UNIVERSITY OF NAIROBI

AN AUDIT OF AMINOGLYCOSIDE USE AND MONITORING IN PAEDIATRIC WARDS OF KENYATTA NATIONAL HOSPITAL

BY

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A thesis submitted in partial fulfillment of the requirements for the award of the Degree of Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance.

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DECLARATION

I declare that this thesis is my original work and has not been presented to any other academic institution for examination.

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This thesis has been submitted for research and examination with our approval as University supervisors.

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DEDICATION

I dedicate this work to my late parents, Mr. and Mrs. Casmir and Gaudencia Oluoch.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AGs`	Aminoglycosides
BPP	Basic Pediatric Protocol (Ministry of Health, Kenya)
HMIS	Health Management Information System
HCW	Health care worker
ICU	Intensive Care Unit
i.v	Intravenous
KNH	Kenyatta National Hospital
NCCMERP	National Coordinating Council for Medication Error Reporting and Prevention
NICE	National Institute for Health and Clinical Excellence
NBU	New Born Unit
PICU	Paediatric Intensive Care Unit
PSU-RU	Paediatric Surgical and Renal Unit
TDM	Therapeutic Drug Monitoring
WHO	World Health Organization

OPERATIONAL DEFINITION OF TERMS

For the purpose of this study **a paediatric patient** means any patient aged 0 to 12 years.A **neonate** means newborns up to one month.

Omission Error means failure to administer a prescribed dose of an aminoglycoside to a patient at the time the next dose is due, assuming there has been no prescribing error. This includes wrong frequency and duration but excludes a patient's refusal to take the medication and failure to administer the dose because of recognized contraindications.

Extra Dose Error means administration of a medication dose after the order was discontinued by the prescriber.

Wrong Dose Error means the patient received an amount of aminoglycoside that is greater than or less than that specified for a particular indication.

Wrong Time Error means failure to administer an aminoglycoside to a patient within a predefined interval from its scheduled administration time.

Prescribing Error means an aminoglycoside prescribed to a patient withknown allergies to aminoglycosides or where aminoglycoside use is contraindicated. It also means wrong or inadequate dosage instructions for use of an aminoglycoside prescribed by a physician or other authorized prescribers.

Monitoring Error means any of the following:

1. Failure to obtain baseline creatinine levels.
2. Failure to monitor creatinine levels at least twice a week after initiation of aminoglycoside therapy.
3. Failure to determine serum aminoglycoside levels.
4. Failure to monitor temperature or white blood cell count while the paediatric patient is on aminoglycoside therapy.

Nephrotoxicity means an increase in serum creatinine bymore than 25-30% above the baseline serum creatinine values.

A High risk medicine is one which poses risk of death or serious harm to a patient when wrongly selected, used, prescribed or administered.

ABSTRACT

Background

Aminoglycosides(AGs) are high risk medicines, which means, they pose a risk of death or serious harm to a patient when wrongly selected, used, prescribed or administered.. Despite their common use in Kenyatta National Hospital (KNH), the largest referral hospital in Kenya,no clinical evaluation has been undertaken to assess compliance to guidelines for AGs use and monitoring.This study aimedmainly to conduct a clinical audit on the use of AGs, obtain healthcare worker (HCW) perceptions on the practice of Therapeutic Drug Monitoring (TDM) of AGs. Further, the study intended to identify gaps and opportunities for the introduction of a protocol on the use of AGs in the paediatric wards of KNH as a basis for suggesting future improvements.

Methods

Phase one was a prospective cohort study conducted at the general pediatric wards (GPW) and the new born unit (NBU). Phase two involved face-face interview with HCWs. Data were analyzed using descriptive statistics and the association between outcome measures and study covariates was assessed using inferential analysis.

Results

A total of 192 participants aged between 0 and 12 years were recruited with 113 (58.9%) of them being male. Overall, the prevalence of AG use was 9.8% (n=227). The main indication for AGs use was neonatal sepsis (n=81, 42.2%). The most common antibiotic combination was gentamicin and benzyl penicillin (n=107, 55.7%).Doses for the majority of the patients (n=102, 53.1%) did not conform to recommendations in the national pediatric protocol. More than half (50.5%) of the patients did not receive all the AG doses within one hour of the prescribed dose

time. About a third (30.3%) of the patients missed at least some AG dose in the course of therapy.The body weight of the majority of patients in the GPWs (n=23, 52.3%) was not recorded. Aminoglycosides related adverse drug reaction (ADR) was suspected in 33.9% (n=65) of the patients. Follow up creatinine level was done in only 17 (8.9%) patients while TDM was not done in any patient. The majority (n=18, 64.3%) of the study participants needed training in how to perform, interpret and use TDM results in clinical practice. All the respondents affirmed the need for an Aminoglycosides use protocol in KNH. The barriers to effective TDM implementation that needs urgent attention in this hospital include knowledge gaps and the lack of required resources such as AG TDM kits.

Conclusion

Use of AGs is common in the pediatric wards at the KNH. Adherence to treatment guidelines in terms of dosing and monitoring was sub-optimal and raises concerns around potential, avoidable harms to patients. The identified barriers, particularly training of healthcare workers and provision of resources need to be adequately addressed before a TDM service for AGs is undertaken in KNH.

1.0 CHAPTER ONE: INTRODUCTION

1.1 Background

Aminoglycoside antibiotics (AGs) are high risk medicines. A medicine is considered high risk if it poses risk of death or serious harm to a patient when wrongly selected, used, prescribed or administered(1).Gentamicin, amikacin and tobramycin are some examples of aminoglycosides. Other medicines also classified as high risk are potassium and other electrolytes, insulin, narcotics, chemotherapeutics, heparin and other anticoagulants.

Aminoglycosides have a narrow therapeutic range. This requires accurate timing in their administration with careful monitoring of blood levels. They can cause permanent hearing loss, vestibular toxicity and reversible nephrotoxicity(2). Surgical and intensive care unit (ICU) patients on aminoglycosides should be monitored for neuromuscular blockade(3). Although these adverse reactions are rare in children(4), close monitoring is required. This is especially important in children from families with a history of hearing loss, poor renal function and elevated blooddrug levels. Concurrentuse of nephrotoxic drugs, large cumulative doses and prolonged duration of therapy are also other indications for close monitoring(3). Paediatric patients are at a higher risk of medication errors compared to adults. Neonates are more vulnerable because they have underdeveloped kidney, liver and immunological functions(5). They have reduced clearance of aminoglycosideswhich may predispose them to higher risk of toxicity(6).

In order to reduce the risk of harmcaused topatientsby the high alert medicines, health facilities are required to have programs that monitor use of such medicines. These should include a register and protocol for all the medicines identified as high risk. Patient monitoring appropriate for the clinicalcircumstances should be done. Mitigation strategies should be put in place to minimise harm that the high risk medicines may pose to patients. It is also required that adverse events involving high risk medicines be reported and be reviewed by the relevant authority(1).

Some of the standards for prescribing and administering high risk medicines include mandatory inclusionofaccurate patient weight, route of administration, dosage regimen and indication for use. Dosage adjustments should be considered for patients with extremes of weight or co-morbidities. Adherence to the therapeutic guidelines is required. Some instances may require

independent double checking of the medication use cycle before the medicine is administered to the patient(1).

1.2 Problem Statement

Kenyatta National Hospital is the largest teaching and referral hospital in Kenya. Many patients in this facility are treated with aminoglycosideswhich are classified as high alert medicines hence their use needs to be monitored. However, to date, no clinical audit on this has been done. The hospital also lacks a protocol for therapeutic drug monitoring of these medicines.Paediatric patients are particularly at risk of aminoglycoside-related toxicity.

Kenyatta National Hospital, being the largest teaching and referral hospital in the country, sets the standards of practice for other health facilities. Lack of a protocol for therapeutic drug monitoring of aminoglycosides in this hospital implies there is no standard way of monitoring patients on such medicines. As a result patients on aminoglycosides are at high risk of harm from adverse events following therapy. If proper monitoring is not done, patients may develop complications such as ototoxicity and nephrotoxicity which can be life threatening or result in permanent damage. The extent of improper medication use and adverse drug reactions (ADRs) associated with aminoglycosides in Kenyatta National Hospital has not been assessed.

1.3 Research Questions

1. What proportion of prescriptions in the paediatric wards of KNH containsaminoglycosides?
2. What is the current practice of prescribing, preparation and administration of aminoglycosides to paediatric patients admitted at Kenyatta National Hospital?
3. Is the use of aminoglycosides monitored according to internationally accepted standards?
4. What proportion of paediatric patients on aminoglycosides experience adverse events in the course of treatment at Kenyatta National Hospital?
5. What are the gaps and opportunities for the implementation of a protocol for aminoglycoside use in KNH?

1.4 Study Objectives

1.4.1 Broad objective

To conduct a clinicalaudit on the utilization and outcome ofaminoglycosides in the paediatric wards of Kenyatta National Hospital and to identify gaps and opportunities for introduction of a protocol on aminoglycoside use.

1.4.2 Specific objectives

1. To determine the incidence of aminoglycoside utilization in the paediatric wardsof KNH.
2. To describe the current practice of prescribing, preparation, administration and monitoring of aminoglycosides in paediatric patients admitted at Kenyatta National Hospital.
3. To determine the incidence of aminoglycoside treatment outcomes among pediatric patients admitted at Kenyatta National Hospital.
4. Identify potential gaps and opportunities for implementation of a protocol on the use of aminoglycosides.

1.5 Study Justification

The opportunities and gaps for implementation of the protocol for therapeutic drug monitoring of aminoglycosides at Kenyatta National Hospital are unknown. Currently there are no protocols for risk minimization or monitoring the use ofaminoglycosides in this hospital. Identification of the existing gaps and risks will form the basis for quality improvement and implementation of protocols that will improve efficiency and patient safety. The identified barriers and challenges will inform the interventions and policies to improve practice.

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1 Drug Use Review and Audit

Drug use review (DUR) is a continuous, systematic process aimed at ensuring rational use of medicines and to detect medication related problems. A pre-determined criterion for appropriate drug use is compared to the patient's medical records. The patient's health history and medical records should be comprehensively reviewed before deciding on any treatment strategy. DUR provides an opportunity for improvement, feedback to prescribers and further evaluations. Improvement in medicine use has the potential of reducing the overall cost of care. DUR can be prospective, concurrent or retrospective. DUR enables healthcare systems to understand, interpret, assess and improve medication use. The findings of a DUR can inform efficient use of scarce resources. It also helps in identifying trends in prescribing of certain medications(7).

Ideally, a prospective review should be performed by assessing the appropriateness of a patient's medicines before dispensing. This enables the pharmacist to detect and resolve any problem before it gets to the patient. These may include issues such as clinical abuse or misuse and drug - disease contraindications. Drug-drug interactions, drug-patient precautions, formulary substitution and inappropriate duration of treatment can also be detected. Concurrent review involves ongoing monitoring of treatment in order to achieve the intended outcomes. It focuses on issues such as drug-drug interactions, duplicate therapy and drug dosage modifications. Drug-patient precautions, under and over utilization or therapeutic interchange can also be addressed. A retrospective review determines medicine use patterns and set standards and interventions to avoid recurrence of inappropriate use. This helps the prescribers to improve the care of their patients(8).

Steps in conducting a DUR involves first identifying or setting a criteria for appropriate medicine use against which the actual use is compared. A minimum acceptable threshold is then set. Actual use is measured and evaluated. The number of users who meet the pre-set criteria is determined and causes for any discrepancies are identified. Patterns of use are identified and interpreted. An intervention is then put in place to correct any problems identified. Finally, theeffectiveness of the DUR program is evaluated. Reasons for the observed outcomes are

documented and any necessary adjustment to the DUR program is done. The final report is then submitted to the relevant authority(8).

2.2 Medication use cycle and Medication Errors

Medication use cycle includes all the processes involved in every stage of patient care. These may range from medicine selection to feedback of its use in patients(9,10). The medication use cycle is presented in Figure 1.

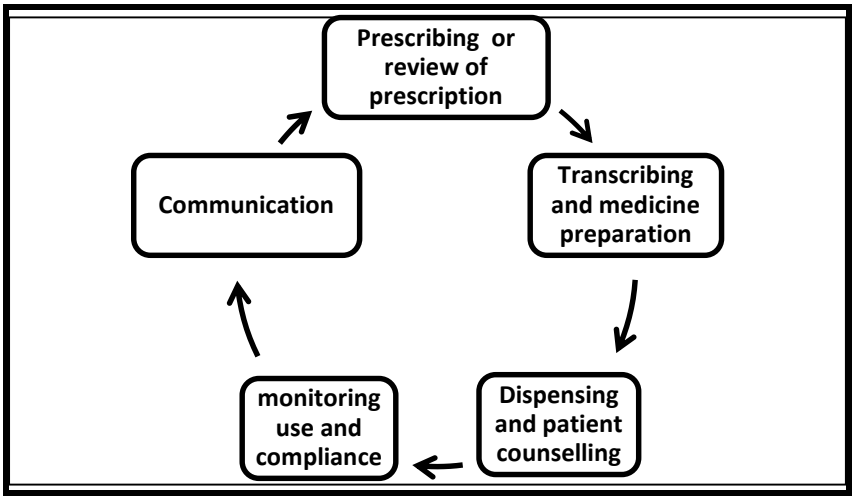


Figure 1 : Medication use Cycle

The most common medical errors are medication errors(11).The National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) defines medication error as "... any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer."Errors can occur at any point of the medication use cycle. They can be due to wrong diagnosis, prescribing errors or wrong dose. Other contributing factors include poor storage and transportation, problems with the drug device or drug itself, wrong administration andmiscommunication(12).

2.2.1 Types of medication errors

Prescribing errors include illegible handwriting and missing or insufficient information about co-prescribed medications. Incorrect drug or dose and complex dose regimen also constitute prescribing errors. Dispensing errors may be errors of commission such as dispensing the wrong

drug or dose. Errors of omission such as failure to counsel the patient and failure to check for interactions or unclear labeling also fall under this category.

