MEDICATION RELATED PROBLEMS AMONG CRITICALLY ILL NEONATES ADMITTED AT KENYATTA NATIONAL HOSPITAL: A PROSPECTIVE COHORT STUDY

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U51/6754/2017

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

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AUGUST, 2021

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DEDICATION

I dedicate this thesis to my loving parents, Daniel and Elizabeth for their earnest support and devotion throughout this academic journey**.**

ACKNOWLEDGEMENT

I am grateful to the Almighty God for His faithfulness and Grace that enabled me to complete this Post Graduate journey. I thank Mombasa County Government for giving me the chance to pursue this course.

My deepest appreciation goes to my principal supervisor, Professor Faith Okalebo, for her teachings on medication related problems, advice and support throughout the study period. I am grateful to Dr Margaret Oluka for her significant guidance and positive criticism throughout the research process. I am also extremely indebted to Dr Slyvia Opanga, who was always ready to offer guidance through the study.

Above all, my parents and brothers Eric and Antony who have given me their unequivocal support throughout. They persevered with me throughout my studies and encouraged me.

I also acknowledge the invaluable contribution of my wonderful colleagues Gratia, Lynn, Fridah ,Nelly, Louis, Kevin, Kelvin ,Preston and Aggrey who were a blessing to interact with.

Finally l would like to thank KNH management for allowing me to conduct the study in the hospital and l especially thank the staff members of NBU for their cooperation.

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LIST OF ABBREVIATION AND ACRONYMS

AAP	Academy of Pediatrics
AEs	Adverse Events
ADRs	Adverse Drug Reactions
AGA	Appropriate for gestational age
BMJ	British Medical Journal
BNFc	British National Formulary for Children
CEO	Chief Executive Officer
DRPs	Drug Related Problems
DWI	Drug Without Indication
DI	Drug Interactions
ERC	Ethics Review Committee
FRD	Failure to Receive Drug
GA	Gestational age
IDS	Improper Drug Selection
IWD	Indication Without Drug
KNH	Kenyatta National Hospital
LBW	Low birth weight
LGA	Large for gestational age
MRP	Medicine Related Problems
NBU	New Born Unit
NCC-MERP	National Coordinating Council for Medication Error Reporting
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
OD	Over-Dosage
PCNE	Pharmaceutical Care Network Europe
PTT	Pediatric Trigger Tool
SCBU	Special Care Born Unit
STD	Sub-Therapeutic Dosage
SSA	Sub-Sahara Africa
VLBW	Very low Birth Weight
WHO	World Health Organization

LIST OF OPERATIONAL DEFINITIONS

Adverse Drug Reaction:	An unintended noxious response occurring after the normal dose of a drug, which is suspected to be associated with the drug.
Full Term Neonate:	This is a baby born between 37 to 42 weeks
Gestational Age:	This is defined as the best obstetrical estimate (OE) of the newborn's gestation in completed weeks based on the birth attendant's final estimate of gestation, irrespective of whether gestation results in a live birth or a fetal death.
Low Birth Weight:	This is defined as first weight recorded within hours of birth of less than 2500 g (up to and including 2499 g) irrespective of the gestational age.
Large For Gestational Age:	This is defined as birth weight greater than the 90^{th} percentile for gestational age
Medication Related Problem:	Is an event or situation involving drug therapy that actually or has potential to interfere with desired health outcomes. Involves medication errors, non-adherence, drug interactions and adverse drug events.
Neonate:	New-born from birth to 28 completed days.
Off-Label Use of Medicine:	All uses of an authorized medicine not described in the approved summary of product characteristics.
Preterm:	These are babies born alive before 37 weeks of gestation.
Very-Low-Birth-Weight:	Neonates born weighing less than 1.5 kg. They are particularly vulnerable to adverse outcomes

ABSTRACT

Background: Neonates are usually at a significant risk for adverse risk for adverse drug reactions since organs required to handle medicine are still under development. Neonates at the neonatal intensive care unit are usually very ill with multiple organ dysfunction. They may be on multiple medications which greatly increases the chances of adverse drug reactions.

Objective: The main objective of the study was to characterize the medication related problems and their associated factors among the neonates admitted to the intensive care units of Kenyatta National Hospital.

Methods: The study was carried out between April and June 2019 and it was a descriptive prospective cohort study. It entailed the prospective review of treatment sheets and patient files of neonatal patients who are critically ill and admitted at the Kenyatta National Hospital. Data collection commenced within 48 hours of admission. Data collection was done by reviewing patient files to extract details such as demographic characteristics and clinical data on medication related problems. Patient records were reviewed daily. Follow-up was done daily for two weeks. Descriptive data analysis was conducted. The relationships between predictor and outcome variables for medication related problems was computed using logistic regression to identify risk factors for Medication Related Problems. The level of significance was set at 0.05.

Results: A total of 70 participants met the eligibility criteria and were enrolled into the study. The most common diagnosis was respiratory distress syndrome (64, (88.8%), which was followed by infections (81.1%). Benzyl penicillin (52, (19%), gentamicin (50, (18.2%) and ceftazidime 32(11.7%) were the most prescribed antibiotics. Aminophylline (21, (5.5%) was the most prescribed respiratory drug. Dosing errors were evaluated and they were most likely to have a negative impact on treatment outcomes. Gastrointestinal (OR **1.5** 95% CI 1.038, 2.165; p=0.031) and congenital disorders (OR **1.368** 95% CI 1.018, 1.837; p=0.037) were strong predictors of underdosing. There was statistical significant association between the use of aminophylline, ranitidine, phenytoin and overdosing. There was no statistical significant between dosing errors and anthropometric measures.

Conclusion: Dosing errors are the most common MRP among critically ill neonates admitted in the neonatal intensive care unit. Specialist pharmaceutical care is needed to identify and manage MRPs.

CHAPTER ONE: INTRODUCTION

1.1 Background of the Study

Drugs are usually prescribed with the intention of doing good to a patient. However, the utilization of medicines can potentially lead to harm. These unwanted effects are known as medication related problems (MRPs) (1). A medication related problem is defined as an event involving pharmacotherapy that interferes with desired therapeutic outcomes (2).

The world of medicine has dramatically changed over the years, and this has led to a sharp increase in drugs and their use. There are also complex drug regimens that have only increased the number of drug interactions and side effects (3). MRPs lead to substantial mortality and morbidity (4). MRPs cause an increase in medical expenditure . An organized review of a patient's medication history is an efficient way of distinguishing MRPs, and disease related problems. There are many classification systems of MRPs and a universal system would be invaluable in the prevention and management of MRPs (5).

MRPs in neonates have not been extensively studied as compared to the adult population since neonatal drug use is often off-label whereby doses are extrapolated from those of adults (6). The dosages of neonates are calculated according to body weight and size. Neonates are at high risk of MRPS due to the changes in the development and maturation of their body systems (7).

MRPs have become a priority among medical professionals and researchers, due to the increasing complexity of symptoms which make it hard to arrive at an accurate diagnosis (8). Problems associated with medical research in neonatal patients have resulted in scanty drug information, which compromises medication safety and efficacy (9). Medication safety analysis is vital in new-borns because of their increased susceptibility to adverse drug reactions (ADRs) and polypharmacy (10).

1.2 Statement of the Problem

Medication related problems are a significant concern since they cause mortality and morbidity among neonates (11). MRPs can have a toll on the economic status of a family, leading to decreased quality of life of the neonate. Neonates are most vulnerable to MRPs, and this susceptibility may be related to clinical heterogeneity, in weight, gestational age and postnatal age determinants of dose selection. There are limited studies on drugs for this age group and the dosing recommendations are often empirical. A large proportion of medications utilized in neonates are available in formulations for adults. This needs a lot of adjustment and has a higher potential for MRPs (12).

Like many other African countries, Kenya is still facing challenges in pharmacovigilance due to the under reporting of ADRs and lack of knowledge among medical personnel in identifying MRPs (13). Health workers often ignore the importance of identifying and documenting MRPs in neonates, which leads to the incidence of drug-related mortality and morbidity (14).

A study conducted at the KNH by Nyakiba et al. reported that the incidence of MRPs was 96% in all medical wards, including the neonatal ward (15). This is an indication that medication use problems are common. The lack of awareness about MRPs among clinicians and pharmacists contributed to the current scenario where there is a lack of active surveillance for the management and prevention of errors in neonatal patients (16). Hence there was a need for data that highlights these problems. This study aimed to measure the prevalence of selected MRPs amongst neonatal patients. The findings of the study will be used to justify the initiation of a pharmacovigilance service for neonates.

1.3 Research Questions

1. Identify patterns of medication use amongst neonates in neonatal intensive care unit.
2. What is the prevalence and different types of MRPs among neonates at KNH, according to Helper and Strand and National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) classification systems?
3. What are the patient factors or correlates associate with MRPs among neonate patients receiving care at KNH

1.4 Objectives of the study

1.4.1 Main Objective

The main objective of the study was to characterize the medication related problems and their associated factors among the neonates admitted to the intensive care units of Kenyatta National Hospital.

1.4.2 Specific objectives

1. Identify patterns of medication use amongst neonates in neonatal intensive care unit.
2. Measure the overall prevalence and different types of Medication related Problems among neonates at Kenyatta National Hospital according to Helper and Strand and NCC-MERP classifications systems.
3. Investigate patient-related risk factors for selected Medication Related Problems among neonatal patients at KNH.

1.5 Justification of the Study

This study demonstrated frequency, types of medication administration, and dosing errors likely to be encountered, and areas that need improvement. The findings highlighted the need for more organized systems for medication use review among neonates. Identification of these MRPs will lead to improved neonatal safety monitoring systems to improve medication use and safety among neonatal in-patients. The findings will aid in the formulation of interventions to promote the detection and prevention of MRPs in this age group (17).

CHAPTER TWO: LITERATURE REVIEW

2.1 Definition and Classification of Medication Related Problems

Medication related problems are undesired events that interfere with desired therapeutic outcomes. In order for an event to qualify as a MRP, at least two conditions must exist. In essence a patient must be experiencing disease or symptoms of a disease, and these conditions must have an identifiable or suspected relationship with a medication therapy (1).

Classification of MRPs helps to identify the most prevalent MRPs and also the best action to be taken. There are various classification systems available. The most commonly used are the Pharmaceutical Care Network Europe (PCNE), National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP), and Helper and Strand classification systems (18) (19).

Strand et al. in 1990 published a landmark article on the first classifications of MRPs. The Strand classification is a simple scheme containing eight types of MRPs and has been the foundation of pharmaceutical care (20). Helper and Strand classification is easier to use in Sub Saharan Africa (SSA) given, the poorly funded healthcare services in Africa.

The other commonly used classification system is provided by NCC-MERP. This classification comprises an order of medication errors to be used in addition with system analysis in tracking medication errors (21). NCC-MERP provides a list of medication errors data use in databases for analyzing medication error report. Helper and Strand classification of medication related problem is presented in Table 2.1.

Table 2.1: Helper and Strand Classification of Medication Related Problem (19)

Untreated indication	This refers to a situation where a patient is not receiving prescribed medication for a medical condition(s) that requires treatment
Improper drug selection	When a patient takes the wrong drug
Subtherapeutic dosage	When a patient is getting too little of the drug
Overdosage	A patient is treated with too much medication that may lead to toxicity
Adverse drug reaction	A medical condition where the patient has experienced an adverse reaction upon use of a drug
Drug interaction	This refers to a medication related condition that happens as a result of two or more drugs acting together
Failure to receive medication	A patient may not receive the prescribed drug due to various reasons within the patient's control or out of their control.
Medication used without indication	This is when a patient is using a drug without a medically valid indication

The NCC-MERP Index for categorizing medication errors is presented in Table 2.2.

Table2.2: National Coordinating Council for Medication Error and Reporting Programme (21)

Category	Description of Category
A	Circumstance that has the ability to cause a mistake.
B	A mistake happened, but the harm did not reach the patient.
C	An error happened that resulted to increased patient monitoring but no patient harm.
D	An error happened that resulted to increase monitoring of patient to confirm no patient harm and/or preclude harm.
E	An error occurred that caused temporary harm to the patient and needed treatment.
F	Error occurred that caused to short term injury to patient and resulted to initial or prolonged hospitalization.
G	A mistake occurred that resulted in patient's permanent harm.
H	A mistake happened that resulted to a near-death event.
I	Harm occurred that resulted in patient's death.

2.2 Types of Errors at the Different Stages of the Medication Use Process

A medication related problem may happen at any stage of the medication use process. The process of prescribing, administering, and monitoring of medicines of medicines are complex. Mistakes can arise in each of the many steps (3). Medication errors can occur at various stages of the medication use cycle, as shown in Table 2.3.

Table 2.3: Types of medication errors at various stages of medication use cycle (3)

Medication use process	Definition	Examples of specific errors
Prescribing, (22)**.** **These are sub-classified into;** **Dosing errors** **Indication errors** **Documentation errors**	Involves choosing an appropriate medication for a given clinical situation	• Inappropriate route • Inappropriate use of units milligrams instead of grams • Lack of neonate-specific drug protocols • Overdose • Underdose • No indication • Untreated indication • Illegible writing • Use of brand names
Administration,(20)	Involves obtaining the medication in a ready-to-use form	• Patient misidentification • An additional dose of medicine • Inappropriate dilution • Wrong time
Monitoring	Involves follow up of the patient to determine if the medication is working (23)	• Failure to review the prescribed regimen (24)

2.3 The Use of Weight and Age for Dosing of Neonates

World Health Organization (WHO) defines a neonate as a new-born infant less than 28 days of age (25). Neonates are considered to be at risk for dosing and dispensing mistakes because they have a fast-changing body surface area and weight, a rapidly developing system of medication use cycle and are unable to speak with the provider; and off-label or unlicensed medication use. Dose adjustments need calculations and have a potential for errors (26,27). In this population, gestational age, body surface area and weight are factors that are to be taken into consideration.

Dosing in neonates is more difficult as compared to adults. This has been due to lack of suitable ways for investigating pharmacokinetics in these populations (27). Five International Guidelines for dosing exist they include; the National Institute for Health and Care Excellence (NICE) (32), the American Academy of Pediatrics (AAP) (28), the British Medical Journal (BMJ) (29) and the British National Formulary for Children (BNFc) guidelines(30) Most guidelines suggest clinicians should rely on data based on locally prevalent pathogens at the institutional level when selecting treatment regimens. Most of the guidelines are in line with WHO recommendations on dosing in neonates.

