Antimicrobial Susceptibility Patterns of Bacterial Isolates from Patients in Medical Wards at Kenyatta National Hospital in 2015-2016

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LIST OF ABBREVIATIONS

AKUHN	Aga Khan University Hospital Nairobi
ASP	Antibiotic Stewardship Program
AST	Antimicrobial Susceptibility Testing
CDC	Centers for Disease Control and Prevention (United States)
CDDEP	Center for Disease Dynamics, Economics & Policy
CI	Confidence Interval
CLSI	Clinical and Laboratory Standards Institute
CoNS	Coagulase-negative staphylococcus
CRE	Carbapenem-resistant Enterobacteriaceae
EPEC	Enteropathogenic *Escherichia coli*
ESBL	Extended-spectrum beta-lactamase
GARP	Global Antibiotic Resistance Partnership
HIV	Human Immunodeficiency Virus
KNH	Kenyatta National Hospital
MRSA	Methicillin-resistant Staphylococcus aureus
SPSS	Statistical Package for the Social Sciences
UoN	University of Nairobi
USA	United States of America
WHO	World Health Organisation

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ABSTRACT

BACKGROUND

There is worldwide concern of rapidly increasing antimicrobial resistance (AMR). However, there is paucity of resistance surveillance data and updated antibiograms in Kenya. This study was undertaken in Kenyatta National Hospital (KNH) to help bridge existing AMR knowledge and practice gaps. This would contribute towards best clinical practice with eventual patient and cost benefits.

OBJECTIVES

1. To document the antimicrobial susceptibility of bacterial isolates in culture specimens obtained from KNH medical wards in a 1-year retrospective review.
2. To describe the antimicrobial susceptibility of bacterial isolates in culture specimens of KNH medical ward inpatients with clinical profiles prospectively over a 3-month period.

METHODS

A retrospective review of laboratory records capturing antimicrobial susceptibility data for the year 2015 was done, and augmented with a prospective cross-sectional descriptive study of medical ward inpatients over 3 months in 2016 to obtain relevant clinical correlates. Data was analysed using WHONET and SPSS version 20.

RESULTS

Retrospective arm

Analysis of 823 isolates revealed AMR rates higher than most recent local and international reports. Eighty-eight percent (88%) of isolates tested were multi-drug resistant (MDR) whereas 26% were extensively-drug resistant (XDR). The critical World Health Organization antibiotic-resistant 'priority pathogens' claimed majority of the resistance burden, with resistant Gram negative enterobacteriaceae surpassing Gram positive bacteria.

Prospective arm

The antimicrobial susceptibility patterns were similar to those in the retrospective arm. Fifty-one percent of patients were empirically treated with cephalosporins yet we documented overwhelming cephalosporin resistance rates, such as ceftriaxone resistance of 82%. Uninformed clinician prescription practices and misuse of antibiotics could possibly be a key driver of AMR leading to increased morbidity and mortality.

CONCLUSION

There is overwhelming resistance to commonly used antibiotics, underscoring the need for antimicrobial stewardship programmes including guided empirical therapy and restricted prescription of reserve antibiotics following culture and sensitivity testing.

1. INTRODUCTION

Antibiotics have for a long time been regarded as the "panacea to cure infections" ever since the discovery of Penicillin by Alexander Fleming(1). With outstanding foresight he predicted that bacteria would soon exhibit resistance to these wonder-drugs. He was right. Over 70 years after Fleming delivered his Nobel Prize speech in 1945, one of the pivotal topical issues faced by the global community is antibiotic resistance. Dr Kejji Fukuda, WHO's Assistant Director-General for Health Security already warned in a press release in 2014, "Without urgent, coordinated action by many stakeholders, the world is headed for a post-antibiotic era, in which common infections and minor injuries which have been treatable for decades will again kill"(2).

Global evidence in recent years has revealed an overall downward spiral in antibiotic effectiveness, as resistance to first and last-resort antibiotics continues to increase. Although there is paucity of data on antibiotic resistance in Africa, there still exists a few local studies that have been done(1,3). From these, it is certain that antibiotic resistance is on the rise in Kenya, however the exact figures or current rates of increasing resistance remain unclear, due to lack of systematic national surveillance(3). As a result, there is a pertinent need to fill the information gap on resistance that exists in our local healthcare facilities.

This study was based in Kenyatta National Hospital (KNH), situated in Nairobi, Kenya. According to the 2006 WHO mortality report, the top five causes of death in Kenya are all infectious diseases, and yet data documenting the proportion attributable to bacterial agents is not collected systematically(3). Being the largest tertiary referral centre in East & Central Africa, KNH thus bears a large morbidity and mortality burden attributable to infections. Therefore there is a need to establish clear-cut guidelines on appropriate antimicrobial therapy for these patients to improve patient care and outcomes. These guidelines can only be arrived at following synthesis of local antimicrobial susceptibility data; hence the timely need to evaluate antibiotic sensitivity and resistance patterns in our setting. They will significantly contribute towards increasing the levels of awareness concerning our local population, as we seek to join efforts with the rest of the world in preventing the arrival of the impending global "post-antibiotic era".

2. LITERATURE REVIEW

2.1. ANTIBIOTIC RESISTANCE

Globally, the role of antibiotics in recent decades has increasingly become widespread, from initially curing simple infections, to a host of other functions such as disease prophylaxis in both humans and animals, as well as promoting growth and well-being of animals. The immediate consequence of this widespread use is antibiotic resistance. Antibiotic resistance is "the result of bacteria changing in ways that reduce or eliminate the effectiveness of antibiotics" and is estimated to contribute to more than 2 million infections and 23,000 deaths annually in the United States alone, according to the U.S. Centers for Disease Control and Prevention (CDC). This translates to a direct cost of $20 billion and additional productivity losses of $35 billion(6). A similar scenario is reflected in Europe, which registers approximately 25,000 deaths yearly and costs to the tune of €1.5 billion annually, all attributable to infections with antibiotic resistance(7). There is a great knowledge gap in the developing world, as data on economic losses is not available. However there is scanty data in various countries in Africa, showing the morbidity and mortality burden of antibiotic-resistant infections. For example, these infections were noted to be a contributor to increased mortality in neonates with suspected neonatal sepsis in a Tanzanian study(8).

Worldwide there was been growth spurt in antibiotic consumption due to increased incomes and access to antibiotics. According to the State of the World's Antibiotics 2015 report by the Center for Disease Dynamics, Economics & Policy (CDDEP), the global use of antibiotics grew from an estimated 50 billion to 70 billion standard units between the years 2000 and 2010; and the greatest rise in consumption was noted to be in low and middle income countries(4). In these countries, approximately 80 percent of antibiotics are consumed by the community either over-the-counter or on a prescription basis, whereas the remainder 20 percent are used in healthcare facilities(5).

Apart from overconsumption and misuse of antibiotics, it has also been noted in our local setting that underuse through lack of access, inadequate dosing, poor drug compliance and substandard antibiotics may also contribute towards emergence of antibiotic resistance(3). The overall consequence of increased resistance is that infections that were once easily cured, are now increasingly posing a challenge to treat. This leads to increased expenses to healthcare facilities and rising mortality(4).

2.1.1. FACTORS CONTRIBUTING TO ANTIBIOTIC RESISTANCE

Healthcare provider factors

Inappropriate prescription of antibiotics occurs worldwide, as medical practitioners overprescribe antibiotics even without confirmed evidence of bacterial infection. Antibiotics tend to be prescribed for inappropriate indications, as is the example of viral respiratory tract illnesses. Such inappropriate practices tend to be driven by diagnostic uncertainty, lack of knowledge on appropriate prescription practices, patient demand, easy access over-the-counter supply, as well as scarce patient follow-up opportunities by these same healthcare providers(9).

Patient factors

Self-medication by patients plays a big role in spread of antibiotic resistance. This self-medication arising from inadequate access to formal healthcare promotes misuse, underdosing and poor compliance(3). Patients thus continue to purchase for themselves readily available drugs without prescriptions. In Kenya, the proportion of pharmacies dispensing antibiotics without a doctor's prescription is approximated to be 70 percent(10). Furthermore noncompliance with already prescribed medication occurs, as seen in erratic dose administration due to forgetfulness, negligence, affordability or even premature discontinuation once patients perceive relief. Patients are also likely to seek medical attention from multiple sources with various therapies prescribed. The above patient factors can be exemplified by a study in Vietnam where a low general knowledge and wrong use of antibiotics was associated with antibiotic resistance of the Enteropathogenic *Escherichia coli* (EPEC) strains isolated(11).

Hospital factors

By virtue of concentrating large numbers of infected individuals in a confined space, hospitals provide a fertile nidus for viable resistant bacterial populations. Moreover, these inpatient healthcare facilities are more likely to treat patients with frequent, intensive and prolonged antibiotic therapy than their outpatient counterparts(9). The resultant selective pressure placed on the micro-organisms makes these healthcare facilities an evolutionary breeding ground for these bacteria. Antibiotic resistance is significantly higher in tertiary and referral hospitals such as KNH. This is likely due to the high number of admissions, overcrowding, severity of illnesses encountered and inadequate infection prevention practices among healthcare workers in their interaction with patients and during instrumentation.

Patient-in-hospital factors

Antibiotic resistance tends to be highest in tertiary care/referral institutions. Various characteristics of the patient in the hospital setting driving resistance have been outlined(9). Hospitalized patients at greatest risk of becoming infected include those with extremes of age, with naturally impaired immunity. Others include patients with acquired immunodeficiency such as transplant and neutropenic patients, HIV, severe trauma or extensive burns. Use of instrumentation (indwelling medical devices) such as indwelling urethral catheters, dialysis catheters, central vascular catheters, endotracheal tubes provide a nidus for bacterial biofilm formation, development of antibiotic resistance (12) as well as their subsequent entry into sterile body sites such as the bloodstream. Ultimately, the highest burden of antimicrobial resistance is borne by specialized units in which there is an interplay of severe morbidity among patients in close proximity, intensive therapy and multiple instrumentation. These include intensive care, burns and transplant units(9).

2.1.2. ANTIBIOTIC RESISTANCE SITUATIONAL ANALYSIS

EPIDEMIOLOGY, HEALTH AND ECONOMIC FACTORS

In efforts to bridge the knowledge gap in Antimicrobial Susceptibility Testing (AST) data and thereby global antibiotic resistance, the World Health Organisation (WHO) in a 2014 report outlined *Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus* as the three major bacterial agents of public health importance and international concern forming majority of hospital and community acquired infections(1). They pose the greatest health and economic burden of antibiotic resistance, and are elucidated further below.

2.1.2.1. Escherichia coli

E. coli is a member of the family enterobacteriacae and it is the most significant species in the genus *Escherichia.* Being part of the normal flora in human and animal intestines, *E. coli* is world-renown as a causative agent of urinary tract infections, bloodstream infections, skin and soft tissue infections, as well as intra-abdominal infections. A recent systematic review undertaken by the WHO outlines significant health outcomes associated with resistant *E. coli* infections globally. These can be summarized as a twofold increase in all-cause mortality, bacterium-attributable mortality and in 30-day mortality(1). Furthermore, this report discussed a twofold risk increase in

ICU admission as a result of fluoroquinolone resistant *E. coli*, as well as a significant increase in septic shock. This shows that *E. coli* has a significant morbidity severity burden, in addition to mortality. On the other hand, an economic impact analysis performed in the WHO systematic review revealed a higher rate of ICU admission thus involving more healthcare resources required to treat the complications such as septic shock, including additional antimicrobial therapy costs, arising from these drug-resistant infections(13,14).

Escherichia coli resistance to fluoroquinolones and third-generation cephalosporins has been quoted as high as more than 50 percent in five of the six WHO regions(1). Fluoroquinolone resistance is acquired through mutations. On the other hand, resistance to penicillins and cephalosporins is conferred by extended-spectrum beta-lactamases (ESBLs) which are enzymes also known to inactivate penicillins, cephalosporins and monobactams.

The median prevalence of *E. coli* resistance to third generation cephalosphorins in Subsaharan Africa ranges from 0 to 47 percent(16). In East Africa, ESBLs were identified in 38-63% of a Kenyan hospital's samples and 6% of community samples(17). WHO 2014 estimates about 60% resistance to cephalosporin in incomplete data surveillance in 2012, (1) whereas a publication in a Kenyan private tertiary hospital realized 87% resistance to cephalosporins in 2007 to 2009 (18). The Department of Pathology in this same facility released an updated 'Antibiotic Susceptibility Report 2015' for data through 2014 showing 49% *E. coli* resistance to third-generation cephalosporins among hospital inpatients(19,20).

According to the WHO 2014 report, Kenyan national data is inadequate as far as *E. coli* resistance to fluoroquinolones is concerned. However, literature from a Kenyan private tertiary hospital revealed 92.7% *E. coli* resistance to ciprofloxacin and 90% resistance to Levofloxacin when testing 109 isolates between the period 2007-2009 (18). For this same hospital, antibiotic susceptibility testing in the year 2014 showed 57% *E. coli* resistance to Ciprofloxacin(19,20). This is comparable to results from a study performed in the year 2013 at the largest public tertiary healthcare facility, Kenyatta National Hospital (KNH) which showed 54.5% fluoroquinolone-resistant *E. coli* isolated from pus specimen samples(21). These statistics may bear implications on choice of empiric antibiotic therapy for urinary tract infections in our local setting, which tends to lean heavily on the fluoroquinolones. Ultimately, there is a need for more studies and antibiogram data to inform the practice of evidence-based medicine.

2.1.2.2. Klebsiella pneumoniae

In Africa, the most commonly reported Gram negative bacteria pathogen is *K. pneumoniae*. It constitutes almost 50% of all Gram-negative neonatal infections(22). *K. pneumoniae* is often found as a commensal in the human gut, like its counterpart *E. coli*. Breaches into other body sites make it a pathogen of important concern, especially in urinary and respiratory tract disorders, and in neonates, bloodstream infections. This pathogen is a key player in healthcare associated infections. It is easily transmitted between patients, thus nosocomial outbreaks are common especially in acute settings such as intensive care units and neonatal facilities. Other vulnerable populations include those who are immunosuppressed, such as those with comorbidities like diabetes and alcoholics(1).

The health burden of resistant *K. pneumoniae* infections has been studied in different centres across the globe. A WHO systematic review has shown a significant increase in mortality, be it all-cause, bacterium-attributable and 30-day as well as increase in ICU admissions and post-infection length of stay in hospital. The studies reviewed did not indicate associated progression to septic shock. On the other hand, the economic burden of resistant *K. pneumoniae* using relevant surrogates of excess cost showed numerically longer length of stay in hospital and intensive care units, however statistical significance was not achieved. However, a USA study which pooled *K. pneumoniae* and *E. coli* with other Gram-negative bacteria revealed an average of US$38,121 higher hospital costs than that realised in treating susceptible infections(23).

K. pneumoniae resistance to cephalosporins and penicillins is facilitated by ESBLs which are genetically encoded into a resistance gene. Thus *K. pneumoniae* resistance is acquired primarily via horizontal transfer of genetic elements such as transposons or plasmids. Apart from extended spectrum penicillins and cephalosporins, these bacteria are also noted to have inactivity against fluoroquinolones, and even more recently, the carbapenems.

K. pneumoniae resistance to third-generation cephalosporins has been reported to be more than 30 percent in most WHO member states, and in some regions this may be higher than 60 percent. National data reported from 13 African countries shows *K. pneumoniae* resistance to cephalosporins ranging from 8 – 77% (1). Kenyan national data is currently unavailable as per the WHO 2014 report. However an Antibiotic Susceptibility Report released by a Kenyan private tertiary hospital in 2014 noted 61% resistance to third-generation cephalosporin ceftriaxone, in 77

confirmed tested isolates (19,20). Another study done in KNH in 2013 testing pus culture isolates revealed 75.9% *K. pneumoniae* resistance to ceftriaxone (21). Some national data in neighbouring Uganda reported about 50% resistance in four tested isolates. A more comprehensive analysis in South Africa revealed 77% resistance among 923 blood culture isolates in the year 2012 (1).

Carbapenems are often the last-resort antibiotics employed in the treatment of severe resistant infections, and these drugs form the mainstay of antibiotic reserve avoided in first-line treatment where possible. Emerging incidence of resistance to carbapenems is on the rise worldwide, which is a cause for morbidity and mortality alarm for clinicians treating resistant infections. Carbapenem resistance is conferred by carbapenemases, thus the term Carbapenem Resistant Enterobacteriaceae (CRE), which is increasingly reported especially in developed countries(24). Presence of CRE is also rising in the developing world. The WHO 2014 report acknowledges substantial gaps in information on *K. pneumoniae* resistance to carbapenems worldwide. Most of the data available is from the region of the Americas and Europe, with reports of more than 50% noted in two WHO regions. In East Africa, national data is currently unavailable for *K. pneumoniae* resistance to carbapenems. However a study by Otieno reporting antibiotic susceptibility testing of blood culture isolates, as carried out in patients with sepsis presenting to the Accident and Emergency department of KNH in 2015, showed that all the carbapenems tested showed excellent efficacy against the entire gram negative and a majority of gram positive bacteria (25). Meanwhile an analysis of pus samples in KNH across the whole hospital for the year 2013 revealed *K. pneumoniae* resistance of 9.5% to meropenem(21). Another study published in 2013 reporting ESBL resistance patterns in a Kenyan private tertiary hospital noted 0.6% resistance to meropenem(18). An Antimicrobial Susceptibility Report for the year 2014 in the same facility documented 8% resistance to meropenem in 77 isolates from inpatient admissions (19). These low rates are similar to WHO 2014 estimates in South Africa which showed 1% resistance to meropenem and 3.8% resistance to ertapenem in an analysis of 923 blood culture isolates in 2012 (1). On the other hand as previously stated, carbapenem resistance is increasingly reported in developed countries, for example the United States of America which whose national data showed 11% resistance to carbapenems in health-care associated infections in the year 2009-2010, among 7932 tested isolates(1). Just as in the case of *E. coli*, there is a conspicuous knowledge gap in *K. pneumoniae* resistance patterns locally, as data in the developing world is greatly wanting.

