

**BUSITEMA
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**DESCRIPTION OF THE CLINICAL SPECTRUM AND OUTCOMES OF
CHILDHOOD SEVERE MALARIA IN EASTERN UGANDA**

By

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ABSTRACT

Severe malaria remains a major public health problem in Sub-Saharan Africa (SSA). It has a wide spectrum of clinical and laboratory features. Commonly reported are; severe anaemia, respiratory distress, convulsions and impaired consciousness. A number of children experience a febrile illness following a severe malaria episode. However, there are no focused studies on determining the post therapeutic malaria parasitaemia in this area. The overarching aim of this study was to determine the clinical spectrum, post-therapeutic malaria parasitaemia and treatment outcomes of childhood severe malaria in Eastern Uganda.

Methodology: I employed a prospective cohort study for 138 children with severe malaria. I studied a population of children aged from 60 days (2 months) to less than 12 years admitted to Mbale Regional Referral Hospital (MRRH) with confirmed *P.falciparum* severe malaria. Follow up of 93 children was done after 28 days to determine post therapeutic malaria parasitaemia. A structured data collection tool was used to capture participant social demographics, current illness history, features of severe malaria, treatment and follow-up details. Laboratory studies included blood slide for malaria, CBC, lactate, glucose, i-STAT, urine dipstick, and biochemistry at day 0. Additional blood slides were carried out at discharge and at follow up to determine malaria parasitaemia at both time points. Data was analysed using STATA V15.0. The univariate, bivariate, and multivariate analyses were carried out.

Results: I recruited 138 participants starting from 01/OCT/2021 to 01 /Mar/ 2022 and analysed data for 138 on the social demographics. I analysed complete data sets for 137, 93, 115 and 99 children for severe malaria spectrum, post therapeutic parasitaemia, prolonged hospitalisation and mortality respectively.

The overall median age was 4.0 years, the eldest being 10.7 years and the youngest 2 months. A big proportion 84/138 (60.9%) were under 5 years, 76/138 (55.1%) males. Many of the participants were from Budaka district with 41/138 (29.7%), Mbale 34/138 (24.6%) and the least were from Serere, Namisindwa, Manafwa, Kumi and Bugweri districts. A big proportion had prostration 109/137 (79.6%), jaundice 84/137 (61.3%), and severe malaria anaemia 75/137 (54.7%). Post therapeutic malaria parasitaemia was found in 31/93 (33.3%) after day 28 of treatment. Prolonged hospitalisation was in 23/115 (20%) and was highly associated with hypoxaemia OR 14.6 95% CI (2.6, 83.0) $P=0.002$, hyperlactaemia OR 5.3 95% CI (1.6, 17.2) $P=0.005$, acidosis OR 6.1 95% CI (1.4, 25.0) $P\text{-value}=0.002$, impaired consciousness OR CI 4.4 (1.5, 12.9) $p=0.007$.

The overall mortality was 6/137 (4.4%). Case fatality rate was high for severe anaemia. However, impaired consciousness OR 3.0 95% CI (1.1, 4.9) $P=0.002$, respiratory distress OR 16.1 95% CI (2.9, 89.3) $P=0.001$, acidosis OR 13 95% CI (2.5, 172.3) $P=0.002$, cerebral malaria OR 8.9 95% CI (1.5, 52.5)

P= 0.015, hypoglycemia OR 16.8 95% CI (1.5, 189.4) P= 0.022 and renal impairment OR 9.9 95% CI (1.1, 90.0) P= 0.040.

Conclusion: The findings affirm the changing trend in the severe malaria spectrum with increased prevalence in children above 5 years, more cases of prostration, jaundice, haemoglobinuria and less of shock. Post therapeutic parasitaemia in a sizeable proportion of 33.3% could suggest recrudescence, new infection or resistance and calls for further research confirming these possibilities. Prolonged hospitalisation was noted in smaller proportion in upto 20%. Overall mortality appears to have come down to 4.4% compared to a decade ago of 9.5%. This mortality though is still high.

Recommendation: Frequent and regular epidemiological and clinical studies on severe and complicated malaria to inform improved case management and aid reduction in mortality.

Keywords: severe malaria, children, post therapeutic parasitaemia, prolonged hospitalization, mortality

DECLARATION

I, NAMAYANJA CATE do declare that the work presented in this book is a result of my own original work. Where I have used the works of other persons, due acknowledgments have clearly been stated. No part of this work has been submitted for any award, qualification or recognition to any University or institute of higher learning.

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We approve that the research work culminating in this book has been developed under our guidance and supervision.

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DEDICATION

To my husband Robert and children Louis and Rita Alexis

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TABLE OF CONTENTS

ABSTRACT	i
DECLARATION	iii
SUPERVISORS' APPROVAL.....	iv
DEDICATION	v
ACKNOWLEDGEMENTS	vi
LIST OF FIGURES.....	x
LIST OF TABLES.....	x
ACRONYMS AND ABBREVIATIONS	xi
OPERATIONAL DEFINITIONS OF TERMS	xiii
CHAPTER 1: INTRODUCTION	1
1.1 BACKGROUND	1
1.1.2 Outcomes of severe malaria	4
1.1.3 Treatment for severe malaria.....	5
1. 2 STATEMENT OF THE PROBLEM	5
1.3 MAIN OBJECTIVE.....	6
1.3.1 Specific objectives.....	6
1.3.2 Research questions	7
1.3.3 Hypothesis	7
1.4 JUSTIFICATION	7
1.5 THEORETICAL, CONCEPTUAL FRAMEWORK	9
CHAPTER 2: LITERATURE REVIEW	9
2.1 SOCIAL DEMOGRAPHIC CHARACTERISTICS	10
2.2 CLINICAL SPECTRUM OF SEVERE MALARIA	11
2.3 DIAGNOSTICS	19
2.4 POST THERAPEUTIC MALARIA PARASITAEMIA	21

2.5 OUTCOMES OF SEVERE MALARIA.....	24
CHAPTER 3: MATERIALS AND METHODS	26
3.1 STUDY DESIGN.....	26
3.2 STUDY AREA	26
3.2 STUDY POPULATION.....	28
3.3 SAMPLING STRATEGY	28
3.4 SAMPLE SIZE	29
3.5 STUDY VARIABLES	29
3.6 DATA COLLECTION	30
3.7 DATA ENTRY	34
3.8 DATA MANAGEMENT AND CLEANING	34
3.9 DATA ANALYSIS	34
3.10 AUTHORIZATION AND ETHICAL CONSIDERATIONS	35
3.11 DATA DISSEMINATION PLAN.....	35
CHAPTER 4: RESULTS	36
4.1 SOCIAL DEMOGRAPHIC CHARACTERISTICS	36
4.2 CLINICAL SPECTRUM OF SEVERE MALARIA	38
4.3 POST THERAPEUTIC MALARIA PARASITAEMIA.....	43
4.4 OUTCOMES OF SEVERE MALARIA.....	46
CHAPTER 5: DISCUSSION	49
5.1 SOCIAL DEMOGRAPHIC CHARACTERISTICS	49
5.2 CLINICAL SPECTRUM OF SEVERE MALARIA	49
5.3 OUTCOMES OF SEVERE MALARIA.....	53
5.4 STUDY STRENGTHS AND LIMITATIONS.....	55
CHAPTER 6: CONCLUSION AND RECOMMENDATIONS.....	56
6.1 CONCLUSIONS	56

6.2 RECOMMENDATIONS.....	56
REFERENCES	58
APPENDICES.....	64
APPENDIX A-1: ETHICAL APPROVAL	64
APPENDIX A-2: APPROVALS	66
APPENDIX A-3: MAPS.....	69
APPENDIX A-4:PHOTOS.....	70
APPENDIX A- 5: WORK PLAN.....	72
APPENDIX A- 6: CONSENT FORMS	73
APPENDIX A-7: DATA COLLECTION TOOLS	82

LIST OF FIGURES

Figure 1: The epidemiological and research definition of the severe malaria spectrum	3
Figure 2: A graph showing the variation of the different severe malaria phenotypes in relation to transmission intensity	4
Figure 3: Conceptual framework showing the relationship of independent and dependent variables.....	9
Figure 4: Hillman urine colour chart	32
Figure 5: Box plot showing Age of the participants	37
Figure 6: A graph showing percentages of severe malaria phenotypes.....	39
Figure 7: Combination of severe malaria features	42
Figure 8: A bar graph showing the variation of parasitaemia at different time points.....	44

LIST OF TABLES

Table 1: Social Demographic characteristics of participants.....	37
Table 2: Characteristics of participants with parasitaemia at follow up	43
Table 3: Table showing a comparison of the clinical features at admission and at follow up....	45
Table 4: Association of post therapeutic malaria parasitaemia and independent severe malaria manifestations	45
Table 5: Table of General in-hospital Outcome	46
Table 6: Multivariate logistic regression for factors associated with prolonged hospitalisation	46
Table 7: Bivariate logistic regression of severe malaria manifestations in relation to mortality	47
Table 8: Multivariate table for predictors of mortality	48

ACRONYMS AND ABBREVIATIONS

ACT	-	Artemisinin Combination Therapy
AKI	-	Acute Kidney Injury
AOR	-	Adjusted Odds Ratio
BS	-	Blood Slide
BUN	-	Blood Urea Nitrogen
CBC	-	Complete Blood Count
CI	-	Confidence Interval
CM	-	Cerebral Malaria
COR	-	Crude Odds Ratio
CSF	-	Cerebral Spinal Fluid
DHAPP	-	Dihydroartemisinin Piperaquine
DRC	-	Democratic Republic of Congo
EDTA	-	Ethylenediaminetetraacetic acid
EIR	-	Entomological Inoculation Rate
G6PD	-	Glucose -6 Phosphate Dehydrogenase
GMS	-	Greater Mekong Subregion
Hb	-	Haemoglobin
ITN	-	Insecticide Treated Nets
LDH	-	Lactate Dehydrogenase
MCRI	-	Mbale Clinical Research Institute
mRDT	-	Malaria Rapid Diagnostics Test
MRRH	-	Mbale Regional Referral Hospital
MRRH-REC	-	Mbale Regional Referral Hospital Research Ethics Committee
MoH	-	Ministry of Health

MUAC	-	Mid Upper Arm Circumference
NMCP	-	National Malaria Control Programme
OR	-	Odds Ratio
p.	-	Plasmodium
PCR	-	Polymerase Chain Reaction
Pfhrp2	-	Plasmodium falciparum histidine-rich protein 2
Pfhrp3	-	Plasmodium falciparum histidine-rich protein 3
RBC	-	Red Blood Cells
RBS	-	Random Blood Sugar
RDT	-	Rapid Diagnostic Test
SCA	-	Sickle Cell Anaemia
SEA	-	South East Asia
SM	-	Severe Malaria
SMA	-	Severe Malaria Anaemia
SSA	-	Sub Saharan Africa
UDHS	-	Uganda Demographic and Health Survey
Vs	-	Versus
WHO	-	World Health Organization

OPERATIONAL DEFINITIONS OF TERMS

Malaria	A febrile protozoal infection caused by <i>Plasmodium</i> species. The following <i>Plasmodium</i> species have been known to cause disease in humans: <i>P.falciparum</i> , <i>P.vivax</i> , <i>P.ovale</i> , <i>P. malariae</i> , and <i>P.knowlesi</i>
Severe malaria spectrum	Severe malaria is an acute infection with asexual form of <i>P.falciparum</i> accompanied by signs of severe illness and or evidence of vital organ dysfunction. There is a presence or history of fever plus a positive blood film for asexual form of <i>P. falciparum</i> malaria with at least one of the following clinical or laboratory criteria(WHO CRITERIA 2014) • Cerebral malaria; It is defined as the presence of unarousable coma (or Blantyre coma scale of less or equal to 2) • Prostration; generalized weakness so that the person is unable to sit, stand or walk without assistance. • Respiratory distress; defined as Kussmaul's breathing manifesting as deep breathing with signs of increased work of breathing . • spontaneous haemorrhage; recurrent or prolonged from nose gums or venipuncture sites; haematemesis or melaena • multiple convulsions; 2 or more convulsions in 24 hours • impaired consciousness; Blantyre coma score <3 in children • Shock; compensated with capillary refill time $\geq$ 3s or temperature gradient and no hypotension. Decompensation shock is defined as systolic blood pressure <70mmHg in children or < 80mmHg in adults with evidence of impaired perfusion(cool peripheries or prolonged capillary refill) • jaundice ;plasma bilirubin >50um(3mg/dl) • haemoglobinuria; Hillman urine Color Chart $\geq$ 5-10 • hyperparasitaemia; > 10% in highly endemic areas • Acidosis ;venous plasma lactate >5mmol/L • hypoglycaemia ;blood glucose <2.2mmol/L or < 40 mg/dL • severe malaria anaemia ;haemoglobin< 5g/dl • renal failure ;serum creatinine >3mg/dL/ BUN >20 mmol/L (Health and Malaria, 2014b)

