PRESCRIPTION PRACTICE AND POTENTIAL DRUG-TO-DRUG INTERACTIONS IN THE MANAGEMENT OF CHILDHOOD MALARIA AT MBALE REGIONAL REFERRAL HOSPITAL: A CROSS SECTIONAL STUDY

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DECLARATION

I the undersigned, declares that this dissertation is my original work, except where due acknowledgement has been made. I declare that this work has never been submitted to this university or to any other institution of higher learning for funding or for partial fulfilment for any other award.

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SUPERVISOR'S APPROVAL

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ACRONYMS AND ABBREVIATIONS

ADRs: Adverse Drug Reactions

BNF: British National Formulary

CI: Confidence Interval

DDIs: Drug-to-Drug Interactions

EML: Essential Medicine List

MoH: Ministry of Health

MoH: Ministry of Health

mRDT: Malaria Rapid Diagnostic Tool

PACU: Paediatric Acute Care Unit

PAR: Paediatric Admission Record

PPDIs: Potential Drug-Drug Interactions

RDT: Rapid Diagnostic Tool

RRH: Regional Referral Hospital

SSA: Sub Saharan Africa

UCG: Uganda Clinical Guidelines

WHO: World Health Organization

OPERATIONAL DEFINITIONS OF TERMS

Term	Definition
Diagnostic approaches	This was defined as the laboratory tests used to determine what the patient is suffering. For the diagnosis of malaria in this study; blood slide means the use of microscope to detect the presence of the malaria parasite, Malaria RDT means the use of the malaria rapid diagnostic strip for the testing of malaria, while the clinical diagnosis means determining if someone had malaria by using the signs and symptoms without testing using laboratory investigations.
Health worker qualification	This was defined by the level of training and vocational education attained, regulation, and activities and task of jobs for the health worker. It was categorized by cadre as clinical officer, intern Doctor, consultant, medical officers, others (e.g. medical students, nurses) and the unknown as those who did not write their names against the prescription or those whose names could not be traced to qualification.
Potential drug to drug interaction	This was defined as the presence of at least two drugs amongst the prescriptions received during the admission period, which have a potential to interact either pharmacokinetically or pharmacodynamically.
Prescription practices	This was defined as the practices surrounding the prescription of medicines, including the trend of drugs prescribed, what informs the prescription in-terms of laboratory investigations.

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ABSTRACT

Background: Malaria remains a leading cause of mortality among the under-fives in Uganda, and yet health professionals do not adhere to the treatment guidelines and standards. The poor prescription practices have led to irrational drug use; polypharmacy, inappropriate medications, high antibiotic and high injection rate. These contribute to drug interactions, overdose, under dose, poor health outcomes, antimicrobial resistance, drug shortage and increased cost of care. This study was done with an aim of describing prescription practices and potential drug-to-drug interactions in the management of malaria among patients admitted at the paediatric department at Mbale Regional Referral Hospital (Mbale RRH).

Methods: This was a cross sectional retrospective study conducted at the Paediatric Acute Care Unit (PACU) of Mbale RRH from October 2017 to April 2018 on 633 Paediatric admission records of in-patients with malaria diagnosis using consecutively sampling. This data was analysed using the STATA statistical analysis software using univariate and bivariate analysis.

Results: The prevalence of malaria was 45.6% with majority being under five (79.5%) but poor documentation of the anthropometric data. The percentage adherence to laboratory tests for malaria diagnosis was at 86.3% with 13.7% diagnosed for malaria without any documented laboratory test, Blood slide at (66.2) and mRDT was at (47.6%). Drug prescription trends were as follows; artesunate (60.3%), paracetamol (42.8%), ceftriaxone (37.9%), gentamicin (36.5%), and ampicillin (24%). It was noted that 70.1% of the patients without a malaria test performed had antimalarials prescribed which is worrysome. There was also a high antibiotic prescription (65.9%). The prevalence of potential drug-drug interactions was 10.7% with 5.5 % of the prescriptions having one potential drug-drug interaction, 4.3% prescriptions having two potential DDIs, 0.6% prescriptions having three potential DDIs, 0.2% prescriptions having four potential DDIs and 0.2% prescriptions having five potential DDIs.