2.1.2.3. Staphylococcus aureus

This Gram positive bacterium forms part of the normal flora on the skin, and has also been found in the nasopharyngeal tract. It has been widely studied internationally for its pathogenic role in skin and soft tissue infections, being the most common cause of postoperative wound infections. It features prominently as well in bloodstream, bone and respiratory tract infections. Initially susceptible to the Penicillin discovered by Alexander Fleming, *Staphylococcus aureus* began to develop resistance as early as the 1940s via the beta lactamase enzyme. This led to the development of drugs inactive to beta lactamase action, such as methicillin, as well as drug combinations with beta lactamase inhibitors such as clavulanic acid. Continual evolution of *S. aureus* through acquisition of a resistance gene (*mecA*) has led to methicillin-resistant Staphylococcus aureus (MRSA) which first emerged during the 1960s. This strain has grown to be an alarming pathogen in as high as 90 percent of all *S. aureus* hospital-acquired isolates and more recently, as high as 80 percent of *S. aureus* community-acquired isolates(4). This makes *S. aureus* a pathogen of international concern, being a major cause of hospital-acquired and community acquired infections.

The health burden attributable to *S. aureus* has been summarised in the WHO 2014 report as significant increased all-cause, bacterium-attributable and ICU mortality; as well as post-infection and ICU length of stay. Further morbidity impact is seen in increased associated septic shock and higher rates of discharge to long-term care, as opposed to Methicillin-susceptible counterparts. The economic impact of MRSA measured through resource-use outcomes showed a longer duration of hospital and ICU length of stay, greater proportion of discharges to long-term healthcare facilities, thus implying higher resources utilization in treatment in the acute setting and long term.

Globally MRSA is reported to have exceeded resistance rates of 20 percent in all WHO regions, and above 80 percent in some regions(1). National data from 9 African countries shows MRSA resistance rates to approximate between 12-80%. Fortunately, MRSA prevalence has been noted to be on a declining trend, as seen in Europe from 22 to 18 percent and in the United States from 53 to 44 percent(4). This has also been reflected locally in sub-Saharan Africa, as seen in the decline from 34 to 28 percent in South Africa since 2011 (4,26). According to the WHO 2014 report, there was no Kenyan national data available. However this report mentioned a Kenyan

publication which registered 20% resistance in 207 isolates from surgical site infections in 2012. A notable number of Kenyan publications reporting MRSA rates are in literature. A fairly recent one included isolates from two Kenyan private hospitals tested between the years 2011 to 2013, which reported Methicillin-resistance of 3.7% (27). An Antimicrobial Susceptibility Report in a private tertiary hospital for the year 2014 revealed MRSA prevalence of 6% among 271 isolates(19,20). In contrast, a study conducted in KNH in 2014 among paediatric surgical patients with wound sepsis primarily isolated *S. aureus*, which showed 50.6% resistance to Oxacillin (a Methicillin testing surrogate) in 79 isolates, thus considered MRSA(28). A more recent study by Mogere performed on MRSA carriage among KNH healthcare workers in the year 2015 showed a resistance rate of 18.9% among 180 isolates(29). Due to its contribution to health and economic outcomes on a global scale, there is a need for collection of updated data on MRSA resistance and its surveillance.

2.1.3. COMBATING ANTIBIOTIC RESISTANCE

Over the last few years, there has been pressure mounted on the antibiotic pipeline with incentives for new antibiotics to be developed by manufacturers, in efforts to wage war against bacterial infections. It was initially thought that the fight against antibiotic resistance would be to innovate new antibiotic drugs, which would continue to cure bacterial infections and retard the arrival of the post-antibiotic era. Despite widely cited analyses which suddenly raised the alarm globally because they portrayed an almost "empty pipeline"(30) there remains contrary evidence to show reasonable production of new antibiotics in the last 30 years(31). For example, seven new antibiotics were approved in 2014 whereas about 37 new antibiotics were in the development pipeline for approval by the end of that same year(4). It is interesting to note that many of the new antibiotics approved in the last few years have been withdrawn as they have failed to meet the needs in the market. The pitfall that exists in reliance on new drugs to maintain the global reserve of antibiotic effectiveness is that they are expensive and highly inaccessible, especially in the developing middle and lower-income countries which bear a high burden of infectious diseases(32). The question hereby still remains- *how can we best combat antibiotic resistance, particularly in our resource-constrained part of the world where the threat is most imminent?*

In cognizance of the health and economic implications of global antibiotic resistance, the World Health Assembly in May 2015 recently sanctioned the Global Action Plan on Antimicrobial

Resistance. This resolution recommends national policies on antibiotics to be undertaken by all countries through various modes of stewardship, to conserve antibiotic effectiveness(1). The Center for Disease Dynamics, Economics and Policy (CDDEP) has taken the mantle of gathering data worldwide on antibiotic consumption and resistance, through The Global Antibiotic Resistance Partnership (GARP). This work of GARP extends from developed to developing countries, including Kenya (The GARP-Kenya Working Group), to "establish the capacity and methods for developing antibiotic resistance policies" as stated in the State of the World's Antibiotics 2015 report(4). Antibiotic stewardship programmes form an essential component of resistance prevention policies. They have been noted to reduce inappropriate prescription practices and confer economic benefits due to shorter treatment periods and less hospital costs(33). For example, a reduction in consumption of antibiotics in critical care units by 11 to 38 percent, and lower costs by $5 to $10 per patient per day has been described in a study undertaken in nine countries(34). Moreover, health benefits of ASPs exist, including a reduction in healthcare associated infections(35). A systematic review on the impact of antimicrobial stewardship in critical care has highlighted a reduction in antibiotic resistance especially for Gram-negative bacilli (34) which contribute a significant burden, in infections treated in these acute settings.

2.1.3.1. Local strategies in combating antimicrobial resistance

The Kenyan government has instituted some policies including vaccination programmes, national hospital infection control guidelines and support of individual efforts in antibiotic resistance surveillance pertaining to humans and livestock. However systematic and up-to-date national surveillance programmes are yet to be fully actualised. On the other hand, local efforts exist on a smaller scale, by non-governmental organisations and various inter-sectoral collaborative partnerships which include facility-level reporting on resistance trends and patterns by entities such as the CDC, KEMRI, CDDEP and facilities such as the Aga Khan University Hospital Nairobi (AKUHN) (3).

Notably, the GARP-Kenya Working Group released a document in the year 2011 involving public and private health sectors detailing a situational analysis and recommendations on antibiotic use and resistance in Kenya. Whereas due credit was given to the Kenyan government's efforts in establishing good management protocols and instituting infection control and medicine and therapeutic committees in hospitals, it was noted that none comprehensively tackled the

fundamental drivers of resistance including inappropriate antibiotic use. Two approaches to tackling these drivers and slowing down resistance are reducing need for and better targeting of antibiotics, in order to reduce the demand for these drugs. In order to achieve this, some of the relevant policy actions outlined include surveillance and monitoring, as well as training and education. Knowledge of the levels and trends of resistance contributes to formation of effective policies and interventions to tackle resistance, promoting behaviour change in antibiotic use, as well as reduction in morbidity, mortality and cost implications attributable to resistant bacteria(3).

2.1.4. THE NEED FOR AN ANTIBIOGRAM

A key component of both resistance surveillance and antibiotic stewardship programs entails "documenting the antibiotic situation and context" (4) as has been exemplified by GARP's recommendations. This includes collection, analysis and dissemination of antimicrobial susceptibility data in healthcare facilities, and application of this information towards creating antibiotic policies. This data exists in an antibiogram, which is defined by the Clinical and Laboratory Standards Institute (CLSI) as the "overall profile of antimicrobial susceptibility results of a microbial species to a battery of antimicrobial agents"(36). As far as a local healthcare facility is concerned, the hospital antibiogram is a "periodic summary of antimicrobial susceptibilities of local bacterial isolates submitted to the hospital's clinical microbiology laboratory" (37).

In 2002, the Centers for Disease Control and Prevention (CDC) instituted the "Campaign to Prevent Antimicrobial Resistance" which highlighted four main strategies: preventing infection, diagnosing and treating infection effectively, using antimicrobials wisely, and preventing transmission(9). These actionable steps are all aimed at motivating a shift in clinician practices in order to prevent resistance. A report undertaken by the CDC Campaign to Prevent Antimicrobial Resistance Team years later analysed data from 9 research projects involving 695 clinicians. A majority of these participants agreed that of the Campaign's four strategies, "Diagnose and Treat Infection Effectively" and "Use Antimicrobials Wisely" were deemed to be the most important than the rest(38). One of the steps under the "Diagnose and Treat Infection Effectively" strategy is to target the pathogen causing infection. This involves obtaining patient specimen cultures, targeting empiric therapy to likely pathogens and local antibiogram, and targeting definitive therapy to known pathogens and antimicrobial susceptibility test results. On the other hand, part of the "Use Antimicrobials Wisely" strategy involves using local data. This entails clinicians

knowing their local antibiogram and patient population. This is because the prevalence of resistance can vary by locale, patient population, hospital unit, and length of stay.

It can therefore be seen that a hospital antibiogram overall plays a major role towards combating antimicrobial resistance (AMR). CDC highlighted two functions of the antibiogram as an integral part of antimicrobial stewardship: tracking AMR and regular dissemination of antibiotic resistance data to hospital staff(39). The antibiogram serves to reflect the needs of patient care and forms the basis of a hospital's formulary, improving policy decisions and empirical treatment guidelines(40) in the absence of patient-specific culture results, or where they may be awaited. In this way, prescription of antibiotics is restricted to address the likely pathogen and their probable susceptibility patterns, with an overall effect of reducing chances of future resistance. When selecting optimal empiric therapy, it is recommended that the clinician considers the hospital antibiogram in concert with patient factors (including type of infection, organism, past medical history and past antibiotic use) (37). This selection ought to be based on accurate and reliable antibiogram data that is updated on an annual basis, if possible(36). Unfortunately, this data in many local scenarios is scarce and wanting, especially in developing countries. In studies involving small hospitals, the lack of antibiogram preparation is attributed to resource constraints, or sending of cultures to external laboratories(41). In Kenyan literature, paucity of data has been attributed to underdeveloped microbiological surveillance services(42). It thereby follows that there is an overwhelming need for more studies looking into antimicrobial susceptibility patterns in our local patient population. This will have a bearing on clinician practice as noted in a study on nosocomial infections at KNH Intensive Care Unit by Ngumi Z. who recognized the need to have an antibiotic policy "strengthened by culture and sensitivity results for effective treatment of patients"(43).

In efforts to standardize preparation and assimilation of antibiogram data, the CLSI consensus group published the M39-A document detailing collection, analysis and presentation of cumulative antimicrobial susceptibility test data. This aims to direct clinicians in the appropriate selection of empirical antibiotics(44).

According to CLSI, the following should be considered during antibiogram preparation: (45)

i. A cumulative antibiogram report should be analysed and presented at least annually
ii. Only final, verified test results should be included.
iii. Only species with testing data for more than 30 isolates should be included.

iv. Only diagnostic (not surveillance) isolates ought to be included.
v. Eliminate duplicates by including only the first isolate of a species per patient per analysis period, irrespective of body site or antimicrobial susceptibility profile
vi. Include only antimicrobial agents routinely tested and calculate the percent susceptible (%S) from results reported
vii. Report the %S and do not include the percent intermediate (%I) in the statistic

2.1.4.1. Problem Statement

Antimicrobial susceptibility reporting as well as resistance surveillance is not systematically conducted in Kenya. Furthermore, many microbiology laboratories in the country are challenged by lack of quality control, inadequate supervision and unreliable agents(3). As a consequence, lack of accurate and timely laboratory diagnoses of infectious diseases leads to a compromise in clinical care(20). Up until the end of the year 2015, there has not been any existing system of regular and updated antibiogram reporting by the KNH. There is a need for continual antibiotic surveillance as exists in other healthcare facilities both locally and in the international arena. As noted earlier, important knowledge gaps in antimicrobial resistance as well as practice gaps in antibiotic stewardship can be bridged by antibiogram reporting. This will confer manifold benefits – health, economic among others– to the patient and the hospital at large as described earlier.

It is important to note that previous antimicrobial susceptibility studies in KNH have been within a limited scope**:** either confined to specific hospital wards or units, or to specific patient specimen types, or to a short duration of time. As a result, the data reported in many of these studies is scanty, with less than 30 isolates per species which falls below the international CLSI guidelines(45). This information is not entirely generalizable so as to influence antibiotic policy making. This underscores the need for more comprehensive antimicrobial susceptibility studies reporting on hospital-wide data, to aid in antibiotic stewardship and combating antibiotic resistance in our setting. The following table highlights previous studies:

Table 1: Recent studies in KNH investigating antimicrobial susceptibility of bacterial isolates

AUTHOR	YEAR	STUDY FOCUS	STUDY DESIGN	SPECIMEN TYPE	ISOLATES
Mogere	2015	Nasal carriage among healthcare workers	Prospective	Nasal swabs, Hand swabs	180
Otieno	2015	Sepsis in Accident & Emergency patients	Prospective	Blood	20
Elamenya	2014	Wounds in Paediatric surgical patients	Prospective	Pus	137
Ratemo	2013	Pus isolates in whole hospital	Retrospective	Pus	518
Bwisa	2013	Bacterial isolates from Sterile sites from whole hospital	Retrospective	CSF, Blood, Peritoneal fluid, Pleural fluid, Synovial fluid	63
Kinyua	2013	Wound infections in burnt patients	Prospective	Pus	81
Njiru	2012	Enterobacteriace isolates from whole hospital	Retrospective	Urine	365
Karimi	2008	Wound infections in orthopaedic units	Prospective	Pus	167
Maigacho	2007	Central Venous Catheter infections in ICU	Prospective	Blood	12
Ngigi	2006	Haemodialysis catheter infections	Prospective	Pus	57
Inyama	2006	Urinary tract infection in ICU	Prospective	Urine	22
Ngumi	2005	Nosocomial infections in ICU	Retrospective & Prospective	Tracheal aspirate, Urine, Pus, Blood, Stool	109
Muthurania	1999	MRSA in KNH	Retrospective	Pus, throat swab, blood	327
Omari et al	1991-1995	Bacterial infections among KNH inpatients	Retrospective	Urine, pus swabs, blood, stool, CSF	7416

3. STUDY JUSTIFICATION

The main justification of this study lies in its contribution towards efforts to combat antibiotic resistance, by providing baseline information of this problem in question. There is an emerging worldwide concern of rapidly increasing antibiotic resistance, from first-line to last-resort drugs. There is therefore an overwhelming need for appropriate antibiotic stewardship and surveillance programmes locally and at a global scale to protect our antibiotics reserve for our sake and that of generations to come. The scarcity of new effective antibiotics, especially in developing countries, underscores the importance of preserving the drugs currently in use.

Locally, the magnitude of the problem is accentuated since our healthcare systems are still developing, with higher morbidity and mortality rates due to infections as compared to Western counterparts. Moreover our knowledge gaps are wider as far as local antimicrobial susceptibility data is concerned. There is paucity of regularly updated antibiograms in many of our local facilities, and proper surveillance systems scarcely exist, even in Kenya's largest public healthcare facility, Kenyatta National Hospital (KNH). This frequently leads to uninformed clinician prescription choices of empiric antibiotic therapy, which are currently governed by external data, personal preference or availability of drugs within our local facilities. As a consequence, unchecked increase in indiscriminate antibiotic consumption promotes antibiotic resistance.

By describing antimicrobial susceptibility patterns in KNH, this study helped to fill existing knowledge and practice gaps relevant to the patient, clinician and the hospital. This would help to optimise patient care by treating bacterial infections using evidence-based informed practice, with numerous benefits accrued thereof. To the patient, this will be reflected as lesser morbidity and mortality rates. To the hospital, financial implications are evident, in terms of reduced cost of antibiotics used, as well as logistics involved in the better managed admissions. To the country, the economic benefits accrued from a healthier population cannot be overstated.

4. RESEARCH OBJECTIVES

4.1. BROAD OBJECTIVE:

To describe the antimicrobial susceptibility patterns of bacterial isolates from culture specimens of KNH medical ward inpatients.

5. RESEARCH QUESTION

What are the antimicrobial susceptibility patterns of bacterial isolates obtained from the medical wards in Kenyatta National Hospital?

5.1. SPECIFIC OBJECTIVES

I. To document the antimicrobial susceptibility of bacterial isolates in culture specimens obtained from KNH medical wards in a 1-year retrospective review from 1st January to 31st December 2015.

II. To describe the antimicrobial susceptibility of bacterial isolates in culture specimens of KNH medical ward inpatients with clinical profiles prospectively over a 3-month period from 15th September 2016 to 31st December 2016.

6. STUDY METHODOLOGY

6.1. STUDY DESIGN:

This was a hybrid study comprising a retrospective arm and a prospective cross-sectional descriptive arm. Data collection was done retrospectively using isolates previously cultured in the year 2015, and prospectively using samples that were collected within the last 3 months of the year 2016.

6.2. STUDY SETTING

Kenyatta National Hospital, situated in Nairobi, Kenya is the largest tertiary and referral centre in East & Central Africa with an estimated 1,800 beds(43). It registers approximately 89,000 admissions per year(46)**.** KNH has approximately 50 wards, 22 outpatient clinics and 24 surgical theatres. Of these, there are 8 adult medical wards with an average of about 60 patients per ward at any given time.