A comparison of international guidelines reveals differing dosing regimens for antibiotics such as gentamicin. The current WHO guidelines recommend a once-daily dosing regimen of 7.5 mg/kg per day according to age and birth-weight. In Kenya, Basic Pediatric Protocol supports the dose for gentamicin, should be 3 to 5mg/kg every 24 hours in neonates (31). The age-groups for dose calculation in neonates is presented in Table 2.4.

Table 2.4: Age group for dose calculation in Neonates (12)

Term	Definition
Appropriate for gestational age	Birth between the 10^{th} and 90^{th} percentile for gestational age
Gestational age (GA)	The measurement of gestation age using the obstetric estimate.
Low birth weight	Birth weight less than 2.5kg
Large for gestational age	Birth more than 90^{th} percentile for gestational age
Preterm neonate	Birth less than 37 weeks of gestational age
Term neonate	38 to 42 weeks gestational age
Very low birth weight	Neonates weighing less than 1500g

2.4 Prevalence and Factors Associated with Medication Related Problems in Neonates

There are varying statistics on the prevalence of MRPs in neonates. Although data on epidemiology and cost of MRPs in this population is still limited, a recent study from the UK and Saudi Arabia found that 21% of neonatal patients experienced MRPs(32). The incidence of MRPs in a survey in Ethiopia was 32%, the frequency reported was higher than in a Hong Kong study (2). The difference in the prevalence may be due to the changes in hospital settings. Male patients (54.4%) with reported MRPs were higher as compared to females (46%), However, the difference was dismal (COR1.5, 95% CI 0.9, 2.6, p=0.089).

Data from other countries is limited. Medications used and healthcare systems vary significantly in different countries. Consequently, the types of Medication-related problems can be different. Hence, strategies in the reduction of MRPs may be needed.

Studies from Australia investigated pediatric hospital admissions as a result of MRPs and found that 4% of paediatric admissions and 3% of Accident and Emergency visits are related to MRPs, and 50% were found to be preventable (33). In Kenya, the magnitude of the problem in neonatal patients is not known. However, a study carried out to determine the incidence and determinants of medication errors among paediatric in-patients aged 0-5 years at Kisii Level 5 Hospital showed there is a significant burden. In this study, 76% of the prescriptions contained errors, and the total number of medication errors was 307 out of 405 (34).

2.5 Drugs Commonly Used in Neonates

There is limited data on medication use in neonates, particularly in the hospital. The number of medication utilization studies in this population is limited (35). Drug use in the neonatal patient must adhere to the fundamentals of rational medicine use (36). The drugs commonly used in neonates are as shown in Table 2.5

Table 2.5: Drugs commonly used among neonates (11)

Drug	Mechanism of action and indications	Dose
Blood and blood-forming organs		
Vitamin K (phytonadione)	Used to treat Hemorrhagic Disease of the Newborn (HDN). Synthesis of coagulation factors II, VII, IX and, X.	Treatment of HDN 0.5-1 mg IM at birth. Ought to be closely monitored.1 hr after birth.
Cardiovascular system		
Furosemide	Utilized in the treatment of edema in the cardiovascular system, hepatic and, renal system.	Initial dose 1-2 mg/kg per dose Maintenance dose: 1 mg/kg
Beta-lactams antibacterial, penicillin		
Benzylpenicillin	It is used in combination with an aminoglycoside as treatment of early sepsis	Bacterial infection: Age less than 6 days :IV/IM infusion 50000 iu/kg/ dose 12 hourly Age 7 days and over 50000iu/kg/dose 6 hourly
Nervous System		
Phenobarbitone	It is recommended for the treatment of neonatal sepsis.	Loading dose:20mg/kg by slow IV infusion Maintenance dose: 5 mg/kg daily IV/IM
Antiparasitic products		
Metronidazole	Used in the management of anaerobic sepsis in the neonate	7.5mg/kg/dose 12hourly.
Antimycotics for systemic use		
Fluconazole	Utilized in the treatment of suspected systemic fungal infection	Treatment: 12 mg/kg/dose 24 hourly.
Aminoglycoside		
Gentamicin	Used in the management of proven neonatal sepsis	Weight <2 kg: 3mg/kg/dose IV. Weight> 2kg: 5mg/kg/dose IV.
Systemic hormonal preparations		
Dexamethasone	Utilized as an immunosuppressant	0.01mg/kg/dose 12 hourly

HDN- Hemorrhagic disease of the newborn**,** IM-Intramuscular, IV-Intravascular

2.6 Off Label and Unlicensed Use of Antibiotics and Other Drugs

Off label use is the use of products outside the marketing authorization not included in the summary of product characteristics with regard to therapeutic indication, age, dose, dosing interval, or route of administration (37). Unlicensed drug use is defined as the modification of a licensed medicine that is administered after the change in the formulation(9).

An example of unauthorized use of administration of furosemide in the form of oral solution prepared from crushed tablets. Off-label and unlicensed use is not unlawful (38). To determine if the use of a drug in neonates was either unlicensed or off-label, the drug's legal status was evaluated using Electronic Medicine Compendium licensed for use in the United Kingdom and USA Food and Drug Administration (39). The incidence of off-label and unlicensed use of medications are summarized in Table 2.6.

Table 2.6: Off label use of antibiotics and other medications in neonates

Drugs	Legal status
Antibiotics	
Benzylpenicillin	Off-label
Gentamicin	Off- label
Amikacin	Off-label
Ceftazidime	Off-label
Metronidazole	Off-label
Meropenem	Off-label
Ceftriaxone	Off-label
Erythromycin	Off-label
Flucloxacillin	Off –label
CVS drugs	
Furosemide	Off-label and Unlicensed
Sildenafil	Off- label and Unlicensed
Dopamine	Off-label
Antimycotics	
Fluconazole	Off-label
CNS drugs	
Phenobarbitone	Off label and Unlicensed
Phenytoin	Off- label
Respiratory drugs	
Aminophylline	Off-label
Analgesic	
Paracetamol	Off-label
Morphine	Off-label and Unlicensed
Ibuprofen	Off-label
Other drugs	
7.1% chlorhexidine	Off-label
Omeprazole	Off-label
Multivitamin	Off-label
Dexamethasone	Off- label
Ranitidine	Off-label
Artesunate	Off-label

2.7 Major Adverse Events Reported in Neonates

An adverse drug reaction (ADR) has been defined by the World Health Organization (WHO) as noxious and unintended response to medicine used for prophylaxis, diagnosis treatment of an illness (38). Some ADRs are considered to be predictable based on the known pharmacology, and these are frequently related to the dose, while others remain unpredictable based on currently available knowledge and are not dose-related (40). Unpredictable adverse drug reactions can be attributed to excipients and drug manipulation errors. Genetic factors play a role in the development of ADRs (41).

Adverse drug reactions often prompt adjustments to therapy. Real-time pharmacovigilance is essential for neonatal care. There are also some medications that cause specific harms in neonates. Despite emerging data regarding medicines that can be harmful to neonates, some of these medicines with published safety warnings are still used in NICUs worldwide. Examples include; meropenem, itraconazole, and sulfadiazine (42). The drugs are known to cause adverse drug reactions that are specific to neonates are as presented in Table 2.7

Table 2.7: Drugs that cause Adverse Drug Reactions that are specific to neonates (38)

Drug	**Recognized neonatal ADR**
Ceftriaxone plus calcium administration	Death due to precipitation of ceftriaxone calcium salts
Chloral hydrate	Encephalopathy
Chloramphenicol	Grey-baby syndrome
Codeine and other opioids	Respiratory depression
Indomethacin	Oliguria
Sulphonamides	Kernicterus

2.8 Formulation Specific and Administration Problems in Neonates

Drug manipulation is the physical alteration of a dosage form in order to achieve the required smaller dose for administration. An example of drug manipulation is dilution of injections when the available dosage does not allow paediatric dose to be measured accurately and splitting of a tablet. It is a common practice among clinical staff. Studies about medication manipulation with the intention of achieving the required dose are limited. Manipulations can be inaccurate, time consuming and have unknown effects on the bioavailability of the drug. This increases the risk of administration and dosing errors. Dosing errors are the most common MRPs in neonatal and paediatric practice (43).

At present, commercially, ready-to-administer neonatal preparations will be unlikely available for all compounds prescribed. It is reasonable to assume that compounding is still going to be a common practice in the near future. Drug formulations contain excipients such as co-solvents, surfactants preservatives, colorants, or sweeteners. Examples of excipients are lactose, aspartame, ethanol, propylene glycol, benzyl alcohol, sorbitol, xylitol, mannitol ,and poly-ethylene glycol. Excipients are added to increase the shelf life of a drug, to make it more palatable or facilitate dissolution or to bulk up formulations. (44). The expected side effects of excipients on neonates are presented in Table2.8.

Table 2.8: Harmful effects of selected excipients in Neonates (44)

Excipient exposure	**Specific clinical syndrome**
Parabens, Sodium benzoate	Hyperbilirubinemia
Propylene glycol,	Seizures, Liver dysfunction, cholestasis
Ethanol	Central nervous system depression
Benzyl alcohol	Metabolic acidosis
Propylene glycol (as an excipient)	Hyperosmolarity, lactic acidosis

2.9 Tools for monitoring Medication use in Neonates

Therapeutic drug monitoring (TDM) is a necessary tool in the intensive care unit. The goal of TDM is to tailor drug dosage to maximize therapeutic benefits and minimize toxicity. Traditionally, this approach has been performed by measuring serum drug concentrations,

applying pharmacokinetic and pharmacodynamics principles, and then adjusting the dose to keep the drug concentration in the therapeutic range. TDM is primarily applicable for medications that possess narrow therapeutic indices. The targeted therapeutic levels for drugs with a narrow therapeutic index are illustrated in Table 2.9.

Table 2.9: Therapeutic Drug Monitoring for medications with narrow therapeutic index (41)

Drug	Serum drug concentration
Theophylline	Serum concentrations of greater than 20 mcg/ml increase the incidence of toxicity.
Aminoglycosides	The prolonged peak level of gentamicin 12 to 14 mcg/mL increases the incidence of adverse drug reaction.
Chloramphenicol	High serum concentrations of 25 mcg/ml increase the risk of bone marrow suppression.
Vancomycin	Trough concentrations of higher than 80mg/l are associated with an increased risk for nephrotoxicity and ototoxicity

There is currently no gold standard method for detecting MRP(45). There are four methods for detecting MRPs, which include a medical chart review, pharmacists' documentation, analysis of incident reports, and trigger tools (46). All of these methods have various limitations. Incidents are notoriously under-reported by staff, perhaps because many fear punishment. Chart reviews and observational studies are highly resource intensive. Indicators based on administrative data may lack clinical relevance, while cases are identified from malpractice claims. Trigger tools have emerged as a strategy to avoid many of these limitations.

The pediatric trigger tool (PTT) was developed by the Institute for Healthcare Improvement (IHP) in the USA for neonatal intensive care and critically ill children. It is an adapted version of NCC MERP. The PTT is applied to clinical records and an adverse events causing harm to the patient, whether or not they are the result of the medication (45, 47).

The PTT consists of various items described in table 2.9. It entails a review of neonatal patient records in the following order: diagnoses and treatment procedures, medication charts, laboratory results, nurse notes, physician notes, and admission notes (47). The tool excludes the first four categories in the NCC-MERP classification system because the medication errors do not cause harm (48).

Table 2.10: Pediatric Trigger Tool user guide(49)

Intensive Care	**Admission to intensive care or high-dependency unit**
Drugs	Vitamin K Naloxone Flumazenil Glucagon or glucose ≥ 10% Antihistamine Antiemetics IV Bolus ≥10 mL/kg colloid An abrupt stop of medication
Lab test	Thrombocytopenia Transfusion An unexpected drop in Hb or Hct
Biochemistry	Rising urea or creatinine Electrolyte abnormalities Hypoglycemia Medicine level out of range
Microbiology	MRSA bacteremia Clostridium difficile VRE Nosocomial pneumonia Positive blood culture

IV-Intravenous, Hb- Hemoglobin, Hct- Hematocrit, MRSA-Methicillin-resistant *Staphylococcus aureus*, VRE-vancomycin-resistant enterococcus

2.10 Conceptual framework

Figure 2.1 is a conceptual map showing the relationship between Medical related problems (MRPs). It illustrates the different types of MRPs.