Conclusion: The percentage contribution of malaria to inpatient admissions is higher and there exist high levels of children with malaria co-infected with other illnesses. There is also non-adherence to the test and treat policy for malaria management with inappropriate prescription of antibiotics.

Key words: Prescription practice, potential drug-drug interactions, malaria, irrational prescription.

CHAPTER 1: INTRODUCTION

1.1 Background

Drug therapy is considered a major component of patient management in formal modern health care settings [1] . Increasing availability of medicines [2], with poor regulatory mechanisms [2], has led to the potential increased misuse of antimicrobials even when there exist guidelines for appropriate prescription. Moreover, inadequate prescription and increased rates of self-medication [3] also increase drug misuse. These practices have contributed to the irrational use of drugs with direct medical consequences such as development of resistance to drugs [2], ineffective treatment and adverse effects [4]. On the socio-economic aspect, there is an increased cost burden on patient care and to society [5].

Malaria remains a major public health challenge in Uganda. Uganda ranks the fourth with the highest number of annual malaria cases globally [6]. The Ministry of Health report indicated that there exists non-adherence to test results. For instance, malaria was being diagnosed clinically and presumptively treated; with some districts recording below 40% malaria cases with laboratory tests done. Eastern Uganda and Northeastern Uganda had the poorest adherence to malaria testing guidelines countrywide [7]. The expected level for the test and treat for malaria is 100%, but it was reported that the average number of malaria cases with a laboratory test in Uganda was only 69% and Mbale district is among the districts with below 90% adherence to the test and treat guidelines for malaria [6]. These test and treat rates for malaria are counterproductive to the efforts on malaria control especially that Malaria is the leading cause of under 5 inpatient mortality in Uganda for the past four years accounting for 26.8% of cases in 2016/17 [6]. Even though inpatient malaria deaths recorded in 2016/17 reduced slightly from those reported in 2015/16 (from 22/100,000 to 20/100,000), it was below the set target of 5/100,000 for 2016/17 [6]. Control of malaria remains a challenge especially with reports of increasing number of malaria cases per 1000 persons, for instance there was a reported increased from 408 in 2015/16 to 433 in 2016/17 [6].

A survey using World Health Organization (WHO) prescription indicators in 1997 showed that irrational use of drugs in the health units in Kabarole was rampant. It indicated that polypharmacy was evident with an average number of drugs of 2.3 per encounter. Inappropriate use of medications was noted with antibiotics being prescribed in 66% some of which had no indication, and injection rate was at 26%. Similarly, another study by Ario and colleagues was done in Tororo district in 1996 in 12 local facilities. It indicated that the average number of drugs per encounter were (2.3), with antibiotics prescription at (48%), while injections prescribed stood at (49%), and an overall conformity to the national standard treatment guidelines of only 50% [8]. These findings are contrary to the desired national standard at the same period of the different indicators in which the average number of drugs per encounter (<1.6), antibiotic rate (<20%), and injection rate (<15%) [9]. Whereas few specific studies have been done on potential drug-to-drug interaction on prescribed medications, one study done at Mbarara Regional Referral Hospital indicated that there was 23% prevalence of potential drug to drug interactions with 10.6% categorised as major [10]. These results portray the same picture as those in other studies done worldwide. For instance, a study conducted in Pakistan in 2014, indicated a level of potential drug-to-drug interaction (at least one potential interacting combination) of 40% (13% major, 17% moderate, and 10% minor) [11]. The same authors also showed a relationship between potential drug-to-drug interaction with age, and polypharmacy [11]. Furthermore, on the Paediatric group, they indicated that a level of potential drug-drug interaction was high (32.1%)[11]. It was also evident that DDIs caused up to 3% of all hospital admissions [12].

It took 30 years before the WHO Essential Medicines List (EML) considered the issue of medicines for children, with the first EML for children being published in 2007 [13]. This shows that drug childcare has lagged the adult model of the drug model of drug care. Only a few studies have been done among children and yet they are considered among the most vulnerable group [14].