This study was based in the KNH Microbiology laboratory, which processed about 20,693 culture specimens in the year 2015. The study then focussed on the results of antimicrobial susceptibility testing (AST) on bacterial isolates cultured from medical ward inpatients.

6.3. STUDY DATA

Both the retrospective and prospective arms of this study focussed on antimicrobial susceptibility test results of bacterial isolates from laboratory culture specimens of patients admitted to the KNH medical wards. Additional clinical data in the prospective arm was derived from the patient files. These patients tend to be diverse, many of whose medical history involves interaction with other sectors of the hospital such as surgical, casualty and outpatient clinics. These clinics vary widely, encompassing specialties such as medical, diabetic, oncological, general and subspecialized surgical, among others.

In KNH, specimens submitted to the laboratory for culture are routinely collected at the clinicians' discretion, based on clinical suspicion of infection or as part of routine workup. By including the culture results of all specimens submitted from the medical wards, this study reflected a true representation of the medical inpatient population, and was not selective.

6.4. SAMPLE SIZE

Both the retrospective and prospective studies reported a census of all positive cultures that met the inclusion criteria. No sampling techniques were employed, but instead inclusion of all isolates available was done. The advantage of a census is that it provides a narrow confidence interval thus higher accuracy at a given confidence level. This augmented the strength of the study, by including all eligible specimen results as opposed to random selection sampling. This has been exemplified locally in Kenyan tertiary private hospitals which report annual antibiograms by including all positive cultures (20) in conformity to international standards and recommendations(45).

6.5. STUDY PROCEDURE

The unit of study was the isolate results of all positive cultures analysed in the KNH Microbiology laboratory for antimicrobial susceptibility testing. The study procedure involved collecting data in two arms, retrospective and prospective, in order to achieve the study objectives as follows:

SPECIFIC OBJECTIVE 1: a retrospective study of all bacterial isolates cultured from patient samples, with corresponding antimicrobial susceptibility data was done in order to report a 1-year antibiogram report (1st January to 31st December 2015) for the medical wards. Laboratory results of various culture specimen types with their bacteria isolates and corresponding antibiotic sensitivity and resistance patterns was documented.

SPECIFIC OBJECTIVE 2: a cross-sectional description of antimicrobial susceptibility data of all positive cultures from laboratory records with corresponding patient characteristics from inpatient files was done prospectively over a period of approximately 3 months (15th September to 31st December 2016). Through this, the investigator was able to describe appropriate patient demographic and clinical information relevant to antimicrobial susceptibility patterns, which could only be done prospectively. Once the positive culture results were reported in the laboratory, the respective patients were traced back to the wards and consent sought in order to recruit their culture results into the study, along with clinical information from their patient files. This was a non-invasive study with no active participation from the patients, as it only involved a review of existing records (from laboratory and patient files). The research participants (medical ward inpatients) did not carry out any activities and any interaction with them was limited to obtaining

consent for extracting relevant data from their existing records. No personal identifiers were captured, in order to preserve patient privacy and integrity.

6.6. RECORDS SELECTION

6.6.1. Inclusion criteria:

- KNH microbiology laboratory records of all pathogenic bacterial isolates from culture specimens obtained from patients admitted to the medical wards from 1st January 2015 to 31st December 2015, and 15th September 2016 to 31st December 2016.
- The first bacterial isolate of a given species per patient per inpatient admission period, in order to minimise duplication.

6.6.2. Exclusion criteria:

- KNH Microbiology laboratory records and hospital inpatient records with incomplete data (for example antimicrobial sensitivity test results) or any instances of mismatched information (such as patient details).
- KNH inpatient records of patients who declined consent to use their information.

6.7. DEFINITION OF STUDY VARIABLES

Factors contributing to antibiotic resistance are numerous and vary in terms of patient, clinician and hospital factors as earlier mentioned. This study described relevant patient characteristics obtained from their hospital records.

6.7.1. Dependent Variables

The following was reported in both the retrospective and prospective arms of the study:

- Bacteria isolated: identity of genus/species of bacteria isolated
- Antibiotic susceptibility result**:** reported as "percent susceptible"

6.7.2. Independent Variables

For the retrospective arm, the independent variables included:

- Specimen type: for example urine, pus, blood
- Date of specimen reporting

For the retrospective arm, the study variables were obtained from existing laboratory records containing the results of antimicrobial susceptibility testing. These were reliably obtained from the in-built archives of the VITEK® 2 (bioMérieux) machine (whose operations have been elaborated in section 6.11).

For the prospective arm, the study variables were obtained from both inpatient files and laboratory records. These details encompassed clinical aspects of the patients' demographic, medical and treatment history:

- Patient Sex: obtained from the patient records
- Patient Age: obtained from the patient records
- Date of hospital admission: obtained from patient records
- Admission diagnosis: obtained from patient file
- Comorbidities: obtained from patient records. These included diabetes, hypertension, HIV status, cancer, organ transplant or any other immunosuppressive conditions
- Use of empirical antibiotic: prescribed in the ward before culture specimen was taken
- Duration of empirical antibiotic (days): retrieved from the patient's treatment sheet
- Instrumentation used: including urinary catheter, central line, dialysis catheter, tracheostomy, nasogastric tube, gastrostomy tube, or none at all.
- Specimen type: for example urine, pus, blood.
- Date of specimen arrival in the laboratory: obtained from laboratory records
- Duration of inpatient stay before specimen collection: calculated from date of hospital admission to date of specimen arrival in the laboratory

6.8. STUDY INSTRUMENTS

A validated data abstraction tool (Appendix C) was used for systematic data collection. This tool was adapted and modified from two previous research studies done by Bwisa (47) and Njiru (48) in the University of Nairobi Institute of Tropical and Infectious Diseases.

6.9. LABORATORY PROCEDURES

The laboratory processes that were undertaken in microbial identification and antimicrobial susceptibility testing were performed by the VITEK® 2 (bioMérieux) machine in the KNH Microbiology laboratory, which is an automated system used for microbial identification and antibiotic susceptibility testing. It can also perform resistance mechanism detection and aid in epidemiologic trending and reporting. At the time of this study, the KNH Microbiology laboratory was only capable of analysing aerobic bacteria.

6.9.1. Lab Definitions

The following terminologies operational in the laboratory processes of this study were defined by the CLSI M39-A4 document: Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data; Approved Guideline – 4th Edition (January 2014) as well as international expert consensus by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) (45,49).

1. Susceptible – the "susceptible" category implies that isolates are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used.
2. Resistant – the "resistant" category implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules, and/or that demonstrate MICs or zone diameters that fall in the range where specific microbial resistance mechanisms (e.g. B-lactamases) are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.
3. Empirical therapy – treatment initiated before determining the diagnosis of infection in a patient and/or before a specific etiological agent is identified and/or characterised as related to an infectious disease.
4. First isolate – refers to the initial microbial isolate of a particular species recovered from a patient during the time period analysed regardless of body source, specimen type, or antimicrobial susceptibility profile.
5. Drug resistant (DR) - refers to non-susceptibility to at least one antimicrobial agent.
6. Multi-drug resistant (MDR) - denotes non-susceptibility to at least one agent in three or more antimicrobial categories.

7. Extensively drug-resistant (XDR) - denotes non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories).
8. Pandrug-resistant (PDR) - denotes non-susceptibility to all agents in all antimicrobial categories.

It is important to note that the above definitions of XDR and PDR categories are based on the various antimicrobial agents locally available in KNH microbiology laboratory testing panel. Most of the antibiotic classes were duly represented during the routine antimicrobial susceptibility testing. However, it has been acknowledged that this being a clinical laboratory with limitations, not all the antimicrobial agents in all known antibiotic classes were available (for example Colistin). This means that in such cases where there is incomplete testing, resistant bacteria isolates can only be characterised as 'possible XDR' and 'possible PDR'. This nomenclature has been recommended and widely accepted in group consensus literature. Ultimately, definitive classification of XDR and PDR bacteria ought to be done in fully-equipped standard reference laboratories with extensive supplementary antibiotic panels(49).

7. QUALITY ASSURANCE

The KNH Microbiology laboratory has existing in-built controls and external quality checks through the World Health Organization – National Institute for Communicable Diseases, South Africa (WHO/NICD) and United Kingdom National External Quality Assurance Service (NEQAS). The laboratory uses the VITEK 2 system which currently conforms to the international recommendations as outlined in the *M100-S24 Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement*(50) produced by the Clinical and Laboratory Standards Institute (CLSI) in January 2014. This document was developed through the CLSI consensus process and provides the current updates to the antimicrobial susceptibility testing standards M02-A11, M07-A9, and M11-A8, for global application. In addition, the laboratory applied specific Standard Operating Procedures (SOPs) below to enhance quality of specimen processing and minimise pre-analytical, analytical and post-analytical errors.

Pre-analytical processes

To minimise pre-analytical errors, the laboratory applied the standard operating procedures entitled *'Collection, Handling and Transportation of Microbiological specimens'* (KNH/LAB MED/MICROB/069P). This document entails details of proper specimen collection by trained clinicians, as well as prompt transport of specimens to the laboratory as soon as possible after collection. Once received in the laboratory, careful scrutiny of the specimens was done, with rejection criteria applied to those which were deemed unfit for processing, such as mislabelled or contaminated specimen. After sorting, proper storage of specimens was ensured before processing, including refrigeration of certain specimens such as urine.

Analytical processes

Quality control during specimen analysis was performed as per the Standard Operating Procedure: *'Media Preparation and Quality Control'* (KNH/LAB MED/MICRO/003P). Standard ATCC (American Type Culture Collection) reference micro-organisms were used to check the performance of culture media. Sterility testing of media was done to ensure that there was no contamination of cultures. It is important to note that contaminated media and inoculation of old cultures can lead to false results and analytical errors. Adequate bacterial cultures grown were processed by the VITEK-2 machine, according to the Standard Operating Procedure quality control document: 'Operation of VITEK-2 Compact' (KNH/LAB MED/MICRO/057P). Verification of VITEK-2 results was done and inter-method comparison performed with offline manual methods such as Kirby-Bauer disk diffusion techniques. External quality assurance and inter-lab comparisons are usually performed on a quarterly basis to check all stages of processing from culture to VITEK reporting, using external reference laboratories. All the above processes were done to ensure that the VITEK results reported were valid.

Post-analytical processes

In the post-analytic phase, the Standard Operating Procedure: *'Results Reporting Format'* (KNH/LAB MED/MICRO/065P) was applied. The machine print-outs were interpreted by both the machine and by the microbiology laboratory technologist. All results were subjected to a second verification and countersigning by a senior laboratory microbiologist. Any contaminants or commensals reported were flagged, and reported to the clinician. The clinician was then advised

to request for a second specimen to be collected and tested in search of pathogenic isolates. Antibiotic susceptibility test results and breakpoints were validated and interpreted as per the latest CLSI *M100-S24 Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement.* Periodic internal quality checks are performed regularly to interrogate culture and sensitivity testing results and locate any discrepancies. In case of any clarifications needed, previous results are retrieved from the manual backups and VITEK storage archives.

8. ETHICAL CONSIDERATIONS

Study approval was sought from the Department of Clinical Medicine & Therapeutics, University of Nairobi, then further permission granted by the KNH/UoN Ethics and Research Committee. For both the retrospective and prospective arm, AST data was extracted from existing KNH Microbiology laboratory records. Permission to extract data from the hospital records was obtained from the KNH Head of Laboratory Medicine, Health Records and the KNH Research Office. Once approved, the study data was collected and analysed whilst maximizing patient confidentiality. Personal identifiers such as patient name were not be captured nor disseminated in any format.

This was a non-invasive study with no risks of body harm. The patients did not actively participate in this study in any way, but only consented to extraction of existing clinical information from their files (See Appendix D for consent form). Patients were informed that if they declined consent, they would have their personal data excluded from the study.

9. DATA MANAGEMENT

9.1. DATA COLLECTION

Data was collected by the Principal Investigator and two research assistants, from VITEK® 2 (bioMérieux) and hospital inpatient files. A data abstraction tool was used to capture all the relevant details. Data collection involved the following steps:

a) The AST data (both retrospective and prospective) was retrieved from VITEK-2, converted into Microsoft Excel format, imported to WHONET[1] software (World Health Organization) and finally input the SPSS database.

b) In the prospective arm:
   - AST data from VITEK 2 was converted into Microsoft Excel and then SPSS format
   - The culture results (using the laboratory number) was used to trace back to the patient in the medical ward
   - Patient consent was obtained for extraction of clinical information from their files
   - Relevant patient data was extracted from patient files & compiled into the abstraction tool
   - Data from the tool was coded into the SPSS database with corresponding AST data

9.2. DATA HANDLING

The data in the abstraction tools was checked and validated at two stages, during the data entry process of each form and again at the end of the data collection process of all the forms, before the analysis commenced. This ensured conformity to the current Clinical and Laboratory Standards Institute (CLSI) standards.

Coding of the data was subsequently performed and input into a SPSS version 20 database primarily accessed by the biostatistician on board. Another system of checks was undertaken on completion of data entry, as the soft copy was compared with the physical forms to detect any inconsistencies. Various methods were employed, such as comparing frequencies via manual and

[1] WHONET software developed by the WHO Collaborating Centre for Surveillance of Antimicrobial Resistance

automated cross-checks and various correlations, as described in the CLSI M39-A4 document. Once the SPSS data was cleaned and inconsistencies removed, analysis was done.

9.3. DATA ANALYSIS

Data analysis was performed using WHONET, SPSS and Microsoft Excel depending on the desired output. Methods for data analysis, results summary and presentation of the antimicrobial susceptibility test data was done according to the standards elaborated in the CLSI M39-A4 document:

I. 1-year retrospective data was analysed to report proportions of bacteria susceptible and those non-susceptible to respective antibiotics. Therefore the primary analysis of the first specific objective documenting antimicrobial susceptibility patterns was based on the retrospective dataset only. The outcome of this was a 1-year antibiogram report.

II. The 3-month cross-sectional (prospective) dataset under study in the second specific objective was used to describe individual patient characteristics as related to antimicrobial susceptibility data obtained for these patients. Here, univariate data analysis of the independent variables included:

- frequencies and proportions for categorical variables such as *patient sex, empirical antibiotic, instrumentation used*.
- measures of central tendency (mean, mode, median) for continuous variables such as *patient age, duration of empirical antibiotic, duration of inpatient stay before culture*.

10. RESULTS

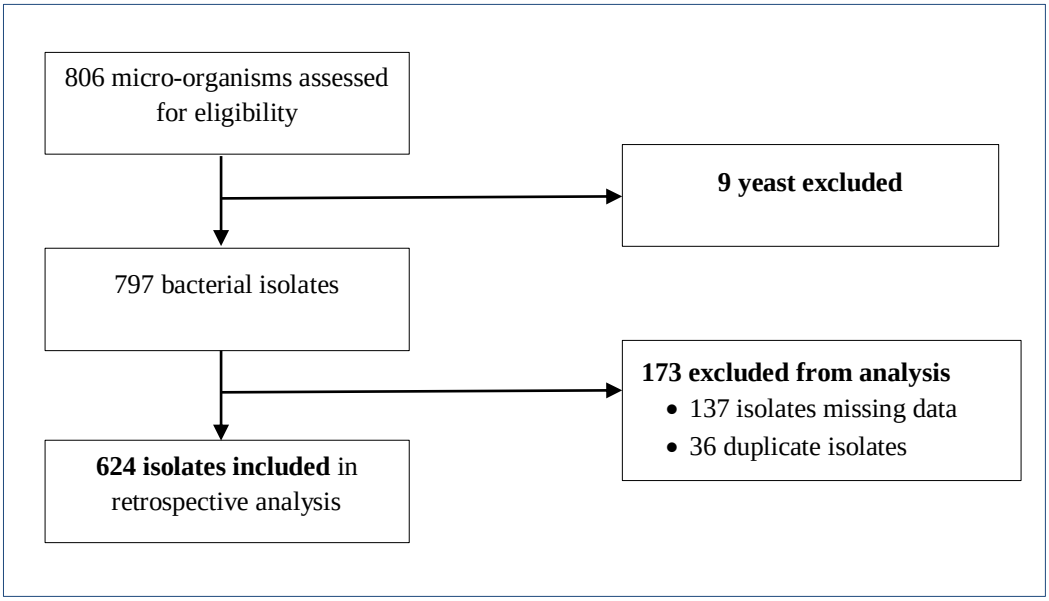
10.1. RESULTS OF OBJECTIVE 1:

To document the antimicrobial susceptibility of bacterial isolates in culture specimens obtained from KNH medical wards in a 1-year retrospective review

10.1.1. STUDY PROFILE

A total of 806 micro-organisms were isolated from culture specimens obtained from medical ward inpatients in the period between 1st January 2015 and 31st December 2015. Of these, 9 isolates were identified as yeast and were excluded from the study. The remaining 797 were bacterial isolates from which a further 137 isolates were excluded from analysis due to missing data. Examples of missing entries included instances of isolate listing without antibiotic susceptibility rates. The remaining 660 bacterial isolates met the inclusion criteria. Following the CLSI guidelines, 36 duplicate isolate entries were excluded so as to remain with one isolate per patient per admission period. The final number of bacterial isolates included into the retrospective dataset was 624.

Figure 1: Study profile - retrospective review



10.1.2. SPECIMEN TYPE

Nine types of specimen were obtained from the medical wards. Most of the bacteria isolated were cultured from urine (254/624, 41%), followed by pus (227/624, 36%) and blood (68/624, 11%). The rest included pleural fluid (37/624, 6%), peritoneal fluid (19/624, 3%), cerebrospinal fluid (10/624, 2%), sputum (6/624, 1%), stool (2/624) and vaginal swab (1 isolate). All the 624 bacterial isolates were cultured from the 8 medical inpatient wards alone in 2015, since the medical critical care unit (CCU) was established in late 2016.