Outcomes	Poor outcomes of severe malaria include; prolonged hospitalisation , mortality and neurologic sequelae
Post-therapeutic parasitaemia	Presence of malaria parasites after initial antimalarial treatment, for artemisinin based combination therapy (ACT) a period of 28 days is considered
Hyperpyrexia	Fever with axillary temperature greater than or equal to 39.5° C (Idro and Aloyo, 2004)
Malaria drug Resistance	This is the ability of a malaria parasite strain to survive and/ or to multiply despite the administration and absorption of medicine given in appropriate doses.
Prolonged hospitalisation	Defined as hospital stay for more than 4 days during a severe malaria episode
Malaria recurrence / relapse	This is the recurrence of asexual parasitaemia following treatment only occurs in <i>P.vivax</i> and <i>P.ovale</i> infections deriving from the persisting liver stages .
Recrudescence	It is the recurrence of asexual malaria parasitaemia 28 days after treatment of the infection with the same infection that caused the original illness.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Malaria is the oldest parasitic disease known to man and is still a global health problem. It is a febrile infection caused by *Plasmodium species*. The most prevalent species is *P.falciparum* which accounts for 91.8% of all infections, while *P.vivax*, *P.ovale*, and *P.malariae* combined account for 8.2% (Asua *et al.*, 2017) . However, this depends on the location, population, and innate characteristics. For instance in Uganda, up to 98% of malaria infections are due to *P. falciparum* with an endemicity of over 95% (‘Malaria in Uganda: Statistics & Facts | Severe Malaria Observatory’, 2020). *P.falciparum* has a higher distribution compared to *P.vivax* in Africa and the reverse occurs in South America. *P.malariae* is co-endemic with *P.falciparum* in Sub Saharan Africa (SSA), South America, Indonesia, South East Asia (SEA),and Western Pacific (Kotepui *et al.*, 2020).In South-East Asia, *P.vivax* accounts for 53% of all infections.

In 2020 the global estimate of malaria cases was 241 million which was a rise compared to the 227 million cases in 2019 with *P.falciparum* as the leading cause of infections and poor outcomes(World Health Organization., 2020; WHO, 2021). These cases were in 85 endemic countries majority in the WHO Africa region (WHO, 2021). An additional 69,000 deaths in 2020 occurred due to disruptions in health care delivery during the COVID –19 pandemic leading to the rise of malaria deaths. The most vulnerable group are children below five years accounting for 77% by 2020 , a reduction of 10% from 87% in 2000 over 20 years (WHO, 2021). Out of the 85 countries, only 26 contributed 96% of all cases globally with six countries contributing to approximately 55% of the mortality that is Nigeria (26.8%), Democratic Republic of Congo (12%), Uganda (5.4%), Mozambique (4.2%), Angola (3.4%), and Burkinafaso (3.4%). This trend has been partly due to the effect on service delivery of the COVID-19 pandemic. Uganda has the 3rd highest malaria morbidity and the 8th highest malaria related mortality. WHO African region contributed 96% (602,000) of all malaria deaths with 80% being children below 5 years (WHO, 2021).

Generally, Uganda is a malaria high burden country. The Eastern Uganda perennial transmission is high with greater than 100 bites per person per year (Olupot-Olupot, 2014). Several factors are responsible for malaria distribution in the community including the intensity, seasonal duration of

malaria transmission, age, and geographical location. The burden, spectrum, and age distribution of severe malaria are also contingent upon these factors(Murray .et al, 2012). *P. falciparum* accounts for 98% of all malaria infections and the rest including *P. vivax* and *P.ovale* do not exceed 2% of all cases in Uganda. There are two malaria transmissions experienced in Uganda; the stable, perennial that exists in 90-95%, and the low, stable with epidemic potential in 5-10% of the country. The transmission peak aligns with the two annual rainy seasons from March to May and from September to November (‘Malaria in Uganda: Statistics & Facts | Severe Malaria Observatory’, 2020). This implies that the onset of rains results in a surge in hospital admissions especially due to malaria(Maitland, 2016).

Severe malaria is a life-threatening condition affecting multiple systems manifesting with different clinical and laboratory features. It is highly associated with mortality if not promptly and effectively managed. The distribution of its syndromes varies with transmission intensities and immunity patterns of a given population Mankhambo *et al.*, 2010 ; Olupot *et al.*, 2020). The majority of the severe malaria cases are predominantly due to *P.falciparum* worldwide endemic in over 85 countries with the majority being in Sub-Saharan Africa (SSA) (WHO, 2021). On average the national prevalence of malaria is 9% , West Nile with a prevalence of 22%, Karamoja 34%(UNICEF, 2020).

The first line treatment for complicated malaria in Uganda is artesunate adopted in 2011. However, alternatives such as quinine are also used and artemether. Additional supportive care with. Pre-referral treatment with rectal artesunate has been where optimal care for severe malaria cannot be availed (WHO, 2016). Due to irregularities in supply, there are stock outs of malaria diagnostic and supportive care commodities like blood transfusion , malaria rapid diagnostic test (RDT) and glucose sticks that put a challenge to management of severe malaria (Idro and Aloyo, 2005; WHO, 2016). COVID -19 has increased the case incidence of malaria from 56 per 1000 population at risk in 2019 to 59 in 2020.

Presence of post-therapeutic malaria parasitaemia after 28 days from initial presentation, could suggest treatment failure, new infection, resistance or recrudescence. Several factors are associated with treatment failure: including incorrect dosage, poor drug quality, poor drug compliance, drug interactions, and resistance (WHO, 2014).

1.1.1 Clinical spectrum

Severe malaria is an acute infection with asexual form of *P. falciparum* accompanied by signs of severe illness and or evidence of vital organ dysfunction. There is a presence or history of fever plus a positive blood film for blood schizonts of *P. falciparum* malaria with at least one of the following clinical or laboratory criteria (**Figure 1**). The outcomes differ depending on the clinical features. The clinical features include one or more of impaired consciousness, cerebral malaria(coma), respiratory distress, repeated convulsions, prostration jaundice, haemoglobinuria, significant bleeding and shock while the laboratory includes: hypoglycaemia, acidosis, severe malarial anaemia (SMA), renal impairment, hyperparasitaemia (Health and Malaria, 2014a)(Health and Malaria, 2014b).

Figure 1: The epidemiological and research definition of the severe malaria spectrum

Table 4 Epidemiological and research definition of severe falciparum malaria

For epidemiological and research purposes, severe malaria is defined as one or more of the following, occurring in the absence of an identified alternative cause, and in the presence of *P. falciparum* asexual parasitaemia:

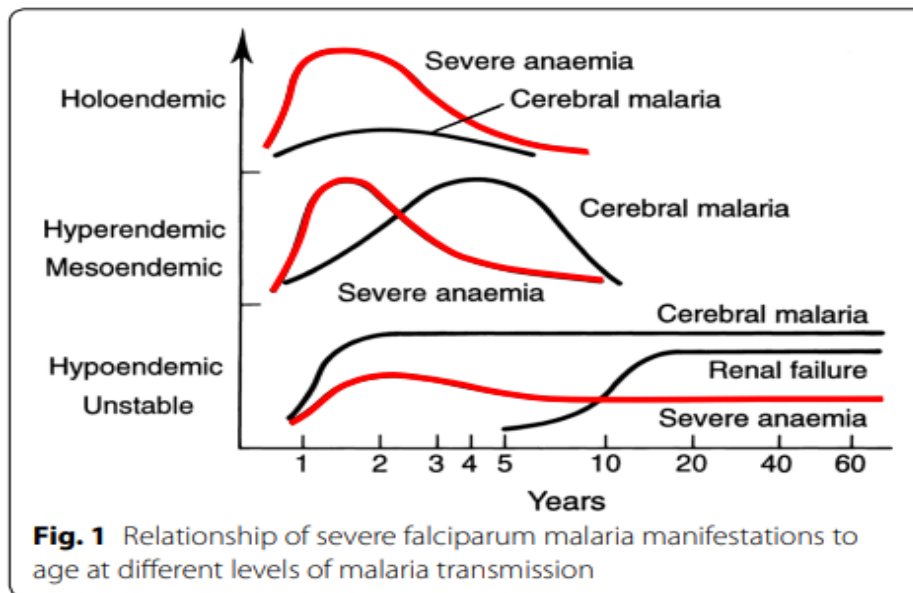
Impaired consciousness:	A Glasgow Coma Score <11 in adults or a Blantyre coma score <3 in children
Acidosis:	A base deficit of >8 meq/l or, if unavailable, a plasma bicarbonate of <15 mM or venous plasma lactate >5 mM. Severe acidosis manifests clinically as respiratory distress – rapid, deep and laboured breathing
Hypoglycaemia:	Blood or plasma glucose <2.2 mM (<40 mg/dl)
Severe malarial anaemia:	A haemoglobin concentration <5 g/dl or a haematocrit of <15% in children <12 years of age (<7 g/dl and <20%, respectively, in adults) together with a parasite count >10 000/μl
Renal impairment (acute kidney injury):	Plasma or serum creatinine >265 μM (3 mg/dl) or blood urea >20 mM
Jaundice:	Plasma or serum bilirubin >50 μM (3 mg/dl) together with a parasite count >100 000/μl
Pulmonary oedema:	Radiologically confirmed, or oxygen saturation <92% on room air with a respiratory rate >30/min, often with chest indrawing and crepitations on auscultation
Significant bleeding:	Including recurrent or prolonged bleeding from nose gums or venepuncture sites; haematemesis or melaena
Shock:	Compensated shock is defined as capillary refill ≥3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mm Hg in children or <80 mm Hg in adults with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitaemia:	<i>P. falciparum</i> parasitaemia >10%

Source 2014 WHO. Tropical Medicine and International Health (Health and Malaria, 2014b)

Descriptions of the clinical spectrum of severe malaria reported are dependent on the geographical location, age, demographics, temporal relationships, and changes in community-level patterns (Purohit *et al.*, 2016; Mpimbaza *et al.*, 2020; WHO, 2021). Currently, data from most settings are over 10 years old and therefore old. There is an urgent need for updating these data, especially from sites that have not previously reported data, for those sites that have reported data there is a need for recent trends, and for sites with incomplete data or descriptions, complementary data is

required. There is directly proportional increase in severe disease with an increase in transmission intensity (WHO, 2021). The relationship between levels of transmission and the possible severe malaria phenotype is depicted in **Figure 2**.

Figure 2: A graph showing the variation of the different severe malaria phenotypes in relation to transmission intensity



source: *anaemia and malaria 2018*(White, 2018)

1.1.2 Outcomes of severe malaria

The outcomes of severe malaria depend on the nature and degree of vital organ involvement, which differs in both children and adults. For example, renal impairment is highly reported among children due to acute tubular necrosis having less mortality as compared to renal impairment in adults (Seidlein *et al.*, 2012). Other outcomes are mortality, disabilities and treatment failure that may be clinical or parasitological. Mortality as an outcome could be during admission or post-discharge in addition to readmission. In the recent past, studies carried show that severe malaria syndromes like acidosis and symptomatic anaemia are highly associated with poor outcomes including mortality (Cserti-gazdewich *et al.*, 2013; Kwambai *et al.*, 2020). Prolonged hospitalisation is another outcome that has been reported in a few studies (Paasi *et al.*, 2022). Neurological sequelae are associated with mainly cerebral malaria (Opoka *et al.*, 2017).

