin			
Moxifloxacin			
Norfloxacin			
Trimethoprim/Sulfamethoxazole			
Trimethoprim			
Colistin			
Nitrofurantoin			
Chloramphenicol			
Tetracycline			
Tigecycline			

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Facebook: ttps://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC

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(To be submitted with Application for ERC Review of Research)

Exempt studies to be defined

KNH-UoN ERC

REQUEST FOR WAIVER OF INFORMED CONSENT

(Not Required for Exempt Studies)

Project Title: *Klebsiella pneumoniae* Resistance Trend at Kenyatta National Hospital ICU from Sept 2013- Sept 2017

Principal Investigator and Institutional affiliation: Herbert Netia Chitere. University of Nairobi UNITID

Date: 19-Jan-18

Under special circumstances, investigators may request one of three types of waivers to obtaining written informed consent from research participants.

1. **Alteration of informed consent.**
   With this waiver, the investigator may provide to the participants a consent which does not include or which alters one or all of the required elements. Examples of when this waiver might be applicable would be, when a researcher is conducting secondary data analysis and the participants cannot be located or when requiring informed consent might somehow actually have negative consequences for research participants.

2. **Waiver of parental permission.**
   This waiver would be used in cases where something may be legal for a child to do (i.e. contraception) without parental permission and obtaining parental permission would violate that privacy. An example of this type of waiver would be a survey on children (which would require parental permission) but the survey is about their experience on contraception usage.

3. **Waiver of written documentation** that informed consent was obtained. With this waiver, the investigator would be required to read or provide the informed consent form to a participant, but would not need to obtain the participant's signature on the consent form. Examples of when this waiver might be applicable would be some internet or phone surveys or when signing the form might have some negative consequence for the participant. It must be emphasized that these waivers will be given only when there are compelling reasons for doing so.

The Ethics and Research Committee determines which type of consent applies to your research, but please indicate the type that you are requesting.

☐ **Waiver or alteration of the informed consent process.** *(Complete Section I)*

☐ **Request for waiver of parental permission.** *(Complete Section II)*

☐ **Waiver of written documentation of consent.** *(Complete Section III)*

I. Request for waiver or alteration of the consent process (Not required for Exempt studies)

I believe that this protocol is eligible for waiver or alteration of required elements of the informed consent process because the protocol meets all of the following criteria: (Provide protocol-specific supporting information for each criterion that justifies the findings for the following :)

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1. The research presents no more than 'minimal risk' of harm to participants.

It's a retrospective study that focusses on collected and analysis of secondary data from the VITEK-2 systems and patients medical records. No harm is expected.

2. The waiver or alteration will not adversely affect the rights and welfare of the participants.

The study is guided by ethical principles and safe guards to ensure confidentiality such as limiting access to retrieved data using passwords are in place.

3. The research could not practicably be carried out without the waiver or alteration.

Given the time frame and nature of the study it s impractical to obtain informed consent from the study participants. The study is interested in participants who are already discharge or have died in the course of care.

4. Whenever appropriate, the participants will be provided with additional pertinent information after participation.

The study is descriptive rather than investigational in nature. As such no new information is expected to arise that is key to the subject's well-being or otherwise. But as much as its practical, additional pertinent information shall be provided if need be to the study participants.

5. Elements of informed consent for which a waiver or alteration is requested and the rationale for each:

Being a retrospective study, there will be no direct contact with the study subjects all of whom are will not be at the facility due to discharge or death. This study poses minimal risks to the participants.

Confidentiality issues will be addressed by minimizing access to the retrieved data to the study personnel including the statistician. There will no disclosure of subject identifying information.

Voluntariness and Autonomy:-since the study aims at looking for outcomes of a disease state mainly discharge or mortality tracking the study participants will not be logistically possible.

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The study focusses on non pediatric study participants admitted at Kenyatta National Hospital main ICU it will not involve non viable neonates.

7. The research is not subject to FDA and/or national research regulation:

Not applicable.

II. **Request for waiver of parental permission** (Not required for Exempt studies)

I believe that this protocol is eligible for waiver of parental permission because the protocol meets all of the following criteria: (Provide protocol-specific supporting information for each criterion that justifies the findings for one of the following two options)

Option 1

1. The research presents no more than "minimal risk" of harm to participants.

2. The waiver or alteration will not adversely affect the rights and welfare of the participants.

3. The research could not practicably be carried out without the waiver or alteration

4. Whenever appropriate, the participants will be provided with additional pertinent information after participation.

5. Elements of informed consent for which a waiver or alteration is requested and the rationale for each:

6. The research does not involve non-viable neonates:

7. The research is not subject to FDA and/or national research regulation:

1. The research protocol is designed for conditions or for a participant population for which parental or guardian permission is not a reasonable requirement to protect the participants (for example, neglected or abused children)

_____

_____

2. An appropriate mechanism for protecting the children who will participate as participant in the research will be substituted

_____

_____

3. The research is not subject to FDA and/or national research regulation:

_____

_____

4. The waiver is consistent with international and national law:

_____

_____

III. Request for waiver of written documentation of consent (Not required for Exempt studies and not required when the consent process is waived.)