10.1.3. ISOLATE SPECIES

Overall, there were twice as many gram negative bacteria (419/624, 67%) as there were gram positive bacteria (205/624, 33%) isolated. The most frequently isolated gram negative bacteria were *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa* and *Acinetobacter baumanii* in descending order. The most frequently isolated gram positive bacteria were *Staphylococcus aureus, Staphylococcus haemolyticus, Enterococcus faecalis, Staphylococcus epidermidis* and *Enterococcus faecium*. For detailed listing of the gram negative and gram positive bacteria isolated see Table 2 and Table 3.

Table 2: Gram negative organisms isolated in the retrospective review (January – December 2015)

SPECIMEN^	*E. coli*	*K. pneumoniae*	*P. mirablis*	*P. aeruginosa*	*A. baumanii*	*E. cloacae*	OTHERS (27 species)**	TOTAL
Urine	92	76	5	2	4	6	27	**212**
Pus	33	26	26	23	18	5	24	**145**
Blood	8	8	1	1	3	2	2	**25**
Pleural fluid	6	3		1	1	3	7	**21**
Sputum		6					0	**6**
Peritoneal fluid	3						2	**5**
CSF*		1					1	**2**
Stool							2	**2**
Vaginal swab	1						0	**1**
TOTAL ISOLATES	**143**	**110**	**32**	**27**	**26**	**16**	**65**	**419**

^ Bacteria isolated from specimens include *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Acinetobacter baumanii, Enterobacter cloacae* among others.

* Cerebrospinal fluid

** Others include insignificant numbers of isolates including *Morganella morganii, Serratia fonticola, Acinetobacter lwoffii, Proteus vulgaris, Serratia liquefaciens, Serratia odorifera, Enterobacter aerogenes, Salmonella sp., Serratia marcescens, Aeromonas hydrophila, Citrobacter freundii, Raoultella ornitholytica, Proteus penneri, Pseudomonas putida, Alcaligenes faecalis (odorans), Acinetobacter haemolyticus, Delftia acidovorans, Pantoea agglomerans, Ewingella americana, Escherichia hermannii, Klebsiella oxytoca, Klebsiella pneumoniae ss. Ozaenae, Raoultella planticola, Myroides sp., Pseudomonas pseudoalcaligenes, Shigella flexneri,* and *Yersinia enterocolitica.*

Table 3: Gram positive organisms isolated in the retrospective review (January – December 2015)

SPECIMEN^	*S. aureus*	*S. haemolyticus*	*E. faecalis*	*S. epidermidis*	*E. faecium*	*Other coagulase negative Staphylococcus*	OTHERS (14 species)**	TOTAL
Pus	56	7	10	2			7	**82**
Blood	7	12	1	9	2	2	10	**43**
Urine	4	1	9	2	14	1	11	**42**
Pleural fluid	2	1	3	3	1	1	5	**16**
Peritoneal fluid		5		4	2		3	**14**
CSF*	1	2	2	2			1	**8**
Sputum								**-**
Stool								**-**
TOTAL ISOLATES	**70**	**28**	**25**	**22**	**19**	**4**	**37**	**205**

^ Bacteria isolated from specimens include *Staphylococcus aureus, Staphylococcus haemolyticus, Enterococcus faecalis, Staphylococcus epidermidis, Enterococcus faecium* among others.

* Cerebrospinal fluid

**Others include insignificant numbers of isolates including *Enterococcus gallinarum, Staphylococcus sciuri ss. lentus, Staphylococcus lugdunensis, Staphylococcus xylosus, Streptococcus pneumoniae, Enterococcus casseliflavus, Enterococcus durans, Staphylococcus saprophyticus ss. saprophyticus, Staphylococcus capitis ss. capitis, Staphylococcus intermedius, Staphylococcus simulans, Staphylococcus cohnii ss. cohnii, Staphylococcus cohnii ss. urealyticum,* and *Staphylococcus warneri.*

10.1.4. ANTIMICROBIAL SUSCEPTIBILITY TESTING (AST)

Antimicrobial susceptibility results of the 624 bacteria were grouped according to the organism types as seen in tables 4 and 5.

10.1.4.1. Antimicrobial susceptibility of gram negative organisms (retrospective review)

Escherichia coli, *Klebsiella pneumoniae* and *Proteus mirabilis* met the threshold for antibiogram reporting (more than 30 isolates per species). Although Pseudomonas aeruginosa and Acinetobacter baumanii were less than 30 isolates each, their AST results have been described below due to their high clinical significance (see table 4).

The results indicated that the *E. coli* and *K. pneumoniae* had poor susceptibility to penicillins (8-48%), cephalosporins (16-43%), monobactams (17-29%), fluoroquinolones (22-44%) and trimethoprim-sulfamethoxazole (7%). *E. coli* had moderate susceptibility to nitrofurantoin (56%). Both *E.coli* and *K. pneumoniae* had high susceptibility to meropenem (76-87%) and excellent susceptibility to amikacin (91-97%).

Proteus mirabilis demonstrated poor susceptibility to cefuroxime (34%) and trimethoprim-sulfamethoxazole (9%); moderate susceptibility to ampicillin-sulbactam (59%), cefepime (53%), ceftriaxone (50%), gentamicin (53%); and high susceptibility to amoxicillin-clavulanic acid (81%), ceftazidime (75%), aztreonam (81%), and ciprofloxacin (72%). *P. mirabilis* showed excellent susceptibility to meropenem (97%) and amikacin (100%).

Pseudomonas aeruginosa was resistant to amoxicillin-clavulanic acid, ampicillin-sulbactam, cefotaxime, ceftriaxone, cefuroxime and nitrofurantoin. It showed moderate susceptibility to piperacillin-tazobactam (56%) and aztreonam (48%); and high susceptibility to cefepime (78%), ceftazidime (70%), meropenem (70%), amikacin (89%) and gentamicin (82%).

Acinetobacter baumanii was resistant to cefuroxime, aztreonam and nitrofurantoin. It had negligible susceptibility to cefotaxime and ceftriaxone. It had poor susceptibility to ampicillin-sulbactam (23%), piperacillin-tazobactam (19%), cefepime (19%), ceftazidime (19%), meropenem (27%), ciprofloxacin (23%), gentamicin (27%) and trimethoprim-sulfamethoxazole (15%). It had high susceptibility to amikacin (89%).

Table 4: Antimicrobial susceptibility of gram negative organisms to various antibiotics (retrospective review)

Gram negative organism	No. of strains	PERCENT SUSCEPTIBLE (%S)*														
		PENICILLINS			CEPHALOSPORINS					AMINOGLYCOSIDES		FQ	CPM	OTHERS		
		Amoxicillin-Clavulanic acid	Ampicillin-Sulbactam	Piperacillin-Tazobactam	Cefuroxime	Cefotaxime	Ceftriaxone	Ceftazidime	Cefepime	Amikacin	Gentamicin	Ciprofloxacin	Meropenem	Aztreonam	Nitrofurantoin	Trimethoprim-Sulfamethoxazole
Escherichia coli	**143**	26	8	48	20	25	25	34	43	97	53	22	87	29	56	7
Klebsiella pneumoniae	**110**	27	-	33	16	18	18	17	36	91	31	44	76	17	8	10
Proteus mirabilis	**32**	81	59	100	34	44	50	75	53	100	53	72	97	81	-	9
*Pseudomonas aeruginosa***	**27**	-	-	56	-	-	-	70	78	89	82	73	70	48	-	-
*Acinetobacter baumannii***	**26**	-	23	19	-	8	8	19	19	89	27	23	27	-	-	15
OTHERS (28 species)†	**81**															
TOTAL	**419**															

Abbreviations: FQ, fluoroquinolones; CPM, carbapenems

* The percent susceptible for each organism/antimicrobial combination was generated by including the first isolate of that organism encountered on a given patient.

(-) drug not tested or drug not indicated

** Calculated from fewer than the standard recommendation of 30 isolates

† Others include insignificant numbers of isolates including *Enterobacter cloacae, Morganella morganii, Serratia fonticola, Acinetobacter lwoffii, Proteus vulgaris, Serratia liquefaciens, Serratia odorifera, Enterobacter aerogenes, Salmonella sp., Serratia marcescens, Aeromonas hydrophila, Citrobacter freundii, Raoultella ornitholytica, Proteus penneri, Pseudomonas putida, Alcaligenes faecalis (odorans), Acinetobacter haemolyticus, Delftia acidovorans, Pantoea agglomerans, Ewingella americana, Escherichia hermannii, Klebsiella oxytoca, Klebsiella pneumoniae ss. Ozaenae, Raoultella planticola, Myroides sp., Pseudomonas pseudoalcaligenes, Shigella flexneri,* and *Yersinia enterocolitica*.

10.1.4.2. Antimicrobial susceptibility of gram positive organisms (retrospective review)

Staphylococcus aureus (70 isolates) was the only species that met the threshold for antibiogram reporting (see table 5). It is likely that a large number of *Staphylococcus haemolyticus*, *Staphyloccus epidermidis* and other *coagulase-negative staphylococcus* species isolated were skin contaminants, and thus their susceptibility rates should be interpreted with caution.

The results indicated that *S. aureus* had poor susceptibility to penicillin G (3%), trimethoprim-sulfamethoxazole (29%) and oxacillin (45%) which is a methicillin surrogate. Moderate susceptibility was seen to fluoroquinolones (59-61%), macrolides (59-64%) and high susceptibility to cefuroxime (70%) and gentamicin (78%). Excellent susceptibility was seen to imipenem (90%), vancomycin (97%), linezolid (99%), nitrofurantoin (100%) and quinupristin-dalfopristin (100%).

Enterococcus faecalis demonstrated poor susceptibility to tetracycline (16%) and quinolones (44-48%), and moderate susceptibility to imipenem (63%). It had high susceptibility to penicillin G (88%), vancomycin (80%), linezolid (84%), nitrofurantoin (84%) and teicoplanin (84%).

Enterococcus faecium was multi-drug resistant to beta-lactam antibiotics, quinolones and aminoglycosides. It demonstrated poor susceptibility to nitrofurantoin (11%) and tetracycline (21%). It showed high susceptibility to quinupristin-dalfopristin (75%), linezolid (90%), vancomycin (95%) and teicoplanin (95%).

Table 5: Antimicrobial susceptibility of gram positive organisms to various antibiotics (retrospective review)

Gram positive organism	No. of strains (n)	PERCENT SUSCEPTIBLE (%S)*																		
		PENICILLINS			CEPH	CPM	QUINOLONES		AMINOGLYCOSIDES			MACROLIDES		OTHERS						
		Ampicillin-Sulbactam	Oxacillin	Penicillin G	Cefuroxime	Imipenem	Levofloxacin	Moxifloxacin	Gentamicin	Streptomycin-High	Tobramycin	Clindamycin	Erythromycin	Vancomycin	Linezolid	Nitrofurantoin***	Trimethoprim-Sulfamethoxazole	Tetracycline	Mupirocin	Quinupristin-Dalfopristin	Teicoplanin
Staphylococcus aureus	**70**	-	45	3	70	90	59	61	78	-	75	64	59	97	99	100	29	51	0	100	97
*Staphylococcus haemolyticus***	**28**	67	0	0	33	100	18	18	32	-	36	39	11	89	100	96	7	54	0	100	96
*Enterococcus faecalis***	**25**	100	-	88	-	63	44	48	-	100	-	-	-	80	84	84	-	16	-	-	84
*Staphylococcus epidermidis***	**22**	-	21	0	67	100	23	23	63	-	84	55	23	100	100	100	36	59	0	100	100
*Enterococcus faecium***	**19**	0	-	0	-	0	0	0	-	100	-	-	-	95	90	11	-	21	-	75	95
*Other Staphylococcus, coagulase negative***	**4**	-	0	0	67	100	25	25	100	-	0	50	0	75	75	100	0	25	0	67	75
OTHERS (15 species)†	**37**																				
TOTAL	**205**																				

Abbreviations: CEPH, cephalosporins; CPM, carbapenems

* The percent susceptible for each organism/antimicrobial combination was generated by including the first isolate of that organism encountered on a given patient.

(-) drug not tested or drug not indicated

** Calculated from fewer than the standard recommendation of 30 isolates

*** Suggested interpretation for urine isolates

† Others include insignificant numbers of isolates including *Enterococcus gallinarum, Streptococcus pneumoniae, Staphylococcus hominis ss. hominis, Staphylococcus sciuri ss. lentus, Staphylococcus lugdunensis, Staphylococcus xylosus, Staphylococcus saprophyticus ss. saprophyticus, Staphylococcus capitis ss. capitis, Staphylococcus intermedius, Staphylococcus simulans, Staphylococcus cohnii ss. cohnii, Staphylococcus cohnii ss. urealyticum, Staphylococcus warneri, Enterococcus casseliflavus,* and *Enterococcus durans*

10.1.5. RESISTANCE PROFILES

Nineteen (19) antibiotic class types were tested in total in various combinations, each isolate being tested with antibiotic panels corresponding to its organism group (i.e. Gram positive vis-à-vis Gram negative panels). Antibiotic classes tested include Aminoglycosides, Penicillins, Monobactams, Non-extended spectrum cephalosporins, Extended-spectrum cephalosporins, Phenicols, Fluoroquinolones, Macrolides, Lincomycins, Lincosamides, Fosfomycins, Carbapenems, Oxazolidinones, Nitrofurans, B-lactam/B-lactamase inhibitors, Streptogramins, Ansamycins, Glycopeptides, Tetracyclines and Folate pathway inhibitors.

The results were as follows: 613(98%) were drug resistant; 549(88%) were multidrug resistant; 163(26%) were possible extensively-drug resistant; and 51(8%) were possible pandrug-resistant. For definitions of these resistance categories, refer to 'Lab Definitions' section 6.11.1.

To summarise the clinically important antibiotic-resistant bacteria isolated in our study, the WHO Priority Pathogens List (PPL) was used. The list contains the 12 most significant antibiotic-resistant bacteria recognised worldwide and the following table highlights their local prevalence in KNH medical wards as derived from the retrospective arm. In the critical category, we found carbapenem resistant *A. baumanii* (73%), *P. aeruginosa* (30%), *E. coli* (13%) and *K. pneumoniae* (24%). In the high category, we isolated 5% vancomycin-resistant *E. faecium*, 3% vancomycin-resistant *S. aureus* and 55% MRSA. There were no other organisms isolated in the high and medium priority categories. See table 6 below and the corresponding figures 2-4.

Table 6: Prevalence of WHO priority antibiotic-resistant organisms: retrospective study

	Antibiotic	%R	Antibiotic	%R
Priority: CRITICAL				
1. ***Acinetobacter baumannii***, carbapenem-resistant	Carbapenem	***73%**		
2. ***Pseudomonas aeruginosa***, carbapenem-resistant	Carbapenem	***30%**		
3. ***Enterobacteriaceae***, carbapenem-resistant, ESBL-producing:				
Escherichia coli	Carbapenem	**13%**	Ceftriaxone	**75%**
Klebsiella pneumoniae	Carbapenem	**24%**	Ceftriaxone	**82%**
Priority: HIGH				
4. ***Enterococcus faecium***, vancomycin-resistant	Vancomycin	***5%**		
5. ***Staphylococcus aureus***, methicillin-resistant, vancomycin-intermediate, and resistant	Methicillin	**55%**	Vancomycin	**3%**
6. ***Helicobacter pylori***, clarithromycin-resistant	Clarithromycin	-		
7. ***Campylobacter* spp**, fluoroquinolone-resistant	Fluoroquinolone	-		
8. ***Salmonellae***, fluoroquinolone-resistant	Fluoroquinolone	-		
9. ***Neisseria gonorrhoeae***, cephalosporin-resistant, fluoroquinolone-resistant	Cephalosporin	-	Fluoroquinolone	-
Priority: MEDIUM				
10. ***Streptococcus pneumoniae***, penicillin-nonsusceptible	Penicillin	-		
11. ***Haemophilus influenzae***, ampicillin-resistant	Ampicillin	-		
12. ***Shigella* spp**, fluoroquinolone-resistant	Fluoroquinolone	-		

%R denotes percent resistant

* In this study, calculated from fewer than the standard recommendation of 30 isolates

(-) organism not isolated in this study

Figure 2: Resistance of gram negative organisms to carbapenems (retrospective review)

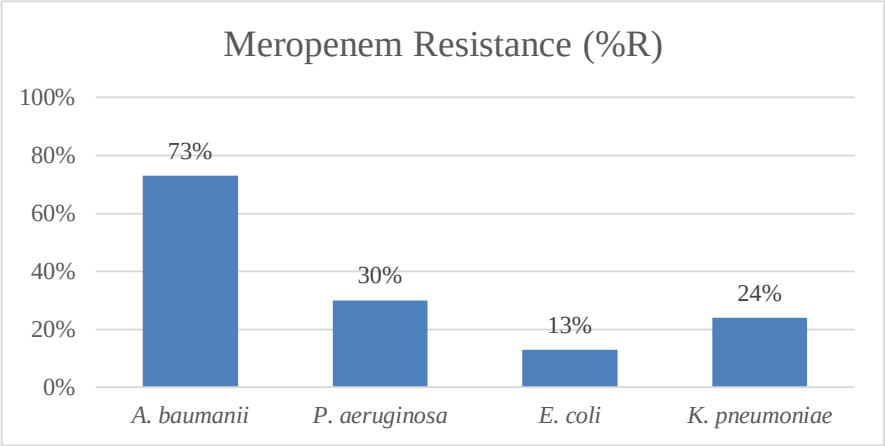


Figure 3: Enterobacteriaceae resistance to cephalosporins (retrospective review)