1.1.3 Treatment for severe malaria

In Uganda, artemisinin combination therapies (ACTs) remain efficacious in treatment of both complicated and uncomplicated malaria. For severe malaria, artesunate is administered intravenously. Children weighing less than 20kg receive 3mg/kg body weight and those above 20kg receive 2.4mg/kg body weight. This treatment regimen is given eight (8) hourly in the first 24 hours and thereafter once daily until the patient can tolerate oral medications. This ensures an equivalent drug exposure. It has an added advantage of rapid onset of action accompanied by faster rate of parasite clearance including ring stages that were poorly cleared by quinine. There are now reports of possible failure of artesunate in the treatment of severe malaria in Uganda.

1. 2 STATEMENT OF THE PROBLEM

Malaria is still a global Health problem with an estimated number of 229 million cases of malaria in 2019 worldwide. In 2018, 93% (213 million cases) were in the African region alone (Alegana, Okiro and Snow, 2020; World Health Organization., 2020). Majority of the earlier studies have reported the most vulnerable to severe malaria being children below the age of five years (Kalinga *et al.*, 2012; Olupot-Olupot, 2014). Most of the studies are dependent on location, age, demographics, temporal relationships, and changes in community-level patterns (Purohit *et al.*, 2016; Mpimbaza *et al.*, 2020; WHO, 2021). Many studies have described severe malaria in the under-five. There is a possibility that the age affected is increasingly getting older.

Numerous studies have been carried out on clinical spectrum of severe malaria worldwide and in Africa (Dzeing-ella *et al.*, 2005; Idro and Aloyo, 2005; Gyapong *et al.*, 2009; Kalinga *et al.*, 2012; Ogah *et al.*, 2013; Olupot-Olupot, 2014; Purohit *et al.*, 2016). Many of these studies were carried out before the artemisinin era. Majority of these were carried out almost a decade ago hence, data available is old. The most recent study (Purohit *et al.*, 2016) was carried out in a slightly older population ages >15 years and not children. The trends of disease could have changed with the advances in severe malaria case management. There is a need to generate data in Eastern Uganda in the artemisinin era to update the existing data on severe malaria clinical spectrum. Lastly, the trends of severe malaria spectrum differ from time to time and place to place.

Many studies have reported the existence of malaria parasitaemia after 28 days of initial treatment (Mugittu *et al.*, 2007; Olliaro *et al.*, 2008;). Other studies carried out in this context were focused

on recrudescence (Cattamanchi *et al.*, 2003; Byakika-Kibwika *et al.*, 2017, 2019; Saito *et al.*, 2019; Mahamar *et al.*, 2021; S Landre *et al.*, 2021). Post therapeutic malaria parasitaemia could suggest a new infection, resistance or recrudescence. However, there is no baseline data on post therapeutic malaria parasitaemia in Eastern Uganda hence need to investigate.

Eastern Uganda had a prevalence of malaria as follows; Busoga 53.1/498, Bukedi 27.1/333, Teso 19.8/236 in the 2016 Uganda Demographic Health Survey (Survey and Indicators, 2016). Malaria has negatively affected Uganda's economy according to the national malaria control program. It leads to loss of workdays due to sickness, decreased productivity and among the children decreased school attendance. Severe malaria impairs the learning and cognitive ability of children by as much as 60% hence affecting their academic performance (Batwala, Magnussen and Nuwaha, 2010). The overall mortality rate in the quarter of 01/ Apr/2020- 30 / Jun/2020 increased to 3/100,000. Mbale was among the districts that presented with the highest mortality per 100,000 at 7.3/100,000 (Bulletin, 2020).

Many studies have been carried out on outcomes of severe malaria (Seidlein *et al.*, 2012; Cserti-gazdewich *et al.*, 2013; Manning *et al.*, 2014; Saravu, Rishikesh and Kamath, 2014; Patel, Dunican and Cunningham, 2020). Some of these studies in Uganda were in Central region (Seidlein *et al.*, 2012; Cserti-gazdewich *et al.*, 2013). The studies were conducted on different populations; children <15 years (Seidlein *et al.*, 2012), 6 months-12 years (Cserti-gazdewich *et al.*, 2013), >18 years (Saravu, Rishikesh and Kamath, 2014). There is no published study in Eastern Uganda on outcomes of severe malaria in general. Therefore there is need to determine post treatment outcomes in Eastern Uganda among young children with severe malaria.

1.3 MAIN OBJECTIVE

The overarching aim of this study is to describe the clinical spectrum, post therapeutic parasitaemia and outcomes of childhood severe malaria in Eastern Uganda.

1.3.1 Specific objectives

1. To describe the social demographic characteristics of children with severe malaria admitted in MRRH.
2. To describe the clinical spectrum of severe malaria among children in Eastern Uganda.

3. To describe the 28-day post therapeutic malaria parasitaemia among children treated for severe malaria.
4. To describe outcomes of severe malaria among children in Eastern Uganda.

1.3.2 Research questions

1. What are the social demographic characteristics of children with severe malaria admitted in MRRH?
2. What is the clinical spectrum of severe malaria among children in Eastern Uganda?
3. What is the 28-day post therapeutic malaria parasitaemia among children with severe malaria 28 days post treatment?
4. What are the outcomes of severe malaria among children in Eastern Uganda?

1.3.3 Hypothesis

The working hypothesis for this study is; **the epidemiological transition of malaria has changed the clinical spectrum of severe malaria, post therapeutic malaria parasitaemia and outcomes.**

1.4 JUSTIFICATION

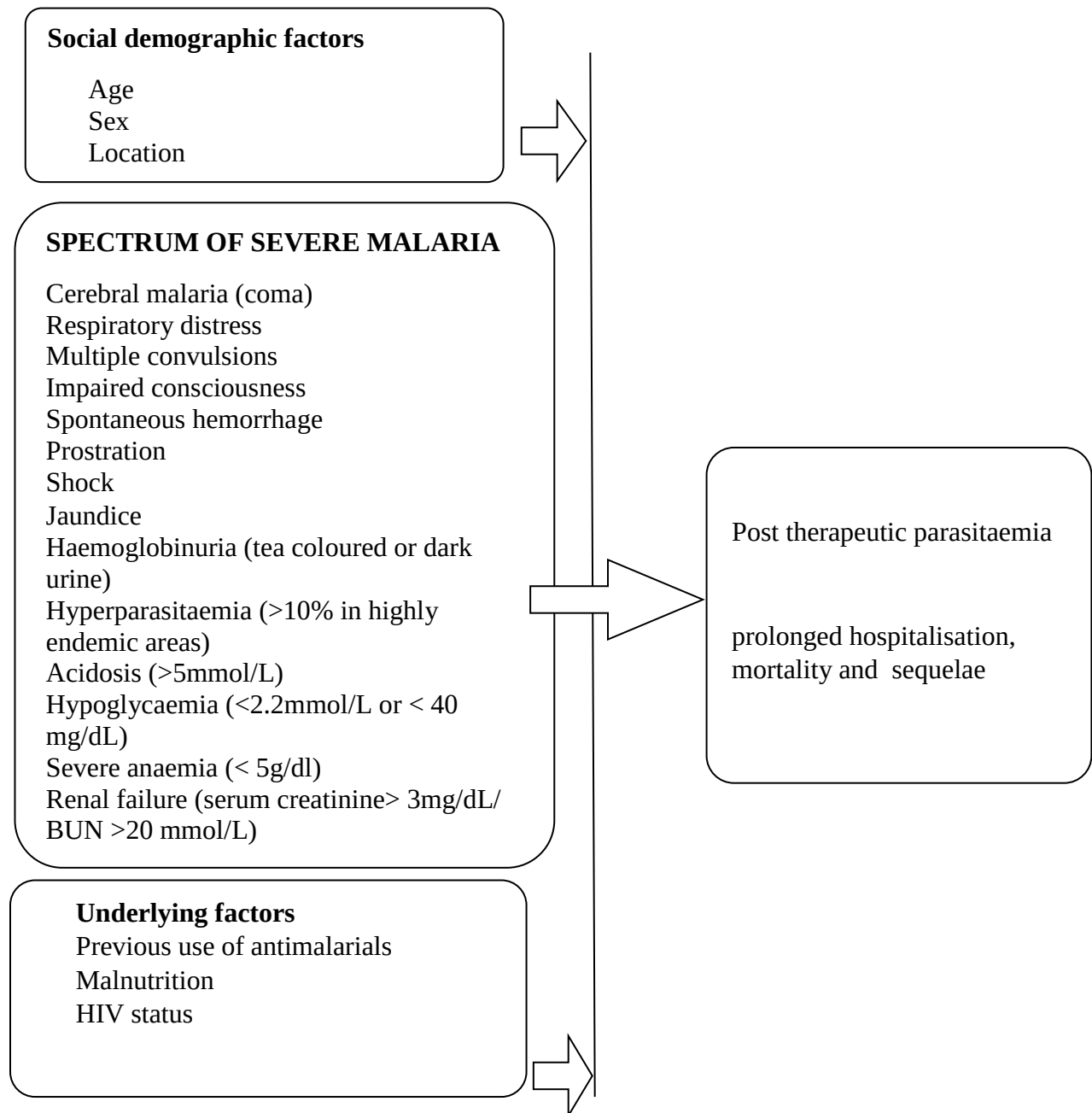
Severe malaria remains a problem of public health importance in East Africa, especially in Uganda. It accounts for up to 10% of total paediatric admissions (Olupot-Olupot, 2014). In Eastern Africa, malaria is endemic and remains a common cause of in-hospital admissions and mortality in children below 12 years with poor outcomes among the under 5 (WHO, 2021). Malaria is endemic in approximately 95% of Uganda, affecting over 90% of the population. Uganda as the third, contributed 5% to the malaria global mortality in 2020 (WHO, 2021). WHO recommends documentation of the severe malaria clinical spectrum from time to time and place to place hence the need to update. Studies on post therapeutic malaria parasitaemia have been carried out in different localities but none in Mbale Regional Referral Hospital (MRRH). This justified the need to determine the post therapeutic malaria parasitaemia. In addition, this type of malaria parasitaemia increases the burden to the community. This has an impact on both individual health and malaria transmission in the community. This also comes with an economic impact due to wastage of funds on the management of the disease, which in most cases may result in a negative

effect especially if it is severe malaria in children. Malaria episodes among children in Africa range from 0 to 40 per cent according to research (Lawpoolsri *et al.*, 2019).

This study focused on current patterns of the social demographics, clinical spectrum, post therapeutic malaria parasitaemia and outcomes of severe malaria.

1.5 THEORETICAL, CONCEPTUAL FRAMEWORK

Figure 3: Conceptual framework showing the relationship of independent and dependent variables



The conceptual frame work in Figure 3 implies that the interaction between independent factors that is social demographic characteristics , underlying factors could contributes to the clinical spectrum and the three would impact the outcome of the participants.

CHAPTER 2: LITERATURE REVIEW

Malaria illness due to *P. falciparum* is the most predominant accounting for majority of severe and complicated malaria. Life threatening malaria due to *P. falciparum* dominates the under -five. This is true even for individuals living in stable transmission areas in Africa (Alegana, Okiro and Snow, 2020; WHO, 2021). Uganda is one of the African countries with the highest malaria morbidity and mortality worldwide (WHO, 2021). *P.falciparum* has a unique pathophysiology and drastic growth of parasite biomass every 48hours.

The pathophysiology involves the deformability of parasitized red blood cells, sequestration, rosetting, and cytoadherence. This occurs in the microcirculation leading to endothelial dysfunction hence manifestations relate to the affected system. Severe falciparum malaria is highly associated with mortality. There are different factors influencing the development of the severe illness and successful management is challenging in a resource-limited setting (Health and Malaria, 2014; Maitland, 2016). The factors include;

- host factors; undernutrition, age <5 years and presence of comorbid illness like HIV
- underlying factors; Health-seeking behavior, environmental aspects,
- health system factors; delayed diagnosis and adequate treatment (Roberts and Matthews, 2016; Access, 2017).

The most affected groups of persons are children under five, pregnant women, people in low transmission areas, children with Sickle cell anaemia (SCA) and the immune suppressed.