Table 2.1: Summary of types of medication errors

Prescribing errors	Dispensing errors	Administration errors	Monitoring errors
Illegible handwriting	Dispensing wrong drug or wrong dose	Wrong route of administration	Failure to monitor plasma drug concentrations where indicated
Missing or insufficient information	Failure to check interactions or contraindications	Wrong administration technique	Failure to monitor laboratory parameters
Wrong drug	Unclear labeling	Wrong frequency of administration	Failure to monitor for adverse drug reactions
Wrong dose	Failure to counsel the patient	Administration of wrong drug	-
Complex dosage regimen	Wrong dose calculations	Wrong time of administration	-

Dispensing errors commonly occur in three ways. The first is dispensing the wrong medicine, wrong strength or incorrect dosage form. The others are wrong dose calculation and failure to check for interactions or contraindications. Administration errors usually occur due to poor communication. Healthcare workers forget to instruct patients how to use their medicines. Most patients do not usually ask questions about the medicines they have been given at the health facility. This contributes to incorrect medicine use(12). The various types of medication errors are summarized in Table 2.1.

2.3 Aminoglycosides

The aminoglycosides are a class of antibiotics that were first isolated from natural sources in 1940s. The first aminoglycoside to be isolated was streptomycin. These antibiotics derive their name from their structure. They contain several amino groups linked to glycoside moieties(13). There are two classes of aminoglycosides. These are natural and semisynthetic aminoglycosides. Natural aminoglycosides include neomycin, kanamycin and paromomycin. Spectinomycin, gentamicin and tobramycin also fall under this category. Netilmicin and amikacin are examples of semisynthetic aminoglycosides(6,14).

2.3.1 Mechanism of action of aminoglycosides

They act by binding to the 30s ribosomal subunit, inhibiting bacterial protein synthesis and misreading of mRNA leading to formation of dysfunctional proteins (3).

2.3.2 Indications foraminoglycosides use

Aminoglycosidesare used for treatment of severe infections due to aerobic gram negative or gram positive bacteria in conditions such as pneumonia, bacteremia and infective endocarditis(3,15). Theirantibacterial activity is limited by drug modifying enzymes and decreased uptake in gram positive bacteria that possess unique membrane components that inhibit aminoglycoside penetration. The anaerobes lack oxygen dependent membrane transport mechanism. Aminoglycosides are highly polar and therefore poorly absorbed orally. They are mainly administeredparentally(13).

Aminoglycoside bactericidal activity and post antibiotic effect is concentration-dependent. This is influenced by the ratio of the peak concentration to minimum inhibitory concentration. In order to achieve high peak concentrations and low trough levels, once daily dosing is preferred. It avoids sustained high trough levels. Aminoglycoside toxicity is related to their uptake in the perilymph and renal cortex. This uptake is saturable and is concentration dependent (4,16).

Aminoglycosidesare often combined with antibiotics that inhibit cell wall synthesis such as vancomycin and β-lactam antibiotics to broaden the spectrum of activity. It is assumed that this enhances bacterial permeability and increases uptake of aminoglycosides(17).

2.3.3 Dosing of aminoglycosides

There are two approaches to dosing of aminoglycosides(18). The conventional dosing is the administration of multiple daily doses, usually after every eight hours. In the extended interval administration, the total daily dose is given once daily. Both approaches achieve comparable cure rates and risk of nephrotoxicity. However, the latter enhances bactericidal activity and post antibiotic effect but one should monitor for additional risk of neuromuscular blockade especially in surgical and intensive care patients; and gram negative endotoxin induced hypotension. The recommended doses for conventional dosing in patients with normal renal function are 3–5 mg/kg/d for gentamicin and tobramycin and 15 mg/kg/d for amikacin. These are divided into

three equal daily doses for gentamicin and tobramycin or two to three equal daily doses for amikacin. Extended interval doses for patients with normal renal function are 4-7mg/kg/d for gentamicin and tobramycin or 11-20mg/kg/d for amikacin(3). Patients older than 65 years or who have altered renal function should have plasma peak levels of less than 1mg/L before the next dose (19).

2.3.4 Toxicity of aminoglycosides

Peak concentrations above 12-14µg/ml for gentamicin and tobramycin or 35-40µg/ml for amikacin are associated with increased risk of ototoxicity. Aminoglycosides can cause permanent auditory and vestibular ototoxicity. Hearing loss resulting from aminoglycosides is usually not detected until the patient cannot hear in the conversational frequency zone(3,20). Ototoxicity is both dose dependent and idiosyncratic. Damage of hair cells in the inner ear is a manifestation of dose dependent toxicity. It is postulated that this could be due to generation of reactive oxygen species(2,21). Nephrotoxicity is caused by accumulation of the drug in the renal cortex. This is usually reversible. When correctly dosed, aminoglycosides induced nephrotoxicity is unlikely before 3-5 days of dose administration(3).

2.3.5 Monitoring of aminoglycoside use

Where culture and sensitivity tests are available, the antibiotic prescribed should be informed by the current test results. If a second antibiotic is added to the treatment schedule, it should be checked for appropriateness. Elevated body temperatures and white blood cell counts is usually common in severe infections. However, this may not be the case in immune-compromised patients. Serial measurement of white blood cell count and body temperature can be used as an indicator of the patient's response to therapy. Steady-state peak and trough concentration of aminoglycosides should be measured in 3-5 estimated half-lives when administered using the conventional dosage approach. This can be done after the third dose which falls between the first and third day after initiation of therapy. Clinical efficacy can also be assessed during this time. Dosage adjustment can then be considered if need be using these parameters(3).

Baseline serum creatinine concentration should be obtained before initiating aminoglycoside therapy. This should be repeated three times weekly. For intensive monitoring, the serum creatinine concentrations can be determined daily. An increase greater than 0.5mg/dL above the

baseline value or more than 25-30% above the baseline for serum creatinine values greater than 2mg/dLafterruling out other causes of nephrotoxicity requires a switch to other treatment alternatives or intense monitoring (3).

2.4 Tools used to audit Aminoglycosides use

Some tools that can be used to audit aminoglycoside use include the World Health Organization's (WHO) tool on how to investigate drug use in health facilities(22), National Institute for health and Clinical Excellence (NICE) clinical audit tool on antibiotics for early-onset neonatal infection(23) and gentamicin specific chart(24). Other tools include neonatal gentamicin care bundle daily audit chart and neonatal gentamicin care bundle compliance chart (25).

2.5 Studies on aminoglycoside use in Africa

Studies that focus on aminoglycoside use in an African setting include a study by Ahiabu et al, 2015(26) and Gwee et al, 2012(27). Others include studies by Donkor et al, 2012(28) and Ojo et al, 2014(29). Irrational drug use is more common among junior doctors compared to senior doctors (29). This is particularly observed for upper respiratory tract infections but varies depending on the type of health facility(27). Irrational drug use can also be as a result of self-medication. About 49% of people who do self-medication have poor knowledge about health implications of irrational use of antibiotics (28). Most prescribers also believe they need more information on the concept of rational drug use (29). Antimicrobial resistance is one of the consequences of irrational use of antibiotics. In a study by Gwee et al (2012) it was noted that gram negative resistance to gentamicin varied between 17- 27% (27).

3.0 CHAPTER THREE: METHODS

Two studies were conducted. The first was a prospective cohort study of pediatric patients on aminoglycosides and the second was a structured interview with the healthcare workers.The prospective cohort study sought to determine the proportion of prescriptions in the paediatric wards that containedaminoglycosides and the proportion of paediatric patients who experienced aminoglycoside related adverse reactions at Kenyatta National Hospital(KNH). It also sought to describe the practice of prescribing, preparation, administration and monitoring of aminoglycosides to children admitted at KNH pediatric wards and the new born unit (NBU). The structured interview attempted to clarify some of the practices which were not clearly described in the cohort study.It also highlighted the barriers and readiness of the staff for therapeutic drug monitoring of aminoglycosides.

3.1 Clinical audit of aminoglycoside use

3.1.1 Study site

The study was carried out at Kenyatta National Hospital Pediatric wards. According to KNH Health Management Information Systems, (HMIS 2016), the hospital has four general paediatric wards (3A, 3B, 3C and 3D), five specialized paediatric wards (surgery, orthopedic surgery, oncology, ICU and renal unit which are located in 4A, 6B, 1E, Paediatric Intensive Care Unit (PICU) and Paediatric Surgical and Renal Unit (PSU-RU) respectively). There are also the general ward NBU and Private wing NBU. The bed capacity of the general paediatric wards is 237patients with an average bed occupancy rate of 133% and an average admission of 174 patients per month. The average number of admissions in the General Ward NBU is 345 patients per month with average bed occupancy of 173.8%. Paediatric oncology ward has 28 beds with an average occupancy of 87.6% and average monthly admission of 10 patients.

3.1.2 Study Design

This was a prospective cohort study done over a three month period. Itinvolved review of files of paediatric patients on aminoglycosidesand observation of the patients for any ADRs.

3.1.3 Target Population

The target population for this study was the patients admitted at the general pediatric wards (GPWs)and general New Born Unit (NBU) of KNH in October to December 2016.

3.1.4 Inclusion and Exclusion Criteria

The study cohort for phase one was patients admitted at the GPWs and NBU of KNH during the study period, the patient was on any AGs and was aged 0-12 years. Patients were excluded if they were discharged before recruitment, not on any AGs during the period of the study, admitted in pediatric wards other than the GPW and general NBU or were older than 12 years.

3.1.5 Sample size determination

The Cochran formula (30) was used to calculate the sample size. This formula was selected because the study was descriptive. According to a study by Erbay et al (31), aminoglycosides were prescribed for 12.1% of all the patients who required antibiotics. This was assumed to be the prevalence of aminoglycosides use.

$$n = \frac{Z^2 * p\,(1-p)}{d^2}$$

Where:

Z = statistic for 95% level of confidence (1.96)

p= estimated prevalence of aminoglycosides use (12.1%);

d= level of precision used in the study and was set at 5%

n= Sample size.

Taking 12.1% as the estimated prevalence of aminoglycoside use in the population, the calculated sample size was 164.

To take care of incomplete data, the calculated sample size was inflated by 10% to target a minimum of 181 patients.

3.1.6 Sampling Method and Plan

Universal sampling method was used. The sampling was done in the afternoon to avoid disruption of ward rounds. All the files of patients meeting the inclusion criteria were sampled and reviewed. The sampling was done within 48 hours after the aminoglycoside antibiotic was prescribed.

3.1.7 Data collection

Data was collected from admission to discharge. Information was abstracted from patient treatment sheets and files using the data collection tool in **Appendix A**. The tool was designed to collect information on patient socio-demographic characteristics, medical history, medications prescribed, prescribing clinician and patient monitoring especially creatinine levels. The tool was developed by combining WHO tool on how to investigate drug use in health facilities(22),NICE clinical audit tool for antibiotics for early-onset neonatal infection(23) and gentamicin specific chart(24). The tools were merged because no single tool was adequate to capture all the required information. Patient files were reviewed daily and data sheet updated. The patients were followed up from the time of recruitment to discharge. Where there were any discrepancies or vague information, the prescribing clinician was consulted.

The information gathered using **Appendix A** and **Appendix B** were compared to standard practice stipulated in aminoglycoside use protocols in Canada(32), Australia(33)and the Kenya Ministry of Health Pediatric Protocol(34). Some of the standards for prescribing and administering high risk medicines includemandatory documentation of patient weight, route of administration, dosage regimen and indication for use. Dosage adjustments should be considered for patients with extremes of weight or co-morbidities. Adherence to the therapeutic guidelines is required. Some instances may require independent double checking of the medication use cycle before the medicine is administered to the patient(1).

3.1.8 Variables

The main outcome variable was the incidence of aminoglycoside use in paediatric wards in KNH. The secondary outcome variables wereaminoglycoside dosing, monitoring of patients on aminoglycosides, outcomes of patients on aminoglycosides, adverse drug reactions and medication errors. The co-variates included patient age, gender, weight, diagnosis and cadre of

prescriber. Other variables were antibiotic combinations, co-medications, co-morbidity and duration of aminoglycoside therapy

3.1.9 Quality Assurance

Pre testing of data collection tools

The data collection tools were pre tested at one of the KNH paediatric wards by purposely sampling 10 patients on aminoglycosides to test their suitability in capturing the required data. The tools were then modified to rectify the observed shortcomings. The research assistants were trained on how to use the tools to correctly capture the required data. They were two male final year Bachelor of Nursing students from the University of Nairobi.

3.1.10 Data Management

The collected data was entered in Epi Info version 7 database. The data was then cleaned and validated. Access to the folders containing the data was controlled by a password known only to the researcher. The data was regularly backed up in flash disks and to email address of the researcher.

3.1.11 Data analysis

The data was analyzed using STATA version 13 software. Descriptive statistical analysis was done. Continuous variables were summarized using median and interquartile range. Categorical variables were summarized as proportions using percentages. Inferential analysis was done using the unpaired student t test for continuous variables that were normally distributed or the Mann Whitney test for continuous variables that were not normally distributed. The Chi square test was used for inferential data analysis for categorical variables. The sign rank test was used to determine if the median doses complied with the recommendations in the guidelines. The level of significance was set at 0.05.

3.2 Interview with the Health Care Workers

A structured interview was conducted with the healthcare workers to determine their current knowledge, practice and attitude towards a protocol on aminoglycoside use and the potential gaps and opportunities for implementation of this protocol.

3.2.1 Study site

The study was carried out at Kenyatta National Hospital Pediatric wardsand the new born units.

3.2.2 Study Population

The study population was the healthcare workers in the general pediatric ward and NBU in KNH. These included pediatricians, senior house officers, pharmacists, nurses, and laboratory technologists.

3.2.3 Inclusion and Exclusion Criteria

The healthcare workers were included in the study if they worked in or served the general pediatric wards or NBU; were allowed to prescribe or contribute to monitoring therapy with aminoglycoside antibiotics and gave informed consent. They were excluded from the study if they did not consent to the interview.

3.2.4 Sample size determination

Universal sampling technique was employed, whereby every health worker meeting the inclusion criteria was approached.

3.2.5 Participant recruitment

The participants were approached after completion of ward rounds and they were briefly informed about the study. They were asked to select the time and place convenient for them for the interview to be administered. They were approached at a time of minimal disruption to ward activity. Before the onset of the interview they were given detailed information about the study and they were asked to sign the appended informed consent form if they were agreeable. **(Appendix C).**

3.2.6 Procedure of the interview

The interviews were conducted by two research assistants. One research assistant conducted the oral interview while the second one recorded all the proceedings. The interview was done at a time and location convenient to the participant. Each participant was given a code known only to the researcher that was used for the data collection and analysis.