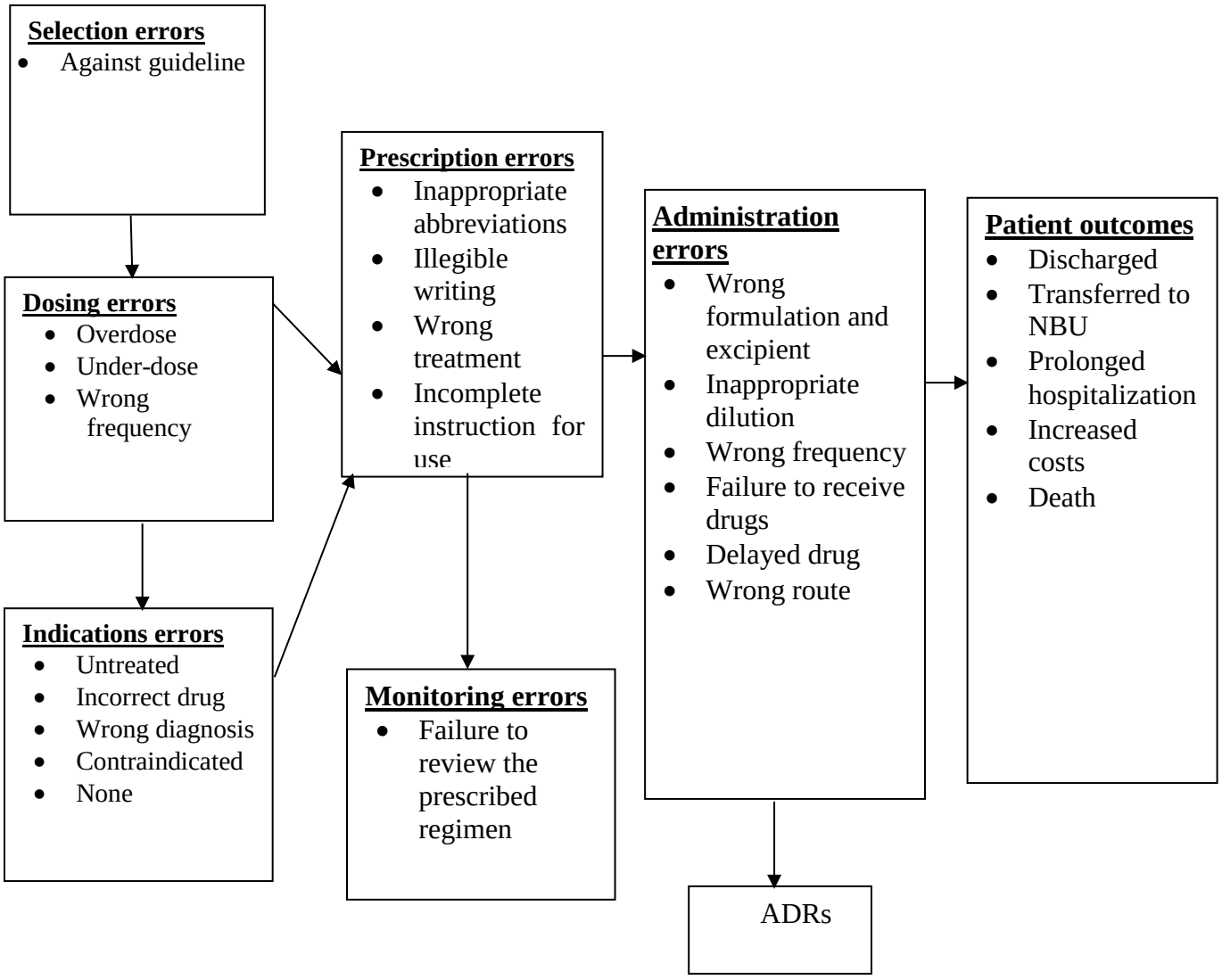

Figure 2.1: Conceptual map for the relationship between medication related problems and their causes at different levels

CHAPTER THREE: MATERIALS AND METHODS

3.1 Study Design

This was a descriptive cohort study which entailed the prospective review of treatment sheets and patient files of critically ill neonatal patients admitted at KNH to determine the overall incidence and patient-related risk factors of medication related problems. Participants were followed from the date of admission to discharge.

3.2 Study Site

The study was conducted at the Kenyatta National Hospital (KNH) which is a 2000 bed National teaching and referral hospital. Kenyatta National Hospital is the largest referral hospital in Kenya. The hospital has close to 2000 inpatients and receives 1500 outpatient patients per day (49). The hospital is the teaching hospital of University of Nairobi, College of Health Sciences and works in collaboration with many other medical institutions countrywide in offering clinical services.

The New-born Unit is on the first floor of the hospital's tower block and it admits babies from the labor ward and theatres as well as from referrals from private and level 5 hospitals. It is subdivided into three sections (48). New Born Unit (NBU) which was designed to care for all well new-borns; Special Care Baby Unit (SCBU) is a specialized unit to care for babies from birth who require intensive care and the New-born Intensive Care Unit (NICU) which receives all critical cases including premature babies. Only participants admitted in the Special Care Baby Unit and New-born Intensive Care Unit were included in the study.

3.3 Target and Study Populations

The target population was neonatal patients requiring critical or intensive care. A neonate was defined as a baby between 0 to 28 days of life and is at its most vulnerable at this point of life (25). The study population included neonatal patients admitted to the special care baby unit and new-born intensive care unit from 1st April to 31st June 2019 who required specialized care.

Eligibility Criteria

Neonates were included if they were 0 to 28 days of age and admitted in the critical or special care units as from 1st April to 30th June 2019. Consent was sought from caregivers who had their neonates admitted to hospital within 24 hours on day of the recruitment. Neonates who were older than 28 days and admitted in the New Born Unit or the Caregiver declined to give consent to participate and admitted for more than 24 hours at the time of recruitment were excluded.

3.5 Sample Size Consideration

The Cochran formula (50) was applied to determine the minimal sample size.

Equation one: Cochran formula for sample size calculation.

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

Where: Z is level of significance (1.96) at a α-value of 0.05 for a two tail hypothesis.
p was prevalence of MRPs
d was precision of estimate around MRPs (5% or 0.05).
n was sample size.

A study conducted at the KNH showed the prevalence of MRPs is 96% in all Medical wards including neonatal wards. This was the value of p. The minimum calculated sample size was 59 patients. The calculated figure was adjusted by 10% to cater for missing information, a total of 70 treatment sheets and files were sampled (50).

3.6 Sampling Method and Participant Recruitment

Convenient sampling method was employed. Every neonatal patient meeting the inclusion criteria outlined in the eligibility checklist (Appendix A) was included in the study until the desired sample size was met. On obtaining Ethics approval the researcher wrote to KNH committee and the Head of Pediatric Department requesting for permission to conduct the study. The list of new admissions was obtained from the nursing station. The records of patients admitted in the last 48 hours were perused every morning on a daily basis. The patient files were

screened to assess for eligibility with the aid of the eligibility checklist in Appendix A. After shortlisting the eligible patients the names of their parents were obtained. The parents were approached whenever they come to the intensive and special care units to visit the baby or express milk. Parents were approached during lunchtime in the waiting area. They were invited in a private room in the neonatal unit and invited to participate in the study. They were informed about the study and requested to provide consent with the aid of informed consent form shown in Appendix G. Recruitment was done privately in the doctor's office when it was vacant. An explanation on the harm, benefits and confidentiality was provided. All parents /caregivers who gave consent for their child to participate were requested to sign the consent form.

3.7 Review of Treatment Records

Treatment records were perused daily and information abstracted from treatment sheets using the data collection tool in Appendix IX. The tool was designed to capture information such as gestational age, birth weight, gender and caregivers traits. Information on medication use such as reason for admission, diagnosis, comorbidities and drug treatment modalities were recorded. The third part of the form was used to capture any changes in medication prescribed. This form was designed to capture prescribing errors, illegible handwriting and inappropriate medication. This information was obtained from prescriptions. To confirm if the dose was appropriate, the app *Pedi STAT*® was used.

Data collection was done in the afternoon when there was no ward rounds and after medications were administered minimizing interruption of services. Research assistants (RAs) were pharmacists who had completed internship and were trained in infection control. The RAs were trained on how to handle questionnaires before commencement of data collection. They were only involved in reviewing patient files to extract details such as demographic characteristics and clinical data on medication related problems after consenting under regular supervision of the researcher.

3.8 Detection of Adverse Effects

The adverse events were divided into two categories. Signals in the PTT (trigger tool) and the expected side effects for a given drug. The latter included creatinine elevation, increase of ALT, convulsions and skin rash.

The expected adverse events associated with selected drugs used in ICU setting were recorded using the data collection tool in Appendix IX. Any unexpected events were recorded. The adverse events were submitted to Pharmacy and Poisons Board, Pharmacovigilance Department. The records were updated daily.

3.9 Quality Assurance and Data Management

The data collection instruments Appendix I were pre-tested on five neonatal patients and optimized appropriately by the researcher, where necessary. The filled instruments were reviewed by the researcher at the end of each day against the source documents for completeness and accuracy. All the raw data collected was entered in Epi-info version 7 (2007-2010) software and a database created. The data was backed up on a weekly basis by the researcher. Data cleaning and validation was done before exporting to STATA (version 14) for analysis.

The health records were protected by reviewing the files in the neonatal wards. No document was removed from the units. All information extracted was coded and patient identifier information was not included. The electronic data was password protected all hard copy documents was restricted to researcher and supervisors.

Backing-up of data was done weekly to protect data from loss. Soft copies of documents were password-protected and encrypted. Hard copies of the interview notes, and questionnaire forms were kept securely locked in a filing cabinet that only could be accessed by the principal investigator.

3.10 Study Variables and Definitions

The main outcome variable was Medication related problems. They were classified using the NCC-MERP and Helper and Strand systems. The predictor variables included age, sex, and disease condition, number of medication per prescription, type of medication, administration route, types and number of diagnosis. In this study outcome variables are defined as follows.

Medication related problems are undesired events that interfere with desired therapeutic outcomes.

Demographic characteristics are the classifiable characteristics of a given population

Gestational age: is defined as measure of the newborn's gestation, which determined by the best obstetrical estimate.

Weight at birth is defined as the first weight recorded after birth, measured within the first hours after birth.

Full term neonate: This is a baby born between 37 to 42 weeks

Large for gestational age: This is defined as birth weight greater than the 90^{th} percentile for gestational age

Preterm: These are babies born alive before 37 weeks of gestation.

Very-low-birth-weight: Neonates born weighing less than 1500gm. They are particularly vulnerable to adverse outcomes

Low birth weight is defined as neonates who weigh less than 2500gm (up to and including 2499gm).

Basal Surface Area measures the total surface area of the body and is used to calculate the drug dosages.

3.11 Data Analysis

The Shapiro-Wilk test was used to check if continuous variables were normally distributed. Descriptive data analysis was done and continuous variables expressed as either the mean and standard deviation, or median and inter-quartile range. Categorical variables were presented as proportions, percentages with the 95% confidence intervals. The main outcome calculated was incidence of various types of medication related problems as a percentage.

Bivariable logistic regression was used to analyze associations between dosing errors and predictor variables identified in the data. Their odds ratio, 95% confidence intervals of the odds ratio and the associated p-values computed.

Multivariable logistic regression were constructed to investigate association while adjusting for possible confounding. The predictor variables associated with medication related problems were determined using Forward stepwise model building. STATA version 14.0 software which was used for data analysis. P values of less than 0.05 were considered to be statistically significant.

3.12 Ethical Considerations

Approval to carry out this study was sought from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC P867/12/2018) in Appendix I. This study was registered with the Research and Programs of the Kenyatta National Hospital and an official research study number given and recorded in the registry as per the hospital research guidelines. To implement the study, permission was sought from the relevant hospital management authorities who are the Chief Executive Officer (CEO), the nurse in charge from the respective neonatal wards. Informed consent for participation was sought from the patients' parents or guardians (Appendix VII). The researcher took utmost care to ensure maximum privacy and confidentiality of the information obtained during the study. Patient codes were used instead of patient identifier information. The data instruments were stored in a password-protected database only accessible to the researcher were to be kept under lock and key. At the end of the study, they were handed over to the Department of Pharmacology, the University of Nairobi for storage for a period of 5 years. A password protected electronic version of the primary data was also deposited to the department e-repository. At the end of the 5 years, the researcher will apply to the KNH/UoN-ERC for the authority to destroy the data.

CHAPTER FOUR: RESULTS

4.1 Participants Enrolled and Reasons For Exclusion

A total of 300 neonatal patients were admitted in the neonatal intensive care unit between the months of April and June, 2019. Convenient sampling was conducted. Two hundred and thirty participants were excluded from the study. Out of the 230 babies, 200 did not meet the inclusion criteria with regard to age and length of admission. The guardians of the remaining twenty seven refused to participate in the study. The 3 participants were excluded because of a language barrier. Figure 4.1 summarizes participant enrolment and exclusion.

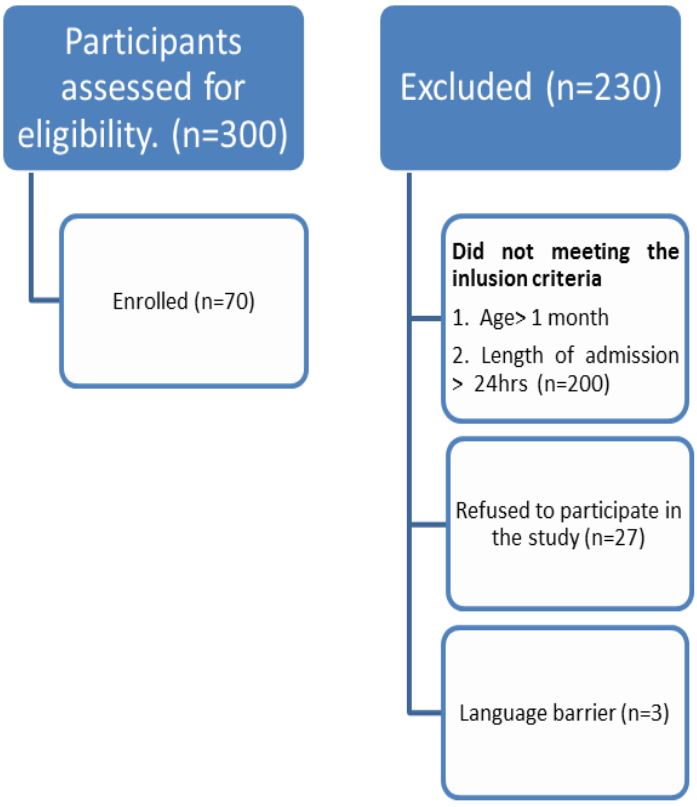

Figure 4.1: Participant enrolment and reasons for exclusion.

4.1.1 Demographic Characteristics of the Neonates

The characteristics of the participants are summarized in Table 4.1. Out of every 10 neonates, nearly 6 were male (41, 58.6%). Nearly 60% of the participants weighed more than 3 kg. A significant fraction were full term (44%). Most of them had a length of above 40 cm. Majority had a body surface area of above $0.17m^2$ (36, 51.4%).

Table 4.1: Demographic Characteristics of Neonates in the Intensive Care Unit

	n	%
Gender		
Male	41	58.6
Female	27	38.6
Ambiguous	2	2.8
Total	70	100
Weight at birth		
Less than 2 kg	15	21.4
2 - 3.0 kg	14	20
Above 3.0 kg	41	58.6
Total	70	100
BSA of the baby		
Less than $0.13m^2$	22	31.4
$0.13\text{-}0.17m^2$	12	17.1
Above $0.17m^2$	36	51.4
Total	70	100
Length of the baby		
Less than 35 cm	16	22.9
35-40 cm	14	20
Above 40 cm	40	57.1
Total	70	100
Gestation Age		
Full term	31	44.3
Preterm	30	42.9
Large gestation	5	7.1
Low birth weight	3	4.3
Very low birth weight	1	1.4
Total	70	100

4.1.2 Reasons for Admission in the Intensive Care Unit

The most common reason for admission was difficulty in breathing at a prevalence of 48.6%, followed by convulsions, fever, prematurity and inability to breastfeed. The reasons for admission are summarized in Table 4.2.