2.1 SOCIAL DEMOGRAPHIC CHARACTERISTICS

Literature from earlier studies shows that severe malaria mainly occurs in children less than 5 years. This has been identified by multiple studies in Central Africa 92.3% (Dzeing-ella *et al.*, 2005), East Africa 86% by Kalinga(Kalinga *et al.*, 2012), and West Africa (Dzeing-ella *et al.*, 2005; Kotepui *et al.*, 2020). Several studies have reported severe malaria to occur slightly more among males and less in females with average age of participants as low as 18 months as reported by Olupot-Olupot (Olupot-Olupot, 2014). Rural settings are specifically linked to higher mortality compared to urban settings, while a low social economic status is associated with more adverse outcomes of Malaria (Ricci, 2012). Peri-urban areas with low social status and slums contribute to

a high morbidity among children. The fatality rate has been found to high in the group below 5 years compared to those above (Olupot-Olupot, 2014).

2.2 CLINICAL SPECTRUM OF SEVERE MALARIA

The clinical presentation of severe malaria in children is non-specific. However, it has clinical and laboratory defining features. The clinical signs include pulmonary edema, prostration, shock, spontaneous hemorrhage, multiple convulsions, impaired consciousness, jaundice, and passing bloody urine (haemoglobinuria). Laboratory defining features include hyperparasitaemia (greater than 10% in highly endemic areas), acidosis, hypoglycaemia ($< 2.2\text{mmol/L}$ or $< 40\text{ mg/dL}$), acidosis ($>5\text{mol/L}$), severe anaemia (less than 5g/dl), renal failure (serum creatinine $>3\text{mg/dL}$ /BUN $>20\text{ mmol/L}$) (WHO, 2015; Olupot-Olupot *et al.*, 2017; Olupot *et al.*, 2020). Earlier studies have described three common features including respiratory distress, cerebral malaria, and severe anaemia. These were found to be highly related to mortality (Olupot-Olupot, 2014; Kotepui *et al.*, 2020). In Eastern Uganda hemoglobinuria, jaundice, and renal involvement were described (Olupot *et al.*, 2020). Respiratory distress was found to be the common feature in Eastern Uganda among 83.7% (Olupot-Olupot, 2014) and Gyapong found 31% in Central Africa (Gyapong *et al.*, 2009).

In Central Africa, renal failure and bleeding were uncommon and no case of shock recorded. This was different from a study carried out in Uganda, where shock was found in 62% of the studied population (Olupot-Olupot, 2014). On the other hand, studies carried out in East Africa and Central reported hyperlactataemia as a common feature of severe malaria (Gyapong *et al.*, 2009; Olupot-Olupot, 2014). Several studies reported significant proportions of severe anaemia ; West Africa 41% (Ajetunmobi *et al.*, 2012), Central Africa 67.8% (Dzeing-ella *et al.*, 2005) and East Africa 51.5% (Olupot-Olupot *et al.*, 2017). Eastern Uganda recorded cases of hemoglobinuria in the FEAST trail in approximately 14.0% of participants. This could be rising in this population (Olupot-Olupot *et al.*, 2017). This was known as black water fever in the era of quinine. Children who suffer from this complication are highly susceptible to multiple readmissions and blood transfusions (Olupot-Olupot *et al.*, 2017; Connon *et al.*, 2021; Paasi *et al.*, 2022).

In summary, several studies have been carried out on the clinical spectrum of malaria. Some in Uganda with unique findings of dark urine (haemoglobinuria) by Olupot *et al.*, 2020. Other studies

elsewhere in Africa more than a decade ago (Gyapong *et al.*, 2009). The trends of the spectrum could have changed hence the need to find out the current trends of severe malaria clinical presentation among children in the Eastern Region.

2.2.1 Severe malaria anaemia (SMA)

SMA is a common feature among children. It is defined by haemoglobin concentration less than 5g/dl or haematocrit less than 15% in children less than 12 years and haemoglobin of less than 7 g/dl or haematocrit <20% in adults. It is common in children aged below 5 years of age (Health and Malaria, 2014a) with a prevalence of 25.5% (Olupot *et al.*, 2020) and 60% in Western Africa (Dzeing-ella *et al.*, 2005). It is associated with high mortality and remains a major complication in Sub-Saharan Africa (SSA) (Connon *et al.*, 2021). It is the leading presentation of severe malaria in children in high transmission areas of *P.falciparum*. Infants have the highest risk in high transmission areas while the risk peaks at 24 months in areas of moderate and low transmission (Health and Malaria, 2014a).

Several mechanisms may result in severe anaemia including hemolysis of parasitized RBCs and non-parasitized RBCs especially for acute cases, phagocytosis of parasitized RBC in the spleen, disruption of the red cell membrane when schizonts are released (Olupot-Olupot P1, 2013 ; Mankhambo *et al.*, 2010), interaction of glycosylphosphatidylinositol toxin with the non-parasitized red blood cell membrane (Purohit *et al.*, 2016). Chronic anaemia occurs in high transmission areas among those with a heavy hookworm infestation. It also occurs due to dyserythropoiesis following bone marrow dysfunction (Handbook, 2012).

Severe malaria anaemia (SMA) is associated with haemoglobinopathies and inherited red cell abnormalities including sickle cell anaemia (SCA) and Glucose 6 phosphate deficiency (G6PD). Sickle cell anaemia is common in Sub-Saharan Africa (SSA) with a birth prevalence of 1-2% and it is highly associated with SMA (Mankhambo *et al.*, 2010). The diagnosis is made when haemoglobin is <5g/dl in presence of *P.falciparum* parasite count >10000/IL (Health and Malaria, 2014b). Children with SMA may have symptoms of tachycardia and dyspnea. It may also contribute to confusion and restlessness due to acidosis (Handbook, 2012).

The treatment specifically involves adequate treatment with antimalarials and blood transfusion. The children are transfused 10ml/kg of packed cells or 20ml/kg of body weight over 4 hours. The

administration depends on the clinical picture where the haemoglobin levels are between 4-6g/dl in presence of respiratory distress, impaired consciousness or shock. In low transmission areas, blood transfusion is carried out for haemoglobin <7g/dl (Health and Malaria, 2014 ; Mankhambo *et al.*, 2010; Handbook, 2012).The outcome is fatal in the first 12 hours of admission, especially in Africa. This is true in areas with scarcity of blood and its products plus logistics (Olupot-Olupot, 2014).

2.2.2 Cerebral malaria

This is a common feature often reported. It is defined as the presence of unarousable coma (or Blantyre coma scale of less or equal to 2 (Health and Malaria, 2014b),in a patient with *P.falciparum* malaria in absence of other causes. This is characterised by a coma at least 1 hour after termination of a seizure in presence of asexual forms of *P.falciparum* (WHO, 2015). The prevalence in an earlier Ugandan study was 7.2% (Idro and Aloyo, 2004) and 24% in Gabon (Dzeing-ella *et al.*, 2005).It is commonly found to occur in older children with a median age of 2.5 years (Olupot-Olupot, 2014). Decreased conscious level may result from metabolic and haemodynamic complications including severe anaemia, metabolic acidosis and hypoglycaemia (Mankhambo *et al.*, 2010). Cerebral malaria results from parasite sequestration and cytoadherence of parasitized RBC in the brain microvasculature. This leads to local endothelial injury, apoptosis, inflammation, blood brain barrier (BBB) dysfunction, and increased intracranial pressure (Idro *et al.*, 2011). It normally presents in conjunction with other complications including; severe malaria anaemia, metabolic acidosis, seizures, electrolytes imbalance, hyperpyrexia, or hypoglycaemia. Coma may occur due to prolonged post ictal state, covert status epilepticus, and metabolic derangement or as a primary neurological syndrome (Idro *et al.*, 2011 ; Olupot-Olupot, 2014).

Cerebral malaria is an emergency, managed with antimalarial and relevant supportive therapy. Other supportive care involves treatment of systemic abnormalities like any organ failure plus convulsions. It also involves the treatment of metabolic abnormalities including hypoglycaemia, hypovolemia, acidosis, hyperpyrexia and severe anaemia (Health and Malaria, 2014 ; Idro *et al.*, 2011).The outcome is fatal without treatment. Failure to correct severe metabolic derangements results in prolonged exposure that leads to neuronal dysfunction. Case fatality in cerebral malaria was reported at 15% and sequelae in 9% by Molyneux (Molyneux *et al.*, 1989). Several

symptoms are associated with adverse outcomes including; coma, absence of corneal reflexes, age under 3, sign of dehydration, convulsions at the time of admission (Molyneux *et al.*, 1989).

2.2.3 Recurrent convulsions/ multiple convulsions

Defined as an occurrence of more than two generalized convulsions in the last 24 hours (WHO, 2015). The prevalence in earlier studies includes ; Aloyo of 13.3% (Idro and Aloyo, 2004), in Gabon of 39.2% (Dzeing-ella *et al.*, 2005) and in Tanzania of 50.9% by Kalinga (Kalinga *et al.*, 2012). The cause of the convulsions is multifactorial including hypoglycaemia, hyperpyrexia, cerebral malaria, and metabolic abnormalities(Health and Malaria, 2014a).The presentation may be subtle with little or no limb movement, repetitive eye movements, twitching of digits, abnormal respiration and increased salivation. The management involves use of antimalarials and anticonvulsants. Supportive care includes treating reversible causes such as hypoglycaemia and hyperpyrexia (Mankhambo *et al.*, 2010; Health and Malaria, 2014).

2.2.4 Respiratory distress

This is one of the common features among children with severe malaria. It is defined as deep breathing known as Kussmaul's breathing. It normally occurs as a compensatory mechanism for metabolic acidosis. It is a common feature in children as compared to adults who have pulmonary edema instead with a prevalence of 83.7% in an earlier study (Olupot *et al.*, 2020).It majorly manifests as deep breathing with signs of increased work of breathing such as nasal flaring, head nodding, intercostal recession. It is highly associated with severe anaemia, cerebral malaria, hyperlactatemia and shock (Health and Malaria, 2014a; Olupot-Olupot, 2014; Patel, Dunican and Cunningham, 2020).In case of available resources, blood gases are measured with continuous pulse oximetry. Management involves correction of reversible causes of acidosis like anaemia and dehydration. Rehydration or blood transfusion are carried out with caution to avoid precipitating pulmonary edema. It has an increased risk of fatal outcome(Mankhambo *et al.*, 2010; Olupot-Olupot, 2014).

2.2.5 Hypoglycaemia

Hypoglycaemia is a common complication of severe malaria among children. It is a random blood glucose level of $< 2.2\text{mmol/L}$ ($< 40\text{ mg/dL}$) (Health and Malaria, 2014b). This was reported in a small portion of 3.6% by Olupot-Olupot (Olupot *et al.*, 2020) and high prevalence by Kunuanunua of 62.2% in the Republic of Congo (Kunuanunua *et al.*, 2015). Common in children under three years of age, those with evidence of undernutrition, metabolic acidosis, coma or impaired perfusion (Handbook, 2012). Hypoglycaemia is highly suspected in children whose conscious level suddenly deteriorates. Several mechanisms contribute to hypoglycaemia. These include failure of hepatic gluconeogenesis as the principal mechanism, parasite consumption of glucose, increased metabolic demand in these patients and increased anaerobic glycolysis (Mankhambo *et al.*, 2010). In addition, there is reduced intake and previous treatment with quinine (Olupot-Olupot, 2014). Diagnosis is by using a glucometer, as clinical presentation is non-specific. However, it is suspected in all children with convulsions or hyperparasitaemia (Olupot-Olupot, 2014; Handbook, 2012). Primary hypoglycaemia is associated with coma. The management involves the administration of 5ml/kg of 10% dextrose immediately. It increases the risk of mortality (Handbook, 2012).

2.2.6 Acidosis

Acidosis is one of the laboratory features. It is defined as plasma bicarbonate level of less than 15mmol/L or venous plasma lactate greater than 5mmol/L or an abnormal base deficit $>8\text{ mmol/L}$ (Health and Malaria, 2014b; WHO, 2015). Acidosis results from tissue hypoxia exacerbated by hypovolemia, anaemia and hypotension. It is augmented by renal or hepatic dysfunction and parasite lactate production (Mankhambo *et al.*, 2010). The presence of acidosis suggests a failure of hyperventilation to compensate for the metabolic acidosis (Handbook, 2012). Severe acidosis clinically manifesting as respiratory distress (rapid, deep and laboured breathing) (Olupot-Olupot, 2014). The management involves the use of antimalarial drugs and supportive care. Blood transfusion is carried out in case of severe anaemia and fluid infusion in those with dehydration (Mankhambo *et al.*, 2010; Handbook, 2012). It is associated with poor outcomes in affected individuals (Olupot-Olupot, 2014).