1.2 Problem statement

There is poor adherence to national guidelines for prescribing in Uganda [9], even though there exist national guidelines like the Uganda Clinical Guidelines, the latest being 2016 [15] and Uganda National

Standard Treatment Guidelines [16]. The poor implementation of these treatment guidelines is aggravated with lots of medicines available and poor monitoring in the health system [17]. This has led to the increased levels of inappropriate medicine use leading to poor health outcomes and drug related problems [18]. Notably, there is an increase in drug related problems like drug resistance [2] and drug-to-drug interactions [10], which result into poor treatment outcomes and high cost of treatment. While drug resistance and drug-drug interactions are on the increase worldwide [19] and in Uganda [20], there exists little literature concerning the trend of drug-drug interactions in Uganda [10]. Studies done in other countries have indicated an increasing number of drug-drug interactions especially among paediatrics [11], while one done in Uganda, among patients of all ages by Lubinga and team in 2007, in Mbarara Regional Referral Hospital, indicated a prevalence of potential drug-drug interaction of 23% (10.6% categorised as major) [10]. The lack of studies in this subject area to inform evidence based awareness creation and practice guidelines [10] is worsened by the poor prescription practices in the region [8]. Poor prescription practices have been reported in the management of childhood malaria, partly because of the non-adherence to the test and treat guidelines [7], with malaria being diagnosed clinically and presumptively treated which was indicated by average number of malaria cases with a laboratory test of only 69%. Eastern Uganda and Northeastern Uganda had the poorest adherence to malaria testing guidelines countrywide [7] according to a report by the Ministry of Health. Mbale district is among the districts with below 90% adherence to the test and treat guidelines for malaria [6]. This makes the control of malaria remain a challenge especially with reports of increasing number of malaria cases per 1000 persons, for instance there was a reported increased from 408 in 2015/16 to 433 in 2016/17 [6].

1.3 Research questions

The overarching research question for this study is that what is the current prescription practice for the management of childhood malaria and its consequences on DDIs? This main research question is broken down for clarity and to inform research objectives as well as methodology of this study for children admitted with malaria at the Acute Care Unit of Mbale RRH, as follows:

- What are the social demographic characteristics of the children admitted with malaria at acute care unit of Mbale RRH?
- Which diagnostic approaches are used to guide the prescription of drugs for children with malaria admitted at acute care unit of Mbale RRH?
- What is the pattern of drugs prescribed for children admitted with malaria at the acute care unit of Mbale RRH at admission?
- What is the prevalence of potential drug-to-drug interactions among inpatient paediatric prescriptions diagnosed with at admission?
- What are the associated risk factors for potential drug-to-drug interactions in the management of malaria in children?

1.4 Objectives

1.4.1 General objective

This study was aimed at describing prescription practices and potential DDIs in the management of malaria among patients admitted at the paediatric department at Mbale RRH, which could inform practice and contribute to the fight against irrational drug use.