Table 4. 2: Reasons for admission to the Intensive Care Unit

Characteristics	N	%
Breathing related problems		
Difficulty in breathing	34	48.6
Rapid breathing	4	5.7
Apnea	3	4.3
Inadequate breathing	2	2.9
Others		
Convulsions	8	11.4
Fever	5	7.1
Inability to breast feed	4	5.7
Prematurity	4	5.7
Lethargy	2	2.9
Congenital defects	2	2.9
Bradycardia	1	1.4
Gastrochisis	1	1.4
Total	**70**	**100**

4.1.3 Types of Diagnosis in the Neonatal Intensive Care Unit

The most common diagnosis was respiratory disorders (88.8%). Nearly 50% of the babies had respiratory distress syndrome followed by perinatal asphyxia, meconium aspiration syndrome cyanosis and pneumonia. The second most common diagnosis was infections with a prevalence of 81.4%. Out of every 10 participants, four had sepsis followed by acute kidney injury, jaundice, meningitis, diarrhea, necrotizing enterocolitis and malaria. The least common diagnosis was congenital deformities. The most common deformity was congenital heart disease with a prevalence of nearly 6% followed by extra digits in both legs and hydrocephaly. The diagnoses are summarized in Table 4.3.

Table 4.3: Diagnosis of Neonates in the neonatal intensive care unit at Kenyatta National Hospital

	n	%
Respiratory disorders		
Respiratory distress syndrome	34	48.8
Perinatal asphyxia	21	30
Meconium aspiration syndrome	4	5.7
Cyanosis	3	4.3
Pneumonia	2	2.9
Infections		
Neonatal sepsis	25	35.7
Acute kidney injury	5	7.1
Neonatal meningitis	3	4.3
Diarrhea	2	2.9
Necrotizing enterocolitis	1	1.4
Congenital malaria	1	1.4
Congenital deformities		
Neonatal jaundice	4	5.7
Congenital heart disease	4	5.7
Extra digits in both legs	4	2.9
Hydrocephaly	2	2.9
Klumpke paralysis	1	1.4
Cleft lip palate	1	1.4
Pierre robin syndrome	1	1.4

4.1.4 Duration Of Treatment Of The Neonates In The Intensive Care Unit

Nearly 70% of the neonates had been on treatment for less than 7 days which was followed by those who received treatment between 7 to 14 days. The duration of treatment is summarized in Figure 4.2.

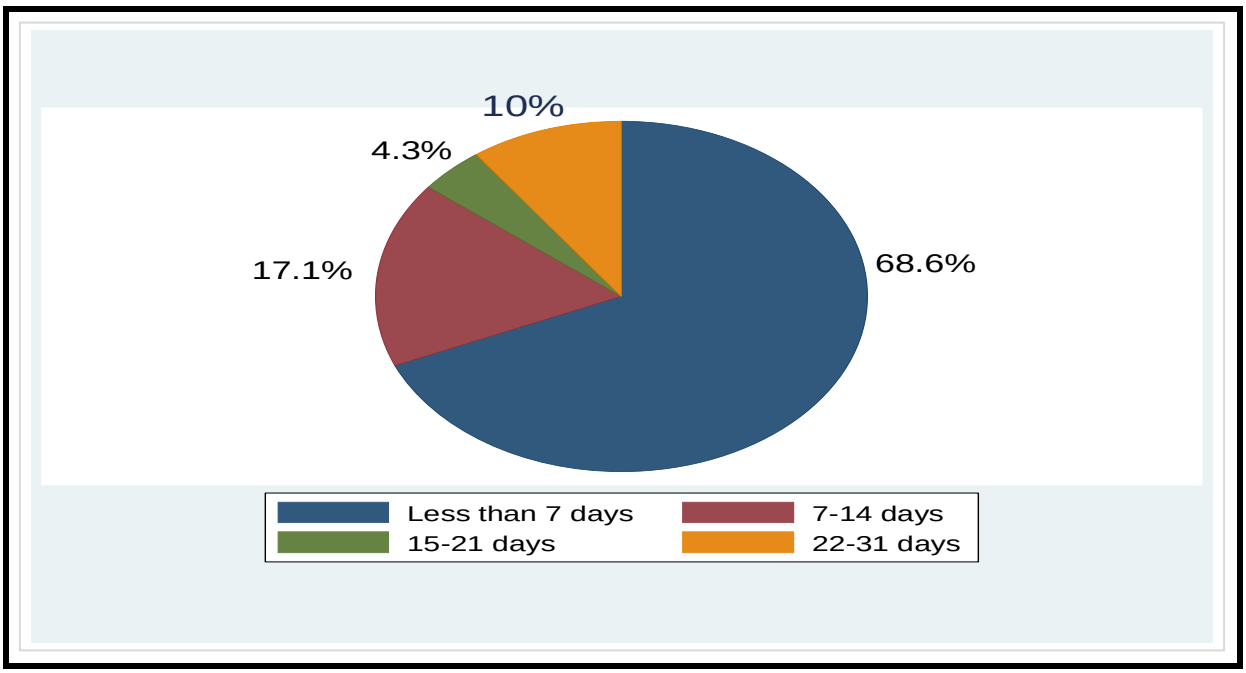

Figure 4. 2: Duration of treatment of Neonates admitted in the Intensive Care Unit of Kenyatta National Hospital.

4.1.5 Medication Use amongst Neonates in the Neonatal Intensive Unit

Antibiotics were the most frequently prescribed medication with a prevalance of 62%. The most frequently prescribed antibiotics were benzyl penicillin and gentamicin. This combination was followed by ceftazidime. Use of meropenem stood at 5.1%. The most frequently used CNS acting drug was phenobarbitone. Aminophylline was the most frequently used respiratory drug. The prevalence of use of other classes of drugs was less than 50%. Central nervous system, hematinics and respiratory drugs followed closely after antibiotics. Types of medicines prescribed are summarized in Table 4.4

Table 4.4: Patterns of Medication Use amongst neonates admitted in the intensive care unit at Kenyatta National Hospital

	n	%	Indication as per Basic paediatric protocols, Kenya
Antibiotics			
Benzyl penicillin	52	19	Early onset neonatal sepsis
Gentamicin	50	18.2	Early onset neonatal sepsis
Ceftazidime	32	11.7	Pseudomonal infection
Meropenem	14	5.1	Late onset neonatal sepsis
Amikacin	9	3.3	Early onset neonatal sepsis
Metronidazole	5	1.8	Necrotizing enterocolitis
Ceftriaxone	3	1.1	Neonatal meningitis and sepsis
Erythromycin	2	0.7	Gastric emptying
Flucloxacillin	2	0.7	Skin and soft tissue infections
CVS drugs			
Furosemide	2	0.7	Fluid overload
Sildenafil	2	0.7	Persistent pulmonary hypertension
Dopamine	1	0.4	Hypotension
Antimycotics			
Fluconazole	11	4	Fungal infections
CNS drugs			
Phenobarbitone	15	9.5	Seizures
Phenytoin	2	0.7	Seizures
Respiratory drugs			
Aminophylline	21	5.5	RDS
Surfactant	1	0.4	RDS
Analgesics			
Paracetamol	5	1.8	Pyrexia and analgesia
Morphine	2	0.7	Sedation and analgesia
Ibuprofen	1	0.4	Patent ductus arteriosus
Other drugs			
Vitamin K	13	4.7	Vitamin K deficiency bleeding
Chlorhexidine (7.1%)	10	3.6	Umbilical cord application
Omeprazole	5	1.8	Gastrointestinal reflux disease
Multivitamin	4	1.5	Vitamin deficiency
Calcium syrup	3	1.1	Mild hypocalcemia
Dexamethasone	3	1.1	Facilitate extubation
Ranitidine	2	0.7	Acute gastrointestinal hemorrhage
Artesunate	1	0.4	Malaria
Tetracycline eye ointment	1	0.4	Neonatal conjunctivitis
Total	274	100	

CNS-Central nervous system CVS-Cardio vascular system RDS-Respiratory distress syndrome

4.1.6 Indications for Antibiotics

The most common indication for an antibiotic was neonatal sepsis. The overall prevalence for use of an antibiotic for sepsis was (41, 93.3%).The most frequently used antibiotics for this condition included benzyl penicillin (14,100%), gentamicin (11, 84.6%) and ceftazidime (5 ,83.3%). The second most common indication among neonatal patients was respiratory distress syndrome (17 ,38.6%) and respiratory distress syndrome at (17,38.6%) which was followed by perinatal asphyxia at (14,31.8%).

Patients who were diagnosed with perinatal asphyxia were prescribed for an antibiotic .The most common antibiotic prescribed was gentamicin (5 ,38.4%) followed by ceftazidime (1,33.3%) and benzyl penicillin(3,21.4%). Treatment guidelines were not followed in this case. The indications are summarized in Table 4.5.

Table 4.5: Indications for the use of Antibiotics in Neonatal Patients at Kenyatta National Hospital

Antibiotic	**Sepsis n (%)**	**RDS n (%)**	**AKI n (%)**	**Perinatal asphyxia n (%)**	**Neonatal meningitis n (%)**	**Pneumonia n (%)**	**Gangrenous feet n (%)**
Benzyl penicillin	14 (100)	6 (42.9)	5 (38.5)	3 (21.4)	1 (7.14)	0	1(7.1)
Gentamicin	11 (84.6)	5 (38.5)	3 (23.1%)	5 (38.5)	0	0	0
Ceftazidime	5 (83.3)	3 (50)	4 (66.7%)	2 (33.3)	1 (16.7)	1 (16.7)	0
Meropenem	4 (100)	3 (10)	3 (75)	1 (25)	0	0	0
Amikacin	3 (100)	0	1 (33.3)	1 (33.3)	0	0	0
Ceftriaxone	1 (100)	0	0	0	0	0	0
Flucloxacillin	1 (100)	0	0	0	0	0	0
Total	41 (93.3)	17(38.6)	17(38.6)	14(31.8)	2(4.6)	1(16.7)	1(7.1)

4.2 Prevalence of Medication Related Problems

4.2.1. Prevalence of Dosing Errors of Antibiotics

Dosing errors were the most common MRPs. This included over and under dosing. For instance, a child weighing less than 2kg was prescribed for 5mg/kg of gentamycin instead of 3mg/kg. Nearly 75% of antibiotics were appropriately dosed. The overall prevalence of overdosing and underdosing were similar with values of 13 (7.6%) and 11 (7.0%) respectively. The combined prevalence of inappropriate antibiotic dosing was 40 (24.2%).This included no dose indicated, overdose and under dose. Gentamicin was most likely to be overdosed given that (6, 12%) of patients treated with were overdosed. The prevalence of inappropriate dosing of antibiotics is summarized in Table 4.6.

Table 4. 6 : Prevalence of dosing errors in antibiotics prescribed for neonates at Kenyatta National Hospital

Antibiotic	Overdose n (%)	Underdose n (%)	No dose indicated n (%)
Benzyl penicillin	1 (1.9)	4 (7.7)	2 (3.9)
Gentamicin	6 (12)	2 (4)	2 (4)
Ceftazidime	1 (3.1)	2 (6.3)	5 (15.6)
Metronidazole	1 (20)	0	1 (20)
Erythromycin	1 (50)	0	0
Amikacin	0	0	1 (33.3)
Meropenem	3 (21.4)	2 (14.3)	1 (7.1)
Ceftriaxone	0	0	1 (33.3)
Flucloxacillin	0	0	2 (0)
Total	**13 (7.6)**	**11 (7.0)**	**16 (9.4)**

For individual antibiotics, overdosing was more common than underdosing with the exception of benzyl penicillin. Three out of 13 patients on meropenem were overdosed and those who were under dosed were 2 (out of 16 prescribing episodes).

The prevalence of not indicating dose overall was 9.4 % (16 episodes out of 171 prescriptions). Amongst antibiotics frequently used by over 30 patients, ceftazidime was the one most likely to be prescribed without documenting the exact dose 5 (15.6%). Prescribers tended not to write the dose of rarely used antibiotics that were prescribed less than 5 times. Flucloxacillin was prescribed twice and in both cases the dose was not written. This is summarized in Table 4.6.

4.2.2 Monitoring of Gentamicin and Amikacin

The only antibiotics for which monitoring errors were studied were the aminoglycosides because they are high risk medicines. Urea, electrolytes and creatinine levels are also meant to be monitored as confirmatory indicators of renal injury. In addition to monitoring renal and liver function tests should be monitored by measuring bilirubin levels. The monitoring tests that were done on patients on aminoglycosides are summarized in Table 4.7.

Out of 22 patients on any of the aminoglycosides only 1 and 3 were monitored for renal and liver function respectively. Only 5 out 22 patients on aminoglycosides had White Blood Cell determined. The findings indicate that the prevalence of treatment monitoring using laboratory parameters was very low. White Blood cells counts should be monitored to confirm infection initially and to determine the efficacy of antibiotic treatment with regard to laboratory parameters. The prevalence of failure to monitor hematological and clinical chemistry parameter ranged from 81.8 to 100% as presented in Table 4.7.

Table 4. 7:Monitoring of Aminoglycoside therapy in neonates at the Kenyatta National Hospital

Indicators	Gentamicin n (%)	Amikacin n (%)	Number of patients not monitored n (%)
UECs			
Creatinine	3 (21.4%)	1 (14.3%)	18(81.8)
Urea	1 (2%)	0	21(95.5)
Sodium	2 (4%)	0	20(90.9)
Potassium	0	1 (1.1%)	21(95.5)
Hematological tests			
WBCs	5 (27.8%)	0	17(77.3)
Thrombocytopenia	2 (4%)	0	20(90.9)
Hemoglobin	3 (6%)	1 (11.1%)	18(81.8)
Liver Function Tests			
Direct bilirubin	1 (2%)	0	21(95.5)
Total bilirubin	1 (2%)	1 (1.1%)	20(90.9)
Total	**18**	**4**	

4.2.3 Incidence of Clinical Conditions that are Suggestive of Adverse Events

The overall prevalence of the trigger conditions were evaluated and summarized in Table 4.8. Evaluation and assessment the cause of the ADR was done using the WHO-UMC causality assessment criteria (52).