3.3 Ethical Considerations

Approval to carry out this study was obtained from the Kenyatta National Hospital/University of Nairobi Ethics Review Committee (**Ref: KNH-ERC/A/330;** Approval number **P563/07/2016**). The approval letter from the ethics committee is attached in **Appendix F.** Approval to collect data was sought from Kenyatta National Hospital management. The approval letter from the hospital **(Ref KNH/PAEDS-AD/48 Vol. II)** is attached in **Appendix G**. Informed consent was given by the healthcare workers and parents or guardians of the pediatric patients before their participation in the interview. The consent was written and signed in either Kiswahili or English depending on which language the respondent was fluent in. One copy of the signed consent form was given to the respondent while another copy was filed by the principle investigator. Care was taken to ensure the information obtained from the participants remained confidential. This was done by keeping the questionnaires locked in a secure place accessible only to the researcher and assigning each participant a code instead of using patient or healthcare worker's name. The folders containing the softcopy of the data were secured by a password known only to the researcher.

4.0 CHAPTERFOUR RESULTS

4.1 Demographical and epidemiological characteristics of Aminoglycoside utilization in the pediatric wards of KNH

4.1.1 Baseline characteristics of the pediatric patients on aminoglycosides in KNH

A total of 2318 pediatric patients were admitted in level 3 wards (3A-3D) and new born unit (NBU) between October and December, 2016; of which the majority (n=911, 39.3%) were in NBU. Among these, 192 who were all on aminoglycosides and aged between 0 and 12 years were recruited. There were 113 (58.9%) male participants. Majority of the patients (n=156, 81.2%) were aged one month and below. The difference in sex distribution across wards was not statistically significant (p = 0.059) but the difference in age distribution was significant (p<0.001). The median age at admission was 3 days. The youngest was less than a day old and the oldest was 12 years old. The baseline characteristics are summarized in Table 4.1.

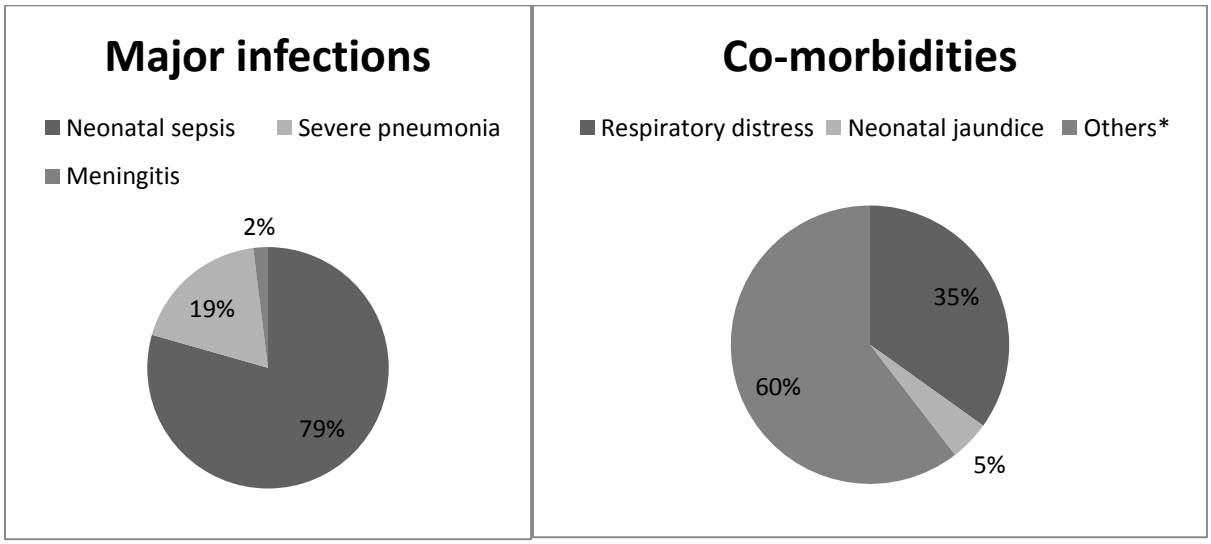
Table 4. 1:Baseline characteristics of the pediatric patients on aminoglycosides at KNH

	Wards n (%)					
	3A	**3B**	**3C**	**3D**	**NBU**	**Total**
Sex						
Male	3(1.6)	5(2.6)	9(4.7)	5(2.6)	91(46.4)	113(58.9)
Female	2(1)	13(6.8)	6(3.1)	1(0.5)	57(29.7)	79(41.1)
Total	**5(2.6)**	**18(9.4)**	**15(7.8)**	**6(3.1)**	**148(77.1)**	**192(100)**
Age category						
0-1 month	0(0)	5(2.6)	4(2.1)	2(1)	145(75.5)	156(81.2)
1 - 24 months	4(2.1)	9(4.7)	4(2.1)	2(1)	3(1.6)	22(11.5)
2- 6 years	1(0.5)	3(1.6)	3(1.6)	1(0.5)	0(0)	8(4.2)
6-12 years	0(0)	1(0.5)	4(2.1)	1(0.5)	0(0)	6(3.1)
Total	**5(2.6)**	**18(9.4)**	**15(7.9)**	**6(3.0)**	**148(77.1)**	**192(100)**
Number admitted	358(15.4)	367(15.8)	334(14.5)	348(15)	911(39.3)	2318(100)
Number recruited	5(2.6)	18(9.4)	15(7.8)	6(3.1)	148(77.1)	192(100)

More than half (n=148, 77.1%) of the pediatric patients on aminoglycosides were admitted in the new born unit (NBU).

4.1.2 Incidence and types of infections and co-morbidities

The main indication for the use of aminoglycosides was neonatal sepsis (n=81, 42.2%). This was followed by respiratory distress syndrome (n=30, 15.6%). Most participants (n=76, 39.6%) had two co-morbidities and 64(33.3%) had one medical condition. The difference in distribution of the medical conditions across the wards was significant ($p<0.001$). Ward 3C had the highest number of medical conditions (seven) to which an aminoglycoside was prescribed while ward 3A had the least (two). Figure 2 illustrates the incidence of the most common medical conditions in the pediatric wards of KNH classified as either an infection or co-morbidity.



*The other co-morbidities were gastroenteritis, prematurity, low birth weight, convulsive disorders, coronary heart disease, anemia, diabetic ketoacidosis, chronic renal failure and acute kidney injury.

Figure 2: Types of infections and other co-morbidities

4.1.3 Types of medicines co- prescribed with aminoglycosides to patients in the pediatric wards of KNH

The median total number of drugs including aminoglycosides per patient was 3 and ranged from 1 to 8. Majority (n=73, 38%) were on two drugs. The median number of antibiotics per patient was 2 and ranged from 1 to 4. Majority of the patients (n=163, 84.9%) were on two antibiotics at a time. The vitamin and mineral supplements that were prescribed included vitamin K injection,

folic acid tablets and hematinic syrup. The drugs acting on the gastrointestinal tract included intravenous omeprazole and domperidone.

Table 4.2: Medicines co- prescribed with Aminoglycosides in pediatric wards of KNH

Ward n (%)	**Vitamins & supplements**	**Aminophylline**	**GIT Drugs**	**Analgesics**	**Anticonvulsants**	**Others***
3A	4(2.1)	0(0)	1(0.5)	3(1.6)	0(0)	0(0)
3B	5(2.6)	0(0)	0(0)	2(1)	0(0)	5(2.6)
3C	2(1)	1(0.5)	3(1.6)	2(1)	3(1.6)	12(6.3)
3D	2(1)	0(0)	1(0.5)	2(1)	1(0.5)	5(2.6)
NBU	47(24.5)	22(11.5)	11(5.7)	4(2.1)	9(4.7)	23(12.0)
Total	**60(31.3)**	**23(12.0)**	**16(8.3)**	**13(6.7)**	**13(6.8)**	**45(24.0)**

*The others were tetracycline eye ointment,saline nasal drops,anti-tuberculosis (Anti-TB), antiretroviral (ARVs), anti-opportunistic infections (OIs) and cardiovascular (CVS) drugs.

Majority of the aminoglycoside prescribers were registrars (n=61, 31.8%) and paediatric specialists (n=55, 28.7%). The others were clinical officer interns (51,26.6%) and medical officer interns(n=25, 13%)

Table 4.3: Characteristics of Prescribers of aminoglycosides in the pediatric wards of KNH

Ward n (%)	**Clinical officer interns**	**Medical officer interns**	**Registrars (pediatrics)**	**Paediatric specialists**
3A	3(1.6)	1(0.5)	0(0)	1(0.5)
3B	8(4.2)	2(1)	0(0)	8(4.2)
3C	4(2.1)	3(1.6)	1(0.5)	7(3.6)
3D	1(0.5)	4(2.1)	1(0.5)	0(0)
NBU	35(18.2)	15(7.8)	59(30.8)	39(20.3)
Total	**51(26.6)**	**25(13)**	**61(31.8)**	**55(28.6)**

4.2 Aminoglycoside prescribing practices in the pediatric wards of KNH

4.2.1 Incidence and patterns of aminoglycosides use in the pediatric wards of KNH

The highest incidence of aminoglycosides use was in NBU (16.2%) and the least was in ward 3A (1.4%). Gentamicin was the most commonly used aminoglycoside (n=118, 5.1%) compared to amikacin (n=109, 4.7%), however, this difference was not statistically significant (p=0.175). The overall incidence of aminoglycosides use in the five wards was 9.8% as illustrated in figure 3.

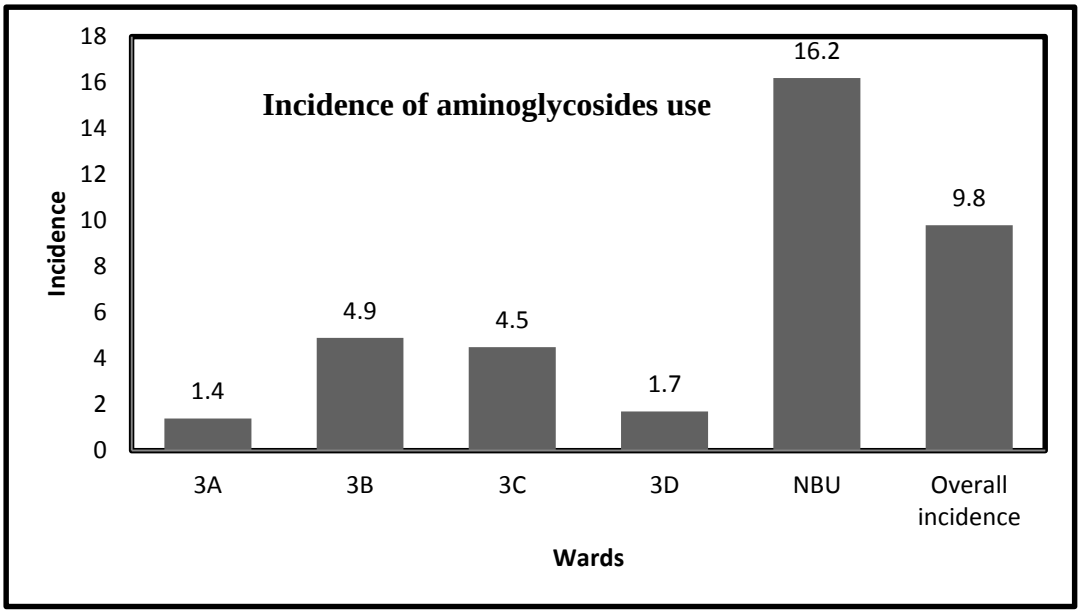


Figure 3: Incidence of aminoglycoside use in pediatric wards and the new born unit of KNH

The use of gentamicin as first line aminoglycoside was significantly higher (n=118, 61.5%) compared to amikacin (n=74, 38.5%) (p=0.001).The incidence of empirical therapy with gentamicin (n=44, 22.9%) was higher compared to amikacin (n=21, 10.9%), however, this difference was not statistically significant (p = 0.317).

4.2.2 Antibiotics administered with aminoglycosides in the pediatric wards of KNH

More than half of the patients (n=107, 55.7%) were started on gentamicin and benzyl penicillin as the first line antibiotic combination. Amikacin and ceftazidime was the second most prescribed (n=29, 15.1%) combination. The antibiotics combined with aminoglycosides are shown in table 4.4.

Only 48(25%) of the patients were switched from one antibiotic combination to another. Out of these, majority (n=17, 35.4%) were switched from gentamicin and benzyl penicillin to amikacin and ceftazidime, followed by a switch to oral antibiotics (n=8, 16.7%). Majority of the patients who had their antibiotics switched experienced only one such change (n=44, 22.9%). A small number of patients (n=4, 2.1%) were retained on the same aminoglycoside at a higher dose while five patients (2.6%) had their doses reduced.

Table 4.4: Antibiotics administered with Aminoglycosides in the Pediatric wards of KNH

	n (%) First line	Second line
Antibiotics combined with Gentamicin		
Gentamicin only	10(5.2)	-
Benzyl penicillin	107(55.7)	-
Other parental antibiotics*	1(0.5)	-
Antibiotics combined with amikacin		
Amikacin only	4(2.1)	1(0.5)
Ceftazidime	29(15.1)	17(8.9)
Meropenem	18(9.4)	4(2.1)
Ceftriaxone	16(8.3)	-
Vancomycin	1(0.5)	-
Vancomycin and meropenem	2(1)	-
Other antibiotics*	4(2.1)	2(1)
Vancomycin and other antibiotics	-	2(1)
Oral antibiotics	-	8(4.2)
Other parenteral antibiotics	-	14(7.3)
Total	192(100)	48(25)

*The other antibiotics combined with aminoglycosides were intravenous metronidazole and flucloxacillin.

4.2.3 Antibiotic combinations used for management of the most common infections in the pediatric wards

Benzyl penicillin and gentamicin was the most commonly prescribed combination for the three most common infections in the pediatric wards as shown in table 4.5.

Table 4.5: Treatment of the most common infections in the pediatric wards of KNH

Initial antibiotic combination	Health problem n (%)		
	Severe pneumonia	Respiratory distress syndrome	Neonatal sepsis
Benzyl penicillin and gentamicin	5(26.3)	22(73.4)	41(50.6)
Gentamicin only	4(21)	0(0)	2(2.5)
Gentamicin and other antibiotics	0(0)	0(0)	1(1.3)
Amikacin only	1(5.3)	0(0)	1(1.2)
Amikacin and ceftazidime	1(5.3)	6(20)	12(14.8)
Amikacin and meropenem	0(0)	1(3.3)	13(16.0)
Amikacin and ceftriaxone	8(42.1)	0(0)	6(7.4)
Amikacin and vancomycin	0(0)	0(0)	1(1.3)
Amikacin and vancomycin and meropenem	0(0)	1(3.3)	0(0)
Amikacin and other antibiotics	0(0)	0(0)	4(4.9)
Total	**19(100)**	**30(100)**	**81(100)**

Some patients (14, 7.3%) had oral antibiotics administered with the aminoglycosides. Erythromycin was the most common of such antibiotics (8, 57.2%). Some were on anti-retroviral therapy (5, 35.7%) and anti-tuberculotics (1, 7.1%)

Nephrotoxic drugs were concurrently administered with the aminoglycosides to 14 patients (7.3%). Such drugs were vancomycin (n=5, 35.7%), intravenous furosemide (n=4, 28.5%), NSAIDs (n=3, 21.5%) and acyclovir (n=2, 14.3%).