1.4.2 Specific objectives

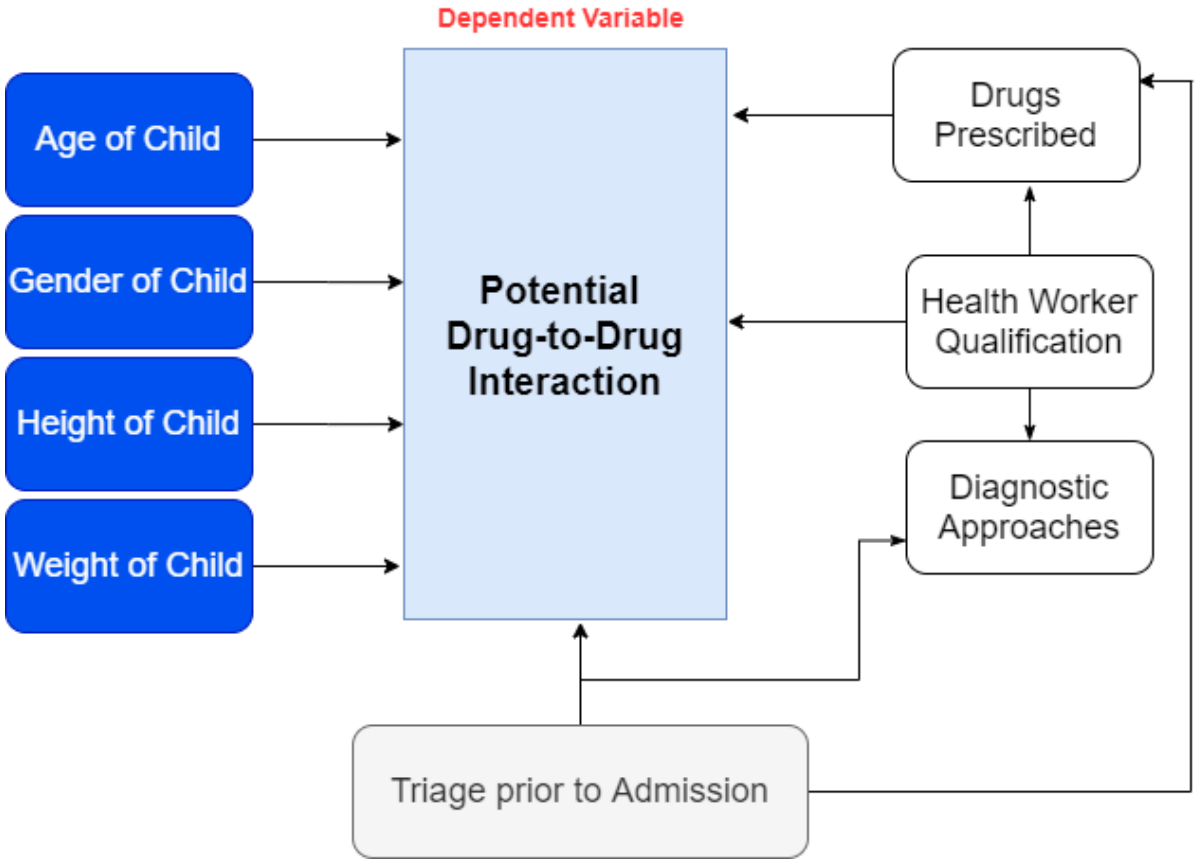
These objectives align the research questions to the methodology used and eventually the reported findings for this study:

1. To describe the social demographic characteristics of the children admitted with malaria at acute care unit of Mbale RRH.
2. To determine the diagnostic approaches that guide the prescription of drugs for children with malaria.
3. To describe the pattern of drug prescriptions for children admitted with malaria at the acute care unit of Mbale RRH at admission.

4. To determine the prevalence of potential drug-to-drug interactions among inpatient paediatric prescriptions diagnosed with at admission.

5. To determine the risk factors for potential drug-to-drug interactions in the management of malaria in children.

1.5 Conceptual framework



Narrative for the conceptual framework

Potential DDIs may result from a number of factors acting individually or in combination. From the previous studies, some of the factors identified include age of the child [21], gender [21], health worker qualification [21], drugs prescribed. Factors that are poorly studied, but have potential contribution to the DDIs may encompass availability, costs and turn-around times for diagnostics and approaches used for malaria and other infections. Besides these, use of anthropometric measurements for dosing and choice of medications especially weight of the child, Mid-Upper arm circumference (MUAC) and

height of the child are poorly documented and used during clinical management of children with malaria. Triage before admission could also be related to the drugs prescribed and diagnostic approaches used for malaria and it could as well contribute to potential drug-drug interactions. Their contributions to DDIs need to be established.

1.6 Justification

Drug to drug interactions (DDIs) seem to be rampant, but are poorly studied especially for the treatment of a common illness like Malaria. In addition, the consequences of poor prescriptions, which are a high risk factor for occurrence of DDIs, are poorly studied in Uganda, especially in rural settings. One such consequence is drug resistance which in the past studies was linked to inappropriate prescription in Uganda [3]. Some studies have been conducted and reported in western Uganda [10], but these data are old. No similar studies have been formally published in Eastern Uganda suggesting that in the picture on DDIs is incomplete in the country. Moreover, where old data exists such as in Western Uganda, there is need for updating such data. Understanding this problem in this current state and era of increased malaria disease burden as well as newer antimalarial drugs and antibiotics will contribute to the reduction of inappropriate use of drugs, drug resistance and reduction of drug related health problems like drug reactions. For the management process, it will reduce on wastage and drug stock outs. Where data on DDIs exists, the consequences are often adverse and lead to poor health outcomes like increased risk for complications and mortality. Given that malaria still contributes to a highest portion of under-five morbidity and mortality in children, evidence from this study will contribute to evidence based pharmacovigilance system to safeguard children from harm due to DDIs.

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