Table 4. 8: Incidence of clinical conditions suggestive of adverse events

Symptoms suggestive of an ADR	Prevalence of suspected ADR n (%)	Medicines patient was taking	Causality assessment	P –value
Rash	5 (13.9%)	Benzyl penicillin	Probable	0.210
		Metronidazole	Possible	
		Meropenem	Possible	
		Vitamin K.	Probable	
Diarrhea	3 (8.3%)	Meropenem	Possible	0.014
		Morphine	Unlikely	
		Omeprazole	Possible	
Vomiting	3 (8.3%)	Gentamicin	Possible	0.235
		Amikacin	Possible	
		Erythromycin	Possible	
Jaundice	3 (8.3%)	Benzyl penicillin	Unlikely	0.379
		Fluconazole	Probable	
		Caffeine citrate	Possible	
Cyanosis	3 (8.3%)	Benzyl penicillin	Unlikely	0.991
		Gentamicin	Unlikely	
		Phenobarbitone	Possible	
Bleeding	2 (5.6%)	Benzyl penicillin	Unlikely	0.185
		Phenytoin	Possible	
Bradycardia	1 (2.8%)	Ceftazidime	Unlikely	0.291

4.3 Medication Related Problems among Neonates According To Helper and Strand and NCC MERP Classification.

A total of 163 MRPs were identified among critically ill neonates admitted at NICU. These are summarized in Figure 4.3. The most common MRP was untreated indication 61 (10.8%); followed by sub therapeutic dosage 34 out of 274 cases (12.4%); adverse drug reaction 20 out of 392 cases (5.1%), overdosage 19 out of 306 cases (6.2%).The least frequently occurring MRPs were failure to receive medication 2, (1%) and drug interactions 2 out of 4 episodes (0.5%).

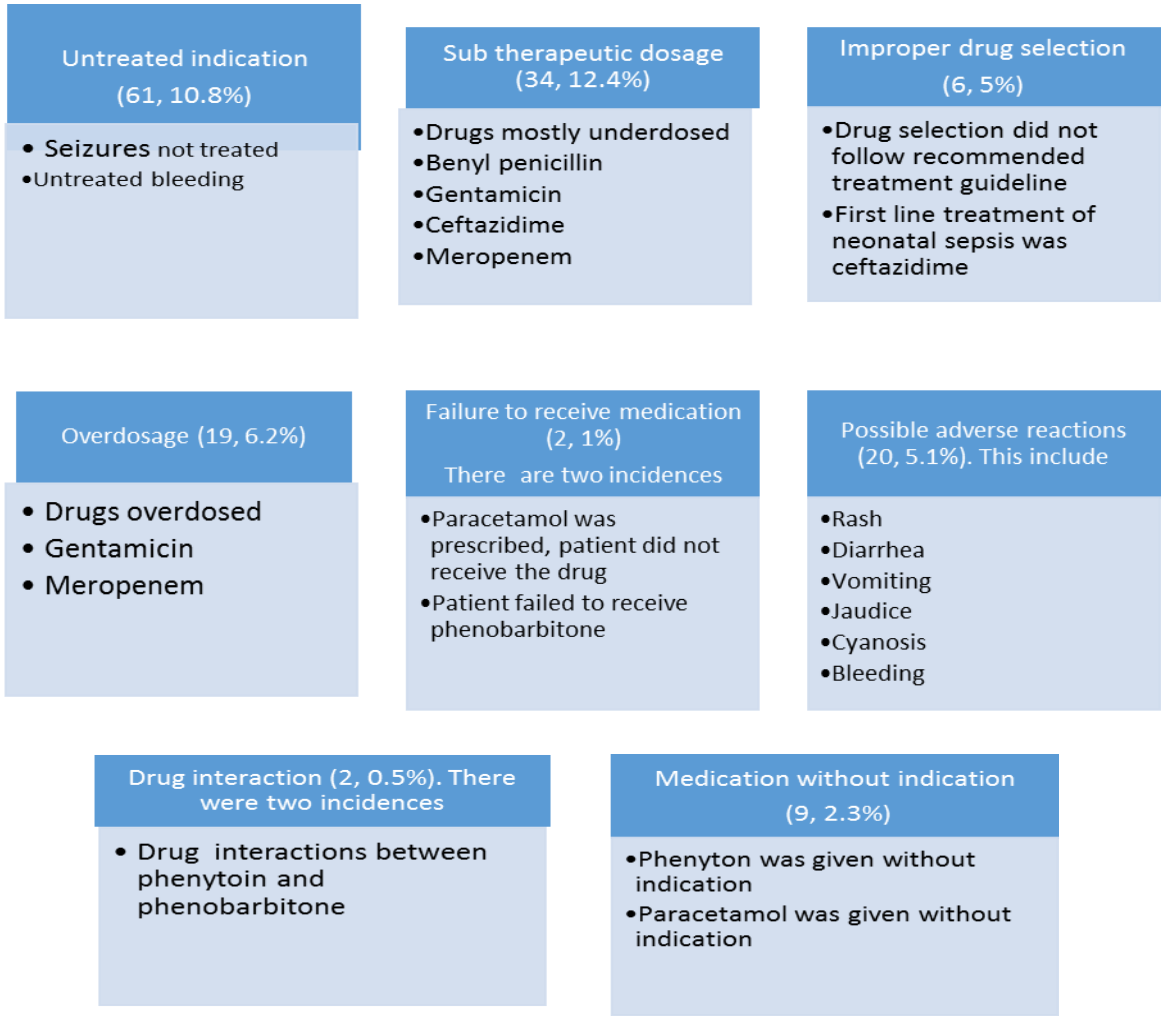

Figure 4.3:Helper and Strand Classification of Medication Related Problems amongst Neonates admitted at the Intensive Care Unit of Kenyatta National Hospital

4.3.1 Prevalence of Medication Related Problem using National Coordinating Council for Medication Error Reporting and prevention (NCC-MERP)

The NCC-MERP classification categorizes MRPs into 14 sub-categories. Only 8 of these categories were assessed for MRPs. Six categories were not measured, because these were not studies. The most common MRPs was improper dose (57,14.5%) which was followed by monitoring errors (22 ,5.6%).This is summarized in Table 4.9 .The most common MRPs was improper dose (57,14.5%) which was followed by monitoring errors (22 ,5.6%).

Table 4. 9: Classification of Medication Related Problem using National Coordinating Council for Medication Error Reporting and Prevention.

Type of MRPs	**(n, %)**
Improper dose	57 (14.5)
Monitoring error	22 (5.61)
Wrong rate of administration	10 (2.6)
Wrong duration	9 (2.3)
Dose omission	9 (2.3)
Wrong route of administration	6 (1.5)
Wrong drug	4(1)
Wrong dosage	16(9.4)
Wrong strength/concentration	ND
Wrong technique	ND
Wrong drug	ND
Wrong patent	ND
Deteriorated drug error	ND
Other	

ND-For this study those were not determined

4.4 Patient-Related Risk Factors for Selected Medication Related Problems

4.4.1 Risk Factors for Underdosing

Bivariable analysis was carried out to determine the predictor variables for dosing errors in the neonates. Separate analyses were done for underdosing and overdosing. There was no statistically significant association between underdosing and anthropometric measures of neonates such as body surface area, length, height, weight at birth and at recruitment. This is summarized in Table 4.10. There was statistically significant association between underdosing and having congenital disorder (OR **1.28** 95% CI 1, 1.64; p=**0.025**) and bleeding (OR **33** 95% CI 1.088, 1000.6; p=**0.045**).

Some neonates who received benzyl penicillin injection experienced underdosing and the association between benzyl penicillin and underdosing was statistically significant ($p<0.05$). Those who also received gentamicin injection, experienced underdosing; however it was not statistically significant ($p=0.063$). Neonates who had gastrointestinal disorders were also likely to experience underdosing but the association was not statistically significant ($p=0.078$). Neonates who had cyanosis, were also likely to be underdosed though the association was not statistically significant ($p =0.081$). However, these findings may be clinically significant.

On multivariable logistic analysis, two predictor variables were found to be significantly associated with underdosing; congenital disorders and gastrointestinal disorders. Neonates who had congenital disorders, were 1.368 times more likely to experience underdosing (OR **1.368** 95% CI 1.018, 1.837; **p=0.037)** compared to those who had no congenital disorder. Neonates who had gastrointestinal disorders, were 1.5 times more likely to experience underdosing (OR **1.5** 95% CI 1.038, 2.165; p= 0.031) compared to those who had no gastrointestinal disorder. This is summarized in Table 4.10.

Table 4. 10:Logistic regression analysis of risk factors underdosing in Neonates admitted in the intensive care unit of Kenyatta Natonal Hospital

Variable	Crude OR (95% CI)	P value	Adjusted OR(95%CI)	P value
Baseline characteristics			-	-
Gender	1.213(0.206-7.149)	0.831		
Body surface area o	2244.06(0-1.04e+13)	0.325	-	-
Gestation age	1.624(0.283-3.716)	0.486	-	-
Length of baby	1.035(0.920-1.165)	0.564	-	-
Weight at birth	1.763(0.653-4.757)	0.263	-	-
Weight at recruitment	1.689(0.6716-4.250)	0.265	-	-
Diagnosis				
Bleeding	33(1.088-1000.6)	**0.045**	22.46(0.679-742.61)	0.081
Congenital disorder	1.28(1-1.637)	**0.025**	1.368(1.018-1.837)	**0.037**
Cyanosis	16(0.708-361.7)	0.081	-	-
Gastrointestinal disorder	1.397(1.02-1.92)	0.078	1.5(1.038-2.165)	**0.031**
Sepsis	0.583(0.06-5.924)	0.649	-	-
Perinatal asphyxia	1.025(0.283-0.970)	0.97	-	-
Drugs				
Benzyl penicillin	0.238(0.055-1.025)	**0.054**	1.272(0.087-18.587)	0.860
Gentamicin	0.5(0.241-1.040)	0.063	-	-
Phenobarbitone	1.03(0.617-1.717)	0.911	-	-
Phenytoin	1.64(0.815-3.3)	0.165		
Ceftazidime	1.10(0.761-1.60)	0.608	-	-
Metronidazole	0.986(0.780-1.246)	0.904	-	-
Amikacin	0.938(0.763-1.154)	0.546	-	-
Meropenem	0.981(0.898-1.072)	0.678	-	-
Aminophylline	1.070(0.942-1.216)	0.300	-	-
Ceftriaxone	1.06(0.947-1.193)	0.300	-	-
Paracetamol	1.03(0.928-1.36)	0.608	-	-

4.4.3 Risk Factors for Overdosing

Bivariable analysis was carried out to determine which independent variables were risk factors for overdosing. There was a statistical significant association between overdosing and having convulsions (OR **4.31** 95% CI 1.07, 17.04; p=**0.04**). Neonates who received aminophylline, were 1.081 times more likely to experience an overdose (OR **1.081** 95%, CI 1.01, 1.160; p = **0.033**) compared to those who did not receive the drug.

Neonates who had jaundice were more likely to experience overdosing, however it was not statistically significant (p=0.081). It was also noted that those who received phenytoin and ranitidine injection, experienced overdosing though this association was not statistically significant (p=0.065).This is summarized in Table 4.11

On the multivariable analysis, those who received aminophylline, phenytoin and ranitidine were found to have statistically significant association with overdosing. It was noted that neonates who received aminophylline, were 1.09 more times likely to experience overdosing (OR **1.09,** 95% CI 1.014, 1.17; p = **0.02**) compared to those who did not receive the drug. Neonates who received phenytoin, were 2.064 times likely to be overdosed (OR **2.064,** 95% CI 1.018, 4.19; p= **0.044**) compared to those who did not receive phenytoin. Those who received ranitidine were 1.17 times more likely to be overdosed compared to those who did not receive the drug (OR 95% CI 1, 1.374; p=**0.044**). This is summarized in Table 4.11.

Table 4.11:Logistic regression anaysis for Overdosing in Neonates admitted in the Intensive Care unit of Kenyatta National Hospital

Variable	Crude OR (95%CI)	P value	Adjusted OR (95% CI)	P value
Baseline Characteristics				
Gender	0.949 (0.227-3.961)	0.942	-	-
Body surface area of baby	138.47 (0-3.28e+08)	0.51	-	-
Gestation age classification	1.404 (0.469-4.204)	0.545	-	-
Length of baby	1.005 (0.909-1.112)	0.917	-	-
Weight birth	0.478 (0.131-2.761)	0.263	-	-
Weight at recruitment	1.40 (0.690-2.845)	0.351	-	-
Diagnosis				
Sepsis	0.271 (0.031-2.389)	0.24	-	-
Convulsions	4.31 (1.07-17.40)	**0.04**	-	-
Gastrointestinal disorder	0.884 (0.536-1.458)	0.628	-	-
Respiratory distress syndrome	0.954 (0.322-2.830)	0.932	-	
Jaundice	16 (0.708-361.72)	0.081	-	-
Duration	1.15 (0.95-1.40)	0.159	-	-
Frequency	1.754 (0.88-3.50)	0.110	-	-
Drugs				
Benzyl penicillin	1.15 (0.365-3.62)	0.811	-	-
Gentamicin	0.712 (0.337-1.507)	0.375	-	-
Phenobarbitone	0.985 (0.492-1.974)	0.967	-	-
Phenytoin	1.938 (0.959-3.915)	0.065	2.06(1.018-4.19)	**0.044**
Amikacin	1.062 (0.838-1.346)	0.620	-	-
Meropenem	1.091 (0.932-1.277)	0.280	-	-
Aminophylline	1.081 (1.01-1.160)	**0.033**	1.09(1.014-1.17)	**0.020**
Ranitidine	1.158 (0.991-1.354)	0.065	1.17(1.00-1.374)	**0.044**

4.5 Treatment Outcomes of Neonates

At the end of the study period, mortality was high at 56% .This was because of an outbreak of drug resistant bacterium *Klebsiella pneumonia*. The observed causes of high mortality by the outbreak included neonates sharing cots which put them at risk of infecting each other, bleeding and bruises in the noses as a result of improvising on feeding tubes and syringes. Six patients were discharged; five to the nursery 5 (7.3%) and one to the general ward 1(1.5%). Twenty four patients were discharged home 24 (34.8%). The treatment outcomes are summarized in Figure 4.4.