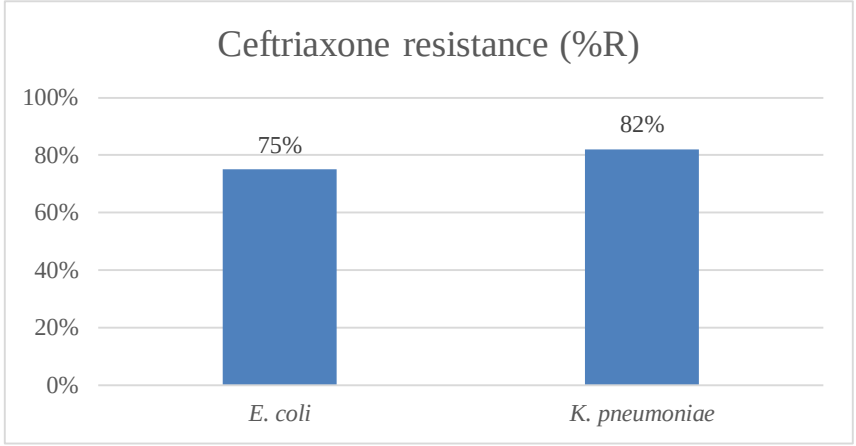
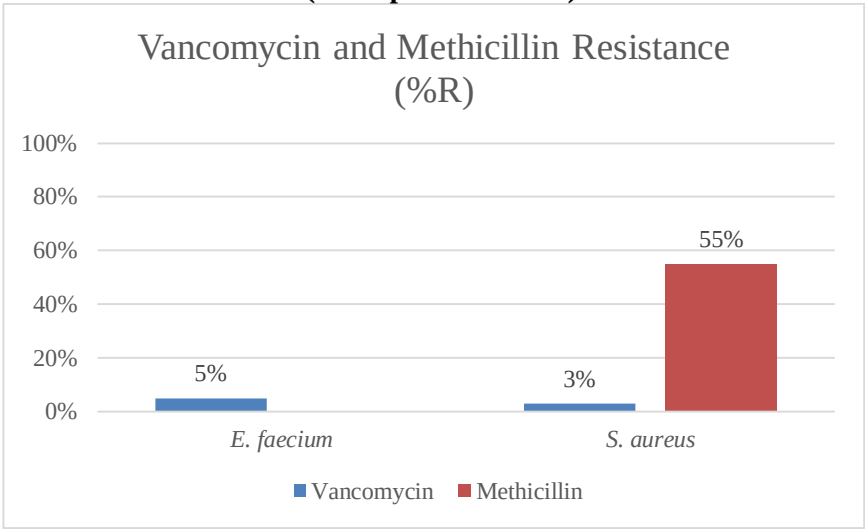


Figure 4: Resistance of gram positive organisms (retrospective review)



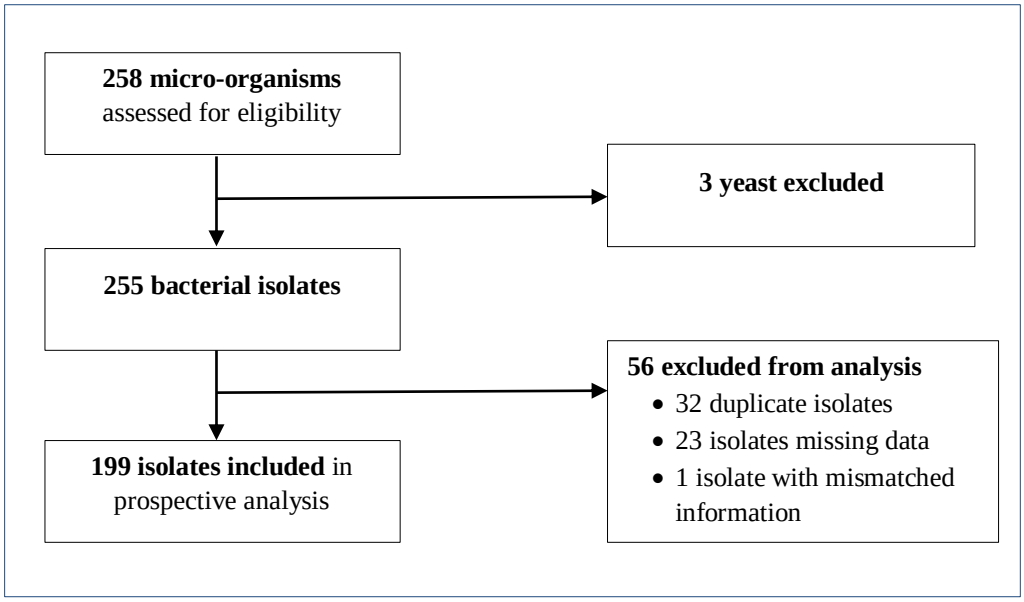
10.2. RESULTS OF OBJECTIVE 2:

To describe the antimicrobial susceptibility of bacterial isolates in culture specimens of KNH medical ward inpatients with clinical profiles prospectively over a 3-month period

10.2.1. STUDY PROFILE

In the prospective arm of the study, 258 isolates were cultured from the total number of culture specimens obtained from medical ward inpatients in the period spanning 15th September 2016 to 31st December 2016. Three isolates were identified as yeast and were excluded from the study. The remaining 255 were bacterial isolates. Of these, 23 isolates had missing data. Examples of missing entries included instances of isolate listing without antibiotic susceptibility rates. The remaining 232 bacterial isolates met the inclusion criteria. For these isolates, corresponding patient clinical information was collected from the patient files in the medical wards. Thirty-two duplicate isolates from the same patient, and one isolate which had wrongly matched clinical information were excluded, leaving a total of 199 bacterial isolates for analysis in the prospective part of the study.

Figure 5: Study profile - prospective study



10.2.2. PATIENT CHARACTERISTICS

The socio-demographic and clinical characteristics of the patients in the prospective part of the study has been summarised in Table 7. Out of the 199 patients recruited, 122 (61%) of them were female and 77 (39%) were male. The median age for females was 45 years (ranging from 13 to 91 years) while that for males was 46 years (ranging from 5 to 100 years).

10.2.2.1. Comorbidities

Majority of patients (144/199, 72%) had recognised comorbidities on admission. Of these, 66 (33%) had renal failure, 41 (21%) had diabetes mellitus, 40 (20%) were HIV seropositive, 24 (12%) had malignancy whereas 48 (24%) had other comorbidities.

10.2.2.2. Empiric antibiotic therapy

One hundred and thirty six patients (68% of the total) had received empiric antibiotic therapy by the time a culture specimen was obtained, and these were grouped into the main antibiotic classes. One hundred and two (51%) patients recruited had been treated with a cephalosporin. Forty-three (22%) patients had been treated with a nitroimidazole such as Metronidazole. Thirty-two (16%) had been treated with a penicillin whereas 24 (12%) had been treated with a carbapenem. Other antibiotics given empirically include macrolides (18/199, 9%), quinolones (15/199, 8%), aminoglycosides (6/199, 3%). Overall, the median duration of empiric antibiotic therapy was 4 days prior to specimen collection for culture.

10.2.2.3. Use of instrumentation and devices

An overwhelming majority of patients (188/199, 94%) had an indwelling device or form of instrumentation. Most of them (181/199, 91%) had an intravenous line in situ. Other forms of instrumentation used include urinary catheters (90/199, 45%), nasogastric tubes (44/199, 22%), endotracheal tubes (33/199, 17%), central venous catheters (32/199, 16%), haemodialysis catheters (31/199, 16%) among others (15/199, 8%).

10.2.2.4. Duration of inpatient stay before specimen collection

The median duration of hospital stay before culture specimen collection was about 5 days. The minimum number of days spent in the ward before specimen collection was one day, whereas the longest admission period realised over the course of this study was 138 days.

Table 7: Sociodemographic and clinical characteristics of the patients with cultured isolates

Prospective study Baseline characteristics	Overall (N)
PATIENT LOCATION	
ALL WARDS	**199**
a) Medical inpatient (8)	155 (78%)
b) Medical Critical Care Unit (1)	44 (22%)
AGE (yrs)	
Median	**46**
Standard deviation (SD)	20
Maximum (Max)	100
Minimum (Min)	5
COMORBIDITIES	
PRESENCE OF A COMORBIDITY:	**144 (72%)**
a) Renal failure	66 (33%)
b) Diabetes	41 (21%)
c) HIV	40 (20%)
d) Malignancy	24 (12%)
e) Other comorbidities	48 (24%)
EMPIRIC ANTIBIOTIC THERAPY	
ALL ANTIBIOTIC CLASSES:	**136 (68%)**
a) Cephalosporin	102 (51%)
b) Nitroimidazole	43 (22%)
c) Penicillin	32 (16%)
d) Carbapenem	24 (12%)
e) Macrolide	18 (9%)
f) Quinolone	15 (8%)
g) Aminoglycoside	6 (3%)
h) Other antibiotic	12 (6%)

DURATION OF EMPRIC THERAPY (days)	
Median	**4**
Interquartile Range	8
Range	95 (1-96)
USE OF INSTRUMENTATION	
USE OF ANY TYPE OF DEVICE:	**188 (94%)**
a) Intravenous line	181 (91%)
b) Urinary catheter	90 (45%)
c) Nasogastric tube	44 (22%)
d) Endotracheal tube	33 (17%)
e) Central venous catheter	32 (16%)
f) Haemodialysis catheter	31 (16%)
g) Other devices	15 (8%)
HOSPITAL STAY BEFORE SPECIMEN COLLECTION (days)	
Median	**5**
Interquartile range	15
Range	138 (1-139)

10.2.3. SPECIMEN TYPE

A total of 199 isolates were cultured from the specimens in the prospective arm. Out of the 9 types of specimen obtained from the medical wards and critical care unit (CCU) under study, the most common was urine (79/199, 40%), followed by blood (39/199, 20%) and pus (38/199, 19%). Others included tracheal aspirates (20/199, 10%), pleural fluid (7/199, 3%), sputum (7/199, 3%), peritoneal fluid (7/199, 3%), cerebrospinal fluid (1/199, 1%) and synovial fluid (1/199, 1%). Majority of isolates were from the samples drawn from medical inpatient wards (155/199, 78%) whereas fewer isolates were obtained from the Critical Care Unit (44/199, 22%).

Nine types of specimen were obtained from the medical wards. Most of the bacteria isolated were cultured from urine (66/155, 43%), followed by pus (35/155, 23%) and blood (30/155, 19%). The rest included pleural fluid (7/155, 5%), peritoneal fluid (7/155, 5%), sputum (7/155, 5%), cerebrospinal fluid (1/155, 1%), synovial fluid (1/155, 1%), and tracheal aspirate (1/155, 1%).

Out of the 44 isolates obtained from the medical Critical Care Unit, majority of them were obtained from tracheal aspirates (19/44, 43%) whereas the rest were cultured from urine (13/44, 30%), blood culture (9/44, 20%) and pus (3/44, 7%).

10.2.4. ISOLATE SPECIES

Overall, there more gram negative organisms (114/199, 57%) than gram positive organisms (85/199, 43%) isolated. The most frequently isolated gram negative bacteria were *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Acinetobacter baumanii* and *Proteus mirabilis* in descending order. The most frequent gram positive bacteria isolated were *Staphylococcus aureus, Staphylococcus haemolyticus, Enterococcus faecalis, Staphylococcus epidermidis* and *Enterococcus faecium*. For detailed listing of the isolated bacteria see table 8 and 9.

Table 8: Gram negative organisms isolated in the prospective study (September - December 2016)

ORGANISM	Isolates (n)	Urine	Tracheal aspirate	Pus	Blood	Sputum	Peritoneal fluid	Pleural fluid	Synovial fluid
Klebsiella pneumoniae	**40**	20	5	5	3	3	3	1	
Escherichia coli	**39**	28	3	1	3		1	3	
Pseudomonas aeruginosa	**9**	1	4	1	1	2			
Acinetobacter baumannii	**7**		4	2	1				
Proteus mirabilis	**5**	3		2					
Enterobacter cloacae	**4**	1	1	1					
OTHERS (9 species)*	**10**								
TOTAL	**114**	**57**	**17**	**15**	**9**	**6**	**4**	**4**	**1**

* Others include insignificant numbers of isolates including *Serratia plymuthica, Citrobacter freundii, Pantoea agglomerans, Pantoea sp., Proteus penneri, Proteus rettgeri, Serratia fonticola, Serratia marcescens* and *Serratia odorifera.*

Table 9: Gram positive organisms isolated in the prospective study (September - December 2016)

ORGANISM	Isolates (n)	Blood	Urine	Pus	Peritoneal fluid	Tracheal aspirate	Pleural fluid	Sputum	Cerebrospinal fluid
Staphylococcus aureus	**19**	3		16					
Enterococcus faecalis	**15**	3	10	2					
Staphylococcus epidermidis	**15**	11	1	1	1		1		
Staphylococcus haemolyticus	**11**	10			1				
Enterococcus faecium	**8**		6	1		1			
Enterococcus gallinarum	**7**	1	4	1	1				
Other Staphylococcus, coagulase negative	**1**							1	
OTHERS (7 species)*	**9**								
TOTAL	**85**	**30**	**23**	**23**	**3**	**2**	**2**	**1**	**1**

* Others include insignificant numbers of isolates including *Staphylococcus intermedius, Staphylococcus sciuri ss. lentus, Enterococcus sp., Staphylococcus saprophyticus ss. saprophyticus, Streptococcus agalactiae, Staphylococcus sciuri ss. sciuri,* and *Staphylococcus xylosus*

10.2.5. ANTIMICROBIAL SUSCEPTIBILITY TESTING (AST)

Antimicrobial susceptibility results of the 199 bacteria isolated in the prospective arm were grouped according to the organism types as seen in tables 10 and 11. Majority of the organisms isolated that were subjected to antimicrobial susceptibility testing (AST) fell below the CLSI threshold of 30 isolates per species. However in general, the AST trends and patterns were similar to those in the retrospective arm for the respective organisms. The prospective arm thus provided a small snapshot of what was realised in the retrospective review.

10.2.5.1. Antimicrobial susceptibility of gram negative organisms (prospective study)

Escherichia coli and *Klebsiella pneumoniae* met the threshold for antibiogram reporting (more than 30 isolates per species). Other clinically significant bacteria that were isolated were *Pseudomonas aeruginosa* (9 isolates), *Acinetobacter baumanii* (7 isolates) and *Proteus mirabilis* (5 isolates). However these three fell way below the significant threshold of 30 isolates each, and thus their AST results in this prospective study cannot be taken into consideration. Their susceptibility rates have been outlined in table 10.

The results indicated that the *E. coli* and *K. pneumoniae* had poor susceptibility to most penicillins (10-43%), cephalosporins (20-49%), monobactams (18-36%), fluoroquinolones (46-50%) and trimethoprim-sulfamethoxazole (13-20%). *K. pneumoniae* had poor susceptibility to nitrofurantoin (28%) while *E. coli* had high susceptibility to nitrofurantoin (72%). Both *E.coli* and *K. pneumoniae* had high susceptibility to meropenem (73-77%) and excellent susceptibility to amikacin (93-97%).

10.2.5.2. Antimicrobial susceptibility of gram positive organisms (prospective study)

None of the few gram positive organisms isolated met the threshold of 30 isolates per species for antibiogram reporting. Coagulase-negative staphylococcus such as *S. epidermidis* and *S. haemolyticus* were considered to be skin contaminants. The only notable organism isolated was *S. aureus* (19 isolates) whose results showed resistance to penicillin G, ampicillin-sulbactam and cefuroxime. *S. aureus* had poor susceptibility to oxacillin (39%), trimethoprim-sulfamethoxazole (21%), quinolones (42-47%). It demonstrated moderate susceptibility to clindamycin (53%) and high susceptibility to aminoglycosides (83-89%) and nitrofurantoin (84%). Excellent susceptibility was seen to imipenem (100%), vancomycin (100%), linezolid (100%), quinupristin-dalfopristin (100%) and teicoplanin (100%). See table 11.

Table 10: Antimicrobial susceptibility of gram negative organisms to various antibiotics (prospective study)

Gram negative organism	No. of strains (n)	PERCENT SUSCEPTIBLE (%S)*														
		PENICILLINS			CEPHALOSPORINS					AMINOGLYCOSIDES		FQ	CPM	OTHERS		
		Amoxicillin-Clavulanic acid	Ampicillin-Sulbactam	Piperacillin-Tazobactam	Cefuroxime	Cefotaxime	Ceftriaxone	Ceftazidime	Cefepime	Amikacin	Gentamicin	Ciprofloxacin	Meropenem	Aztreonam	Nitrofurantoin	Trimethoprim-Sulfamethoxazole
Klebsiella pneumoniae	**40**	43	-	38	20	23	20	25	43	93	50	50	73	18	28	20
Escherichia coli	**39**	41	10	67	31	39	36	49	46	97	62	46	77	36	72	13
*Pseudomonas aeruginosa***	**9**	-	-	44	-	-	-	56	67	67	78	44	44	22	-	-
*Acinetobacter baumannii***	**7**	-	14	0	-	0	0	0	14	57	0	14	14	-	-	14
OTHERS (11 species)†	**19**															
TOTAL	**114**															

Abbreviations: FQ, fluoroquinolones; CPM, carbapenems

* The percent susceptible for each organism/antimicrobial combination was generated by including the first isolate of that organism encountered on a given patient.