4.2.4 Duration of antibiotic use and completion of therapy in pediatric wards of KNH

The median prescribed duration of aminoglycosides and the actual duration on therapyper patient were 7 days and 6 days, and ranged from 2 to 17 days, and 1 to 17 days respectively. This difference was significant ($p<0.001$).

Most of the patients (n=139, 88.0%) were on aminoglycosides for at least72 hours. The number of patients on aminoglycosides for at least 7 days was 76(39.6%).

Slightly less than half (90, 46.9%) of the patients did not complete the prescribed duration of therapy. The three most common reasons for this finding were discharge (n=29, 32.2%), change to other drugs (n=27, 30%) and death (n=26, 28.9%).

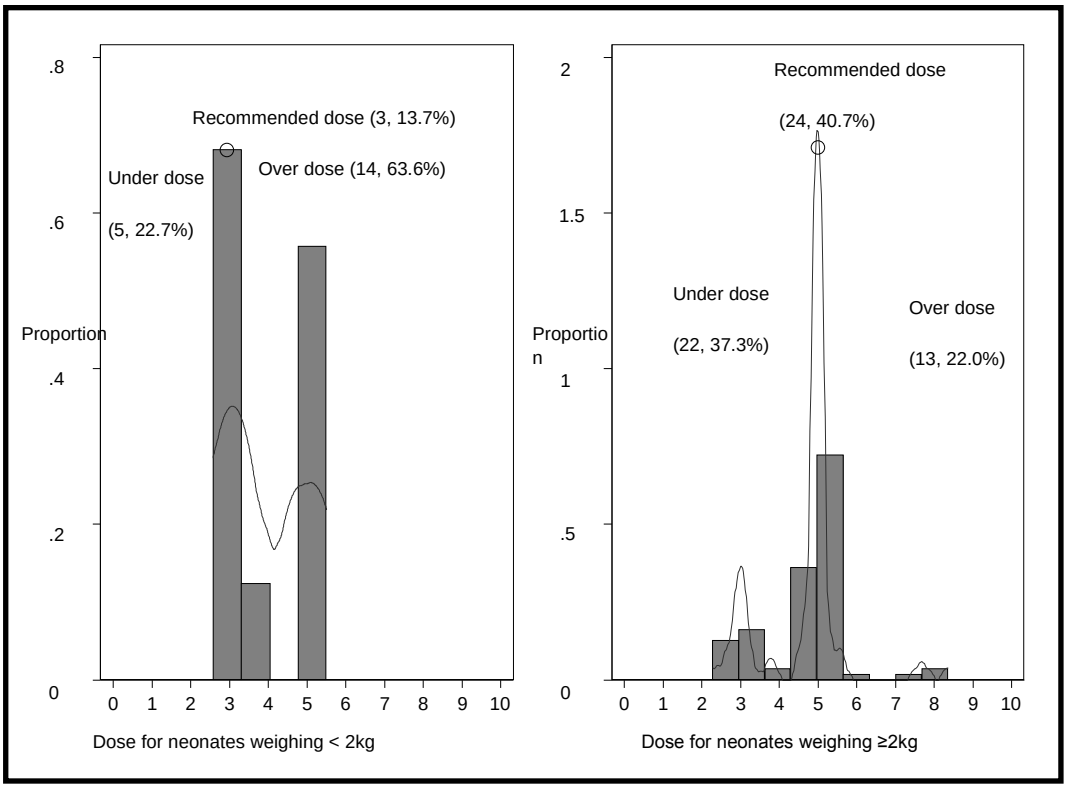
Table 4.6: Duration of Aminoglycosides Therapy in pediatric wards of KNH

Variable	Median[IQR]	Range
Prescribed aminoglycoside duration (days)	7[5,10]	2, 17
Actual duration on aminoglycosides(days)	6[5, 10]	1, 17
Length of admission(days)	14[9, 21]	2, 74
Duration on gentamicin (days)	5[3, 7]	1, 10
Duration on amikacin (days)	6[4, 9]	1, 10

4.2.5 Dose of aminoglycosides prescribed to pediatric patients in KNH

The median dose [IQR] of gentamicin per body weight for neonates aged <7 days post-delivery and weighing <2 kg was 3.4 [3, 5]mg/kg/day and ranged from 2.6 to 5.5mg/kg/day. Neonates aged<7 days post-delivery and weighing at least two kilograms received a median dose [IQR] of 5 [5, 5] mg/kg/day and ranged from 2.3 to 8.4mg/kg/day. The median gentamicin dose [IQR]per body weight for children aged above seven days post-delivery was5.2 [4.2, 7.5] mg/kg/day and ranged from 2.9 to 9.5mg/kg/day. The median amikacin dose [IQR] per body weight was 15 [14.2, 15.6] mg/kg/day and ranged from 1.9 to 26.4mg/kg/day.

A one sample sign rank test was done to compare the dose of gentamicin and amikacin against the recommended doses (34). The prescribed gentamicin dose per body weight for neonates <7 days and weighing at least two kilograms was not significantly different from the recommended 5mg/kg/day (p= 0.197) while that for a similar category weighing <2kgwas significantly higher than the recommended 3mg/kg/day (p= 0.006). The gentamicin dose for children aged above seven days was not significantly different from the recommended 7.5mg/kg/day (p= 0.068). Similarly, the prescribed amikacin dose per body weight was not significantly different from the recommended 15mg/kg/day (p= 0.552). These doses are summarized in figures 3-5.



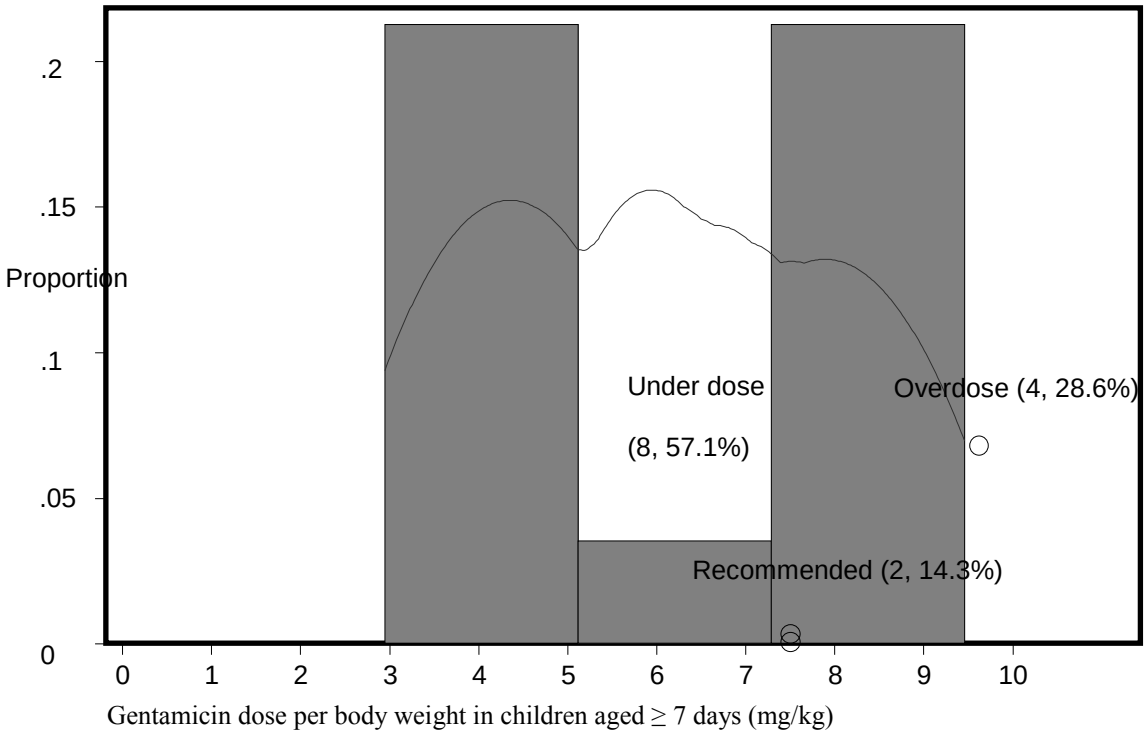
*The recommended dose for neonates <2kg is **3mg/kg/day** and that for neonates ≥2kg is **5mg/kg/day**

Figure 4: Gentamicin dose per kg body weight for neonates aged < 7 days in pediatric wards of KNH

Only 24 (40.7%) neonates aged <7 days post-delivery and weighing ≥ 2kg received the recommended gentamicin dose of 5mg/kg/day. About 22 (37.3%) were under dosed while 13 (22.0%) were over dosed. Neonates aged <7 days post-delivery and weighing < 2kg who

received the recommended gentamicin dose of 3mg/kg/day were 3 (13.7%). Most of them (n=14, 63.6%) were over dosed while 5 (22.7%) were under dosed.

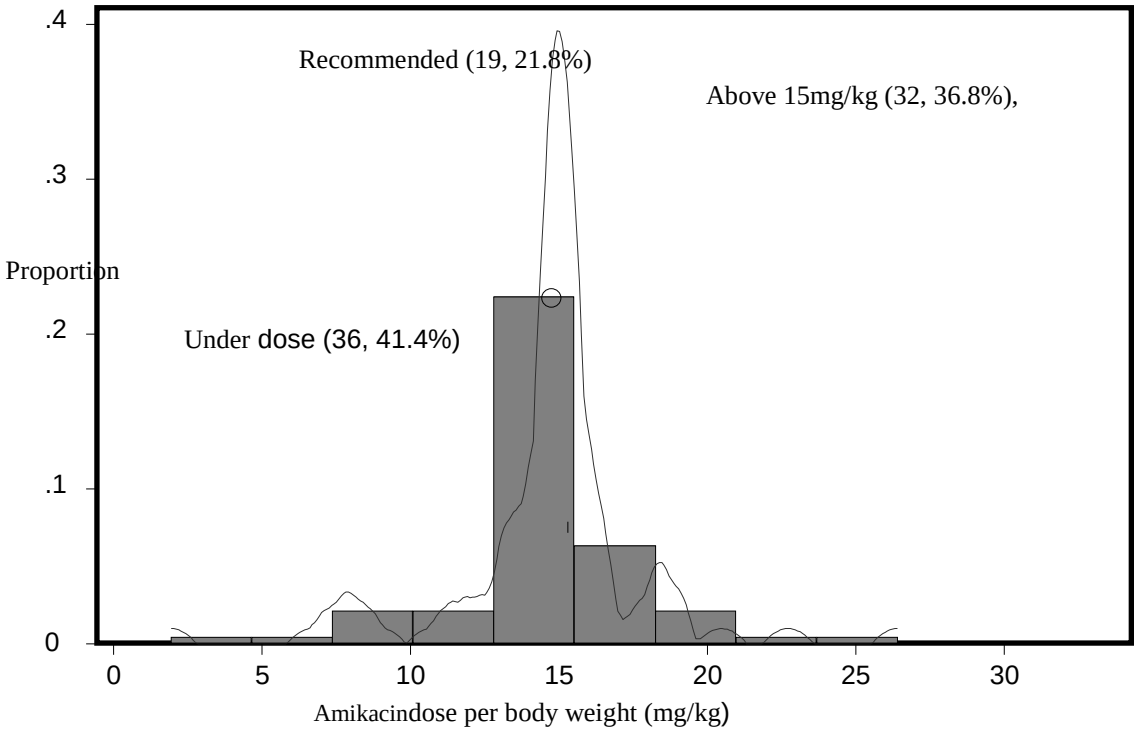
Children aged 7 days or older who received the recommended gentamicin dose of 7.5mg/kg/day were 2 (14.3%). Most of them (n=8, 57.1%) were under dosed while 4 (28.6%) were over dosed.



*The recommended dose for children aged ≥ 7 days is **7.5 mg/kg/day**

Figure 5: Gentamicin dose per kg body weight in children aged ≥ 7days in pediatric wards of KNH

About 19 (21.8%) children on amikacin received the recommended dose of 15mg/kg/day. Less than half (n=36, 41.4%) were under dosed while 32(36.8%) received doses above the recommended 15mg/kg/day. None of them was over dosed.



***The recommended dose is **15-30 mg/kg/day**

Figure 6: Amikacin dose per kg body weight in pediatric wards of KNH

4.2.6 Patient weights in the pediatric wards of KNH

The median weight of the patients [IQR] was 2.55 [1, 11] kg and ranged from 0.95 to 13.8 kg. A majority of the patients (n=169, 88%) had their weight documented. However, the weight of a significant number (n=23, 52.3%) of patients in the general pediatric wards was not recorded. The weight of all the patients in NBU was recorded. Failure to record the body weight meant that doses could not be calculated correctly.

4.3 Administration of aminoglycosides

4.3.1 Dilution and time of administration of aminoglycosides in the pediatric wards of KNH

Kenyatta National Hospital stocks gentamicin in ampoules of 80mg/2ml and 20mg/2ml. Amikacin is stocked in ampoules of 500mg/2ml, 125mg/2ml and 100mg/2ml. There is a

prepared guide attached to the treatment trolley on how to dilute the various antibiotics. An extract of this guide is shown in table 4.7. The full guide is annexed in Appendix E.

All the instructions on dilution were correct except for gentamicin 20mg/2ml in which the diluent per ml was overestimated in the dilution guide. The correct dose should have been 1mg per 0.1ml. Neonates treated with this preparation were therefore under dosed.

All the patients received aminoglycosides once daily intravenously. In all cases gentamicin and amikacin were administered as a bolus in less than half a minute. Slightly less than half of the patients (n=95, 49.5%) received all the daily doses of the aminoglycoside within one hour of the prescribed administration time. Less than half of the participants (n=32, 16.7%) missed some aminoglycoside dose in between treatment.