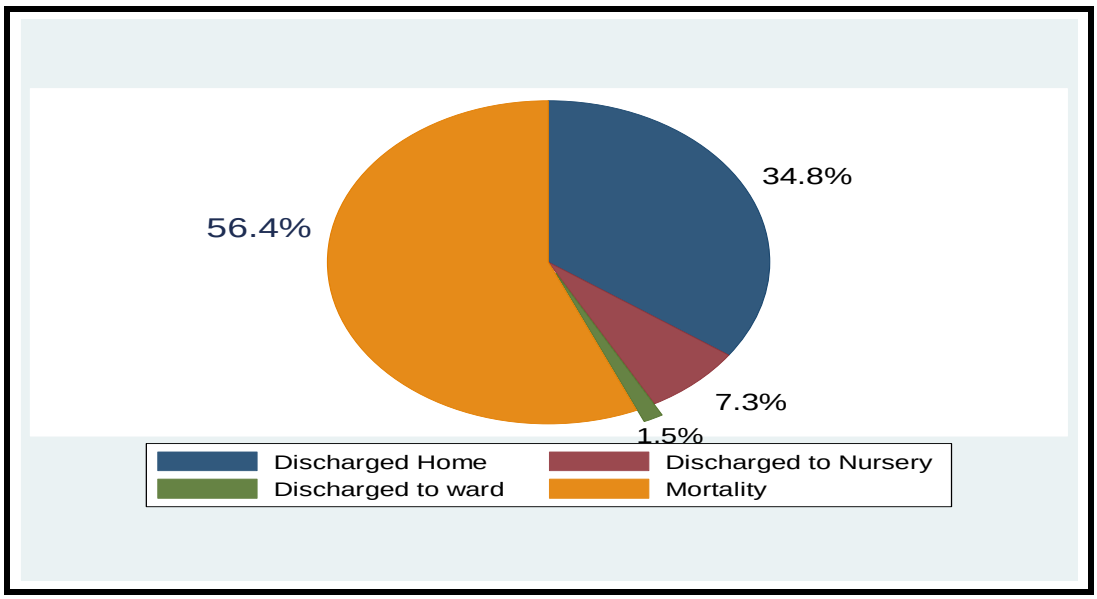

Figure 4. 4: Outcome of Neonates at the Intensive Care Unit.

CHAPTER FIVE: DISCUSSION

5.1 Baseline and medical characteristics of neonates

The present study shows that out of 70 neonates admitted in the intensive care unit, 41 (58.6%) were males. This was consistent with a study carried out in Kisii Level 5 in 2014, where males were predominant (34). A similar study carried out in Brazil in 2016, found out that 89 (52.2%) of neonatal patients sampled were males and 63 (47.8%) females (11). In yet another study carried out in India in 2015, 215 (53.8%) were males and 185 (45%) were females (53). Admission rates for female neonates are generally lower compared to males. A study carried out in South Asia shows parents are likely to seek care for males than females (54). Newborn females have also been reported to have stronger immunity than males and less likely to be seriously ill. (55).

Majority of neonates were 31 (44.3%) full term and were followed by preterm neonates at 30 (42.9%). These findings were in agreement with a study carried out in Germany where majority of the patients admitted in NICU recruited were full term (56.8%), followed by preterm term patients (31.1%) (56) .The most common reason for admission in the intensive care was difficulty in breathing at 34 (48.6%) which correlates with the study carried out in Kisii Level 5 hospital at 16 (32%) (34).

The most common diagnosis was respiratory distress syndrome 64 (88.8%).This was followed closely by infections 37 (81.1%). These findings were similar to study carried out in India in 2016 where respiratory distress syndrome was common (57). A similar study carried out in Hong Kong in 2013 showed that respiratory distress syndrome was most common diagnosis amongst neonatal patients. This is because RDS is common in premature neonates due to deficiency of surfactant in the lungs (58).

The duration of treatment of neonates in the intensive care unit was generally less than 7 days for 68.6% of the neonates. This was similar to a study carried out in India (62) where the duration of treatment was less than 7 days for 80.8% of the neonates. This could be attributed to the very high mortality rates amongst critically ill neonates.

5.2 Medication Use amongst Critically Ill Neonates

The most commonly prescribed class of medications was antibiotics at 62% which was followed by central nervous system drugs at 17%. The findings of this study corresponds to a study carried out in India, where antibiotics were the most commonly prescribed class at 60.3% followed by drugs acting on the nervous system at 7.8% (59). A similar study carried out in Pakistan in 2018, reported that antibiotics were the most frequently prescribed antibiotics at 73% followed by CNS drugs at 12.3% (37). The high prevalence of antibiotic use is due to the common practice of empirical prescribing especially for management for respiratory distress (60). RDS commonly affects neonates, therefore empiric prescribing of antibiotics is advised (57). Majority of cases of respiratory distress syndrome were managed with benzyl penicillin followed by ceftazidime, meropenem and gentamicin. The use of these antibiotics did not follow the recommended Kenya Pediatric Protocols, which recommends combination of benzyl penicillin and gentamicin as first line treatment. The most commonly used antibiotic for treating sepsis was ceftazidime followed by benzyl penicillin and gentamicin .This did not comply with the Kenyan Pediatric Protocols and WHO guidelines which recommends benzyl penicillin and gentamicin for empiric treatment of neonates with suspected clinical sepsis.

The most common indication for an antibiotic in neonatal patients was neonatal sepsis with overall prevalence of 41 (93.2%). The antibiotic with the highest prevalence of appropriate dosing included, benzyl penicillin followed by gentamicin, ceftazidime and amikacin. This is because these drugs are frequently used and therefore clinicians may have experience with appropriate dosing. In addition, gentamicin and amikacin are toxic and therefore clinicians maybe cautious when dosing.

5.3 Medication Related Problems among Neonates

A systematic review by Krzyzaniak et al (2016), found that most prevalent type of MRPs at 14-71% (23). It was also observed that dosing errors resulting in overdosing and underdosing were also common with a prevalence of 40 (42%). A similar study carried out in South Africa reported, dosing errors as the most common medication related problem at 452 (39%) (61). Rashed et al, demonstrated that majority of MRPs reported were related to dosing errors at 21% and this corresponded to studies carried out in UK and Saudi Arabia where incidence of dosing

errors was at 35 (42.5%) (2). Birarra et al, showed dosing errors was the most common MRPs with a prevalence of 45 (42.5%) (24). This could due to inaccurate weight dose calculations, fractional dosing and incorrect recording of patient's weight.

In this study the proportion of off-label prescription was high as compared to unlicensed prescription use. Similar results were obtained in a study conducted in Pakistan where the proportion of unlicensed use (33.4%) and was comparatively low as compared to off-label use (52.1%) (37). Similar results were obtained for studies conducted in Ireland where off-label use was high (76%) and 47% of neonates received unlicensed drugs in NICU (62). Costa et al, demonstrated a high incidence of off-label prescription use (96.4%) and unlicensed use was at 66.8% (38). This is clear evidence that prescription of off-label and unlicensed drug use is a worldwide practice.

5.4 Medication Monitoring Errors amongst Neonates

The only antibiotics for which monitoring errors were studied were the aminoglycosides because they are high risk medicines. Urea, electrolytes and creatinine levels are also meant to be monitored as they also confirmatory indicators of renal injury. The prevalence of treatment monitoring using laboratory parameters was very low for these drugs. This is could be due to the parent's not having enough money and are paying from their pockets.

Clinical conditions that were suggestive of suspected adverse events were only 20 out of 36 treatment episodes. A similar study carried out in Spain was in agreement with the findings of this study with only 22 adverse drug reactions affecting 4% of the participants. This is due to different hospital settings.

5.5. Dosing Errors in Neonatal Patients.

In this study, the most common MRP according to Helper and Strand was sub therapeutic dosage at (12.4%) .In relation to NCC-MERP classification improper dose at 14.5% was the most prevalent. Leopoldino et al, showed there was high incidence of sub-therapeutic dosage not optimal reported at (13.5%) (63). A study conducted in South Africa showed the most prevalent MRP was sub therapeutic dosing at 34% (61). Several studies in the paediatric population have shown a high frequency of MRPs mainly due to sub-optimal doses due to inappropriate dose

selection. Treatment sheets should contain important information such dose, dosage form, route and frequency of administration, age, length and weight of neonate.

5.6 Risk factors for Medication Related Problems

On logistic regression analysis, gastrointestinal and congenital disorders were strong predictors of underdosing. This is attributable to inaccurate weight dose calculation. Phenytoin, aminophylline and ranitidine were positive predictors for overdosing. This could be as a result of formulations that are not suitable for neonatal population and the frequency of administration. There are no comparator studies on dosing errors in neonates and therefore it is difficult to compare with the study.

5.7 Strengths and Limitations of the Study

The main strength of the study was data collected prospectively. Also it was the first study to quantify and investigate the potential risk factors for the occurrence of MRPs amongst critically ill neonates admitted in the intensive care unit of KNH. The limitations of this study was a low sample size for more accurate descriptive analysis. The study was conducted in NICU which limits generalization to all pediatrics. The data was collected from patient files, treatment sheets and nursing records which were prone to incomplete records thus lowering quality of data. Therapeutic drug monitoring is not usual practice in NICU in KNH, so the true prevalence of some MRPs are likely to be underestimated.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusions

The most common MRPs among critically ill neonates admitted in the NICU of KNH were dosing errors. Neonates who had gastrointestinal and congenital disorders were likely to experience underdosing. While those who received phenytoin, aminophylline and ranitidine were likely to experience overdosing. The full term neonates (44.3%) were not exactly different from preterm neonates at (42.9%). The most common indication for antibiotics was neonatal sepsis at 93.2%. RDS was the most common cause of illness which was followed closely by infections.

6.2 Recommendations for Policy and Practice

1. Regular training of health care workers who are specifically providing care to neonatal patients is needed in order to keep up with the emerging trends of management of MRPs.
2. Recommendations from prescribers is the need of a ward based drug safety personnel who can capture and intercept MRPs.
3. The need to avail tools that aid in the identification and reporting of MRPs.
4. Monitoring of high alert medicines to limit MRPs.

6.3 Recommendation for Future Research

1) Studies on the incidence, prevalence and outcomes of MRPs among neonatal patients are required across all Kenyan hospitals.
2) A follow up study is appropriate to determine the extent of MRPs in Kenyan Hospitals

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APPENDICES

Appendix I: Ethical Approval Letter

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21st March, 2019

Emma Mutheu Kivuva
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Dear Emma

RESEARCH PROPOSAL: MEDICATION RELATED PROBLEMS AMONG NEONATES ADMITTED AT KENYATTA NATIONAL HOSPITAL (P867/12/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 21st March 2019 – 20th March 2020.

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. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. 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*).
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 Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmacology and Pharmacognosy, UON
Supervisors: Prof.F.A. Okalebo, Dr. Margaret Oluka, Dr. Sylvia Opanga

Protect to discover

Appendix II: Reviewer Comments on Research Proposal

Resub P 867/12/2018

Emma Mutheu Kivuva
U51/6754/2017
C/o Department of Pharmacology & Pharmacognosy
School of Pharmacy
University of Nairobi.
6th March, 2019.

Ref: KNH-ERC/RR/131

To,
Prof. M. L. Chindia
The Secretary
KNH-UON Ethics and Research Committee

KENYATTA NATIONAL HOSPITAL APPROVED 21 MAR 2019 KNH/UoN-ERC P. O. BOX 20723

KENYATTA NATIONAL HOSPITAL RECEIVED 08 MAR 2019 KNH/UON-ERC P.O. Box 20723-00202 NRB.

Dear Sir,

RE: RESPONSE TO REVIEWER COMMENTS ON RESEARCH PROPOSAL (P867/12/2018)

I acknowledge receipt of your letter dated 19th February, 2019 which contained reviewer comments on the research proposal: **"Medication related problems among neonates admitted at Kenyatta National Hospital".**

Below, kindly find my point-by-point responses to the reviewer comments, and the corresponding changes and corrections to the research proposal:

1. **Reviewer Comment**: Address several typographical and grammatical mistakes in the write up e.g. last sentence on page 12.
   Response: The last sentence has been revised to: - **Unpredictable adverse drug reactions can be attributed to excipients and manipulation.**
   (Page no. 12).

2.Reviewer Comment: Recruitment procedure- Rewrite for clarity

Response: The recruitment procedure has been rewritten for clarity as recommended (Pages no. 20 and 21).

3.Reviewer Comment: Ethical considerations- Explain how the health records will be protected and the services will not be interrupted, especially for critically ill neonates

Response: Information on how health records will be protected and services will not be interrupted for critically ill has been added (Pages no. 26 and 27).

4.Reviewer Comment: What is your dissemination plan of study findings?

Response: The dissemination plan of the study findings has been clearly outlined (Page no. 28).

5.Reviewer Comments: Research assistants are budgeted for. Who are they; their qualifications, training in research, infection control, etc? What is their role in the study?

Response: The research assistants have clearly been explained who they are, their qualifications, training in research, infection control and their role in the study. (Page no.26)

6.Reviewer Comments: Appendix A: Eligibility checklist: Add title, date and screening ID

Response: The title, date and screening ID has been added. (Page no.35)

7.Reviewer Comments: Appendix B: Informed consent

i. Translate to local language (provide at least, a Kiswahili translation)

Response: The Kiswahili translation has now been provided. (Page no.40, 41,42,43,45).

ii. Give a clear statement on study procedures that the participants should expect

Response: A statement on study procedures that the participants should expect has now been explained in detail. (Page 37 and 38)

8.Reviewer Comments: Appendix C, Data collection form: Recheck as there are some inappropriate parameters e.g. BMI for neonates.

Response: The section has been corrected and inappropriate parameters deleted. (Page no. 44).