I believe that this protocol is eligible for a waiver of written documentation of informed consent because the protocol meets one of the following criteria: (Provide protocol-specific supporting information for each criterion that justifies the findings for one of the following two options :) **(NOTE: Even when documentation of informed consent is waived, the investigator is required to give participants full consent information, and to obtain their voluntary consent orally.)**

Option 1

(Example: Conducting interviews with street children engaged in drug abuse. The only record of the name or other identifying information of the participants would be the signed consent form and knowledge of an individual's participation or information provided could lead to potential legal, social, or physical harm.)

Explain:

1. The only record linking the participant and the research would be the consent document.

2. The principle risk would be potential harm resulting from breach of confidentiality.

3. Each participant will be asked whether the subject wants documentation linking the participant with the research and the participant's wishes will govern.

4. The research is not subject to FDA and / national research regulation.

Option 2

(Example: Using an anonymous survey consent or conducting telephone interviews with politicians about how constitutional provision for funding of political parties will affecting the campaign process of smaller parties

1. The research presents no more than minimal risk of harm to participants.

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}

2. The research involves no procedures for which written consent is normally required outside of the research context.

_____

_____

Approval (KNH-UoN ERC Chairperson: Check all that apply to indicate that the waiver or alteration is approved and to indicate agreement with the investigators protocol specific findings justifying the waiver.)

☐ Waiver or Alteration of the Consent Process

☐ Waiver of parental permission

☐ Waiver of Written Documentation of Consent

NOTE: To approve a waiver of written documentation of informed consent the investigator must provide a written document describing the information to be disclosed. This document has to include all required and appropriate additional elements of consent disclosure, unless the consent process has been altered.

Chose one of the following when approving a waiver of written documentation:

☐ The investigator must provide a written description of the information provided orally to the participant.

☐ The investigator does not have to provide a written description of the information provided orally to the participant.

APPROVED BY CHAIR KNH-UoN ERC:

Name: _____ Signature _____

KENYATTA NATIONAL HOSPITAL APPROVED 05 FEB 2018 KNH/UoN-ERC P373/23-00202 NRB

Date and Stamp: _____

KENYATTA NATIONAL HOSPITAL
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OFFICE OF THE HEAD OF DEPARTMENT – HEALTH INFORMATION

Ref: KNH/HI/50/VOL. 1 Date: Monday, January 15th, 2018

Secretary
KNH-UON ERC

RE: AUTHORITY TO ACCESS MEDICAL RECORDS
Research Proposal: Klebsiella Pneumoniae Resistance at Kenyatta National Hospital-ICU (P630/11/2017)

Reference is made to your letter ref KNH-ERC/RR/806 dated 19/12/ 2017 item No. 6 on the above subject.

This is inform you that authority to access medical records will be granted to the researcher (Mr. Herbert Netia) upon presenting the ERC approval and fulfilling other hospital requirements.

Margaret Mbugua
FOR: HOD- HEALTH INFORMATION

Kenyatta National Hospital

OFFICE OF THE HEAD OF DEPARTMENT – LABORATORY MEDICINE

"Email: laboratoryknh@gmail.com" - Exten: 44121

Ref: KNH/DLM/60/VOL./232

Date: 16th January, 2018

Herbert Netia Chitere
Institute of Tropical and Infectious Diseases
College of Health Sciences
University of Nairobi

Mobile No.0726064506

Dear Herbert

RE: Consent for release of Laboratory Data for a Research Study

Refer to your letter dated 12th January, 2018.

The department has given consent for the release of laboratory data from the VITEK-2 System for your study entitled **"Klebsiella pneumonia resistance trend at Kenyatta National Hospital ICU from September 2013-September 2017 (P630/11/2017)"**. As a researcher, you are advised to follow the Department of Laboratory Medicine regulations for conducting research and ensure compliance.

Kindly liaise with the in-charge of Microbiology Section for further assistance and facilitation.

Yours sincerely,

Dr A.K. Gachii
HOD – LABORATORY MEDICINE

CC:
HOD- Research and Programs
I/C Microbiology Laboratory Section

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Ref: KNH-ERC/A/49

5th February, 2018

Herbert Netia Chitere
Reg. No.W64/80481/2015
Institute of Tropical and Infectious Diseases (UNITID)
College of Health Sciences
University of Nairobi

Dear Herbert

Research proposal : "*Klebsiella pneumoniae* Resistance Trend at Kenyatta National Hospital ICU from September 2013 - September 2017 (P630/11/2017)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above revised proposal. The approval period is from 5th February 2018 – 4th February 2019.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

turnitin Turnitin Originality Report

Klebsiella pneumoniae Resistance Trend at Kenyatta NationalHospital ICU from September 2013 to August 2017 by Herbert Chitere

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