Table 4.7: Antibiotics dilution guide in the pediatric wards of Kenyatta National Hospital

Drug name and strength	Amount of water for injections to add	Final dosage(mg) per 0.1ml
Gentamicin 80mg/2ml	Add 2ml	2
Gentamicin 20mg/2ml	Do not dilute	2
Amikacin 500mg/2ml	Add 8ml	5
Amikacin 125mg/2ml	Add 3ml	2.5
Amikacin 100mg/2ml	Do not dilute	5

Majority (n=19, 9.9%) missed one dose followed by 9(4.7%) who missed two doses. No reason was given for the missed dose for a majority of cases (n=19, 59.4%). A missing intravenous line was a reason in ten cases (31.3 %).

4.4 Monitoring treatment response to aminoglycosides in the pediatric wards of KNH

Assessment of patient response to aminoglycosides was done by reviewing creatinine level, white blood cell count (WBC), body temperature and culture and sensitivity testing.

4.4.1 Creatinine levels of patients in the pediatric wards of KNH

Baseline creatinine levels were done and recorded for majority of the cases (n=132, 68.8%). The normal range for creatinine levels for males and females is 50-120 µmol/L and 50-100µmol/L

respectively. Eleven patients (5.7%) had a documented baseline creatinine levels above 120 µmol/l. The majority of these patients were male (n=8, 72.7%) and had neonatal sepsis (n=10, 83.3%), while one female patient had a baseline creatinine level of 105µmol/L. Out of these, aminoglycoside therapy was discontinued in one patient after one dose while in two patients therapy was discontinued after two doses. It was not documented whether the discontinuation was informed by the elevated creatinine level or other patient factors.

Table 4.8: Number of patients with monitoring creatinine levels in the pediatric wards of KNH

	Number of patients n (%)		
Ward	Baseline	At least one follow up	At least twice a week
3A	5(2.6)	1(0.9)	1(1.3)
3B	18(9.4)	4(3.8)	3(3.9)
3C	15(7.8)	3(2.8)	1(1.3)
3D	5(2.6)	0(0)	0(0)
NBU	89(46.4)	9(8.5)	4(5.3)
Total	**132(68.8)**	**17(16.0)**	**9(11.8)**

Patients on aminoglycosides for at least 72 hours with at least one follow up creatinine level documented were 17 (16.0%). Out of the 17, 2 (11.8%) had follow up creatinine levels above 100µmol/l,while 5 (29.4%) had an increase in creatinine level from baseline(from 11.7% to 405%).Patients on aminoglycosides for 7 days or more and at least twice a week creatinine level follow up were 9 (11.8%).

The median baseline creatinine level was 56µmol/l and ranged from 17 to 239.7µmol/l. The median follow up creatinine level was 62.2µmol/l and ranged from 26 to 128.3µmol/l.

4.4.2 Culture and sensitivity testing and Temperature monitoring in the pediatric wards of KNH

Culture and sensitivity testing was done for a very small number of patients (n=8, 4.2%). In all the cases, the organisms were sensitive to the prescribed aminoglycoside. Resistance to gentamicin was detected in one case (12.5%); however, the patient was not on gentamicin. No resistance to amikacin was detected.

The temperature chart was reviewed daily and the highest temperature in 24 hours recorded. Only 53 patients (27.6%) developed a fever in the course of treatment. The fever resolved in all the cases. The fever could have been due to an existing infection, or a new hospital acquired infection. Resolution of the fever in all these cases is an indicator of the effectiveness of the prescribed AG.

4.4.3 White blood cell count (WBC) monitoring in the pediatric wards of KNH

The median baseline WBC [IQR] for the patients was 12.4 [9.6, 15.4] units and ranged from 3.4 -56.7 x 10^9/L while the follow up WBC [IQR] was 9.9[8.4, 11.8] and ranged from 3.97-23.3 x10^9/L. The number of patients with a baseline WBC>11 X10^9/L was 103(53.6%) and the majority(79, 76.7%) were in NBU. The normal range for WBC is 4-11 x 10^9/L. Values above this range are indicative of a bacterial infection. Even though the number of patients with documented follow up WBC was lower compared to baseline WBC, the decrease in the number of patients with follow up WBC > 11 x 10^9/Lis an indicator of the effectiveness of the prescribed aminoglycoside.

Baseline WBC was measured for a majority (n=163, 84.9%) of the patients. The number of patients with follow up WBC results was 38(19.8%).

4.4.4 Pharmacist's review of aminoglycoside use in the pediatric wards of KNH

There were no comments or documented review by a pharmacist in all the sampled patient files. On enquiry with the pharmacist in charge of the pediatric wards, interventions done by the pharmacist are documented in the intervention register kept at the pharmacy. A review of the register identified three instances of intervention by the pharmacist for amikacin dosing between October and December 2016.

4.5 Treatment outcome of pediatric patients on aminoglycosides in KNH

Majority of the patients (n=131, 68.3%) was cured with the first line antibiotic combination and were discharged home without switching to other drugs. About 65 (33.9%)patients were suspected to have ADRs. Fever resolved in all the 53 patients who were febrile. Some patients (26, 13.5%) died during treatment.

Table 4.9: Treatment outcome of pediatric patients on Aminoglycosides in KNH

	Treatment outcome n (%)			
Ward	**Cured with first line drugs**	**Suspected ADRs**	**Fever resolved**	**Died**
3A	4 (2.1)	2(1)	2(3.8)	0(0)
3B	12(6.3)	6(3.1)	4(7.5)	2(1)
3C	13(6.8)	6(3.1)	7(13.2)	2(1)
3D	4(2.1)	2(1)	2(3.8)	1(0.5)
NBU	98(51)	49(25.5)	39(73.6)	21(11)
Total	**131 (68.3)**	**65(33.9)**	**53(100)**	**26(13.5)**

Outcome of patients with aminoglycoside under dosing and over dosing in the pediatric wards of KNH

The number of patients <2kg and aged <7days who received gentamicin under dose were 5. Out of these, only one had neonatal sepsis while the other four were treated empirically. All of them were on combination of gentamicin and benzyl penicillin. None of them were switched to another regimen. The patient with neonatal sepsis died while the other four were discharged home. The birth weight of the patient who died was 1400g, while the others had birth weights ranging from 1105g to 1810g.

The number of patients ≥2kg and aged <7days who received gentamicin under dose were 22. Out of these, 8 had neonatal sepsis while the other 14 were treated empirically. 21 of them were on a combination of gentamicin and benzyl penicillin while one was on gentamicin only. The patient on gentamicin only was treated empirically and was not switched to another antibiotic. Out of the 8 patients who had neonatal sepsis, 5 were switched to other antibiotics while three were retained on the same antibiotics. 2 patients in this group died, one of them having neonatal sepsis.

The number of patients aged ≥7days who received gentamicin under dose was 8. Out of these, 4 had neonatal sepsis, 1 had severe pneumonia while the other three were treated empirically. Amongst these, 4 were on a combination of gentamicin and benzyl penicillin, 3 were on gentamicin only while one was on gentamicin and flucloxacillin. Out of the 8, 5 were switched to other antibiotics including 2 of the 3 patients started on gentamicin only. These included the

patient with severe pneumonia, two patients with neonatal sepsis and two patients who were treated empirically.

The number of patients with amikacin under dosing was 36. Out of these, 23 had neonatal sepsis, 4 had severe pneumonia while the other 9 were treated empirically. 10 patients, including 8 with neonatal sepsis and one with severe pneumonia were switched to other antibiotics while two died.

The number of patients <2kg <7days who received gentamicin over dose were 15. Out of these, 4 had neonatal sepsis while the other 11 were treated empirically. Out of the 6 patients who were switched to other antibiotics, 2 had neonatal sepsis while 4 were on empirical treatment. 4 patients died.

The number of patients ≥2kg <7days who received gentamicin over dose were 13. Out of these, 6 had neonatal sepsis while the other 7 were treated empirically. 2 patients with neonatal sepsis were switched to other antibiotics while 4 died.

The number of patients ≥7days who received gentamicin over dose was 4. Out of these, two had neonatal sepsis while two were treated empirically. One patient with neonatal sepsis was switched to another regimen while none died.

4.6 Aminoglycoside related Adverse Drug Reactions in pediatric patients admitted in KNH

Adverse drug reactions (ADRs) were suspected in 65 patients (33.9%). Fever was the most common suspected ADR (53, 27.6%) followed by nausea and vomiting (8, 4.2%) and electrolyte imbalance (5, 2.6%).

There was one case each of nephrotoxicity (1, 5.9%) and rash (1, 0.5%). The former had 405% increase in creatinine level. The patient with the facial rash was 3 days old on admission. He had respiratory distress syndrome and was on gentamicin and benzyl penicillin. The rash appeared on the fourth day of therapy and he was discharged home a day after.

One patient with acute kidney injury (AKI) was on gentamicin for two days before discharge while another with chronic renal failure (CRF) was on amikacin for seven days. The baseline creatinine level for the two was 134.8 and 140.2µmol/l respectively. Follow up creatinine level

for the patient with AKI was 126.4µmol/l. Follow up creatinine level for the patient with CRF was not recorded.

There was one case with a 405% increase in creatinine levels. The incidence of nephrotoxicity was 1 out of the 17(5.9%) children whose kidney function was adequately monitored. The increase was from a baseline of 20µmol/l on the first day to 101µmol/l on the fourth day. The levels dropped to 81µmol/l on the sixth day of aminoglycoside therapy. The patient was on gentamicin and benzyl penicillin for two days then amikacin and ceftazidime for six days before being changed to meropenem for another seven days. This was the only case with an increase more than 30%. The patient was a preterm female neonate presenting with low birth weight and scleroderma.

Electrolyte imbalance occurred in 5(2.6%) patients. Out of these, 3(60%) had elevated potassium levels, 1(20%) had decreased potassium levels while 1(20%) had elevated sodium levels. Majority of them (4, 80%) were on gentamicin and benzyl penicillin while 1(20%) was on amikacin and ceftazidime. All of them were admitted in NBU.

More males (39, 60.0%) were suspected to have ADRs compared to females (26, 40.0%). However, this difference was not statistically significant (p=0.790). The new born unit had the highest incidence of suspected ADRs (49, 25.5%).

4.7 Summaryof Aminoglycoside related Medication errors in the pediatric wards of KNH

The most common type of medication error was monitoring errors as shown in table 4.10 below. This was followed by wrong dose and wrong time errors respectively.

Table 4.10: Summary of medication errors in pediatric patients at KNH

Error	Ward n(%)					
	3A	**3B**	**3C**	**3D**	**NBU**	**Total**
Omitted doses	0(0)	1(0.5)	0(0)	2(1)	29(15.1)	32**(16.7)**
Extra dose	1(0.5)	0(0)	1(0.5)	0(0)	22(11.5)	24**(12.5)**
Wrong time	2(1)	5(2.6)	7(3.6)	5(2.6)	78(40.6)	97**(50.5)**
Suspected ADRs	2 (1)	6 (3.1)	6 (3.1)	2 (1)	49 (25.5)	65 (33.9)
Wrong combinations	0 (0)	1 (0.5)	6 (3.1)	1 (0.5)	6 (3.1)	14 (7.3)

Wrong dose errors						
Under dose	4(2.1)	6(3.1)	1(0.5)	0(0)	60(31.3)	71**(37.0)**
Over dose	2(1)	1(0.5)	1(0.5)	0(0)	27(14.1)	31**(16.1)**
Total	**6(3.1)**	**7(3.6)**	**2(1)**	**0(0)**	**87(45.4)**	102**(53.1)**
Monitoring errors						
NoBaseline creatinine levels						
	0(0)	0(0)	0(0)	1(0.5)	59(30.7)	60**(31.2**)
NoFollow up creatinine levels						
	4(2.1)	14(7.3)	12(6.3)	6(3.1)	138(71.9)	174**(90.6)**
No serum aminoglycoside levels						
	5(2.6)	18(9.4)	15(7.8)	6(3.1)	148(77.1)	192**(100)**
No baseline WBC						
	0(0)	0(0)	0(0)	1(0.5)	28(14.6)	29**(15.1)**
No follow up WBC						
	2(1)	12(6.3)	8(4.2)	5(2.6)	127(66.1)	154**(80.2)**

4.8: Health Care Workers' Knowledge, Attitude and Practice of Therapeutic Drug Monitoring of Aminoglycosides in Kenyatta National Hospital

4.8.1 Participant recruitment and Response rate

A list of all pediatricians (from KNH and University of Nairobi)and their contacts was obtained from the KNH Department of Pediatrics. They were contacted by phone and were given an overview of the study and asked about their availability and willingness to be interviewed at a place and time of their choice. Universal sampling was attempted. Out of the 40 specialists, only 7 consented and were interviewed. A total of 15 senior house officers were approached after ward rounds out of which eight consented and were interviewed. The other healthcare workers were visited at their stations of work. All the four pharmacists, six nurses and three laboratory technologists approached consented and were interviewed. The target was 15-30 healthcare workers. A total of 28 participants were recruited. The response rate is presented in Figure 7.

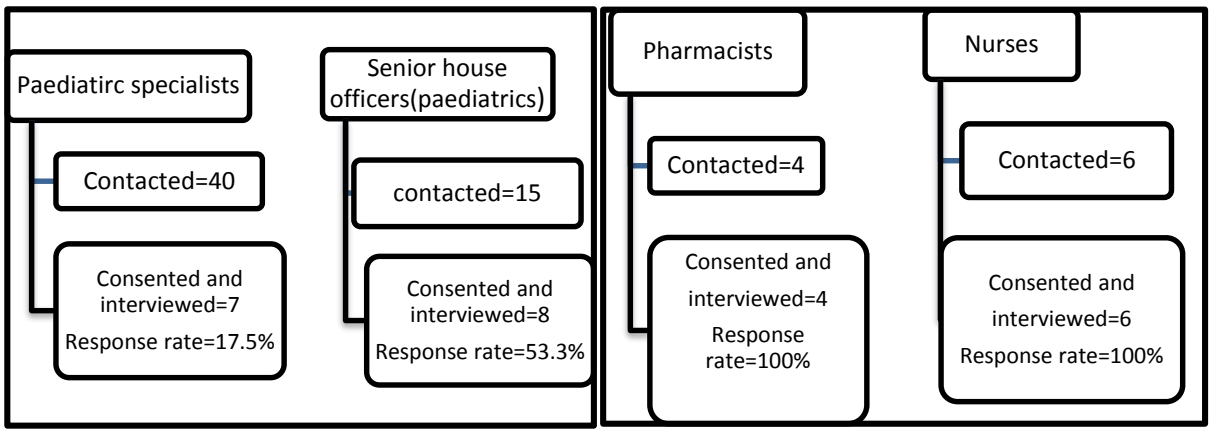


Figure 7: Flow chart of participant recruitment and response rate of HCWs working in the pediatric wards of KNH

4.8.2Baseline characteristics of the health staff interviewed at Kenyatta National Hospital

The majority of the participants were female (18, 64.3%). The median age was 38.5 and ranged from 26 to 74 years. The majority were senior house officers (8, 28.6%) followed by pediatricians (7, 25%) and the least in number were the laboratory technologists (3, 10.7%). The median duration of practice was 12.5 years and ranged from 3 to 45 years. The baseline characteristics of the healthcare workers interviewed are summarized in table 4.11.