2.2.7 Hyperparasitaemia

Hyperparasitaemia is a feature of severe malaria defined in relation to endemicity. In areas of stable endemicity, a parasitaemia $>10\%$ without the other signs of severity described above indicates severe malaria (Health and Malaria, 2014b). In non-immune or low-moderate endemicity, peripheral parasitaemia $\geq 4\%$ is considered hyperparasitaemia and may be suggestive of sequestered biomass (Sowunmi *et al.*, 2011; Health and Malaria, 2014b). The prevalence of hyperparasitaemia was 62.4% by Olupot-Olupot (Olupot *et al.*, 2020) and 6.1% by Kalinga (Kalinga *et al.*, 2012). Hyperparasitaemia, confirmed with a count on blood slide as the gold standard. The relationship of parasitaemia to the severity of illness differs in different populations and age groups. A delay in parasite clearance by antimalarials leads to increasing parasitaemia. It highly poses a risk of recrudescence following treatment (Sowunmi *et al.*, 2011).

2.2.8 Prostration

Prostration is defined as a generalised weakness so that the person is unable to sit, stand or walk without assistance and failure to breastfeed in infants (WHO, 2015). It also includes mild cerebral impairment that results in the inability to sit unsupported. It may progress to coma. It can also be present in the post-ictal phase. Although it is highly reported in severe malaria, it is subjective (Patel *et al.*, 2020). In earlier studies prostration was found in 29.1% by Kalinga in Tanzania (Kalinga *et al.*, 2012) and 6.5% by Olupot-Olupot in Eastern Uganda (Olupot *et al.*, 2020). However, not much is found in the description of recent studies.

2.2.9 Haemoglobinuria (Dark urine/tea coloured urine/ black water fever)

This is one of the features that has been noticed in the recent past accounting for 14.0% in a study by Olupot-Olupot, 2014. However, it appears on a rise as a feature of severe malaria. In other studies carried out in Africa, the findings are 25.3% (Kunuanunua *et al.*, 2015), 19.1% in Nigeria (Ajetunmobi *et al.*, 2012), and 8% in Tanzania (Kalinga *et al.*, 2012) of haemoglobinuria. It is highly associated with severe anaemia, jaundice, recurrent admissions, /multiple transfusions prolonged hospitalisation, and high mortality (Paasi *et al.*, 2022). This feature has been noted among children in Uganda and some parts of West Africa majorly Nigeria. These are endemic countries for malaria. It is highly seen in high transmission areas. However, there has been no difference across transmission intensities in Uganda (Olupot-Olupot, 2014; Ajetunmobi *et al.*,

2012). The syndrome comprises acute intravascular haemolysis, fever and the passage of dark- or red-coloured urine. It is recognised as a complication in patients with recurrent or recent malaria infection. Black water fever was a classical association with the long-term use of quinine in non-immune people during the quinine era. It has been linked to the presence of genetic disorders like G6PD deficiency (Ajetunmobi *et al.*, 2012). It is less in the homozygous thalassemia and carriers for sickle cell anaemia (genotype HbAS). Mechanisms involved may include intravascular related hemolysis and immune-mediated lysis following Quinine. It is associated with severe anaemia and acute renal failure (Olupot-Olupot *et al.*, 2017). Confirmed by comparing a urine sample from an individual with Hillman Colour Chart (HCC) grade 5-10 (Paasi *et al.*, 2022).

2.2.10 Jaundice

Jaundice is defined as a plasma or serum bilirubin >50IM or 3mg/dl with a parasite count greater than 100,000uL (Health and Malaria, 2014b). The prevalence by Kalinga In Tanzania was 1.2% (Kalinga *et al.*, 2012), 26.7% by Olupot-Olupot (Olupot *et al.*, 2020) and 20.1% by Kunuanunua in Congo (Kunuanunua *et al.*, 2015). Genetic conditions like G6PD deficiency and sickle cell anaemia among others are highly associated with jaundice in severe malaria (Olupot-Olupot, 2014). Jaundice has multifactorial causes in severe malaria. It could be related to hepatocyte damage during the hepatic stage (Viriyavejakul, Khachonsaksumet and Punsawad, 2014), increased intravascular and extravascular hemolysis of parasitized and non-parasitized Red blood cells (RBCs) and micro-angiopathic haemolysis leading to disseminated intravascular coagulation (DIC). It could also result from hepatic dysfunction, G6PD deficiency haemolysis, or drug-induced. Lastly, jaundice could result from co-existing septicemia-induced hepatitis (Viriyavejakul, Khachonsaksumet, and Punsawad, 2014; Patel, Dunican and Cunningham, 2020; Olupot *et al.*, 2020).

2.2.11 Renal impairment

Renal impairment defined as plasma or serum creatinine 3mg/dL or blood urea > 20 mmol/L, is one of the rare occurrences as a complication in severe malaria (Health and Malaria, 2014b). The relationship between elevated creatinine and BUN highly indicates renal impairment (Olupot-Olupot, 2014). Its prevalence was 6.25% by Ajetunmobi in Nigerian children with haemoglobinuric severe malaria (Ajetunmobi *et al.*, 2012). Many studies have portrayed an

increasing risk of renal impairment with increasing age (Batte *et al.*, 2021) . It is highly prevalent in hyperendemic areas less in meso-endemic regions (Maitland, 2015). Male gender and hemoglobin levels less than 7.5g/dl are associated with AKI at 48 hours and low platelet count less than 25000mm^3 from baseline (Muhamedhussein *et al.*, 2019).The causes could be tubular necrosis, interstitial nephritis, or glomerulonephritis(Patel, Dunican and Cunningham, 2020). There are multiple mechanisms involved including hypo perfusion due to hypovolemia, parasite sequestration, nephrotoxins, and hemolysis that contribute to ischaemic injury. Other mechanisms include inflammation, immune activation, endothelial activation, and microcirculatory dysfunction (Batte *et al.*, 2021). The mechanisms above are responsible for pre-renal and intra-renal renal failure seen in severe malaria. Sequestration has been described among the adult population as compared to children. The treatment is mainly supportive of eliminating nephrotoxic agents like non-steroidal anti-inflammatory drugs, proper rehydration, and adequate treatment with antimalarial drugs and at times dialysis (Maitland, 2015; Batte *et al.*, 2021). However, there are no clear treatment guidelines for paediatric population. The outcome is excellent when well managed and a minority of patients may need dialysis (Muhamedhussein *et al.*, 2019). The prognosis is poor with increased mortality if it occurs in combination with other complications.

2.2.12 Shock

This is a rare occurrence but life threatening among the manifestations. It is compensated with a capillary refill of ≥ 3 seconds with a temperature gradient, with no hypotension. It is decompensated when the systolic blood pressure is less than 70mmhg in a child with cold peripheries and prolonged capillary refill ≥ 3 s after adequate rehydration. However, the assessment of capillary refill is subjective and varies between observers. Accurate blood pressure measurement in young children depends on using the correct sphygmomanometer cuff size (Health and Malaria, 2014b).

2.2.13 Significant bleeding/Disseminated Intravascular coagulation (DIC)

This includes spontaneous, recurrent, or prolonged bleeding from the nose, venipuncture sites, hematemesis or melaena. Bleeding is uncommon but can be secondarily due to multiple mechanisms including thrombocytopenia, platelet dysfunction, impaired fibrinolysis, and a coagulopathy. This can manifest as bleeding from mucous membranes and venipuncture sites,

normally indicative of more severe disease. It has been mainly reported among the adult population and less in children (Angchaisuksiri, 2014).

2.3 DIAGNOSTICS

There are several approaches to malaria diagnosis ranging from clinical, RDT, microscopy, culture, and PCR. These have different implications on specificity, sensitivity, the cost attached, and the accuracy that determines applicability in a given situation.

2.3.1 Clinical diagnosis/ clinical evaluation

This is the presumptive diagnosis usually not accompanied by a blood slide or RDT confirmation. Clinical diagnosis is very common in many malaria endemic areas, especially in remote zones. In malaria-endemic regions with limited resources and trained health personnel, the presumptive diagnosis is the most realistic option. Malaria has nonspecific clinical features including a fever as the major clinical symptom. This may result in over-diagnosis and overtreatment with misuse of antimalarial, especially in moderate and low endemic areas. In highly endemic areas like Sub Saharan Africa, clinical suspicion of malaria occurs in cases presenting with a fever greater than or equal to 37.5° C. Clinical diagnosis offers an easy, speedy and low-cost service as compared to all diagnostics (WHO, 2015; Report, 2020). Clinical assessment follows a standard format of history taking, identifying symptoms and clinical examination. Recording of anthropometric measurements including weight, MUAC and vital signs (temperature, respiratory rate, blood pressure, heart rate and oxygen saturation). This is important in categorizing the severity of disease.

2.3.2 RDT (Rapid Diagnostic Test)

Recently the malaria RDTs as a diagnostic of choice is replacing microscopy, especially in resource-limited areas. However, many countries have considered shifting their diagnostic policy for malaria to implementing RDTs as a standard diagnosis. The commonly used RDTs detect antigens circulating in the blood namely: p. falciparum histidine-rich protein -2 and 3. Others are ; the pan-specific or species-specific plasmodium lactate dehydrogenase (pLDH) or pan-specific aldolase (WHO, 2021). Good quality malaria RDTs provide a rapid and reliable way to demonstrate the presence or absence of malaria antigens at all levels of health service. Hence,

RDTs are a good alternative for microscopy but have limitations such as poor storage conditions, low quality, availability and cost affect implementation (Byakika-Kibwika *et al.*, 2017).

2.3.3 Microscopy

Laboratory diagnosis by examination of blood smear using a microscope is still the gold standard in malaria diagnosis. It involves making thick and thin blood films commonly stained using Giemsa stain. This examination can identify some species of *Plasmodium* precisely and at the same time, the parasite counts so that the degree of parasitaemia can be known, differentiating clinically important asexual forms from gametocytes that may persist. However, it is difficult to distinguish morphological changes of the *P.knowlesi* from *P.falciparum* and *P.malariae* making diagnosis difficult by only relying on the microscopy diagnostic technique (Lawpoolsri *et al.*, 2019). The advantages are key in assessing parasitological response to treatment and proper case management. Microscopic examination can only detect the presence of the *Plasmodium* at the level of 20 parasites/mL of blood, the results also depend on the expertise and interpretation of the examiner (Moyeh *et al.*, 2019). Microscopic examination is limited in detecting *Plasmodium*, especially when a blood smear are prepared poorly or the low degree of parasitaemia or mixed infection occurs. In addition, the processes of collecting a sample, staining and preparing the slide are time-consuming and needs electricity. It reduces misuse of antimalarial drugs (Ssempiira *et al.*, 2017; Report, 2020).

Reading malaria blood films; Prepared Giemsa-stained or field stained thin and thick films are read identifying asexual and sexual parasites using microscopy (magnification of 1000×). Parasitaemia read on a thin blood film for more than 200 parasites per 10 fields on a thick film seen per 2000 red blood cells (RBCs). Below this threshold, it is counted per 500 white blood cells (WBC) on the thick film. Slides are negative after examination of at least 200 high-power microscopy fields. For quality control, two qualified microscopists read all the slides independently.

2.3.4 PCR (polymerase chain reaction)

PCR is a bio molecular examination test. It is highly more effective than microscopic examination techniques in case of mixed infection and malaria infections with a low degree of parasitaemia. It obtains more results that are accurate especially in drug resistance. It differentiates recrudescence from a new infection and resistant strains (Alemu *et al.*, 2014; Report, 2020) and has been highly used in detecting mixed infections, and differentiating between new infections and recrudescence. The major disadvantage is high cost, high degree of training required, need for special equipment, an absolute requirement for electricity and the potential for cross-contamination.

To differentiate between new infections and recrudescence, dried blood spots on Whatman R3 MM filter paper (Whatman International Ltd, Maidstone, UK) is prepared on day 0 before treatment and after day 7 in case of resurgence of parasite confirmed by microscopy. Genotyping for recurrent infections will be done following the standard protocol as previously demonstrated by characterising the length of polymorphism of the Msp1, Msp2 and Glurp genes in samples at day 0 and day of recurrent infection (Chebore *et al.*, 2020).