9. **Reviewer Comments:** It is mentioned in the protocol that there will be observation procedures. Provide an observation checklist.

   Response: The observation checklist has been provided. (Page no. 41).

Yours sincerely,

Emma Mutheu Kivuva
U51/6754/2017
+254711229 227

c.c Supervisors: Prof. Faith Okalebo, Dr. Margaret Oluka, Dr. Sylvia Opanga

Appendix III: Medication Related Problems among Neonates Admitted at Kenyatta National Hospital

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300

KNH-UoN ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERCs

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9 Ext 44355, 44102
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/RR/131

19th February, 2019

Emma Mutheu Kivuva
Reg. No. U51/6754/2017
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Emma,

Research Proposal: **Medication related problems among neonates admitted at Kenyatta National Hospital (P867/12/2018)**

This is to acknowledge receipt of your research proposal and to inform you that upon review by the KNH- UoN Ethics and Research Committee during the 240th ERC meeting held on 13th February, 2019, the following observations and suggestions were made:

1. Address several typographical and grammatical mistakes in the write up e.g. last sentence on page 12.
2. Recruitment procedure: Rewrite for clarity.
3. Ethical considerations: Explain how the health records will be protected and the services will not be interrupted, especially for critically ill neonates.
4. What is your dissemination plan of study findings?
5. Research assistants are budgeted for. Who are they; their qualifications, training in research, infection control, etc.? What is their role in the study?
6. Appendix A, Eligibility checklist: Add title, date and screening ID.
7. Appendix B, Informed consent:
    i. Translate to local language (provide, at least, a Kiswahili translation).
    ii. Give a clear statement on study procedures that the participant should expect.
8. Appendix C, Data collection form: Recheck as there are some inappropriate parameters e.g. BMI for neonates.
9. It is mentioned in the protocol that there will be observation of procedures. Provide an observation checklist.

Recommendations

Revise and resubmit three (3) copies of the full proposal within a period of four (4) weeks with effect from the date of this letter. Include a cover letter that summarizes how you have addressed the comments and note the page number(s) where the changes have been made.

Yours sincerely,

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

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chair, KNH- UoN ERC
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmacology and Pharmacognosy, UoN
Supervisors: Prof. Faith Okalebo, Dr. Margaret Oluka, Dr. Sylvia Opanga

Appendix IV: KNH-Uon ERC Application Form

UNIVERSITY OF NAIROBI (UoN)
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Website: http://www.erc.uonbi.ac.ke
Facebook:
ttps://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC

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

KNH-UoN ERC APPLICATION FORM

ETHICS RESEARCH COMMITTEE

Application Number P87/12/2018

I. PRINCIPAL INVESTIGATOR: Provide the information requested below:

Last Name	*First name*	*Academic degrees*
KIVUVA	**EMMA**	**Bachelor of Pharmacy**

Professional titles and/or work position within your home institution

Doctor, Pharmacist-Port Reitz Sub County Hospital, Mombasa.

Home institution(s) and or department (s) approving this research project.

Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi

Mailing address, telephone and fax numbers, and email address

Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: ttps://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC

All correspondence shall be addressed to the Principal Investigator. Research Administrators may have delegated signatory authority only when listed as Co-investigators.

ADDRESS **41598-80100 MOMBASA**
TEL. **+254711229227**
Email **kivuvaemma@gmail.com**

II. PROJECT TITLE

MEDICATION RELATED PROBLEMS AMONG NEONATES ADMITTED AT KENYATTA NATIONAL HOSPITAL.

As the Principal Investigator in this research I declare that:

1. Any change to this protocol and/or procedure shall be notified to and effected only after approval by the KNH-UoN ERC.
2. I shall notify the KNH-UoN ERC of intended publication, or any other form of dissemination of results of this study and provide the draft contents.
3. Other members of the research team are bound by 1) and 2) above.

_____ Date 28/02/2019

Principal Investigator's Signature

III. RESEARCH PERSONNEL.

Supervisor's name	Work Position	Institution approving research	Contacts	Signature and Date
Dr. OLUKA MARGARET, PhD	Chairman, Department of Pharmacology and Pharmacognosy	School of Pharmacy	olikamarga@yahoo.com 0722 604 216	28/02/019
Dr. OPANGA SYLVIA ,PhD	Senior Lecturer, UON	School of Pharmacy	sylvia.adisa@gmail.com 0721 296 448	08/03/2019
Prof. OKALEBO FAITH, PhD	Senior Lecturer, UON.	School of Pharmacy	okalebof@yahoo.com 0737 434 204	26/02/2019

IV. FUNDING INFORMATION

Funding for the study will be done by the principal investigator. However, opportunity for funding will be sought in the course of the study.

V. DESCRIPTION OF RESEARCH PROJECT

Background and Purpose of Research

Medication Related Problems (MRPs) are not a common cause of admission of neonates to either the new born unit or the neonatal intensive care unit. However the neonate is usually at a significant risk for adverse drug reactions since organs required to handle drugs are still under development. Neonates at the Neonatal Intensive Care Unit are usually very ill with multiple organ dysfunction. They may be on multiple drugs which greatly increases the chances of adverse drug reaction.

This study is likely to demonstrate frequency and types of medication manipulation errors, describe methods of dosing and possible errors likely to be encountered and areas that need improvement. These findings will highlight the need for more organized systems for neonatal care.

These areas include improved drug administration and monitoring .The study aims to provide data on prevalence of MRPs at Kenyatta National Hospital as well as demonstrate that neonates need specialist pharmaceutical care. The study will demonstrate the need for more vigilance in order to decrease the number of mortality and morbidity cases related with medication related problems among critically ill patients.

Appendix V: Research Questions

Research question

1. What are the patterns of medication use amongst neonates in neonatal intensive care unit?
2. What is the prevalence of MRPs among neonatal patients admitted at KNH?
3. What are the different types of MRPs among neonates at KNH according to Helper and Strand and NCC-MERP classifications?
4. What patient-related risk factors are associated with MRPs among neonate patients receiving care at KNH?

Objective

Main objective

The study aims at identifying and characterizing MRPs and their related risk-factors among critically ill neonatal patients.

Specific objectives

The specific objectives are to:

1. Identify patterns of medication use amongst neonates in NICU.
2. Measure the overall prevalence of MRPs among neonatal patients admitted at KNH.
3. Identify the different types of MRPs among neonates at KNH according to Helper and Strand and NCC-MERP classifications systems
4. Investigate patient-related risk factors associated with different types of MRPs among neonatal patients at KNH.

Research Ethics

Approval to carry out this study will be sought from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC). This study will be registered with the Research and Development Department of the Kenyatta National Hospital and an official research study number given and recorded in the registry as per the hospital research guidelines. Information obtained during the study will be treated with utmost confidentiality.

Research Methodology and Procedures

The study will be carried out between February and March 2019 and it is a descriptive cohort study. It entails the prospective review of treatment sheets and patient files of neonatal patients who are critically ill and admitted at the Kenyatta National Hospital. Data collection will commence within 24 hours of admission. Patient records will be reviewed daily. No medication or material of any nature will be administered by the researcher. No specimens will be taken from the patient.

Participants in the project

The study will not directly deal with humans. Patient records will be used. Neonates will be included if they are;

1. 0 to 28 days of age.
2. Admitted at critical and special care units as from 1st February to 30th May 2019.
3. Guardians provide consent to participate.
4. Admitted to hospital within 24 hours of day of recruitment.

Neonates will be excluded if they are;

1. Older than 28 days.
2. Admitted in the New Born Unit.
3. Caregiver declines to participate.
4. Admitted for more than 24 hours at the time of recruitment.

The study will be conducted at the Kenyatta National Hospital (KNH) which is a 2000 bed National teaching and referral hospital.The hospital is the teaching hospital of University of Nairobi, College of Health Science and works in collaboration with many other medical institutions countrywide in offering clinical experience.

Risks and benefits of the study

There are no anticipated direct benefits or risks to the patients whose records will be used but the findings will aid in the formulation of interventions to promote the detection and prevention of MRPs in this age group and improve medication use and safety among neonatal in-patients.

Potential adverse events and proposed interventions,

a) **Nature and Degree of Risk**: this is a minimum risk study since secondary data will be used. Confidentiality of the information obtained will be observed at all times during and after the study.

b) **Minimization of Risk**: There is no anticipated risk in participating in this study.

c) **Unknown Conditions**: Collaborate with the other health care providers to carry the necessary management plans.

Benefits: This study will lead to more vigilance which will lead to organized systems for neonatal care and also improve drug administration and monitoring

d) **Adverse Events Treatment**: The study will not be interventional in nature therefore no adverse events are anticipated.

e) **Adverse Events Facilities**: The study will not be interventional in nature therefore no adverse events are anticipated.

f) **Financial Responsibilities**: No financial responsibilities or burdens are anticipated in this study.

Confidentiality of research data

Data obtained will be treated with confidentiality at all times. Data collection documents will be stored under lock and key at all times. Information in computers will be password protected. Unique patient identifiers will be used.

1) **Ethical consideration**: Summarize the ethical issues arising from the study and how they will be dealt with.

The health records will be protected by reviewing the files in the neonatal wards. No document will be removed from the units. All information extracted will be coded and patient identifier information will not be included. The electronic data will be password protected all hard documents will be restricted to principal investigator and supervisors.

Consent to use patients medical records will be sought from Kenyatta National Hospital/ University of Nairobi Ethical and Research Committee.

2) **Additional information** (where applicable e.g. radiation exposure, access and use of private records, audio- visual recordings, etc.)
None

3) **Consent /assent forms and waiver** (Justify what applies):

- ☐ **Written**
- ☐ Oral
- ☐ Waiver

The consent will be in the written form since it is considered suitable as the principal investigator will be able to capture the express consent of carrying out the study first hand. It is also suitable for purposes of record keeping.

Appendix VI: Eligibility Checklist

Title: Eligibility Checklist

Date:

Screening ID:

All subjects who meet eligibility based on the inclusion criteria

	Yes	No
Age below 28 days	[ ]	[ ]
Admitted at NICU and SCBU	[ ]	[ ]
Guardians provide consent to participate	[ ]	[ ]
Neonates admitted to hospital within 24 hours of day of recruitment	[ ]	[ ]

All subjects who meet eligibility based on the exclusion criteria

	Yes	No
Older than 28 days	[ ]	[ ]
Admitted at NBU	[ ]	[ ]
Caregivers fail to participate	[ ]	[ ]
Admitted for more than 24 hours at the time of recruitment	[ ]	[ ]

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Appendix VII: Informed Consent Form

To be read in a language that the respondent is fluent in.

Title of the study: Medication Related Problems among Neonates admitted at Kenyatta National Hospital

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

University of Nairobi, P.O BOX 30197-00400, Nairobi.

Investigator: Dr Emma M Kivuva, P.O BOX, 30197-00400, Nairobi.

Supervisors:Prof Faith Okalebo, Dr.M.O.Oluka, and Dr.Sylvia Opanga - Department of

Pharmacology and Pharmacognosy;

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 minutes

Introduction: My name is Emma Kivuva, a postgraduate student in the School of Pharmacy at the University of Nairobi I am inviting your child to take part in this research study and would like

to give you information that will help you decide whether or not your child will participate in this study. Feel free to stop me and ask any questions about the purpose of this study, any risks or benefits, what happens if your child participates and anything else about the study that is not clear. Once I have answered the questions to your satisfaction, you may then decide to sign your name on this form to agree for your child to take part in the study. It is also good to understand that your decision for your child to participate in this study is voluntary; your free to withdraw your child from the study at any time without giving a reason. Refusal to participate will not in any way affect the services your child is entitled to at Kenyatta National Hospital. I will give you a copy of this form for your record.

May I continue? YES/NO

This study has been approved by Kenyatta National Hospital-University of Nairobi Ethics and Research Committee protocol No.....

Purpose of the study: The researcher listed above is carrying out this study to find out medication problems in Neonates. The purpose of the study is to find out if the medication they are taking is working and whether they have experienced or are experiencing any side effects from their medication. We also want to check if the dose is correct and if there are any other problem related to the medicines given.

Procedure: If you agree for your child to participate in this study, the following things will happen: You will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. To obtain your permission for your child to participate. You will be taken through the recruitment process whereby procedures will be explained to you .There

after the researcher will assess your child's records and document the drugs prescribed. The researcher will document also reason for admission and any other disease related condition, age and length of the baby. The approximate length of the baby might be measured using a tape measure. If the researcher notices that he/she may wish to discuss with clinicians this will be reported directly to clinicians to nurse and if appropriate changes will be made to treatment. Researcher may observe how drugs will be administered to see if it's correctly done. There will be no direct procedures that will be done to the child by the researcher.

Risks: One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. To ensure privacy, your child's name will not be filled on the data collection instruments. For this study, your child will be assigned a unique number that I will use to identify him/her in a password-protected database. All the records will be kept under lock and key and only I will be able to access and use it. The results from this study may be published or presented at professional meetings but your child's name will not be used or associated with the findings.

Benefits: Your child may benefit. If any problems are detected the chief doctor will be informed and this may be of benefit to your child. This information is a contribution to science and may help in making future decisions on the choice of medication through identification and management of medication related problems 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 her study. Dr Emma Kivuva 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----------

Kiambatisho VIII: Fomu iliyokubaliwa ya kibali

Iweze kusomwa kwa lugha ambayo mhojiwa anaelewa.

Kichwa cha utafiti: Matatizo yanayohusiana na dawa kati ya watoto wachanga katika Hospitali ya Taifa ya Kenyatta

Taasisi: Idara ya Famakologia na Famakognosia, Shule ya Famasia, Chuo Kikuu cha Nairobi, S.L.P 30197-00400, Nairobi.

Mtafiti: Dkt. Emma M Kivuva, S.L.P, 30197-00400, Nairobi.