Table 4.11: Baseline characteristics of healthcare workers interviewed

Characteristic	Proportion n(%) or median[IQR]
Cadre	
Pediatricians	7(25)
Senior house officers	8(28.6)
Pharmacists	4(14.3)
Nurses	6(21.4)
Laboratory technologists	3(10.7)
Total	28(100)
Age	38.5[31, 50]
Duration in the profession	12.5[7, 19]
Sex	
Male	10(35.7)
Female	18(64.3)

4.8.3 Current practice for determining aminoglycoside doses in the pediatric wards of KNH

Only a minority of the study participants (n=5, 17.9%) mentioned the use of existing pediatric protocols and guidelines in determining aminoglycoside doses while almost half of them (n=13,

46.4%) specified that they determine the dose based on weight and age of the patient. Four respondents (14.3%) mentioned consideration of renal function tests when determining the dose.

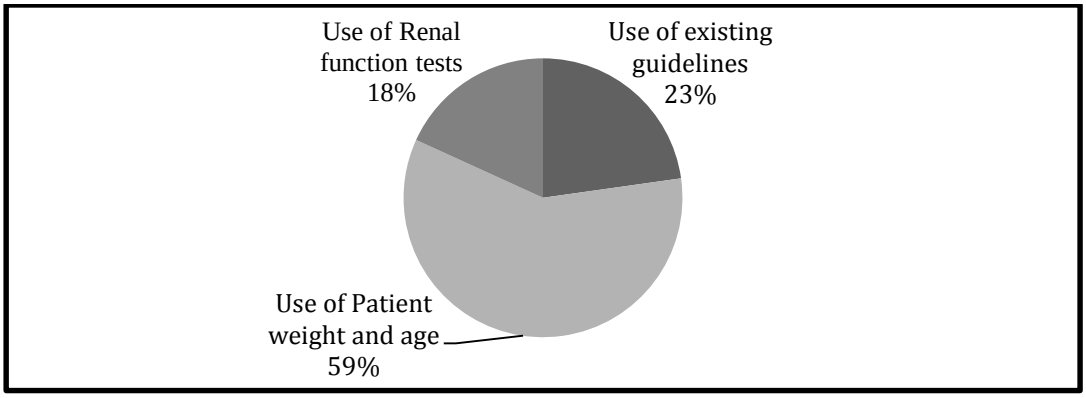


Figure 8: Opinion of respondents on how dose of aminoglycosides is currently determined in KNH

4.8.4 Monitoring of patients on aminoglycosides in the pediatric wards of KNH

The respondents were asked how monitoring of patients on Aminoglycosides is currently performed in KNH. The majority (n=15, 53.6%) were not sure about it while 6 (21.4%) said it is not currently performed. Of those respondents who thought monitoring is undertaken, seven (25%) mentioned renal function tests.

The respondents were also asked if there is a system in KNH for double checking the prescribed and prepared AG dose before administration. The majority (n=15, 53.6%) said there was no system, 7 (25%) affirmed this while 6 (21.4%) were not sure. The group that affirmed mentioned a review by consultants during ward rounds (4, 57.1%), confirmation by nurses before administration (1, 14.3%) and cross checking by pharmacy staff before issuance of the drugs (n=2, 28.6%).

4.8.5 Knowledge and experience with TDM of aminoglycosides in the pediatric wards of KNH

Twelve respondents (42.9%) had been involved in TDM before. This included three pediatricians and three laboratory technologists. Four respondents (14.3%) had requested for TDM before. These were performed in KNH (1, 25%), Aga Khan Hospital (2, 50%) and outside the country

(1, 25%). Eighteen respondents (64.3%) said they needed training on TDM while 7 (25%) were not sure of this.

Respondents were asked to list the drugs they thought needed therapeutic drug monitoring in KNH. Aminoglycosides were mentioned by 14 respondents out of 28 (50%).

Table 4.12: Opinion of respondents on drugs that need monitoring in KNH

Opinion	Number of times mentioned n (%)
Aminoglycosides	14(50)
Anticonvulsants	8(28.6)
Cytotoxic drugs	7(25)
Digoxin	6(21.4)
Antibiotics (general)	4(14.3)
Vancomycin	4(14.3)
Cyclosporine	4(14.3)
Tacrolimus	3(10.7)
Meropenem	3(10.7)

An internal memo from the office of the chief pharmacist in KNH to the assistant director, laboratory medicine and dated 11th May, 2016(Ref: KNH/PHARM/1B/VOL.1/56) requested for reagent strips for therapeutic drug monitoring of vancomycin and amikacin. Other drugs listed in the letter were phenytoin, sodium valproate and methotrexate.

4.8.6 Healthcare workers p erceptionsand barriers to implementation of a protocol for aminoglycosides use in the pediatric wards of KNH

The respondents were asked if they thought there was a need for a protocol on aminoglycoside dosing and monitoring in KNH. All the respondents affirmed the need for this protocol. They were then asked to list what they thought needed to be included in the institutionalized protocol. Dose calculation and how to monitor patients were each mentioned eleven times (39.3% of respondents). This was followed by the side effects and ADRs to watch out for (5, 17.9%). The responses are summarized in figure 9.

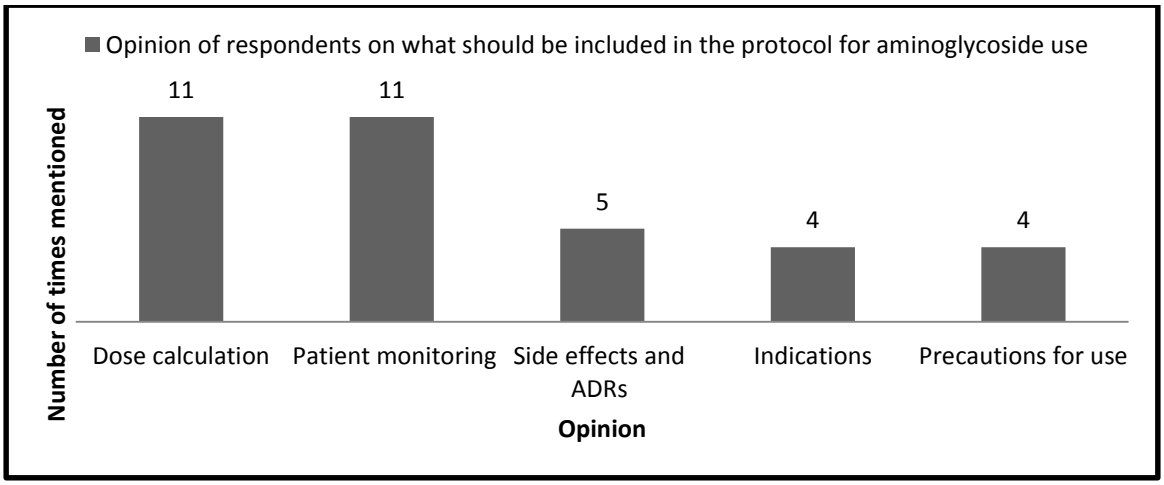


Figure 9: Opinion of healthcare workers on what should be included in the Institutionalized aminoglycosides use protocol in KNH

The respondents were also asked to list what could prevent the effective implementation of such a protocol in KNH. Knowledge gap was listed 12 times (42.9%) followed by lack of good will (9, 32.9%). The other barriers are summarized in figure 10.

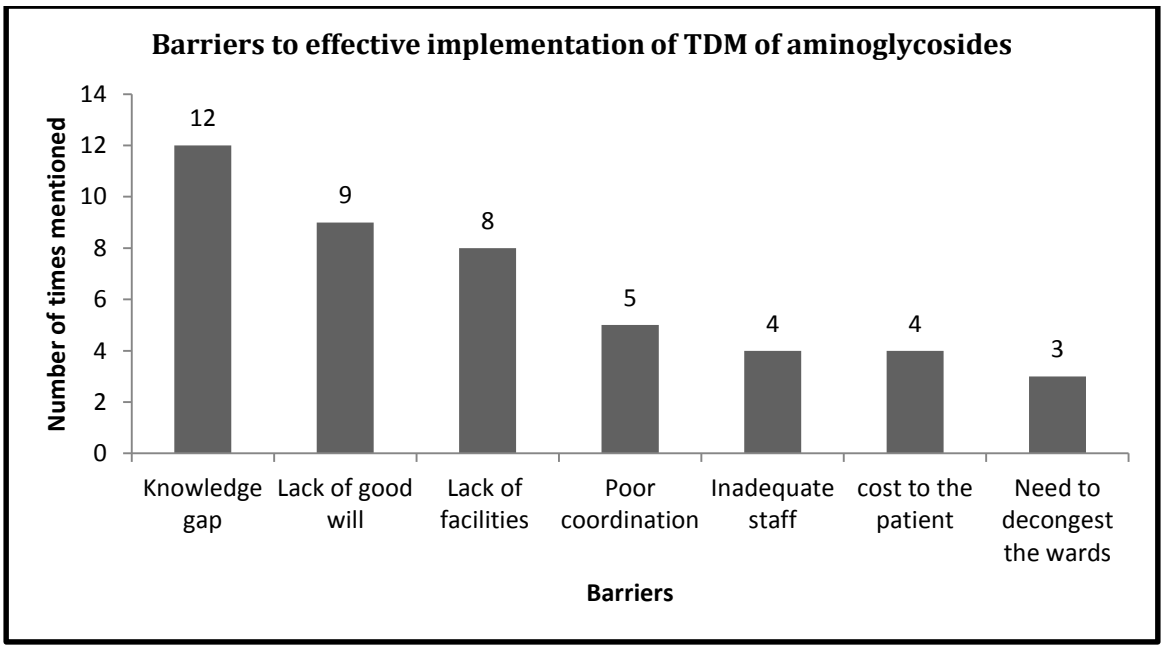


Figure 10: Opinion of the respondents on what can prevent effective implementation of a protocol on aminoglycoside dosing and monitoring in KNH

5.0 CHAPTER FIVE DISCUSSION

5.1 Significant findings

The aim of this study was to evaluate the use of aminoglycosides in the pediatric wards of the largest national referral hospital in Kenya. It also attempted to assess the gaps and opportunities for the introduction of a protocol on aminoglycosides use and the perceptions of the health care workers towards TDM for aminoglycosides monitoring. Some of the significant findings were firstly that: doses for the majority of the patients (102, 53.1%) did not conform to recommendations in the national pediatric protocol and this raises concerns about potential avoidable harm to the patients, especially the neonates who are very vulnerable. In addition, TDM of aminoglycosides is not currently performed in KNH. The healthcare workers affirmed the need for TDM of aminoglycosides, but listed knowledge gaps, lack of willingness and poor coordination as some of the threats to the effective, and the future implementation of this service.

The overall incidence of aminoglycoside use in the pediatric wards of KNH was 9.8%. This was lower than 12.1% (31) and 33.7% (36) reported in other studies. This difference could be attributed to concerns about aminoglycoside safety by pediatricians owing to lack of TDM of aminoglycosides and they therefore opt to use other antibiotics that have lower risk compared to aminoglycosides. This will be followed up in future research, with the availability of TDM services for aminoglycosides potentially avoiding this.

5.2 Consequences of under dosing and missed aminoglycoside doses

Other issues included the fact that more than half (50.5%) of the patients did not receive all the aminoglycoside doses within one hour of the prescribed dose time. This was because of rescheduling administration to specific times for the particular wards. Some patients also missed a dose for the entire day. About a third (30.3%) of the patients missed some aminoglycoside dose in the course of therapy. This may contribute to treatment failure and consequently increase in mortality rates or antibiotic resistance. Such practices need to be urgently addressed.

The national pediatric protocol does not specify whether aminoglycosides should be prescribed in lower doses when used in combination with other antibiotics. It only states a specific dose for a particular weight and age band. The effect of aminoglycoside under dosing may not be detected immediately if the causative organism is responsive to the second antibiotic used in the correct

dose, but it can be a cause for concern if the organism is not responsive to the second antibiotic. In the majority of the patients with gentamicin under dosing (n=21, 60%), the gentamicin was used empirically compared to treatment of known infections (n=14, 40%). Therefore, in as much as less than a half (n=10, 28.6%) of patients with gentamicin under dosing were switched to other antibiotics, more patients with gentamicin under dosing who were actively treated for an infection (n=8, 57.1%) were switched to other antibiotics compared to those who were treated empirically (n=2, 9.5%). In addition, a bigger proportion of patients (n=2, 50%) with gentamicin under dosing who were on gentamicin only were switched to other antibiotics compared to those who received gentamicin in combination with other antibiotics (n=8, 25.8%). The switching of the patient to other antibiotics could be an indicator of non-response due to under dosing. In a minority of the patients with amikacin under dosing (n=9, 25%), the amikacin was used empirically compared to treatment of known infections (n=27, 75%). Due to the empirical use of the aminoglycosides, the actual difference in patient outcomes resulting from under dosing and over dosing of aminoglycosides based on the number of patients switched to other antibiotic regimens was difficult to establish. It is not clear whether; the switch to other antibiotics was necessitated by non-response to the inadequate aminoglycoside dose or change to more appropriate antibiotics.

Failure to record the body weight of the majority of patients in the GPWs (n=23, 52.3%) meant that aminoglycosides doses could not be calculated correctly. Slightly less than half of the patients (46.9%) received doses that conformed to the national pediatric protocol. This is higher compared to 23% (37) and 25% (38) reported in other studies. This difference could be attributed to variations in familiarity with aminoglycoside dosing in different patient populations or heavy work load together with time pressure at KNH leading to medication errors. Some of the reasons listed for non-compliance include knowledge gap and time constraint (37), which was also highlighted by our study participants in the current study

5.3 Resistance to aminoglycosides

There was only 1 case of gentamicin resistance out of 8 (12.5%) for which culture and sensitivity testing was done. Some of the reasons that can be attributed to this low number of patients with culture and sensitivity test results are the high patient turnover at the NBU such that by the time the results are out, the patients would have been discharged as well as poor documentation, where the test was ordered and undertaken but the results were not documented in the patient's

file. The ultimate impact of this in clinical practice is the possibility that some cases of aminoglycoside resistance went undetected especially among the 58 (30.2%) cases that were not cured with the first line treatment. Consequently, I recommend an improvement in utilization and documentation of culture and sensitivity testing where applicable, which is already starting to happen. One study(39) reported considerable variation in the prevalence of gentamicin resistance across laboratories (1.1-27.6%). This was consistent with this study and the study undertaken by Gwee et al, (27) which noted that gram negative resistance to gentamicin varied between 17- 27%, however; different from 50.3% as reported by Gamal et al,(40). Resistance to amikacin was not detected in any of the samples tested in the current study. Gamal et al,(40) reported the prevalence of amikacin resistance was 17.3%. The results of these two studies are consistent with the findings of Kim et al, (41) which noted that resistance to amikacin across hospitals varied from 0 to 45%.