2.4 POST THERAPEUTIC MALARIA PARASITAEMIA

World Health Organisation (WHO) targets a cure rate of 95% 28 days after initial malaria infection. Presence of parasitaemia after 28 days from initial infection (post-therapeutic malaria parasitaemia) is likely multifactorial. It could suggest treatment failure, new infection, resistance or recrudescence. Therapeutic efficacy studies have addressed most factors associated with treatment failure: including incorrect dosage, poor drug quality, poor drug compliance, drug interactions, and resistance (WHO, 2014).

2.4.1 Malaria drug resistance

This is a major concern in malaria treatment. This has occurred with different generations of antimalarial therapy including quinine, chloroquine, fansidar (sulfadoxine/pyrimethamine combination) first noted in 1910, 1965, and 1999 respectively. The pattern of resistance generally arises from the Greater Mekong Sub region (GMS) in SEA spreading to Africa. This region (GMS) consists of six countries: Cambodia, China (Yunnan Province), Lao People's Democratic Republic, Myanmar, Thailand, and Viet- Nam. In the recent past, findings show that Africa has

resistance to all these drugs. For instance, chloroquine resistance was first noted in 1965 in Thailand and noted in the African countries such as Uganda, Sudan, and Zambia by 1983 (Arrow, Panosian and Gelband, 2004; J. *et al.*, 2011; World Health Organization, 2017). In the artemisinin era, drug resistance is now a major concern. This could have emerged as early as 2001 however, many studies since 2006 have reported the presence of partial resistance due to delayed parasite clearance from the bloodstream (Ashley *et al.*, 2014). This reduces effectiveness in clearing all parasites within three days among people with artemisinin-resistant malaria strains first reported in 2008 GMS (Ashley *et al.*, 2014; World Health Organization, 2017; Report, 2020). The partial ACT resistance in GMS evolved rapidly since the detection of PfKelch13 mutations in this region of which some have disappeared as others are increasing. Other mutations related to resistance emerging from this region include F446I, M476I, R561H, Y493H, P553L, and R539T. Other mutations are N458Y, I543T, and C580Y the most observed in Africa being A578S (Woodrow and White, 2017; Lawpoolsri *et al.*, 2019; Report, 2020).

Multiple studies in the recent past show that the ring stage of malaria parasites is the only stage affected in the parasite cycle in humans. Partial artemisinin resistance occurs due to multiple factors including substandard drugs, poor adherence to the prescribed drug, widespread misuse of oral ACT, monotherapies and poor treatment policies. Resistance is also related to pfhrp-2/3 gene deletions hence some parasites are not detected by the histidine-rich protein 2-based RDTs. In Peru and Eritrea, the prevalence of dual deletion is as high as 80%. The presence of these deletions is associated with false-negative malaria RDT (Asua *et al.*, 2017; Olupot-Olupot *et al.*, 2017; World Health Organization, 2017) leading to sub optimal management or no treatment when in the early stage resulting in progression to severe malaria. There are incidences of artemisinin resistance due to the presence of Pfkclh13 mutations in countries like Rwanda, Papua New Guinea, and Guyana. Rwanda our neighbor in the Southwest has already reported cases of this mutation, it could have spread to other countries like Uganda. This would be a contributing factor to recrudescence.

2.4.2 Recrudescence

Recrudescence is the reappearance of parasitaemia after decreasing to microscopically undetectable levels (sub patent) in thick blood smears (Wellems *et al.*, 2020), the asexual parasitaemia re-occurrence of the same genotype that caused an original illness. Recently, recrudescence has been identified to peak at 28 days (Saito *et al.*, 2019). Following treatment with rapidly eliminated drugs, most recrudescence occurs within four weeks. However, following treatment with slowly eliminated antimalarial drugs, the recrudescence may be delayed (Report, 2020). According to Byakika *et al.*, recrudescence among children with severe malaria was estimated at 26.8 % in Eastern Uganda (Byakika-Kibwika *et al.*, 2017). In *P. falciparum* infection, there is persistence of schizonts as compared to *P. vivax* and *P. ovale* where relapse occurs due to dormant hypnozoites in the liver (Saito *et al.*, 2019). Blood gametocytes do not cause symptoms or recrudescence. However, the persistence of *P. falciparum* parasites in the bloodstream, and cryptic parasites in the spleen and bone marrow that may not respond to chemotherapy could be a source of recrudescence (Wellems *et al.*, 2020).

Low concentrations of lumefantrine on day 7, underweight, the very young <3 years and those with hyperparasitaemia are identified risks for recrudescence. The increased risk was observed more in low transmission areas (Antimalarial *et al.*, 2015). In addition, incomplete or inadequate treatment and *P. falciparum* characters, which could be parasite density, genetic diversity, or polymorphism may contribute to recrudescence (Kyabayinze *et al.*, 2008). Recrudescence is commonly associated with the use of monotherapies and persistence of the ring stage of the parasite population following treatment with an antimalarial. This is a parasite dormancy phenomenon common reflected across all artemisinin based combinations (Mahamar *et al.*, 2021). Monotherapies may contribute to 40%-50% of all cases at day 28. In Burkina Faso, high rates of recrudescence were seen with artesunate +chloroquine (AS+CQ) (Sophie Landre *et al.*, 2021). Recrudescence occurs at different times in relation to drug used in the management of malaria: quinine-20 days, artemether-lumefantrine- 21 days and 29 days for dihydroartemisinin /piperaquine (Saito *et al.*, 2019).

Earlier studies on recrudescence were during the period of quinine (Purohit *et al.*, 2016) and chloroquine (Woodrow and White, 2017). Recrudescence has often been linked to malaria resistance (J. *et al.*, 2011). For instance, when the recrudescence was highest in South East Asia

(SEA) in 1980 (Asia, 2018) resistance to antimalarial including chloroquine, antifolates, and mefloquine was reported (J. *et al.*, 2011). In the era of artemisinin combination therapies (ACTs), a similar trend has been reported in SEA (Great Mekong Sub region) which is spreading in Africa (Ashley *et al.*, 2014). By the 1990s, *P.falciparum* malaria parasites resistant to multiple drugs (chloroquine, antifolates, and mefloquine) were prevalent in Southeast Asia (J. *et al.*, 2011).

2.5 OUTCOMES OF SEVERE MALARIA

Severe malaria syndromes have been associated with poor clinical outcomes including prolonged hospitalisation and mortality. Many factors influence the outcome. These include parasite species, host genetics, innate and acquired immunity, and parasite genetics, presence of comorbidities, access to appropriate treatment, and antimalarial resistance. For instance, severe acidosis, and symptomatic anaemia are major mortality predictors (Olupot-Olupot, 2014). According to earlier studies, shock, hyperlactatemia, hypoglycaemia, respiratory distress, impaired consciousness have been associated with mortality in addition to renal impairment. Presence of chronic illnesses in children with severe malaria is associated with poor outcomes including mortality (Dondorp *et al.*, 2005; Cserti-gazdewich *et al.*, 2013; Patel, Dunican and Cunningham, 2020). The presence of bacteremia in children as comorbidity in severe malaria evidenced by leukocytosis, is associated with higher mortality and prolonged hospitalisation (Olupot-Olupot, 2014; Maitland, 2015; Paasi *et al.*, 2022). Hypoglycaemia highly predicts mortality according to findings in several earlier studies. The severity of malaria in relation to the combination of the clinical or laboratory features highly predict the outcomes (Patel, Dunican and Cunningham, 2020). However, these outcomes depend on nature together with the degree of vital organ dysfunction and differ in both children and adults. For example, renal impairment among children reported in severe malaria is due to acute tubular necrosis but is associated with less mortality as compared to renal impairment in adults (Seidlein *et al.*, 2012). The quality of pre-referral and emergency in-hospital care contribute to the malaria case fatality (Idro and Aloyo, 2004).

Hyperparasitaemia is associated with increased symptomatic malaria and may be associated with mortality. However, this works well as a predictor of outcome in presence of other features. Findings of elevated serum tumour necrosis factor (TNF) levels and histidine-rich protein 2 (HRP-2) plus pigmented neutrophils are highly associated with poor outcomes (Seidlein *et al.*, 2012; Patel, Dunican and Cunningham, 2020). There is also increased post-discharge morbidity that may

require hospitalization or outpatient visits that have been highly associated with syndromes of cerebral malaria and severe anaemia malaria. Other outcomes include treatment failure either clinical or parasitological and in children with cerebral malaria, malaria retinopathy was noted in 61% (Opoka *et al.*, 2017). Majority of Studies carried out in Uganda on severe malaria outcomes were in Kampala mainly in the last decade (Seidlein *et al.*, 2012; Cserti-gazdewich *et al.*, 2013; Opoka *et al.*, 2017). There are no studies on outcomes of severe malaria in Eastern Uganda with MRRH as a focus with its catchment area in the past decade. The trends of outcomes could have changed greatly hence the need for new documentation.

CHAPTER 3: MATERIALS AND METHODS

3.1 STUDY DESIGN

The study was a prospective study nested with-in a large malaria study “Malaria Epidemiological, Pathophysiological and Intervention studies in High Endemic Eastern Uganda” (MEPIE) at MRRH. It targeted patients admitted with *P.falciparum* severe malaria aged 2 months to 12 years. There was a follow up on day 28 post discharge from the hospital. This follow up had a window period of from 26-35 days (28-2/+7). This was to enable us to determine the post therapeutic malaria parasitaemia following severe malaria admission among the study participants.

3.2 STUDY AREA

The study area was the paediatric unit of Mbale Regional Referral Hospital (MRRH) in Eastern Uganda. It is about 222 kilometres (138 miles) from Kampala with coordinates: 1°04'36.0"N, 34°10'35.0"E (Latitude 1.076667; Longitude 34.176389). The majority of the area's inhabitants are of the Bantu ethnic group with >90% living in a rural agrarian community and less than 10% living in the urban areas. The hospital is one of the fourteen Regional Referral Hospitals in the country. It is a teaching hospital for Busitema University and among the 15 internship-training hospitals and a public clinical paramedical teaching hospital in Uganda.

The hospital serves as a referral unit for the catchment area that covers about 16 districts; Budaka, Busia, Bukwo, Kapchorwa, Kween, Kibuku, Manafwa, Mbale, Butaleja, Sironko, Bulambuli, Pallisa, Namisindwa, Bukedea, Butebo and Tororo. It also serves several lower level, government-run health centres, private not for profit health units and patients from outside its catchment area in Eastern Uganda having a total population of 4.5million with about 17,000 pediatric admissions annually. It has a hospital bed capacity of 400 beds with four major general specialties: internal medicine, obstetrics and gynaecology, paediatrics and surgery. The hospital also offers other specialist services like radiology, pathology, ophthalmology, ear nose and throat (ENT) and psychiatry. The geographical elevation of this area is 900- 2,000m above sea level with a tropical highland climate. The staff consist of nurses , resident junior house officers (JHOs), senior house officers (SHOs), specialists and consultants.

3.1.1 The Paediatric unit –MRRH

The Paediatric Unit of MRRH is composed of two wards; the acute care unit and the stable ward (ward 3). The acute care unit (ACU) was where the screening and recruitment of study participants took place. This ward is composed of two wings a general side and a High dependency unit (HDU). In this ward, there is triage at reception and stabilisation in HDU or the general ward. Patients from the HDU either are monitored further on the ACU general ward or ward three (3) before they are discharged. The HDU has an oxygen supply system and resuscitation equipment like the bag and mask, an emergency trolley containing emergency drugs together, patient monitor with other equipment that may be required in resuscitation. Activities at the unit include outpatient care and in-patient with a high dependency unit. The acute ward is an emergency paediatric ward with activities like triaging, emergency care, and resuscitation.

The Paediatric unit admits all children ages 1 month to 12 years and all sickle cell anaemia (SCA) patients irrespective of age. It has weekly clinics for children who have had severe anaemia episodes, chronic illnesses like sickle cell anaemia, epilepsy, cardiac disease and renal disease among others. The unit is managed by Paediatrician (3) including medical officer (1), paediatric residents (7), intern doctors (6), nurses (16) and medical students.

The unit has a 90-bed capacity with current monthly paediatric admissions of 1000-1500. Severe malaria accounts for approximately 10% of all paediatric admissions. Severe malaria at this site is managed according to the national treatment guidelines.