Wasimamizi: Profesa Faith Okalebo, Dkt.M.O.Oluka, and Dkt.Sylvia Opanga- Idara ya Famakologia na Famakognosia,

Idhini ya Maadili: Hospitali ya Taifa ya Kenyatta/ Chuo Kikuu cha Nairobi Maadili na Utafiti

Kamati, S.L.P 20723-00100, Nairobi. Nambari. 2726300/2716450 Ext 44102

Ruhusa imeombwa kutoka kwako kujiandikisha katika utafiti huu wa utafiti wa matibabu. Unapaswa kuelewa kanuni zifuatazo za jumla, ambazo zinatumika kwa washiriki wote katika utafiti wa matibabu

i. Mkataba wako wa kushiriki katika utafiti huu ni kwa hiari

ii. Unaweza kujiondoa kwenye utafiti wakati wowote bila lazima kutoa sababu ya uondoaji wako.
iii. Baada ya kusoma maelezo, tafadhali jisikie kuuliza maswali yoyote ambayo itawawezesha kuelewa wazi asili ya utafiti.

iv. Mahojiano inatarajia kudumu dakika 15

Utangulizi: Jina langu ni Emma Kivuva, mwanafunzi wa uzamili katika Shule ya Famasia katika Chuo Kikuu cha Nairobi. Ninakaribisha mtoto wako kushiriki katika utafiti huu wa na ningependa kukupa maelezo ambayo itakusaidia kuamua ikiwa mtoto wako atashiriki katika utafiti huu. Jisikie huru kunismamisha na kuuliza maswali yoyote kuhusu madhumuni ya utafiti huu, hatari yoyote

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au faida, kinachotokea kama mtoto wako atashiriki na kitu kingine chochote kuhusu utafiti usio wazi. Mara baada ya kujibu maswali kwa kuridhika kwako, unaweza kuamua kusaini jina lako kwen0ye fomu hii ili kukubaliana na mtoto wako kushiriki katika utafiti. Pia ni vizuri kuelewa kwamba uamuzi wako kwa mtoto wako kushiriki katika utafiti huu ni hiari; wako huru kumondoa mtoto wako kutoka kwenye utafiti wakati wowote bila kutoa sababu. Kukataa kushiriki si kwa njia yoyote kuathiri huduma ya mtoto wako ana haki ya Hospitali ya Taifa ya Kenyatta. Nitawapa nakala ya fomu hii kwa rekodi yako

Naweza kuendelea? NDIO/ LA

Utafiti huu umekubaliwa na Hospitali ya Taifa ya Kenyatta -Chuo Kikuu cha Nairobi Itafaki cha Maadili na Utafiti wa Kamati nambari .....

Kusudi la utafiti: Mtafiti aliyeorodheshwa hapo juu anafanya utafiti huu ili kupata matatizo ya dawa katika watoto wachanga. Kusudi la utafiti ni kujua kama dawa wanazochukua zinafanya kazi na ikiwa wamepata au wanapata madhara yoyote kutoka kwa dawa zao. Pia tunataka kuangalia kama kipimo ni sahihi na ikiwa kuna shida nyingine yoyote kuhusiana na madawa yaliyotolewa.

Utaratibu: Ikiwa unakubaliana na mtoto wako kushiriki katika utafiti huu, mambo yafuatayo yatatokea: Utaulizwa na mhojiwaji mwenye ujuzi katika eneo la kibinafsi ambako unasikia kujibu maswali. Ili kupata ruhusa yako kwa mtoto wako kushiriki. Utachukuliwa kupitia mchakato wa kuajiri ambapo utaratibu utakuelezea .Hapo baada ya mtafiti atafuta rekodi za mtoto wako na hati ya dawa zilizowekwa. Mtafiti ataandika sababu ya kuingizwa na hali nyingine yoyote ya ugonjwa, umri wa mtoto. Ikiwa mtafiti anatambua tofauti kati ya dawa anazojadiliana na daktari na muuguzi na mabadiliko sahihi yatafanywa kwa matibabu. Mtafiti anaweza kuchunguza jinsi madawa ya

kulevya atakavyotumiwa ili kuona kama imefanywa kwa usahihi. Matatizo yoyote yaliyotajwa katika faili pia yatashughulikiwa. Hakutakuwa na taratibu za moja kwa moja ambazo zitafanyika kwa mtoto na mtafiti.

Hatari: Hatari moja ya kuwa katika utafiti ni kupoteza faragha. Tutaweka kila kitu unachotuambia kama siri iwezekanavyo. Ili kuhakikisha faragha, jina la mtoto wako halitajazwa kwenye vyombo vya kukusanya data. Kwa ajili ya utafiti huu, mtoto wako atapewa namba ya pekee ambayo nitatumia kumtambulisha kwenye databti iliyohifadhiwa na nenosiri. Kumbukumbu zote zitahifadhiwa chini ya kufungwa na ufunguo na mimi tu nitakayeweza kuitumia. Matokeo kutoka kwa utafiti huu yanaweza kuchapishwa au kupelekwa kwenye mikutano ya kitaaluma lakini jina la mtoto wako halitatumiwa au kuhusishwa na matokeo.

Faida: Mtoto wako anaweza kufaidika. Ikiwa matatizo yoyote yamegunduliwa, daktari mkuu atatambuliwa na hii inaweza kuwa ya manufaa kwa mtoto wako. Taarifa hii ni mchango kwa sayansi na inaweza kusaidia kufanya maamuzi ya baadaye juu ya uchaguzi wa dawa kupitia utambuzi na usimamizi wa matatizo yanayohusiana na dawa ambayo yanaweza kutokea wakati wa mazoezi.

Uhakikisho wa siri: Taarifa zote zitapatikana kutoka kwako zitahifadhiwa kwa usiri. Hakuna jina ambalo litatajwa au kutumika wakati wa utunzaji wa data au katika machapisho yoyote yanayosababisha. Kanuni zitatumiwa badala yake.

Mawasiliano: Ikiwa unahitaji kuwasiliana na mimi, idara yangu ya kitaaluma au Hospitali ya Taifa ya Kenyatta / Chuo Kikuu cha Nairobi Maadili na Kamati ya Utafiti kuhusu utafiti huu tafadhali jisikie kutumia anwani zilizotolewa hapo juu.

TAARIFA YA IDHINI

Mimi ---------- ---------- kutoa ruhusa kwa uchunguzi kuuliza mimi na kutumia habari zilizopatikana katika utafiti wake. Dkt. Emma Kivuva ameelezea asili ya utafiti kwangu

Saini ---------- Tarehe ------ ----------

Ninathibitisha kwamba nimeelezea asili na athari za utafiti.

Saini ---------- Tarehe ----- ----------

Appendix IX: Data Collection Form

Study title: Medication related problems among neonates admitted at KNH.

Principal investigator: Emma Mutheu Kivuva

Signature .....

Date of screening .....

Code.....

Section A: Patient Biodata

Patient unique number .....

Gender Male [ ] Female [ ]

Weight at birth .....

Length of the baby.....

BSA of the baby .....

Weight at recruitment .....

Gestation age:

Classified as LBW [ ]

VLBW [ ]

Preterm [ ]

Full term [ ]

Large for gestation (LGA) [ ]

Reason for Admission to ICU .....

Date of admission .....

Diagnosis .....

Others .....

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Appendix X: Medication History

Drugs	Date		Route	Dose	Duration	Frequency	Calculated dose Mg/kg	Comments (1=too low, 2=acceptable 3=High)	Indication (if not clear, put ND
	Started	Stopped							
Antibiotics									
Benzylpenicillin									
Gentamicin									
Amikican									
Ampicillin									
Ceftriaxone									
Meropenem									
CVS Drugs									
Furosemide									
Hydrochlorothiazide									
Dopamine									
Hematinic & Hormones									

Ranitidine									
Vitamin K									
Dexamethasone									
Antimycotics									
Fluconazole									
Amphotericin B									
Musculoskeletal System									
Indomethiacin									
Pancuronium									
Nervous System									
Midazolam									
Pethidine									
Phenobarbitone									
Respiratory Drugs									
Aminophylline									
Caffeine									

Antiparasitic									
Metronidazole									
Analgesic									
Paracetamol									
Acetylsalicylic									

LAB REPORT SIGN

	Day 1	2	3	4	5	6	7	8	9	10	Comments
INR											
ALT											
Bilirubin											
WBC											
Creatinine											
Na^+											
K^+											
Hb											
Neutropenia											

Appendix XI: Additional Assessments

	DOCUMENTATION ERRORS		
Legibility			
Date written			
Frequency			
Completeness			
Dose			
Name of prescriber			

Appendix XII: Examination of Drugs for the following Excipients

Drug	Present excipient	Not present
Parabens		
Sodium benzoate		
Propylene glycol		
Benzyl alcohol		

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Microbiology report sign

Microbiology	Day 1	2	3	4	5	6	7	8	9	10
MRSA bacteraemia										
Clostridium difficile										
VRE										
Nosocomial pneumonia										
Positive blood culture										

Outcome

Date of admission ……Date of Discharge/ death ……

Outcome

Discharge ……

Transferred to NBU ……..

Death ……

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Appendix XII: Drug Therapy problems Checklist

	Yes	No
No medical indication	[ ]	[ ]
Duplicate therapy	[ ]	[ ]
Nondrug therapy	[ ]	[ ]
Untreated condition	[ ]	[ ]
Dosage form inappropriate	[ ]	[ ]
More effective drug available	[ ]	[ ]
Drug not effective for condition	[ ]	[ ]
Wrong dose	[ ]	[ ]
Frequency inappropriate	[ ]	[ ]
Drug interaction	[ ]	[ ]
Duration inappropriate	[ ]	[ ]
Undesirable effect	[ ]	[ ]
Unsafe drug for patient	[ ]	[ ]
Drug interaction	[ ]	[ ]
Dosage administered rapidly		
Allergic reaction	[ ]	[ ]
Contraindications present	[ ]	[ ]
Incorrect administration	[ ]	[ ]
Directions not understood	[ ]	[ ]
Nurse forgets to administer	[ ]	[ ]
Cannot swallow/administer	[ ]	[ ]

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DILUTION OF INJECTION

Name of injection .....

How was volume of dilution calculated? .....

Who calculated?.....

How was it calculated?.....

Were the calculations filed? .....

Were the calculations counter checked .....

Type of diluent:

Was diluent appropriate?.....

How was the diluted drug obtained?.....

Describe how the dilution was carried out .....

Is there dilution protocol for the drug?.....

DILUTION OF ORAL DRUGS

Name of the oral drug .....

How was volume of dilution calculated? .....

Who calculated?.....

How was it calculated?.....

Were the calculations filed? .....

Were the calculations counter checked .....

Type of diluent:

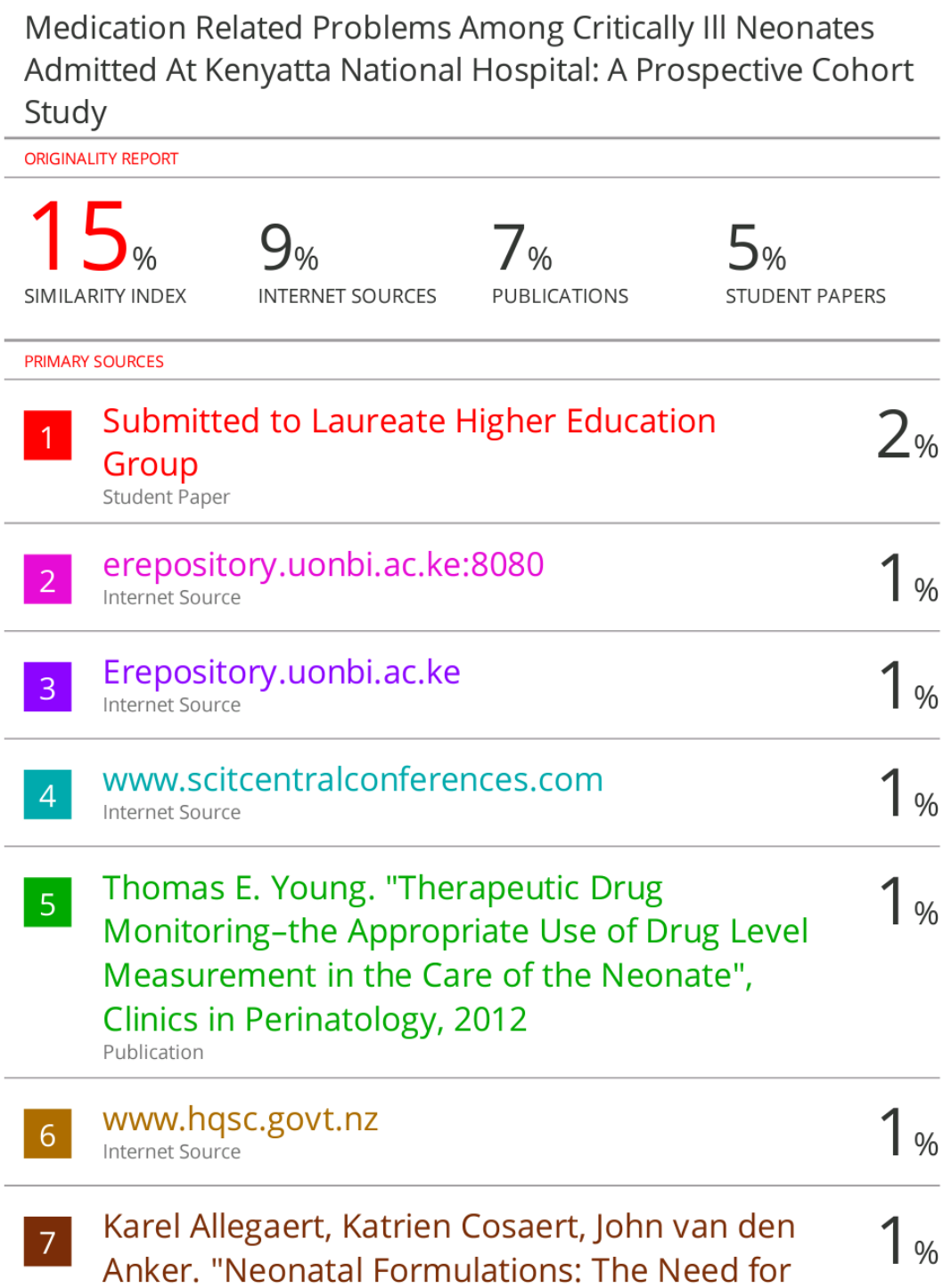
Was diluent appropriate?.....

How was the diluted drug obtained?.....

Describe how the dilution was carried out .....

Is there dilution protocol for the drug?.....

Appendix XIV: Turnitin Report



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