5.4 Aminoglycoside toxicity and treatment monitoring

The present study found out that 14 (7.3%) patients were on other nephrotoxic drugs, out of which 5 (35.7%) were on vancomycin. This was lower compared to the findings of Oliveira et al, (42) and Gerlach et al, (43) who both reported an incidence of 51%. This difference could be attributed to less co-morbidity in the pediatric patients as compared to adults. Only 1 patient out of 17 (5.9%) whose creatinine levels were followed up had nephrotoxicity. This may not be the true incidence of nephrotoxicity because of the poor patient monitoring. It was higher though, than the findings by Rybak et al, (44) and Contopoulos et al, (45) which reported an incidence of 0.0% and 1.6% respectively. The study by Rybak et al,(44) also reported 6 cases of nephrotoxicity out of 39 patients (15.4%) who were on aminoglycosides for at least 72 hours on a twice daily dosing schedule. In the current study, all the patients were on a once daily aminoglycoside dosing schedule. According to Rybak et al, the significant predictors of nephrotoxicity were the schedule of aminoglycoside administration, the daily area under the plasma concentration time curve and concomitant use of vancomycin. This is supported by the findings of Gerlach et al,(43) which found out that the risk of aminoglycoside associated nephrotoxicity is increased by the concurrent use of aminoglycosides with other nephrotoxins. In KNH, the concurrent use of nephrotoxins, coupled with poor monitoring poses a great risk to the patients, which needs to be addressed. Consequently, there is need to minimise concurrent use of

such drugs or promote close monitoring of the patients. This is a subject for future interventions and research in this hospital.

Electrolyte imbalance occurred in 5(2.6%) patients. Hyponatremia and derangement of potassium levels could be a pointer of nephrotoxicity. Hypernatremia could have been as a result of diarrhea or vomiting(46).It was difficult to monitor treatment response using white blood cell count (WBC) because this was only followed up in 38 (19.8%) of the patients.

Currently, TDM is only undertaken for tacrolimus and cyclosporine but not for aminoglycosides at KNH. This implies that aminoglycoside related toxicity in patients may not be detected early enough for swift intervention. The Kenya Ministry of Health Basic Paediatric Protocol(BPP) recommends monitoring of amikacin trough levels where available (34). The limiting factors are the availability of the necessary resources such as aminoglycoside test kits and the contract agreement of the machines on placement which dictates the drugs that can be analyzed. Aminoglycosides are currently not among the drugs under the contract agreement of the machines despite being high risk medicines. Introduction of TDM for aminoglycosides will greatly improve practice because the blood drug levels will inform swift interventions geared towards patient safety and the intended treatment outcomes. However, it is essential to address and overcome the barriers identified in this current study before the introduction of such a TDM service in order to ensure effective and efficient uptake and implementation. This is especially as all the healthcare workers interviewed affirmed the need for implementation of TDM of aminoglycosides but there were identified barriers. This is consistent with the findings of Phillips et al,(47) and Venisse et al, (48) which appreciated the role of TDM in minimization of toxicity and dose optimization. Grossberg et al,(49)lists some of the barriers to TDM as knowledge gap, high out of pocket costs, delay of results and non-coverage by insurance which is consistent with the findings of the current study.

Successful implementation of TDM of aminoglycosides in KNH will depend on how these challenges are addressed including key stakeholder education. This will be the subject of future studies once TDM for aminoglycosides is introduced in KNH.

Strengths and limitations of the study

This was a prospective cohort study and therefore data was collected in real time. One of the challenges faced during the study was incomplete medical records. This was especially with regard to patient weight and creatinine levels. Unavailability of therapeutic drug monitoring and minimal follow up creatinine levels was a limitation to monitoring patients for aminoglycoside toxicity. Some respondents may not have given accurate response to the interview questions. There was low response rate by the paediatric specialists. Nephrotoxicity may not have been detected in patients on aminoglycosides discharged earlier than seven days after initiation of aminoglycoside therapy. Follow up of such patients after discharge was not feasible in this study due to resource constraints.

6.0 CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Use of AGs is common in the pediatric wards at the KNH. Adherence to treatment guidelines in terms of dosing and monitoring was sub-optimal and raises concerns around potential, avoidable harms to patients. The identified barriers, particularly training of healthcare workers and provision of resources need to be adequately addressed before a TDM service for AGs is undertaken in KNH.

6.2 Recommendations

The following recommendations are made to KNH management based on the findings of this study:

1. I recommend an improvement in utilization and documentation of culture and sensitivity testing where applicable, which is already starting to happen.
2. Improvement in creatinine level monitoring is recommended before aminoglycoside TDM is implemented. Do baseline creatinine level for patients anticipated to be on aminoglycosides for at least 72 hours, at least one follow up creatinine level for those on aminoglycosides for less than a week and at least twice weekly follow up creatinine level for patients on aminoglycosides for 7 days or more.
3. Co-administration of nephrotoxic drugs together with aminoglycosides should be minimized especially due to the poor patient monitoring.
4. Sensitize the prescribers on therapeutic drug monitoring of aminoglycosides.
5. Include aminoglycosides monitoring in the contract agreement for the machines on placement.

6.2.1 Recommendations for future research

Larger prospective studies are recommended to determine the true incidence of aminoglycoside related side effects because in this set up, the renal functions were not routinely measured

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APPENDICES

APPENDIX A: GENERAL INDICATORS FORM

Patient Code_____

PART 1: ELIGIBILITY CHECKLIST

Criteria	**Yes**	**No**
Patient admitted in general paediatric ward,PICU,PSU-RU or general NBU		
Patient is on any aminoglycoside antibiotic(s)		
Patient is aged 0 to 12 years		

PART 2: CASE REPORT FORM

Ward _____ Date of recruitment_____

Investigator_____

Date of admission	Date of discharge	Duration on aminoglycosides therapy	Patient weight	Age	Sex	Prescriber
Health Problems	Health Problem Description					
Drugs	Drug Name	Strength	Frequency	Duration		

PART 3: QUALITY OF CARE

1.	Aminoglycoside dosing(Circle appropriately)	8 hourly	12 hourly	24 hourly	36 hourly	48 hourly		
2.	Route of admin							
				Day 1	Day 2	Day 3	Day 4	Day 5
3.	Culture and sensitivity done (Y/N)							
4.	If yes above, are the organisms sensitive to the prescribed aminoglycoside							
5.	Switched to another aminoglycoside							
6.	Switched to other antibiotics							
8.	Baseline Creatinine levels(mg/dl)							
	Creatinine levels during therapy (mg/dl)							
	White blood cell count							
	Daily temperature (^{0}C)							
9.	Time of daily dose of aminoglycoside							
10.	Received daily dose within 1 hour of prescribed dose time							
11.	Reviewed by a pharmacist							
13.	Any suspected ADR on the patient							
	Description of suspected ADR							

Continuation of Part 3

		Day 6	Day 7	Day 8	Day 9	Day 10
3.	Culture and sensitivity done (Y/N)					
4.	If yes above, are the organisms sensitive to the prescribed aminoglycoside					
5.	Switched to another aminoglycoside					
6.	Switched to other antibiotics					
8.	Baseline Creatinine levels (mg/dl)					
	Creatinine levels during therapy (mg/dl)					
	White blood cell count					
	Daily temperature (^{0}C)					
9.	Time of daily dose of aminoglycoside					
10.	Received daily dose within 1 hour of prescribed dose time					
11.	Reviewed by a pharmacist					
13.	Any suspected ADR on the patient					
	Description of suspected ADR					

APPENDIX B: INTERVIEW GUIDE FOR HEALTHCARE WORKERS

Dear colleague,

Kindly spare a few minutes to truthfully complete this questionnaire on aminoglycosides use in the paediatric wards of Kenyatta National Hospital.

PART 1: DEMOGRAPHIC DETAILS		
Gender	Male ☐	Age
	Female ☐	
Cadre	Pediatrician ☐	
	Senior House Officer ☐	
	Medical officer☐	
	Pharmacist ☐	
	Registered clinical officer ☐	
	Nurse ☐	
	Laboratory technologist ☐	
Duration in the profession		

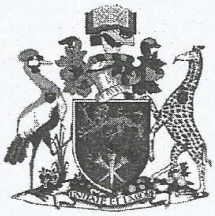
PART 2 CURRENT KNOWLEDGE AND PRACTICE		
	Yes	No
Have you ever been involved in therapeutic drug monitoring before?		
Have you ever requested for TDM?		
If yes, where was it done		
For which drugs do you think TDM is critical in KNH? 1.		
2.		
3.		
4.		
5.		

	Yes	No	Not sure
Do you need training on therapeutic drug monitoring			
How do you determine dose of aminoglycosides in paediatric patients in KNH currently?			
How is monitoring of patients on aminoglycosides currently done in KNH?			

	Yes	No
Is there a system for double checking the prescribed dose and preparation of aminoglycosides before administration to paediatric patients in KNH currently?		

PART 3: ATTITUDE AND BARRIERS TO IMPLEMENTATION OF PROTOCOL FOR AMINOGLYCOSIDES USE		
	Yes	No
Do you think there is need for a protocol for aminoglycosides use in KNH?		
What do you think should be included in the protocol?		
1. 2.		
3.		
4.		
5.		
What are the barriers that can prevent implementation of such protocol in KNH?		
1.		
2.		
3.		
4.		
5.		
6.		

APPENDIX C: CONSENT FORM FOR INTERVIEW WITH HEALTHCARE PROFESSIONALS IN THE PAEDIATRIC WARDS OF KNH



UNIVERSITY OF NAIROBI

COLLEGE OF HEALTH SCIENCES

SCHOOL OF PHARMACY

DEPARTMENT OF PHARMACOLOGY AND PHARMACOGNOSY

Serial No._____ **Version 01** **August2016**

Title of the study: An Audit of Aminoglycosides Use in the Paediatric Wards of Kenyatta National Hospital.

Institution: Department of Pharmacology and Pharmacognosy, School of Pharmacy,

University of Nairobi, P.O BOX 30197-00400, Nairobi. Tel:020 4915027

Investigator: Dr.Onyango Joseph Elias, P.O BOX, 30197-00400, Nairobi. .

Mobile Phone: +254 727 061 699.

Supervisors: 1. Dr.FaithOkalebo - Department of Pharmacology and Pharmacognosy; UoN

Mobile Phone: +254 737 434 204

2. Dr. Margaret Oluka - Department of Pharmacology and Pharmacognosy; UoN

3. Dr. Rosaline Kinuthia – Department of Pharmacy, Kenyatta National Hospital

Ethical Approval: Kenyatta National Hospital/ University of Nairobi Ethical and Research Committee, P.O BOX 20723-00100, Nairobi. Tel 2726300/2716450 Ext 44102

Permission is requested from you to enroll in this medical research study. You should understand the following general principles, which apply to all participants in a medical research:

i. Your agreement to participate in this study is voluntary.
ii. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal.
iii. After you have read the explanation, please feel free to ask any questions that will enable you to understand clearly the nature of the study.
iv. The interview is anticipated to last 15-30 minutes

Introduction: In this study, I am assessing use of aminoglycosides at paediatric wards and NBU in KNH.

Purpose of the study: The purpose of this study is to audit aminoglycosides use at paediatric wards of Kenyatta National Hospital and to identify gaps and opportunities for introduction of a protocol on aminoglycosides use.

Procedure: With your permission, I will engage in a discussion about aminoglycoside use in paediatric patients. I will take some notes on pen and paper. All information obtained will be handled with confidentiality.

Risks: There will be no risks involved in this study,

Benefits: There will be no direct benefits to you but the findings will be useful in improving the quality of care among children less than 12 years, through identification and mitigation of medication errors that may occur during practice.

Assurance of confidentiality: All information obtained from you will be kept in confidence. At no point will your name be mentioned or used during data handling or in any resulting publications. Codes will be used instead.

Contacts: In case you need to contact me, my academic department or the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee concerning this study please feel free to use the contacts provided above.

STATEMENT OF CONSENT

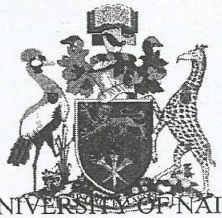
I----------give consent to the investigator to interview me and use the information obtained in his study. Dr. Onyango Joseph Elias has explained the nature of the study to me.

Signature---------- Date----------

I confirm that I have explained the nature and effect of the study.

Signature---------- Date----------

APPENDIX D: CONSENT FORM FOR PARENTS/CAREGIVERS AT PAEDIATRIC WARDS IN KNH



UNIVERSITY OF NAIROBI

COLLEGE OF HEALTH SCIENCES

SCHOOL OF PHARMACY

DEPARTMENT OF PHARMACOLOGY AND PHARMACOGNOSY

Serial No._____ **Version 01** **August 2016**

A copy of this document will be availed in a language that the parent / guardian of the participant is fluent in.

Title of the study: An Audit of Aminoglycosides Use in the Paediatric Wards of Kenyatta National Hospital

Institution: Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi, P.O BOX 30197-00400, Nairobi. Tel: 020 4915027

Investigator:Dr.Onyango Joseph Elias, P.O BOX, 30197-00400, Nairobi.

Mobile Phone: +254 727 061 699

Supervisors: 1. Dr.FaithOkalebo - Department of Pharmacology and Pharmacognosy; UoN

Mobile Phone: +254 737 434 204

2. Dr. Margaret Oluka - Department of Pharmacology and Pharmacognosy; UoN

3. Dr. Rosaline Kinuthia – Department of Pharmacy, Kenyatta National Hospital

Ethical Approval: Kenyatta National Hospital/ University of Nairobi Ethical and Research

Committee, P.O BOX 20723-00100, Nairobi. Tel 2726300/2716450 Ext 44102

Permission is requested from you to enroll your child in this medical research study. You should understand the following general principles, which apply to all participants in a medical research:

i. Your agreement to allow your child to be enrolled in this study is voluntary.

ii. You may withdraw your child from the study at any time without necessarily giving a reason for doing so.

iii. After you have read the explanation, please feel free to ask any questions that will enable you to understand clearly the nature of the study.