3.1.2 Mbale Clinical Research Institute (MCRI) laboratory

The laboratory tests were carried out in the MCRI laboratory. This laboratory has certified technologists and technicians that are GCP (Good Clinical Practice) and HSP (Human subject protection) trained. It is equipped with high quality machines used in the analysis for example the Cobas111 for biochemistry, Beckman coulter model DxH 500 haematology analyzer among others. It has the ability to store various samples and carry out tests like microbiology, parasitology and biochemistry. It has well calibrated machines that undergo routine servicing to ensure quality results. The laboratory has been able to deliver results in high quality different trials including FEAST ISRCTN69856593, TRACT ISRCTN84086586, REACH NCT01966731, PAC

ISRCTN11594437 and still has very many ongoing studies. Two readers, the first and second person, read blood slides. For some cases, a third reader is considered as a tiebreaker.

3.2 STUDY POPULATION

The study targeted children ages between 2 months to less than 12 years admitted to MRRH with *P.falciparum* severe malaria. These children were from the catchment area of MRRH. These were accessible during the study period was from 01/OCT/2021 to 01/March/2022 (5 months). Only children available at the time of screening that is 8:00 am to 5:00 pm for each given day were recruited.

3.2.1 Inclusion criteria

Participants were included in the study having fulfilled all the criteria below at screening.

- Presence of one or more clinical or laboratory features for severe malaria
- Children aged from 2 months to less than 12 years
- Positive blood slide for *P.falciparum* malaria at admission
- Guardian or parent willing and able to provide consent

3.2.2 Exclusion criteria

Participants excluded had any of;

- Presence of surgical conditions
- History of allergy or known contraindication to ACT

Eligible participants were those who fulfilled the inclusion and exclusion criteria.

3.3 SAMPLING STRATEGY

All children admitted to ACU ward of MRRH with a positive RDT with features of severe malaria/ complicated malaria were screened. WHO 2014 severe malaria criteria was used in identifying cases for screening for both clinical and laboratory features. A blood slide with 10% Giemsa stain was carried out to confirm the diagnosis of *P.falciparum* asexual parasitaemia. Those with a positive blood slide for *P.falciparum* malaria were further assessed for eligibility. Eligible participants were randomly sampled from 8:00 am to 5:00pm every day during the study period.

3.4 SAMPLE SIZE

The sample size was derived using Kish Leslie formula: $n = (Z^2 pq)/e^2$

This is valid where:

n is the sample size

Z is the z- score for 95% confidence interval=1.96

e is the desired level of precision =5% (0.05)

p is the estimated prevalence of severe malaria among all children admitted cases (10% of the admitted cases -Olupot-Olupot, 2014).

q =1-p

$$n = (1.96)^2 \times \{0.1(1-0.1)\} / (0.05)^2$$

$$n = 138$$

The sample size calculated was **138** for the study.

3.5 STUDY VARIABLES

3.5.1 Independent variables

These included:

1. **Social demographic factors:** age, sex, home location.
2. **Clinical spectrum of severe malaria:** cerebral malaria, respiratory distress, prostration, shock, spontaneous hemorrhage, multiple convulsions, impaired consciousness, jaundice, hemoglobinuria. Laboratory features hyperparasitaemia (>10% in highly endemic areas), acidosis, hypoglycaemia (random blood sugar <2.2mmol/L or < 40 mg/dL), acidosis (lactate level>5mol/L), severe anaemia (< 5g/dl), renal failure (serum creatinine >3mg/dL/ BUN > 20 mmol/L).
3. **Underlying factors;** previous use of antimalarial, malnutrition, and HIV status

3.5.2 Dependent variables

The dependent variables for this study were; mortality, prolonged hospitalisation and a positive parasitaemia at day 28.

3.6 DATA COLLECTION

This was accomplished using different forms including screening forms, enrollment forms, case report forms, and source documents (Appendix A-7). Eligible patients were consented to participate in the study. A two-stage consent was obtained for patients who were critically ill or in case where the parents are too anxious to understand. This included a verbal/emergency consent, which was a brief document representing acceptance to participate in the study from a parent or legal guardian followed by detailed full consent from eligible participants (Appendix A-6). The data was collected at admission, discharge, and follow up.

3.6.1 Data collection tools and pretesting

Questionnaires used for data collection were first pretested to check the ability to provide the research answers and adjustments made accordingly.

3.6.2 Data collection procedures

Laboratory procedures

The laboratory tests for the study included; rapid diagnostic test (RDT), blood slide for malaria, complete blood count (CBC), and biochemistry. A total of approximately 3.5mls of blood was collected from the participants during the study period. This included 2.5mls at day 0 where 0.5 ml EDTA was for blood slide and complete blood count, 2ml for biochemistry.

Bedside tests: Some of the bed side tests carried out at screening on all eligible patients for proper care and further description of the severe malaria syndromes including;

- i) Lactate using a lactometer Xpress (mmol/L) model manufactured by Nova BIOMEDICAL cooperation USA.
- ii) Malaria RDT; carried out as above with SD - Bio line malaria –AG-pf/pan manufactured by standard diagnostics.

- iii) Random blood sugar (RBS) using glucometer Xpress (mmol/L) model manufactured by Nova BIOMEDICAL cooperation USA. A blood sample obtained by finger prick was used for this.
- iv) Haemoglobin was obtained using hemocue hb 301 manufactured by Hemocue AB, Angelholm Sweden.
- v) i-STAT was carried out using an analyser manufactured by Abbott point of care Inc, a product of the USA. The test was carried out on the sample collected in a lithium heparin vacutainer in a space of 10 minutes from sampling.
- vi) Urine dipstick was carried out on urine samples collected in a clean container using the siemens multistix10SG reagent strips.

All the above test kits are depicted in Appendix A-4.

Clinical assessment; The clinical assessment data on symptoms, signs and working diagnosis were obtained using a questionnaire (Appendix A-7). Clinical examination and anthropometry were carried out and recorded in the questionnaire. Anthropometry was done using the standardized equipment; well calibrated weighing scale height/length using the stadiometer, MUAC (Mid Upper-Arm Circumference) with WHO MUAC tapes, and head circumference with a tape measure. The vital observations were carried out using well calibrated machines, an automated blood pressure machine, a pulse oximeter, and a thermometer. Upon clinical evaluation of the patients and available results, we checked the diagnosis, which was either one or more. The screened eligible patients were further classified according to WHO 2014 severe malaria criteria. The treatment while in the ward was extracted from the patients' ward records.

3.6.3 Data collection methodology

The eligible patients were further classified according to the 2014 WHO severe malaria criteria; cerebral malaria, prostration, shock, spontaneous hemorrhage, multiple convulsions, impaired consciousness, jaundice, hemoglobinuria, and respiratory distress. In addition, using the same criteria laboratory defining features included hyperparasitaemia (>10%), acidosis, hypoglycaemia (2.2mmol/L or < 40 mg/dL), acidosis (>5mol/L), severe anaemia (< 5g/dl), renal failure (serum creatinine> 3mg/dL/ BUN > 20 mmol/L) (Health and Malaria, 2014). Clinical jaundice was defined as yellowing of the mucous membranes in sufficient daylight. Respiratory distress is

defined as the presence of deep breathing or any sign of increased use of accessory muscles. Unconsciousness was evaluated using the Blantyre coma scale where a score of <3 . Hypoxaemia was defined as abnormally low oxygen in peripheral blood with $\text{Spo}_2 < 90\%$ reading the on the pulse oximeter. Febrile seizures were defined as seizures occurring between 6 months to less than 6 years with a fever not caused by an infection of the central nervous system (World Health Organization, 2016). Pyrexia was defined as an axillary temperature of $\geq 37.5^\circ\text{C}$ using a digital thermometer. Hemoglobinuria was defined as urine colour grade ≥ 5 - 10 using the Hillman urine colour chart below (**Figure 5**).

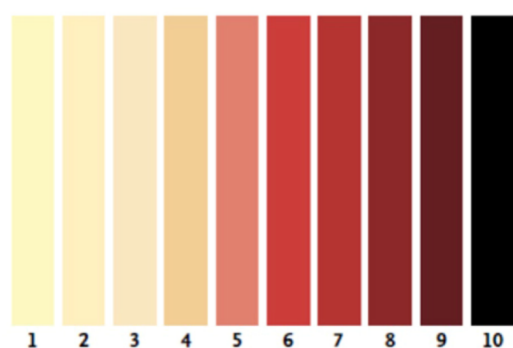


Figure 4: Hillman urine colour chart ; *source (Paasi et al., 2022)*

Eligible patients with any of the above features of severity were invited to participate after informed consent was sought from the patient's parent or guardian. The data was captured on case report forms that captured the socio-demographics features, laboratory results, clinical evaluation, treatment and follow up together with the outcome of the participants. The blood slide (BS) for malaria was carried out on day 0 during the screening period, discharge, and day 28. Other bedside tests were carried out including lactate levels, random blood glucose, hemoglobin level, and urine dipstick. Further laboratory tests included CBC and biochemistry on blood. Screening for Sickle Cell Anaemia (SCA) was carried out in some instances. Blood cultures and cerebral spinal fluid studies were not done.

Procedures

Blood slide and RDT; All patients screened had a malaria RDT carried out. A blood slide was further carried out for those who had a positive RDT. This was to confirm the positivity, species and parasite count. The RDT was carried out on the ward as a point of care test. This was carried out using the SD - Bio line malaria –AG-pf/pan 05FK60 manufactured by standard diagnostics.

This detects histidine-rich protein 2 (hrp-2) and pan lactic dehydrogenase (LDH) antigens. A finger prick sample was used for the test. Using a pipette provided in the RDT a sample was collected and mounted on the sample well. This was followed by 2-3 buffer drops and read after a maximum of 15 minutes. The RDT test was positive when the test for *P.falciparum* and control lines all showed a reaction and negative without a reaction. We collected 0.5 ml of blood in a 0.5ml EDTA that was submitted to the laboratory for microscopy from possible participants with positive RDTs. The blood slide for malaria was prepared with 10%Giemsa, a stable methanol-based Romanowsky stain at pH7.2. The stained smears were examined microscopically under x400 and x1000 lenses. The *P.falciparum* parasites were identified based on the staining and counted against 200 WBC or 500 RBCs. Two experienced microscopists carried out the reading before results were dispatched. The blood slide was positive when *P.falciparum* trophozoites were seen . Slides with only gametocytes were also considered negative.

Case management

All patients were managed in the ACU following the local treatment guidelines from MoH (Ministry of Health). Patients who were hypoxemic had oxygen administered during screening or in the course of admission; dextrose 10% was administered 5ml/kg for those at risk of hypoglycaemia and those who were hypoglycaemic. The additional dose was administered according to patient's need. Antibiotics for co-existing bacterial infections or suspected sepsis was administered in some cases. Blood transfusion was administered for severe anaemia either 20ml/kg of whole blood or 10ml/kg of packed cells. Intravenous artesunate 3mg/kg for children less than 20kg and 2.4mg/kg for children greater than 20kg was administered as per guidelines. All patients were discharged on oral artemisinin- based combination therapy either dihydroartemisinin / piperaquine (DHAPP) or Artemether/lumefantrine (A/L) prescribed in relation to weight. Additional haematinics were prescribed for those who were previously anaemic.

Microscopy for malaria parasites

Parasitaemia on the blood slide was recorded at admission, at discharge, and at follow up to assess parasite clearance. The follow up post discharge was on day 28 from the recruitment date. This follow up had a window period of 26-35 days (28-2/+7). This was to enable us to describe factors and the different types of severe malaria in relation to parasitaemia. In Addition, we tracked the

antimalarials prescribed during hospital stay and discharge. Post therapeutic parasitaemia was defined as a positive blood slide on day 28/follow-up.

Record of outcomes; Case report forms were used to record outcomes in severely ill patients like the lactate levels, random blood glucose, haemoglobin levels, Blantyre coma scale, hypoxaemia. Also recorded were;

- Duration of hospitalisation
- Mortality events
- Other treatment modalities
- Patient status on follow-up

Prolonged hospitalisation was defined as a hospital stay for $\geq$ to 5 days, an adaptation from Gyapong *et al.*, 2009.

3.7 DATA ENTRY

This was carried out by GCP (Good Clinical Practice) trained team using redcap software v 12.2.1. Data was captured and entered using redcap formatted to capture all the variables needed.