(-) drug not tested or drug not indicated

** Calculated from fewer than the standard recommendation of 30 isolates

† Others include insignificant numbers of isolates including *Proteus mirabilis, Enterobacter cloacae, Serratia plymuthica, Citrobacter freundii, Pantoea agglomerans, Pantoea sp., Proteus penneri, Proteus rettgeri, Serratia fonticola, Serratia marcescens* and *Serratia odorifera.*

Table 11: Antimicrobial susceptibility of gram positive organisms to various antibiotics (prospective study)

Gram positive organism	No. of strains (n)	PERCENT SUSCEPTIBLE (%S)*																		
		PENICILLINS			CEPH	CPM	QUINOLONES		AMINOGLYCOSIDES			MACROLIDES		OTHERS						
		Ampicillin-Sulbactam	Oxacillin	Penicillin G	Cefuroxime	Imipenem	Levofloxacin	Moxifloxacin	Gentamicin	Streptomycin-High	Tobramycin	Clindamycin	Erythromycin	Vancomycin	Linezolid	Nitrofurantoin***	Trimethoprim-Sulfamethoxazole	Tetracycline	Mupirocin	Quinupristin-Dalfopristin	Teicoplanin
*Staphylococcus aureus***	**19**	-	39	0	0	100	47	42	83	-	89	53	47	100	100	84	21	42	0	100	100
*Staphylococcus epidermidis***	**15**	-	20	0	-	-	47	47	87	-	73	27	13	100	93	100	20	73	0	-	100
*Enterococcus faecalis***	**15**	60	-	20	-	20	27	20	-	100	-	-	-	73	73	73	-	13	-	-	73
*Staphylococcus haemolyticus***	**11**	-	0	0	-	-	0	0	9	-	46	9	9	100	100	100	18	64	0	-	100
*Enterococcus faecium***	**8**	0	-	0	-	0	0	0	-	100	-	-	-	63	75	0	-	50	-	40	75
*Other Staphylococcus, coagulase negative***	**1**	-	0	0	-	-	100	100	100	-	100	100	100	100	100	100	0	100	0	-	100
OTHERS (8 species)†	**16**																				
TOTAL	**85**																				

Abbreviations: CEPH, cephalosporins; CPM, carbapenems

* The percent susceptible for each organism/antimicrobial combination was generated by including the first isolate of that organism encountered on a given patient.

(-) drug not tested or drug not indicated

** Calculated from fewer than the standard recommendation of 30 isolates

*** Suggested interpretation for urine isolates

† Others include insignificant numbers of isolates including *Enterococcus gallinarum*, *Staphylococcus intermedius*, *Staphylococcus sciuri ss. lentus*, *Enterococcus sp.*, *Staphylococcus saprophyticus ss. saprophyticus*, *Streptococcus agalactiae*, *Staphylococcus sciuri ss. sciuri* and *Staphylococcus xylosus*

10.2.6. BACTERIAL RESISTANCE AND PATIENT CLINICAL PROFILES

The following is a summary of the 199 resistant isolates in the prospective study, matched to respective patients they were isolated from and highlighting their clinical profiles thereof. Of these, 98.9% (197/199) were classified as drug resistant, 86.9% (173/199) were multi-drug resistant, 24.1% (48/199) were possible extensively-drug resistant whereas 3% (6/199) were possible pandrug-resistant. The following table illustrates the proportions of resistant bacteria that were isolated from patients with characteristics relevant to antimicrobial resistance (presence of comorbidities, use of empiric therapy and instrumentation). More than two-thirds of the resistant bacteria in all resistance categories (DR, MDR, XDR, PDR) were isolated from patients with comorbidities and who had used empirical antibiotics and indwelling devices (instrumentation) during the course of their treatment.

Table 12: Correlation of isolate resistance profiles with patient clinical characteristics

ISOLATE CHARACTERISTIC	Resistance Profile	Total (N)	PATIENT CHARACTERISTIC				
			Sex		Any comorbidity	Empirical antibiotic	Any instrumentation
			Male n (n/N)%	Female n (n/N)%	n (n/N)%	n (n/N)%	n (n/N)%
	Drug resistant (DR)**	**197**	77 **(39.1%)**	120 **(60.9%)**	144 **(73.1%)**	135 **(68.5%)**	186 **(94.4%)**
	Multi-DR (MDR)†	**173**	69 **(39.9%)**	104 **(60.1%)**	127 **(73.4%)**	121 **(69.9%)**	164 **(94.8%)**
	Extensively-DR (XDR) β	**48**	18 **(37.5%)**	30 **(62.5%)**	33 **(68.8%)**	38 **(79.2%)**	47 **(97.9%)**
	Pandrug-DR (PDR) ‡	**6**	2 **(33.3%)**	4 **(66.7%)**	4 **(66.7%)**	4 **(66.7%)**	5 **(83.3%)**

*Antibiotic classes used in resistance testing include Aminoglycosides, Penicillins, Monobactams, Non-extended spectrum cephalosporins, Extended-spectrum cephalosporins, Phenicols, Fluoroquinolones, Macrolides, Lincomycins, Lincosamides, Fosfomycins, Carbapenems, Oxazolidinones, Nitrofurans, B-lactam/B-lactamase inhibitors, Streptogramins, Ansamycins, Glycopeptides, Tetracyclines and Folate pathway inhibitors.

** Drug resistant (DR) denotes resistance to more than one antibiotic category/class.

† Multi-drug resistant (MDR) denotes non-susceptibility to at least one agent in three or more antimicrobial categories.

β XDR denotes non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories).

‡ PDR denotes non-susceptibility to all agents in all antimicrobial categories.

11. DISCUSSION

The discussion of the study results has been summarised in three main subsections, focussing on the specific objectives of this study – documentation of antimicrobial susceptibility patterns (section 11.1) as well as description of the patterns with clinical profiles correlated (section 11.2). The clinical implications of the above results have been discussed in section 11.3.

11.1. Antimicrobial susceptibility patterns

The overall objective of this study was to describe the antimicrobial susceptibility patterns of bacterial isolates from culture specimens of KNH medical ward inpatients. This was accomplished whereby the 1-year retrospective review provided a picture of resistance patterns for antibiogram construction with adequate numbers of isolates. A total of 1064 isolates were reported during the 15 months under study, and 241 of them were excluded due to reasons such as duplicate isolates or missing data. By the time of publication, this was the highest number of isolates ever collected in a research dissertation since the laboratory surveillance by Omari which studied 7416 organisms cultured from the year 1991 to 1995. It is important to bear in mind that this was a real-world scenario study, where specimen collection in the wards and subsequent testing in the laboratory was done as per routine, without any influence or intervention.

The three bacterial agents of greatest concern in global antibiotic resistance (*E. coli*, *K. pneumoniae* and *S. aureus*) outlined by WHO (1) formed the majority of the bacteria isolated in both the retrospective and prospective arms of the study. *E. coli* and *K. pneumoniae* collectively contributed over 60% of the Gram negative isolates (34% and 26% respectively in the retrospective part of the study, 35% and 34% in the prospective) whereas *S. aureus* formed the bulk of the Gram positive isolates (34% in the retrospective, 22% in the prospective). This spectrum of isolates has also been demonstrated locally (18,20) and internationally (4) in other facilities where these three bacteria were the most common pathogens causing infection. Therefore, these organisms are of important consideration to a clinician when prescribing therapy to treat bacterial infections, especially those caused by gram negative organisms whose outer membrane confers additional resistance to antibiotics as compared to gram positive organisms which lack it(51). Emphasis will

be placed on discussing the resistance patterns in the retrospective data over that in the prospective, since the retrospective review met the 1-year time period required for antibiogram reporting according to the CLSI standards. However as previously mentioned, the patterns seen in both datasets were similar.

A number of the antibiotic-resistant organisms belonging to the 12 WHO priority pathogens list published in February 2017 were reported in our study, forming the basis of the discussion on resistance patterns(52). This list contains bacteria that pose the greatest threat to human health, and for which new antibiotics are urgently needed. There is paucity of data on these organisms in our region, and thus this study has contributed to filling these knowledge gaps (table 6). Further discussion on the main antibiotic-resistant organisms has been elaborated under the main antibiotic classes below.

11.1.1. Carbapenem resistance

The paucity of data on carbapenem-resistance organisms in our region has been previously acknowledged in the WHO 2014 report (1). Our study helped to contribute towards filling of these existing knowledge gaps. We demonstrated significant rates of antimicrobial resistance to carbapenems, mostly in *A. baumanii* (73%) followed by *P. aeruginosa* (30%), *K. pneumoniae* (24%) and *E. coli* (13%). A local private tertiary hospital Aga Khan University Hospital Nairobi (AKUHN), reported less rates of carbapenem resistance(19) among inpatients in 2014 for *A. baumanii* (55%), *P. aeruginosa* (15%), *K. pneumoniae* (8%) and *E. coli* (2%). AKUHN has an inpatient capacity of 300 beds with patients drawn predominantly from upper middle and high socioeconomic groups of mixed race (20) whereas KNH has a 1800-bed capacity with primarily low-middle income African Kenyan patients as the majority. These differences in resistance rates could be accounted for by differences in hospital infrastructure and patient demographics in the private facility (higher sociodemographic status with fewer total inpatients) as compared to KNH. AKUHN also has stronger antibiotic stewardship programmes which include restricted prescription of reserve antibiotics such as carbapenems, and better hand sanitisation practices (29).

The results in our study depicted higher local rates of resistance to carbapenems in KNH as compared to previous studies. The few KNH studies previously done have documented lower rates

of resistance to carbapenems among various organisms such as Ratemo's study in 2013 which showed resistant *A. baumanii* (41.2%), *P. aeruginosa* (18.9%), *K. pneumoniae* (9.5%) and *E. coli* (0%) (21). A 2013 publication reporting ESBL resistance patterns in a Kenyan private tertiary hospital noted 0.6% resistance to meropenem(18). This is comparable to WHO 2014 estimates in South Africa which showed 1% resistance to meropenem and 3.8% resistance to ertapenem in an analysis of 923 blood culture isolates in 2012(1). However, the little global data available from WHO is from the region of the Americas and Europe, with some reports of more than 50% resistance to carbapenems in two WHO regions(1).

Ultimately, the worrying trends in our public facility underscore the pertinent need for antibiotic stewardship, more so as indiscriminate consumption of carbapenems in KNH has been on the rise over the past few years. For instance, KNH Pharmacy records showed approximately 177% increase in money spent to procure meropenem in KNH between 2013 to 2015 (53). Among other things, this increase could reflect the levels of high carbapenem use in our setup, thus highlighting the economic implications of unchecked clinician prescription practices in treating infections caused by bacteria, which may be resistant to these drugs.

11.1.2. Third-generation cephalosporin resistance

Cephalosporins, especially the third-generation such as Ceftriaxone and Ceftazidime, are among the most prescribed antibiotics in KNH by most cadres of clinicians and this is reflected as well in other local hospitals (18). More than half (51%) of the patients included in the prospective arm had Ceftriaxone as their empiric antibiotic prescribed in the medical ward. Consequently there were alarming rates of Ceftriaxone and Ceftazidime resistance reported for *E. coli* (75% and 66%) and *K. pneumoniae* (82% and 83%) respectively. These rates surpass those seen in other private local facilities such as AKUHN which registered 49% *E. coli* and 61% *K. pneumoniae* resistance to Ceftriaxone among inpatients in 2014 (19). The disparity in antibiotic resistance rates could be possibly attributed to the differences in patient characteristics, disease burden, infrastructure, clinician prescription practices and antibiotic policies between these facilities. Meanwhile, a systematic review of antimicrobial resistance among clinically relevant isolates in sub-Saharan Africa published in 2014 reported median prevalence of third-generation cephalosporin resistance ranging between 0% to 22% in East Africa, between 6% and 15.4% in central South Africa and

between 0% and 46.5% in West Africa(16). This is in contrast to the global estimates of 50% and 30-60% for *E. coli* and *K. pneumoniae* respectively(1). Overall, the rates of cephalosporin resistance in this study surpass both regional and global estimates, and this could possibly be fuelled by the indiscriminate prescription of cephalosporins like ceftriaxone by clinicians in KNH. This underscores the need to explore such and other aggressive drivers of antimicrobial resistance in our setup and their effective mitigation thereof through practices such as informed empirical therapy prescriptions. For instance, nitrofurantoin has been recommended in both local and regional reports to be a favourable option for uncomplicated urinary tract infections caused by E. coli(16,20). Inasmuch as the antibiotic nitrofurantoin has been widely cited to have high sensitivity *in-vitro* (54–57), it has low efficacy in complicated urinary tract infections since it has poor concentration in tissues and blood, whereas high concentration in urine (56). This makes nitrofurantoin the preferred option for empiric therapy of uncomplicated urinary tract infections, as supported by the Infectious Disease Society of America (IDSA) and European Society for Microbiology and Infectious Disease(58). Ultimately, the use of nitrofurantoin reduces selection pressure off other drugs such as cephalosporins, fluoroquinolones and beta-lactams, thus allowing them to regain their lost sensitivity(57).

11.1.3. Methicillin-resistant staphylococcus aureus (MRSA)

Staphylococcus aureus has been known for the last half century to be "notorious" for its ability to rapidly develop antibiotic resistance, since it adapts very well to antibiotic pressure(59). This was noted with concern in the KNH medical wards, which documented 55% methicillin-resistance among 70 *S. aureus* isolates. This resistance rate compares to the 50.6% MRSA found among KNH paediatric surgical patients in 2014 (28), and also represents an increase from the 46.5% MRSA reported by Rutare who tested for the *mecA* resistance gene in *S. aureus* isolated from paediatric patients in ICU(60). Reports of MRSA have been on the rise in past studies carried out in various parts of KNH since the 27.7% MRSA rate published in 2003 (61). The presence of MRSA locally has been augmented by studies involving molecular gene typing of MRSA in both private and public healthcare setups, showing marked genetic diversity and significant presence of epidemic clones locally in Kenya(62). Although data from Africa is scarce, the WHO 2014 AMR report mentioned national data from 9 African countries ranging between 12-80% (1). A

systematic review of MRSA in Africa published in 2013 documents prevalence as high as 82% in some countries (63).

There is a sharp contrast between methicillin resistance reported in public hospitals such as KNH versus other private hospitals in Nairobi(27). The overwhelming high resistance of MRSA in 3 other Kenyan public health facilities was documented in a 2013 publication which reported 84.1% MRSA prevalence through molecular characterisation of the *mecA* gene(64). On the other hand, 2 private hospitals maintained low prevalence of about 3.7% during 2011-2013 and about 6% in 2014 using the automated identification system VITEK-2 (bioMérieux) (20,27,65). KNH introduced this automated system in 2013, as it confers the advantage of greater accuracy, reliability and speed of isolate identification and antimicrobial susceptibility(66) than conventional manual methods which may be subjective, as corroborated by other local facilities such as AKUHN (27). VITEK-2 (bioMérieux) accuracy has been widely reported in literature showing between 95% - 99% correct *S. aureus* species identification(67,68), 98.3% categorical agreement for staphylococcus testing(69) and negligible rates of false positives as low as 1.1% (70).

It can be hypothesised that the contrasting sociodemographics of the patient population in public versus private hospitals, as well as differences in healthcare workers' practices, antibiotic pressure, hospital environment (including infection control/antibiotic stewardship policies and infrastructure) may play a role contributing to this resistance. A 2013 literature review assessing burden of MRSA in Africa suggested socioeconomic conditions, communicable and non-communicable diseases and selection pressure due to antibiotic overutilization as factors influencing variable MRSA prevalence in the different localities(63). Of note, KNH is a tertiary referral public hospital which receives patients of low to middle income status directly from the community as well as referrals from other public primary and secondary healthcare facilities with a higher burden of comorbidities such as HIV, TB and malignancy. This makes it a melting pot for both community-acquired and nosocomial infections from other facilities as well as itself. All these reasons, together with high antibiotic consumption in the facility, can easily translate to higher burdens of antimicrobial resistance.

On the other hand, one can also speculate that there is a possible risk of overestimation of MRSA, through confounding by methicillin-resistant coagulase-negative staphylococcus (CoNS) species misidentified as *S. aureus*. CoNS are commensals found on anterior nares, skin and mucous

membranes and frequently cohabitate with *S. aureus*. As a result, both CoNS and *S. aureus* are frequently isolated together from the same clinical specimen(71). Misidentification occurs even when using chromogenic agar plates(72) as well molecular PCR methods(71). Since methicillin resistance gene *mecA* is detectable on resistant strains of CoNS as well as *S. aureus*, this presents a challenge in true MRSA reporting. False positives have been described (73). Since molecular detection of *mecA* alone is insufficient for true identification of MRSA, additional *S. aureus*-specific gene markers such as *nuc* (71) and *orfX* (73) have to be included during testing. These genetic assays improve accuracy, they are expensive and scarcely available. Ultimately, it has been suggested that the background local or regional MRSA prevalence should always be taken into account during reporting(71).

Another important consideration during MRSA interrogation is its inherent low susceptibility to all B-lactam antibiotics such as cephalosporins and even carbapenems(74). In our study, carbapenem sensitivity was lower for *S. aureus* (10% resistant) than for CoNS (0% resistant). One could argue from this that is possible that this small proportion of carbapenem-resistant *S. aureus* could be inferred to be MRSA. This 10% estimation is much lower than the 55% MRSA reported through oxacillin testing by the VITEK-2 (bioMérieux) system. It is also important to note that cefoxitin testing is currently preferred to oxacillin, since it is more accurate in detecting *mecA*-mediated resistance(50). The VITEK-2 (bioMérieux) system in the KNH laboratory was unable to carry out cefoxitin testing during the course of this study.

The controversy on true versus false MRSA identification in our setup can only be clearly settled by combined multiple gene sequencing, which is very expensive, and not widely available. Molecular methods were beyond the reach of the principal investigator. Building the capacity of our local microbiology laboratories to involve molecular methods in resistance testing would be ideal in our setup, and is highly recommended to improve diagnostic accuracy. Some noteworthy efforts towards molecular characterisation of resistant *S. aureus* have already began on a small scale in some local private healthcare facilities, notwithstanding financial challenges(62). Ultimately, there is a need for standard external reference laboratories which can perform molecular testing and surveillance of such critical isolates from various local laboratories, eventually contributing towards a central national database of resistance data.