Preamble: We are requesting you to voluntarily give permission for your child to be enrolled in this study. Before you make a decision, we would like to provide you with information about the study. This document is a consent form; it has information about the study and will be discussed with you by the investigators. Please, study it carefully and feel free to seek any clarification especially concerning terminologies or procedures that may not be clear to you. If you agree to allow your child to be enrolled in this study, you will be asked to sign this consent form and a copy will be given to you.

Purpose of the study: The purpose of this study is to look at the use of aminoglycoside antibiotics in the children's wards of Kenyatta National Hospital and to identify existing challenges and opportunities for introduction of a guideline on the use of these medicines.

Procedure: A medical history of your child will be taken from you to determine if your child is experiencing any adverse effects from the medicines he/she is receiving currently in the ward. Please be as truthful as possible during this process. In addition, we will review your child's treatment sheets such that information on the medical history, diagnosis, and treatment will be obtained. The Doctor in the ward will also be consulted as need arises. Your child will be followed up from admission to discharge.

Risks: There will be no risks involved in this study. The study staff will take utmost care to keep your child's participation in this study confidential. Information on your child's health will be identified only by a coded number. This study's findings may be used in reports, published papers or presented in public but information identifying you or your child will never be used. Such information will be kept confidential by the investigator.

This study does not in any way introduce a new intervention or treatment to your child's care plan. The care offered to your child will be as per the KNH procedures. We will only ask questions and observe your child's treatment.

Benefits: Study may be of benefit to your child in that your child will be evaluated during the study and any problems with his/her medication addressed or communicated to the attending doctor. The findings of this study will primarily be of benefit to the Kenyan health system in terms of improved safety of medicines and quality of care and therefore improved performance.

Questions: You are free to ask any questions at any time about the study and regarding your rights as a research volunteer. You will not be giving up any of your child's legal rights by signing this consent form.

Contacts: In case you need to contact me, my academic department or the Kenyatta National Hospital / University of Nairobi Ethics and Research Committee concerning this study please feel free to use the contacts provided above.

STATEMENT OF CONSENT OF PARENT / GUARDIAN

I, the undersigned,voluntarily give consent for my child to be enrolled in this study. Dr. Onyango Joseph Elias has explained to me and I have understood the nature of the study, my responsibilities and the risks involved in the study. I will truthfully respond to any questions I will be asked. I understand that I can withdraw my child from this study at any time without giving any reasons or being penalized in any way. I understand the information collected will be used for research purpose only and high level of confidentiality will be maintained.

I will be given a copy of this signed form.

Name.....

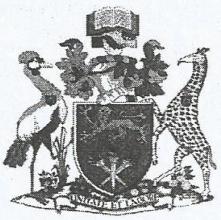
Signature---------- Date----------

I confirm that I have explained the nature and effect of the study.

Name.....

Signature---------- Date----------

KIAMBATANISHO D: HATI YA IDHINI YA WAZAZI/WALEZI KATIKA WODI YA WATOTO HOSPITALI KUU YA KENYATTA



CHUO KIKUU CHA NAIROBI

CHUO CHA SAYANSI YA AFYA

SHULE YA APOTEKET

IDARA YA MASOMO YA DAWA ZA KISASA NA ZA KIASILIA

Mzazi / mlezi wa mshiriki atasoma au kusomewa nakala hii kwa lugha anayoielewa.

Mada ya Utafiti: Ukaguzi wa matumizi ya dawa aina ya Aminoglycosides katika wodi ya watoto Hospitali Kuu ya Kenyatta

Chuo: Idaraya Masomo ya Dawa za Kisasa Na za Kiasilia, Chuo Kikuu Cha Nairobi

, S.L.P. 30197-00400, Nairobi. Simu:020 4915027

Mchunguzi: Dkt. Onyango Joseph Elias, S.L.P, 30197-00400, Nairobi.

Simu ya rurnunu: +254 727 061 699

Waelekezi:

1. Dkt. Faith Okalebo - Idara ya Masomo ya Dawa za Kisasa Na za Kiasilia,Chuo Kikuu Cha Nairobi. Simu ya rununu: +254 737 434 204

2. Dkt. Margaret Oluka - Idara ya Masomo ya Dawa za Kisasa Na za Kiasilia, Chuo Kikuu Cha Nairobi.

3. Dkt. Rosaline Kinuthia – Idara ya Dawa, Hospitali Kuu ya Kenyatta

Maadili ya utafiti yameidhinishwa na Kamati ya utafiti namaadili, Hospitali Kuu ya Kenyatta / Chuo Kikuu Cha Nairobi, S.L.P 20723-00100, Nairobi. Simu: 2726300/2716450 Ext 44102

Naomba idhini yako ilikukuhusisha mtoto wako katika utafiti huu wa kiafya.Unafaa kuelewa mambo yafuatayo ya kimsingi yanayofaa kuzingatiwa na washiriki wote.

i. Kukubali mtoto wako kushiriki utafiti huu nikwa hiari.

ii. Unaweza kuondoa mtoto wakokwa utafiti huu wakati wowote pasipo kuhitajika kutoa sababu za kumuondoa.

iii. Baada ya kusoma au kusomewa maelezo, una uhuru wa kuuliza maswali yoyote yatakayokuwezesha kuelewa vizuri utafiti huu.

Utangulizi: Tunakuomba kwa hiari yako mtoto wako ashiriki katika utafiti huu. Kabla ya kufanya uamuzi, tungependa kukuarifu habari zaidi kuhusu utafiti huu.

Nakala hii ni hati ya idhinisho. Inayo habari kuhusu utafiti huu ambayo wachunguzi katika utafiti huu watajadiliana nawe. Tafadhali uisome au usomewekwa makini, kisha ujisikie huru kuuliza mahali haulewi haswa kuhusu ufafanuzi na taratibu zitakazotumika ili uelezewe vizuri.

Ukikubali mtoto wako kushiriki katika utafiti huu, utaombwa kuweka sahihi yako katika hati hii ya idhini kisha utapewa nakala yako.

Lengo la Utafiti huu: Lengo la utafiti huu ni kukagua matumizi ya dawa aina ya Aminoglycosides katika wodi za watoto Hospitali Kuu ya Kenyatta na kubaini changamoto na nafasi zilizopo za kuweka mwongozo wa taratibu za kutumia dawa aina hizi katika Hospitali Kuu ya Kenyatta

Taratibu: Utaulizwa kuhusu historia ya afya ya mtoto wako ili kubaini uwezekano wa kuwa na athari yoyote ya dawa anazotumia kwenye wodi. Unaombwa kuelezea kwa ukweli mambo yote utakayoulizwa. Zaidi ya hayo tutakagua nakala ya matibabu ya mtoto wakoili kupata habari zaidi kuhusu historia yake ya afya,ugonjwa wake na matibabu anayopokea. Ikihitajika, tutashauriana na dakatari wake kwenye wodi. Tutafuatilia matibabu yake kuanzia kulazwa kwake kwenye wodi hadi atakaporuhusiwa kwenda nyumbani.

Athari: Hakuna athari yoyote katika utafiti huu. Wachunguzi wataweka makini kuhakikisha wameweka habari yote kuhusu mtoto wako katika utafiti huu kwa siri. Habari kuhusu afya ya mtoto wako utawekwa kama ujumbe ghushi kama kwamba hautatambulika na mtu yeyote isipokuwa mchunguzi mwenyewe. Matokeo ya utafiti huu yanawezakutumika katika ripoti,nakala za kuchapishwa au kuonyeshwa kwa umma lakini habari kukuhusu au kuhusu mtoto wako kamwe haitatumika popote. Ni wachunguzi pekee yao watakaojua habari kukuhusu wewe na mtoto wako na sio mtu mwingine yeyote.

Utafiti huu hauzindui aina mpya ya matibabu au kubadilisha taratibu iliyowekwa kutibu mtoto wako. Matibabu atakayopewa ni kulingana na taratibu zilizopo katika Hospitali Kuu ya Kenyatta. Tutauliza tu maswali na kutazama taratibu za matibabu yake.

Faida: Utafiti huu unaweza kuwa na faida kwa mtoto wako kama kwamba matibabu yake itajadiliwa na ikiwa shida yoyote itapapatikana itaweza kurekebishwa au daktari wake kuarifiwa.

Matokeo ya utafiti huu kimsingi yatakuwa ya faida kwa mpangilio wa afya katika taifa la Kenya kwa kuboresha usalama wa dawa kwa umma na ubora wa matibabu.

Maswali: Uko huru kuuliza maswali wakati wowote kuhusu utafiti huu na kuhusu kujitolea kwako kwa hiari kushiriki katika utafiti huu. Hautapoteza haki zako za kisheria kwa kutia sahihi hati hii ya idhini.

Mawasiliano: Ikiwa utahitaji kuwasiliana nami, idara ninayosomea au Kamati ya maadili nautafiti katika Hospitali Kuu ya Kenyatta/Chuo Kikuu Cha Nairobi kuhusu utafiti huu, uko hiari kutumia nambari za mawasiliano zilizopeanwa kwenye nakala hii.

IDHINI YA MZAZI/MLEZI

Mimi niliyetia sahihi kwa hiari nakubali mtoto wangu kushiriki utafiti huu. Nimeelezwa na kuelewa kinachohusiana na utafiti huu, majukumu yangu katika utafiti huu, athari zinazoweza kutokana na kujitolea kwangu na kuwa maswali yote yanayohusiana na utafiti huu nimeyajibu kama inavyotakikana. Naelewa kuwa naweza kuchagua kuacha kushiriki katika utafiti huu wakati wowote bila kutoa sababu au kupigwa penalti kwa njia yoyote. Naelewa kuwa ujumbe uliokusanywa utatumika kwa lengo la utafiti pekee na usiri wa hali ya juu utadumishwa.

Nitapokea nakala ya fomu hii iliyotiwa sahihi.

Jina la mzazi / mlezi _____

Sahihi_____tarehe_____

Nadhibitisha kutoa maelezo kamili kuhusiana na utafiti huu kwa mzazi / mlezi wa mshiriki.

Jina_____

Sahihi_____Tarehe_____

Appendix E: Drugs Dilution Guide

NEWBORN UNIT DRUGS DILUTION

Drug(name &strength)	amount of water for injection to add	dosage per 0.1 ml
X-pen —1 MU	add 4mls	0.1 ml=25,000 iu
X-pen —5MU	add 20mls	0.1ml=25,000 iu
Gentamycin – 80mg	add 2mls	0.1 ml= 2mg
Gentamycin – 20mg	do not dilute	0.1ml=2 mg
Fortum—2gm	add 10mls	0.1ml=20mg
Fortum – 1gm	add 10mls	0.1ml= 10mg
Fortum– 500mg	add 5mls	0.1ml=5mg
Amikacin – 500mg/2mls	add 8mls	0.1ml=5mg
Amikacin – 125mg/2mls	add 3mls	0.1ml=2.5mg
Amikacin—100mg/2mls	do not dilute	0.1ml=5mg
Rocephine – 1 gm	add 10mls	0.1ml=10mg
Rocephine – 500mg	add 5mls	0.1ml=10mg
Zinacef – 750mg	add 7.5mls	0.1 ml=10mg
Flexapen – 500mgs	add 5mls	0.1ml=10mg
Flexapen – 250mgs	add 2.5mls	0.1ml=10mg
Orbenin – 500mgs	add 5mls	0.1ml=10mg
Orbenin – 250mg	add 2.5mls	0.1ml=10mg
Augmentine– 1.2gm	add 12mls	0.1ml=10mg
Augmentine—600mgs	add 6mls	0.1ml=10mg
Imipenem—1gm	add 10ml	0.1ml=10mg
Imipenem—500mgs	add 5ml	0.1ml=10mg
Meropenem—1gm	add 10mls	0.1ml=10mg
Meropenem—500gm	add 5mls	0.1ml=10mg
Vancomycin—500mg	add 5mls	0.1ml=10mg
Phenobarbitone 200mg/ml	add 3mls	0.1ml=5mg
Vitamin k— 10mg/ml	add 3mls	0.1ml=0.25mg
Zantac—50mg/2ml	add 3mls	0.1ml=1mg
Dexamethasone 40mgs/1ml	Add 3mls	1ml= 4mgs (0.1ml=0.4mg

COMPILED BY; CATHERINE NGUGI SENIOR NURSING OFFICER NEW BORN UNIT

Appendix F: KNH/UON-ERC letter of Approval

KENYATTA NATIONAL HOSPITAL APPROVED 23 AUG 2016 KNH/UoN-ERC P.O. Box 20723-00202

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
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Tel:(254-020) 2726300 Ext 44355

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Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/330

23rd August, 2016

Onyango Joseph Elias
Reg. No.U51/81301/2015
Dept.of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Joseph

REVISED RESEARCH PROPOSAL: "AN AUDIT OF AMINOGLYCOSIDES USE IN THE PAEDIATRIC WARDS OF KENYATTA NATIONAL HOSPITAL" (P563/07/2016)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above revised proposal. The approval period is from 23rd August 2016 – 22nd August 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.

"Protect to discover"

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 Pharmacy, UoN
The Chair, Dept.of Pharmacology and Pharmacognosy, UoN
Supervisors: Dr.Faith Okalebo, Dr. Margaret Oluka, Dr.Rosaline N. Kinuthia

Appendix G: Permission to collect Data in KNH Pediatrics Department

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Ref: KNH/PAEDS-AD/48 Vol.II

Date: 3rd October, 2016

Dr. Onyango Joseph Elias
Department of Pharmacology & Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Dr Onyango

RE: PERMISSION TO COLLECT DATA IN PAEDIATRICS DEPARTMENT

Following approval by the KNH/UON-Ethics & Research Committee for your Research Proposal, this is to inform you that authority has been granted to collect data in **Paediatrics Department**, on your study titled ***"An Audit of Aminoglycosides use in the Paediatric wards of Kenyatta National Hospital"***.

Kindly liaise with the Senior Assistant Chief Nurse, Paediatrics for facilitation and forward to this office a report of your findings.

DR. IRENE INWANI
HEAD OF DEPARTMENT, PAEDIATRICS

Cc. Senior Assistant Chief Nurse, Paediatrics