11.2. Correlates of antimicrobial resistance

Owing to its intended design, the smaller prospective arm of the study captured valuable patient data and clinical information, thus clinical correlates could be inferred to the pre-existing retrospective data, providing a richer clinical approach to a largely microbiological study.

11.2.1. Patient comorbidities

Seventy-two percent of the patients in the prospective arm had at least one comorbidity. Renal failure was the most frequent comorbidity (33% of all patients), followed by diabetes (21%), HIV (20%) and malignancy (12%). There was a high prevalence of drug-resistant bacteria isolated from the patients with comorbidities. About seventy-three percent (73%) of the drug-resistant organisms, 73.4% of the MDR organisms, 68.8% of the XDR organisms and 66.7% of the PDR organisms were isolated from these patients. The numbers of isolates in the prospective arm were too few to demonstrate association, thus worth exploring in further studies. It has been recognised in literature that comorbidities conferring immunodeficiency favour antibiotic resistance during the course of their treatment(9). For instance, a literature review assessing MRSA prevalence in Africa cited comorbidities such as HIV, TB and non-communicable diseases like cancer, as some of the factors which make it difficult to control resistant strains in the sub-Saharan countries(63).

11.2.2. Instrumentation

An overwhelming majority (94%) of the patients had used a form of indwelling medical device. Ninety-one percent (91%) of the total patients had an intravenous line in situ, whereas other forms of devices used included urinary catheter (45%), nasogastric tube (22%), endotracheal tube (17%), central venous catheter (16%) and haemodialysis catheter (16%). A large proportion of these patients' specimens grew resistant isolates. About 94.8% of the multidrug-resistant (MDR) organisms, 97.9% of the extensively-drug resistant organisms and 83.3% of the pandrug-resistant organisms were isolated from patients with indwelling devices. Increased incidence of device-related antibiotic resistant organisms such as *S. aureus* (75) and *K. pneumoniae* (76) have been reported widely in literature and are associated with biofilm colonisation of these indwelling devices that are used extensively and for longer periods of time(12).

11.2.3. Empirical antibiotic therapy

There was high utilisation of antibiotics before culture (68% of all patients). Cephalosporins were the most frequently prescribed medications (51% of all the patients) followed by Nitroimidazoles (mainly Metronidazole in 22% of patients), Penicillins (16%), Carbapenems (mainly Meropenem in 12%), Macrolides (9%), Quinolones (8%) and Aminoglycosides (3%). Other antibiotics used sparingly (6% of patients) included Vancomycin, Linezolid and Mupirocin.

About 68.5% of drug-resistant isolates, 69.9% of MDR, 79.2% of XDR and 66.7% of PDR isolates were obtained from patients exposed to empirical antibiotics. The median duration of antibiotic therapy in these patients was about 4 days. The antibiotics prescribed most frequently by clinicians revealed higher resistance patterns (such as 75% *E.coli* and 82% *K. pneumoniae* ceftriaxone resistance) than those least prescribed (such as 1% *S. aureus* linezolid resistance). Since this study captured community-acquired infections as well, the high *E. coli* resistance to ciprofloxacin (78%), amoxicillin/clavulanic acid (74%) and trimethoprim-sulfamethoxazole (93%) may possibly point towards overexposure especially in the community where these drugs are largely used for urinary tract infections, respiratory illness and HIV prophylaxis respectively(20). High antimicrobial resistance rates to these drugs was similarly noted in recent studies in AKUHN which revealed high *E.coli* resistance rates such as to amoxicillin (78%) and trimethoprim-sulfamethoxazole (77%) (20).

Excessive antibiotic consumption in Kenyan hospitals and in the community at large was clearly recognised by majority of KNH doctors in a Knowledge, Attitude and Practice (KAP) survey by Genga (77) thus supporting the earlier-stated implications of antibiotic overutilization on AMR rates. Although this study was not designed to establish direct associations between antibiotic exposure and drug resistance, the above data implies a correlation between the two, and should be studied further to establish significance. Apart from the morbidity and mortality due to accelerated AMR, it is important to note that inappropriate antibiotic prescription has been further associated with increased risk of adverse effects, increased patient re-attendance and self-medication which should be avoided (78).

11.2.4. Duration of inpatient stay before culture

The median duration of inpatient stay before culture specimens were taken was about 5 days. Although longer durations of hospitalisation have been associated with development of resistance, this study was not designed to assess hospital stay and establish corresponding associations of significance. Further studies are recommended to this effect.

11.3. Clinical implications

In public tertiary facilities such as KNH with high rates of antimicrobial resistance, the onus falls on the clinician to promote antibiotic stewardship and other modifiable factors to preserve the efficacy of these vital drugs. This is pertinent since non-modifiable factors such as patient comorbidities, socioeconomic and health-seeking behaviours may be harder to mitigate. Clinician practices can still play a significant role to curb this mixed picture of resistance, which threatens to grow to alarming levels in our facility. The following describes the implications of the results of this study as a whole, with specific emphasis on both the laboratory and clinician practices.

11.3.1. Specimen collection and laboratory testing

Out of the 1064 isolates collectively reported in both arms of the study, 241 of them were excluded from analysis for the reasons aforementioned. It is important to note that processing of specimen that do not reach clinical decision making is regrettable because resources have been used, with less than optimum benefit accorded to the patient. At research level, these excluded isolates may have influenced the exact antimicrobial resistance patterns of certain microbes. However, the major bacterial species were well represented with more than the CLSI minimum recommendation of 30 isolates each, thus giving adequate information that was deemed clinically significant.

The majority of isolates reported were from urine and pus specimens (77% of total isolates in 1 year). Very few isolates from sanctuary sites (such as cerebrospinal, peritoneal, pleural fluid) were reported. Clinicians in our setup ought to be encouraged to be aggressive in looking for causes for infection in these sites, which may be difficult to access during specimen collection. This also holds true for respiratory tract infections, since we noted that sputum formed a small proportion of specimens received in the laboratory for testing, despite the high burden of these infections in our setup. Blood cultures contributed the third highest number of isolates tested (11% of total isolates in 1 year). These were relatively few in number, yet bloodstream isolates ideally make an

important contribution towards antibiogram construction. Considering all the above, had clinicians collected larger numbers of valid specimens, the laboratory would have been able to generate enough significant data to construct a comprehensive antibiogram that would greatly aid clinical practice in treating infections caused by multi-drug resistant organisms.

Inasmuch as external validation and quality assurance of the laboratory procedures was done using international bodies (WHO/NICD and NEQAS outlined in Section 7), our study highlighted key areas that need to be addressed in order to improve the quality of specimen tested and subsequent results generated. This study was a real-world scenario study without any direct interventions, thereby enabling the principal investigator to interrogate ward and laboratory practices, and compare it to standard practice and literature worldwide. A key component for accurate laboratory diagnosis involves proper adequate collection and transport of high quality specimen to the microbiology laboratory,(79) which was not a study objective in this case. A large proportion of the gram positive isolates were coagulase negative staphylococcus (*S. epidermidis, S. haemolyticus* and others) forming about 26.3% of the gram positive bacteria that were isolated in the retrospective arm. This may suggest indiscriminate specimen collection of pus and blood samples done by clinicians in the ward, which may not have been carefully carried out using the proper procedures that are aimed to collect only the pathogenic bacteria. As a result, a lot of commensals were presented to the laboratory for isolation and antibiotic susceptibility testing, and naturally the laboratory could only report what had been presented to it. This bears pertinent implications for the clinicians, who need to be educated on proper specimen collection techniques in order to increase chances of isolating true pathogenic bacteria causing disease vis-à-vis commensals. This would greatly increase the quality of culture results reported, leading to improved patient care. For accurate antibiotic susceptibility reporting that can influence policy recommendations, we recommend a larger prospective study in which sensitized clinicians would carefully collect specimen from the wards and careful interrogation done in the laboratory in order to tease out non-pathogenic species. It is important to note that antibiograms are largely constructed using retrospective annual data, and thus factors contributing to suboptimal results (such as poor specimen collection) should be remedied in order for acceptable antibiogram construction.

Some prominent bacterial species were conspicuously absent in the laboratory reports. These include anaerobic bacteria and fastidious organisms such as *Neisseria* and *Streptococcus*

pneumoniae. This points to the current laboratory capacity which currently can only cater for aerobic cultures. Additionally, it is plausible that many of the fastidious organisms may not have been isolated by the laboratory due to the lack of their respective transport media and culture media supporting fastidious growth. For instance, the pus specimen collection in the wards was done using dry swab sticks, and there was no transport media available for the isolates that required it. The variable transit time and delays between ward and eventual laboratory testing could also have potentially compromised the quality of specimen to be tested. Therefore, our study underscores the need to build capacity in our setup to cater for anaerobic cultures, as well as swab transport systems and appropriate culture media to increase yield of fastidious organisms, all done in a timely manner with minimal delays. Such transport systems and culture recovery of fastidious organisms has been outlined in CLSI recommendations and in literature worldwide(80,81).

11.3.2. Informed prescription practices

Empirical antibiotic therapy should be checked and limited to patients in which there are clear indications for it. An accurate diagnosis of bacterial infection is paramount above all else. Restriction of antibiotic prescription, especially of reserve broad-spectrum antibiotics such as the carbapanems ought to be done to preserve their potency. As seen in this study, penicillins, cephalosporins and fluoroquinolones which ought to be among the first-line of empiric antibiotic therapy demonstrated alarming rates of declining susceptibility. Clinician choices when selecting empirical therapy should be guided by updated antibiograms pending culture and sensitivity results, while considering the most likely organisms and type of infection to be treated with acceptable antibiotic susceptibility rates. This algorithm has been duly packaged into a sample clinician pocket antibiogram for the WHO priority-pathogens isolated from medical wards in Figure 6 below. A caveat exists in that such antibiograms can only be created after careful interrogation by a duly-constituted multi-disciplinary Antibiotic Stewardship committee. Such a document could be a quick handy reference guide for clinicians prescribing antibiotic therapy for medical ward inpatients.

For severe infections, a de-escalation strategy of empirical therapy would apply, where the broad-spectrum antibiotic with highest susceptibility in the antibiogram would be initially selected. Once culture & sensitivity results are available, the therapy would then be de-escalated to the narrow-

spectrum antibiotic with the highest susceptibility seen in the AST results. For instance, according to the sample antibiogram for medical wards (Figure 6), the choice of empiric therapy for severe *E.coli, K. pneumoniae, P. aeruginosa* and *A. baumanii* infections would include amikacin and meropenem. Severe *S. aureus* infections would include imipenem, vancomycin or linezolid as options for empiric therapy. Empirical therapy for severe *P. mirabilis* infections would include amikacin, meropenem and piperacillin-tazobactam.

For less severe infections, it would be favourable to choose an empiric antibiotic with modest susceptibility in order to reduce broad-spectrum antibiotic selection pressure on organisms. These antibiotics ought to be preserved at all costs. The findings from this study have shown overwhelming resistance to cephalosporins, fluoroquinolones and penicillins such as amoxicillin, which is most likely attributable to their indiscriminate use. According to the proposed antibiogram for medical wards, the choice of empiric therapy for less severe *P. aeruginosa* would include ceftazidime and ciprofloxacin, which have moderate antibiotic susceptibility. *E. coli* urinary tract infections for example would be treated with nitrofurantoin (which has moderate susceptibility) and not ciprofloxacin or amoxicillin-clavulanic acid (low susceptibility). Less severe *S. aureus* infections would be empirically treated with erythromycin, clindamycin or levofloxacin.

It is imperative to note that the heterogeneous definition of disease severity needs to be taken within clinical context, considering symptomatology, probable causative species among other factors. For instance, Acinetobacter infections presenting with "less severe" symptoms, would still need broad-spectrum therapy. Ultimately, empiric prescribing ought to be based on hospital-driven guidelines for the individualised management of various conditions. It can therefore be seen that a paradigm shift is required in utilisation of antibiotics by clinicians in order to combat antibiotic resistance.

11.3.3. Use of indwelling medical devices

Instrumentation should be done only for patients in whom there are clear indications for insertion of indwelling devices. This should be done for the minimum length of time as possible, as this reduces the chances of biofilm development which promotes growth of resistant organisms.

Figure 6: Sample Pocket Antibiogram for Clinicians - Antimicrobial susceptibility patterns for KNH medical wards in 2015

ORGANISM CHARACTERISTICS						PERCENT SUSCEPTIBLE (%S)*																						
ISOLATE DETAILS		SOURCE OF INFECTION				PENICILLINS					CEPHALOSPORINS				CARBAPENEMS		FLUOROQUINOLONES			AMINOGLYCOSIDES		MACROLIDES		OTHERS				
Organism	No. of strains	Urine	Wound	Blood	Resp	Amoxicillin-Clavulanic acid	Ampicillin-Sulbactam	Oxacillin	Penicillin G	Piperacillin-Tazobactam	Cefuroxime	Ceftriaxone	Ceftazidime	Cefepime	Meropenem	Imipenem	Ciprofloxacin	Levofloxacin	Moxifloxacin	Amikacin	Gentamicin	Clindamycin	Erythromycin	Vancomycin	Linezolid	Nitrofurantoin	Trimethoprim-Sulfamethoxazole	Tetracycline
E. coli	**143**	64%	23%	6%	0%	26	8	-	-	48	20	25	34	43	87	-	22	-	-	97	53	-	-	-	-	56	7	-
K. pneumoniae	**110**	69%	15%	7%	5%	27	-	-	-	33	16	18	17	36	76	-	44	-	-	91	31	-	-	-	-	8	10	-
S. aureus	**70**	6%	80%	10%	0%	-	-	45	3	-	70	-	-	-	-	90	-	59	61	-	78	64	59	97	99	100‡	29	51
P. mirabilis	**32**	16%	81%	3%	0%	81	59	-	-	100	34	50	75	53	97	-	72	-	-	100	53	-	-	-	-	-	9	-
P. aeruginosa~	**27**	7%	85%	4%	0%	-	-	-	-	56	-	-	70	78	70	-	73	-	-	89	82	-	-	-	-	-	-	-
A. baumannii ~	**26**	15%	69%	12%	0%	-	23	-	-	19	-	8	19	19	27	-	23	-	-	89	27	-	-	-	-	-	15	-

KEY:

* The percent susceptible for each organism/antimicrobial combination was generated by including the first isolate of that organism encountered on a given patient.

‡ Suggested interpretation for urine isolates

~ Limited interpretation: Calculated from fewer than the standard recommendation of 30 isolates

12. CONCLUSION

In conclusion, this study addressed the current knowledge gaps regarding the antibiotic susceptibility patterns in the medical wards at KNH. The results revealed overwhelming resistance to commonly used antibiotics such as penicillins and cephalosporins, with possible drivers such as inappropriate clinician prescription of antibiotics. This underscores the need for standard guided empiric therapy only where indicated, as well as restricted prescription for reserve antibiotics following culture and sensitivity testing. Overall, collaborative efforts are essential to strengthen antimicrobial stewardship, and promote regular surveillance and further research towards combating antimicrobial resistance for the present and future generations to come.

13. RECOMMENDATIONS

13.1.1. Adequate prospective antimicrobial susceptibility studies

We recommend larger prospective AMS studies (spanning at least one year) which will involve sensitised clinicians who are trained in proper specimen collection. This will minimise isolation of commensals and aim at increasing yield of pathogenic bacteria from various body specimens including those from sanctuary sites. These isolates will include adequate numbers (more than 30 isolates) of clinically significant species such as Acinetobacter and Pseudomonas which ought to be included in antibiogram data. Adequate and proper specimen collection will also aim to increase yield of bloodstream isolates which make a significant contribution towards antibiograms. Lastly, such studies could help determine culture isolation rates, by analysing both culture positive and negative reports, thus helping to form recommendations for the clinician on how to improve culture yield in our setup.

13.1.2. Antibiotic Stewardship and Infection Control practices

Robust antibiotic stewardship programmes in KNH promoting proper antimicrobial utilisation will go a long way to reduce the antibiotic pressure causing selection of resistant organisms. Strengthening of infection control practices plays a big role towards curbing antimicrobial resistance as exemplified by South Africa's declining MRSA resistance attributed to effective

infection control(63). Simple practices such as handwashing have been noted in literature to have an impact.

13.1.3. Education and sensitization of healthcare professionals

A knowledge gap among KNH doctors in matters concerning antimicrobial resistance, antibiotic prescription, infectious diseases, microbiology was noted by Genga in 2016 (77). Empowerment of these clinicians and healthcare professions through university teaching curriculums, frequent symposiums and workshops will go a long way in changing inappropriate practices that drive AMR. Clinicians should also be educated on adequate specimen collection practices and techniques which will increase the accuracy and relevance of laboratory testing and reporting.

Circulation of updated antibiograms constructed by a multidisciplinary Antibiotic Stewardship committee to the various clinical areas of the hospital will enhance appropriate antibiotic usage as well as curb unnecessary prescription and loss in potency of these vital drugs. These antibiograms should be individualised for each of the various units in the hospital and disseminated to the respective clinicians working in those areas for their daily use.

13.1.4. Continuous AMR surveillance

Regular surveillance of antimicrobial resistant organisms should be undertaken in the various clinical areas of the hospital, including the critical care units. This will help raise awareness on the current trends in the hospital and appropriate notification where necessary. Surveillance is key to monitoring and checking antibiotic resistance.

13.1.5. Building KNH laboratory capacity

Molecular typing of resistant organisms, archiving of isolates for further testing and reinforcement of both automated and biochemical laboratory methods are some of the initiatives that would strengthen the diagnostic capacity of the microbiology laboratory and increase the accuracy of the data reported. External validation has a role to play in quality control and accuracy checks. These external reference laboratories in conjunction with KNH laboratory would carry out strict surveillance of MDR organisms such as MRSA, as well as provide extended testing of MDR species with supplementary antibiotic panels that are not routinely available in local clinical laboratories. Clinicians and patients will also benefit from expanding local laboratory resources to regularly avail biomarkers such as C-reactive protein, procalcitonin as adjunct guides to antibiotic therapy.

14. STUDY STRENGTHS AND LIMITATIONS

Strengths of this study include:

1. High clinical relevance and application value: the prospective arm of this study augmented the purely microbiological retrospective review by providing valuable patient and clinician information from which clinical applications could be derived.
2. Statistical benefit of a census: By reporting census data from all isolates, narrower confidence intervals were achieved thus attainment of a higher degree of statistical significance.
3. Real-world scenario: Since the processes involved from specimen collection in the ward to the laboratory reporting of isolates was not under the direct intervention of the investigator, this study informally audited the usual practices in our setup. This brought out additional key issues for discussion and suggestions for improvement of clinical and laboratory services.
4. Wealth of microbiological data: To the best of the investigator's knowledge, this is the largest dissertation study on antimicrobial resistance carried out in KNH, which collected data on 1064 bacterial isolates in total.
5. Use of reliable automated systems: This study employed the use of a reliable, accurate and rapid automated microbial identification and susceptibility testing - VITEK-2 (bioMérieux) which has manifold advantages.

Limitations of this study and setbacks encountered include:

1. Limited specimen profile and isolation of pathogenic species: Blood and respiratory isolates were relatively few in number despite the burden of these infections in our setup. Furthermore, improper specimen collection by clinicians led to some laboratory reporting of commensals which bear little clinical significance.
2. Few number of isolates for certain species, and specimen types: Some species such as *Acinetobacter* and *Pseudomonas* were less than 30 isolates each in number. By virtue of being less than the CLSI recommended 30 isolates per species, the antibiotic susceptibility results for these two organisms should be interpreted with caution. On the other hand, the few blood culture isolates in general that were reported also forms a limitation in this study.

3. Laboratory limitations: The laboratory was unable to perform anaerobic cultures, and could not provide swab transport systems and culture media for fastidious organisms, thus reducing yield of some potential growths. Despite being capable of performing coagulase testing and cefoxitin disk screening on staphylococcus isolates, the laboratory did not routinely use this method due to its reliance on VITEK-2 for microbial identification and antibiotic susceptibility testing. Failure of the laboratory to archive specimens meant that controversial isolates (such as MRSA) could not be retrieved and retested in case of any clarifications after a certain period of time had elapsed. Another limitation encountered was missing laboratory reagents. The microbiology laboratory lacked VITEK-2 identification and AST cards for a large period in 2016, hence significantly delaying recruitment in the prospective arm. Inasmuch as the laboratory tested a majority of the major antibiotic classes, some reserve antibiotics such as colistin were unavailable for testing due to their scarce utilisation in our setup.
4. Lack of novel molecular genotyping methods in the hospital meant that confirmation and further characterisation of resistant strains (such as MRSA) could not be achieved, as is the gold standard in other parts of the world.
5. Lack of generalisability: The study was carried out in one clinical area of the hospital (medical wards) and thus the results may not be generalizable to the rest of the hospital.
6. Incomplete data: There was data loss at the clinician level, where some patient details were not captured in patient files; and at the laboratory level, where some specimen details were not input into the laboratory system. Some patient files were also untraceable in the health information department. Isolates with missing data was excluded from the study.
7. Force majeure events: The 2016 nationwide doctor's strike affected operations in the hospital, hence less patient recruitment than what was initially envisaged.

15. BIBLIOGRAPHY

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16. APPENDIX

A. STUDY TIMELINES

The following represents the various phases of this research study with estimated timelines for each:

Figure 7: Study Timeframe

	Apr '16	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan '17	Feb	Mar	Apr	May	Jun	Jul
Protocol presentation	X															
Ethical approval	X	X	X	X												
Data collection						X	X	X	X							
Data analysis										X	X	X				
Dissertation development													X	X	X	
Results presentation																X
Correction & submission																X

B. STUDY BUDGET

Figure 8: Budgetary expenditure for study implementation

ITEM	COST (Ksh)
Ethics fees	2,000
Operating costs (stationary, photocopy etc)	20,000
Data collection procedures	30,000
Data analysis procedures	30,000
TOTAL	**82,000**

C. DATA ABSTRACTION TOOL

Laboratory No: _____

I. PATIENT INFORMATION

1. **Patient Age:** ……Yrs
2. **Patient Sex:** Male ☐ Female ☐
3. **Patient Ward Location:** 7A ☐ 7C ☐ 8A ☐ 8C ☐
   7B ☐ 7D ☐ 8B ☐ 8D ☐
   8A CCU ☐
4. **Admission Date (dd/mm/yy):** _____
5. **Admission Diagnosis:** _____
6. **Presence of comorbidities**:
   If yes, specify: Diabetes ☐ HIV ☐ Malignancy ☐
   Renal failure ☐ Other _____
7. **Use of empirical antibiotic:** YES ☐ NO ☐
   If yes, Duration of empirical antibiotic (days): _____
8. **Use of instrumentation:** YES ☐ NO ☐
9. If yes, Type used: Urinary catheter ☐ Central Venous Catheter ☐
   Intravenous line ☐ Haemodialysis catheter ☐
   Nasogastric tube ☐ Other _____
10. **Duration of inpatient stay before culture taken (days):** _____

II. SPECIMEN INFORMATION

1. **Specimen Type:** Urine ☐ Pus Swab _____ ☐
   Blood Culture ☐ Pleural Fluid ☐
   Sputum ☐ Peritoneal fluid ☐
   Cerebrospinal Fluid ☐ Synovial Fluid ☐
   Stool ☐ Other _____

2. Date of specimen arrival in laboratory (dd/mm/yy): _____

3. Organism isolated: _____

4. Reporting date (dd/mm/yy): _____

5. Antibiotic Susceptibility Result:

DRUG	**%S**	**DRUG**	**%S**	**DRUG**	**%S**
Benzylpenicillin		Amikacin		Ampicillin	
Cefoxitin Screen		Amoxicillin/Clavulanic acid		Ampicillin/Sulbactam	
Clindamycin		Ampicillin		Benzylpenicillin	
Erythromycin		Ampicillin/Sulbactam		Cefuroxime	
Fosfomycin		Aztreonam		Clindamycin	
Fusidic acid		Cefazolin		Erythromycin	
Gentamicin		Cefepime		Gentamicin	
Inducible Clindamycin Resistance		Cefotaxime		Imipenem	
Levofloxacin		Cefoxitin		Levofloxacin	
Linezolid		Ceftazidime		Linezolid	
Moxifloxacin		Ceftriaxone		Moxifloxacin	
Mupirocin		Cefuroxime		Nitrofurantoin	
Nitrofurantoin		Ciprofloxacin		Quinipristin/Dalfopristin	
Oxacillin		Gentamicin		Streptomycin	
Rifampicin		Meropenem		Teicoplanin	
Teicoplanin		Nitrofurantoin		Tetracycline	
Tetracycline		Piperacillin/Tazobactam		Tigecycline	
Tigecycline		Trimethoprim/Sulfamethoxazole		Trimethoprim/Sulfamethoxazole	
Tobramycin				Vancomycin	
Trimethoprim/Sulfamethoxazole					
Vancomycin					

D. CONSENT FORM

Antimicrobial Susceptibility Patterns of Bacterial Isolates from Patients in Medical Wards at Kenyatta National Hospital in 2015-2016

Introduction

Hello, my name is Dr Frederick Wangai. I am a post-graduate student currently pursuing a Masters' degree in Internal Medicine at the University of Nairobi. I am conducting a research project for which I request your participation. Make sure you thoroughly read this form and feel free to ask any questions/ clarifications at any point, before going ahead and taking part in the study.

Objectives of the study

This study will assess the antimicrobial susceptibility patterns of bacterial isolates obtained from medical ward inpatients. This involves research which will aid doctors in making informed decisions while prescribing antibiotics and improve on management and outcomes of patients with bacterial infections. In order to do this, I am required to review patient sociodemographic and clinical information from their files. You will not be required to actively participate in this study and hence I will not take any of your time after signing this consent.

Confidentiality

If you choose to be in the study, I will only collect relevant clinical information in your file without any personal identifiers that can be linked to you. I will only be reviewing relevant laboratory and clinical information from your file. The data extracted will be completely anonymous and your privacy will be maintained. We respect your privacy and will uphold utmost confidentiality.

Risks

There are no foreseeable risks with no bodily harm, as this is a non-invasive study. I will not draw any specimen from you.

Benefits

There are no financial benefits to you for participating in this study. There is no cost or payment to you. However, the results of this study will greatly positively impact patient management in this ward and hospital and help our doctors treat bacterial infections more effectively.

Voluntariness of participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. If you choose not to participate all the services you receive in this hospital will continue and nothing will change. If you decline consent, we will not access your file in any way for purposes of this study.

Reimbursements

You will not be provided any incentive to take part in the study.

Who to Contact

If you have questions about this research study you may contact the Principal Investigator Dr Frederick Wangai on cellphone number 0722 465699. The Kenyatta National Hospital-University of Nairobi Ethical Review Committee (KNH-UON ERC) is responsible for this study. If you feel as if you were not treated well during this study, or have questions concerning your rights as a research participant call the KNH/UoN-ERC Chairperson on Tel. No. 2726300 Ext 44102. Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate. May I continue?

CERTIFICATE OF CONSENT (THIS SECTION IS MANDATORY)

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study. If I have questions later on about the research I can ask the investigator below.

Signature of subject_____ Date_____

Name of subject_____

Witness (Principal Investigator or Research Assistant) _____

If illiterate,

Print name of witness_____ Thumbprint of participant

Signature of witness _____ Date _____

Declaration statement by the researcher/person taking consent
I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

For further clarification, kindly contact

Principal Investigator:

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FOMU YA IDHINI

Jinsi Vimelea vya bakteria kutoka wagonjwa wa wodi za utabibu katika Hospitali ya Kenyatta vinavyoathiriwa na dawa za antibiotiki kutoka mwaka 2015-2016

Mwanzo

Jina langu ni Dkt Frederick Wangai. Mimi ni mwanafunzi wa chuo kikuu cha Nairobi katika shahada ya pili. Niko katika kitengo cha utabibu. Ninafanya uchunguzi ambao unahitaji kujiunga kwako. Tafadhali soma fomu hii kwa makini na uwe huru kuuliza maswali yoyote kabla ya kujiunga na utafiti huu.

Malengo ya utafiti huu

Utafiti huu utachunguza jinsi vimelea vya aina ya bakteria vinavyotibiwa na dawa mbalimbali. Uchunguzi huu utawasaidia madaktari kufanya uamuzi bora wanapochagua dawa za kutibu magonjwa ili wagonjwa wapate nafuu. Nitafanya huu uchunguzi kwa kuangalia mambo ya kiasili na ya matibabu yanayohusu mgonjwa katika rekodi za faili yake. Wewe hutahusika kwa namna yoyote katika utafiti huu na sitachukua muda wako baada ya kunipa idhini.

Usiri

Ukikubali rekodi zako kutumika katika utafiti huu, nitazichukua kwa siri ili usijulikane kamwe. Nitakagua rekodi za maabara na za matibabu yako yanayokuhusu kutoka faili lako. Hakuna mtu yeyote ambaye atakutambua kutokana na rekodi katika uchunguzi huu. Habari yoyote itakayopatikana katika utafiti huu kutoka katika faili lako na kutoka kwako itawekwa kisiri. Tunaheshimu haki zako za usiri na tutahifadhi mambo yako.

Athari

Hakuna athari zozote za kushiriki katika uchunguzi huu kwa vile mwili wa mgonjwa hautaguswa, bali tu kuangalia rekodi mbalimbali zinazohusu mgonjwa.

Manufaa

Hakuna malipo yoyote kwako utakapojiunga katika utafiti huu bali kujiunga kwako na utafiti huu itawasaidia madaktari kuboresha huduma zao kwa wagonjwa haswa wanapotibu magonjwa yanayoletwa na bakteria.

Hiari ya kuungana mkono

Kujiunga na utafiti huu ni kwa hiari yako .Ni chaguo lako kujiunga na utafiti huu. Ukichagua kutojiunga na utafiti huu, utaendelea kupata huduma zote katika hospitali na hakuna kitu kitakachobadilika. Ukikataa kunipa idhini, hatutatumia rekodi zako kwa njia yoyote katika utafiti huu.

Malipo

Hatutakushawishi kwa njia yoyote kujiunga na utafiti huu.

Mawasiliano

Iwapo una maswali yoyote kuhusu uchunguzi huu, unaweza kuwasiliana na Mtafiti Mkuu Dkt Frederick Wangai kupitia nambari ya simu 0722 465699. Kamati ya Maadili ya Utafiti katika Hospitali ya Kenyatta na Chuo kikuu cha Nairobi inasimamia uchunguzi huu. Ukihisi ya kwamba umedhulumiwa katika harakati za utafiti huu, ama ukiwa na maswali kuhusu haki zako unapojiunga na uchunguzi huu, unaweza kuwasiliana na mwenyekiti wa Kamati ya Maadili ya Utafiti kwa nambari ya simu 2726300 Ext 44102. Kujiunga katika utafiti huu ni kwa hiari yako, na huwezi kudhulumiwa wala kupoteza mafanikio yoyote usipotoa idhini ya kujiunga. Ninaomba idhini ya kuendelea?

CHETI CHA MAKUBALIANO (LAZIMA UJAZE SEHEMU HII)

Idhini

Nimekubali kujiunga na utafiti huu ambao umeelezwa kwa ukamilifu kwangu. Nimesoma na kuelewa maelezo yote. Maswali yangu yote yamejibiwa kwa ukamilifu na mtafiti. Nikiwa na maswali yoyote kuhusu uchunguzi huu, nitamwuliza Mtafiti Mkuu.

Sahihi_____ Tarehe _____
Jina _____
Shahidi (Mtafiti Mkuu/Msaidizi)_____

Kwa mgonjwa asiyeweza kusoma wala kuandika,

Jina la Shahidi _____ Kidole cha gumba
Sahihi ya Shahidi _____
Tarehe _____

Thibitisho la mtafiti/ anayeomba idhini

Ninahakikisha mtu huyu hajalazimishwa kunipa ruhusa ya kujiunga na utafiti huu. Amekubali kujiunga na utafiti huu kwa hiari yake. Nimethibitisha ya kwamba nimepewa ruhusa na mgonjwa.

Mtafiti /aliyepewa kibali_____

Sahihi _____

Tarehe _____

Ukiwa na maswali yoyote ya ziada, unaweza kuwasiliana na wafuatao:

Dkt Frederick Wangai (Mtafiti Mkuu)
SLP 62610-00200 Nairobi
Tel 0722 465 699

Taasisi:

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
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KNH/UON-ERC
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Website: http://erc.uonbi.ac.ke

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Ref: KNH-ERC/A/258

13th July 2016

Dr. Fredrick K. Wangai
Reg. No. H58/74412/2014
Dept. of Clinical Medicine and Therapeutics
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Wangai,

REVISED RESEARCH PROPOSAL: ANTIMICROBIAL SUSCEPTIBILITY PATTERNS OF BACTERIAL ISOLATES FROM PATIENTS IN MEDICAL WARDS AT KENYATTA NATIONAL HOSPITAL (P310/04/2016)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and approved your above proposal. The approval period is from 13th July 2016 – 12th July 2017.

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.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF M.L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Assistant Director, Health Information, KNH
The Chair, KNH- UoN ERC
The Dean, School of Medicine, UoN
The Chair, Dept. of Clinical Medicine and Therapeutics, UoN
Supervisors: Dr. Emma Karari, Prof. Godfrey Lule, Prof. Walter Jaoko

INTERNAL MEMO
Kenyatta National Hospital

OFFICE OF THE ASSISTANT DIRECTOR – LABORATORY MEDICINE SERVICES

Exten: 44121

Ref: KNH/DLM/60/VOL.1/137 **Date: 22nd June, 2016**

Dr. Fredrick K. Wangai
(H58/74412/2014)
P. O. Box 62619-00202, KNH
NAIROBI

RE: AUTHORIZATION TO UNDERTAKE RESEARCH IN KNH MICROBIOLOGY LABORATORY

The department of laboratory medicine has perused the methodology in your proposal for research study entitled **"Antimicrobial Susceptibility of Bacterial Isolates from Patients in Medical Wards at KNH – 2015-2016".**

We have noted that your study will involve a retrospective audit of bacterial isolates and a cross-sectional description of bacterial isolates with the corresponding antibacterial susceptibilities data of routinely requested culture samples from the inpatients, which will have already been invoiced. There will therefore no further laboratory user fee charges required for payment.

You are therefore advised to get in touch with the in charge of microbiology section for further technical advice on the laboratory procedures involved.

Thank you.

Dr. A. K. Gachii
AD LAB. MEDICINE

cc.
The Research & Programs
KNH

I/C Microbiology Lab.
KNH

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From the Desk of: Dr Mark Mudenyo *Asst Director Health Information*

Tuesday, June 21, 2016

Prof M.L. Chindia
Secretary KNH-UON-ERC

Dear Sir

RE: Dr. Fredrick Kimani Wangai
Reg No. H58/74412/2014

Research Topic: ANTIMICROBIAL SUSCEPTIBILITY PATERNS OF BACTERIAL ISOLATES FROM PATIENTS IN MEDICAL WARDS AT KNH (P310/04/2016)

This is to inform you that Health Information department will have no objection in providing access to patients records to the researcher upon getting clearance from research and ethics committee of which research proposal has been submitted.

Thank you,

ASSISTANT DIRECTOR: HEALTH INFORMATION SERVICES
KENYATTA NATIONAL HOSPITAL
★ 21 JUN 2016 ★
P. O. Box 20723 - 00202
NAIROBI

Dr. M.O. MUDENYO