3.8 DATA MANAGEMENT AND CLEANING

After collection, data was entered using an electronic database. Thereafter, electronic data was cleaned by identifying wrong entries, repeated unique identifiers, out of range data, spelling discrepancies, missing and missing data using STATA 15.0 (Statacorp, college station, TX, USA). The sources of the data were traced and cross-checked against the entries to ascertain accuracy. The forms filled were kept under lock and key to ensure confidentiality.

3.9 DATA ANALYSIS

Data was analysed using STATA V15.0 (Statacorp, college station, TX, USA) software. Significant p- value was 0.05. Univariate, bivariate and multivariate analyses were done. The Chi-square test was carried out for the bivariate analysis. Multivariate logistic was regression carried out to determine the factors associated with post therapeutic malaria parasitaemia.

3.10 AUTHORIZATION AND ETHICAL CONSIDERATIONS

- Approval was obtained from my Supervisors followed by the Paediatric department of Busitema University College of Health Sciences, Higher Degrees Committee of Busitema University and lastly Mbale Regional Referral Hospital Research and Ethics Committee (MRRHREC). The accreditation number is MRRH 2021-76.
- Consent was sought from all the participants in this study before enrollment. There was a prospective informed consent from guardians of children when stable. A two-stage consent adopted from the TRACT trial was obtained since the children were presenting with life-threatening emergency cases. For children 8 years and above, a child assent was sought. For this study, the primary risk was minimal pain during blood sampling for the tests. However, no other risks were encountered as no other interventions were carried out on the participants. All care was provided in line with the hospital standards of care.
- Benefits: The patients will not benefit directly from the study. However, benefits will be to society by providing information about post therapeutic parasitaemia in childhood severe malaria thus enhancing proper case management.
- Confidentiality: Participant confidentiality was ensured by not stating the patient's name but rather initials and inpatient number or a designated Identification number. Also we ensured data protection and proper data management. All records generated were stored as per good clinical practice (GCP) and only the research personnel at the site had access to the research information.

3.11 DATA DISSEMINATION PLAN

The data will be disseminated through; presentations at Busitema University faculty of health Sciences, Journal clubs, presentations to Mbale RRH, workshops and other research dissemination conferences. This data will be published in several research journals. Copies will be provided to the Paediatrics department of Busitema University College of Health Sciences, the University Library, MRRH Research and Ethics Committee.

CHAPTER 4: RESULTS

Data of 138 participants was analysed for objective one (1), 137 for objective two (2), one patient was excluded since most of the parameters were missing. For objective three (3), that of ninety-three (93) was analysed, 115 for the prolonged hospitalisation and 99 for mortality. We had a difference in the denominators of various objectives; 137 for objective 2 (two) was excluded since missed most of the parameters. For objective 2; data from 93 participants was analysed. This data belonged to those who came for follow-up review. For prolonged hospitalisation, all patients whose discharge status was captured were evaluated and these were 115. We excluded data for five (5) who died during the admission and eighteen (18) who self-discharged. For the mortality 99 were analysed this comprised the 6 who died and the 93 whose status was known until the follow up day.

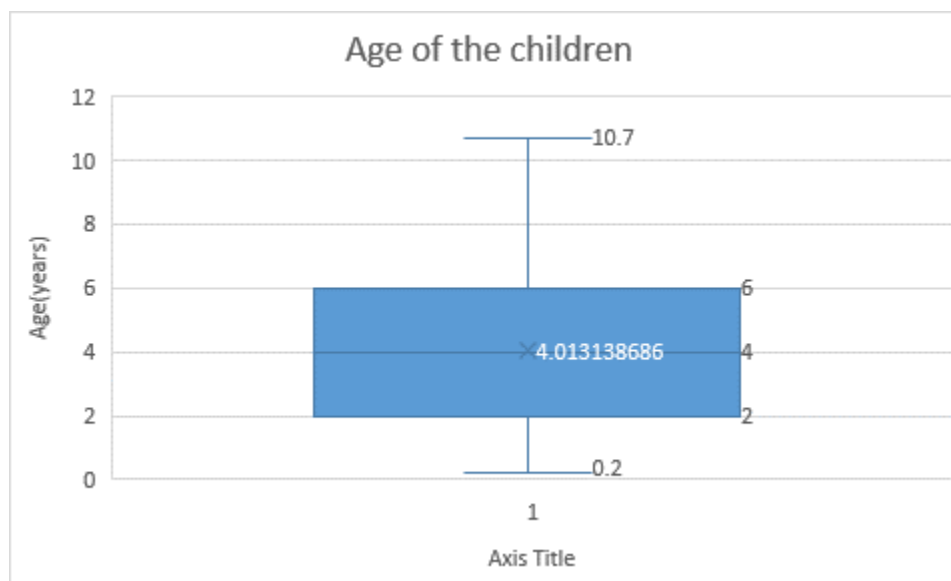
4.1 SOCIAL DEMOGRAPHIC CHARACTERISTICS

I enrolled 138 participants starting from 01/OCT/2021 to 01/Mar/2022. The participants were children from 60 days (2 months) to less than 12 years old. The overall median age in this study was 4.0 years, the eldest being 10.7 years and the youngest 2 months (**Figure 5**). In total 84/138(60.9%) were under 5 years and 54/138(39.1%) were five years or older (**Table 1**). More than half 76/138 (55.1%) were males and 62/138 (44.9%) were females. Majority of the participants were from Budaka district with 41/138 (29.7%), followed by Mbale 34/138 (24.6%), Butaleja 17/138 (12.3%), Butebo 9/138(6.5%), Kibuku8/138(5.8%). Other districts including Namutumba had 7/138(5.1%), Bukedea 7/138(5.1%), Sirinko 4/138(2.9%), Tororo 3/138(2.2%) and Pallisa (3/138(2.2%)) (**Table 1**).

Table 1: Social Demographic characteristics of participants

Variable	Frequency n=138	Percent (%)
Age		
<5 year	84	60.87
=>5 years	54	39.13
Gender		
Male	76	55.07
Female	62	44.93
District		
BUDAKA	41	29.71
MBALE	34	24.64
BUTALEJA	17	12.32
BUTEBO	9	6.52
KIBUKU	8	5.8
BUKEDEA	7	5.07
NAMUTUMBA	7	5.07
SIRONKO	4	2.9
PALLISA	3	2.17
TORORO	3	2.17
BUGWERI	1	0.72
KUMI	1	0.72
MANAFWA	1	0.72
NAMISINDWA	1	0.72
SERERE	1	0.72

Figure 5: Box plot showing Age of the participants

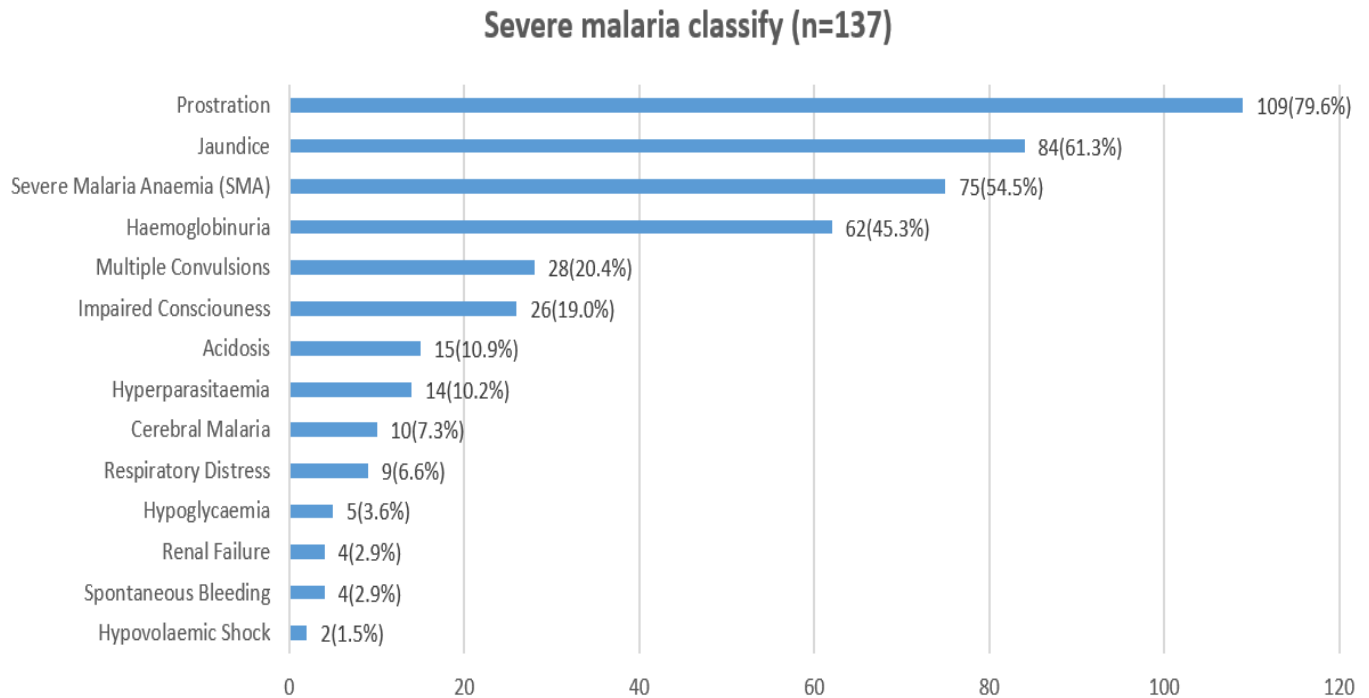


4.2 CLINICAL SPECTRUM OF SEVERE MALARIA

The clinical spectrum of severe malaria among our participants is summarised in **(Figure 6)**. Overall results show that prostration 109/137 (79.6%), jaundice 84/137(61.3%), severe malaria anaemia 75/137(54.7%), haemoglobinuria 62/137 (45.3%) were the leading manifestations. Others were multiple convulsions 28/137(20.4%), impaired consciousness 26/137(19.0%), lactic acidosis 15/137(10.9%), hyperparasitaemia 14/137(10.2%), cerebral malaria 10/137(7.3%), respiratory distress 9/137(6.6%), hypoglycaemia 5/137(3.6%), spontaneous bleeding 4/137 (2.9%), renal failure 4/137(2.9%), and hypovolemic shock 2/137(1.5%). Majority of the participants 136/137(99.3%) presented with history of fever. Other general features were loss of appetite in 124/137(90.5%) and 90/137 (65.7%) presented with abdominal pain and vomiting, 77/137(56.2%) had cough.

In the past medical history, 47/137(34.3%) had history of two or more admissions in the preceding year. A sizeable number 46/136 (33.6%) had received a blood transfusion before with 15/46 (32.6 %) of these having received blood five (5) or more times. Majority of those 37/46 (80.4%) received the blood transfusion in the recent past 3months. Oral antimalarial drugs were received by 89/137 (65%), 81/137(59.6%) had been treated with either intravenous quinine or artesunate and 29/137 (21.2%) with oral antibiotics prior to admission. Four 4/137 (2.9%) participants were known to have sickle cell disease and on chronic care. A sizeable proportion of 33/137 (24.1%) were afebrile (axillary temperature $<37.5^{\circ}\text{C}$) on physical examination despite fevers being reported in 99.3%.

Figure 6: A graph showing percentages of severe malaria phenotypes



* **Haemoglobinuria** (dark urine/ tea coloured urine), **cerebral malaria** (presence of coma / BCS ≤ 2)

Prostration

Prostration was the most commonly observed in 109/137 (79.6%). Majority of these 108/109 (99.1%) had reported a fever, 102/109 (93.6%) loss of appetite, 72/109 (66.1 %) vomiting and 71/109 (65.1%) had abdominal pain. Also 60/109 (55.0 %) had severe anaemia and 79/109 (63.3%) had received a blood transfusion in the current illness.

Jaundice

Jaundice was the second commonest among the clinical features observed in 84/137(61.3%) participants. Of those with jaundice 52/84 (61.9%) had severe malaria anaemia, 65/84 (77.4%) had reported abdominal pain or vomiting. Majority of those with jaundice 71/84 (93.4%) had elevated LDH, 42/84(50%) leukocytosis and 25/84(30.5%) had thrombocytopenia.

Severe malaria anaemia

This was observed in 75/137(54.7%) participants. Fifty-eight 58/75 (77.3%) had reported abdominal pain, 50/75 (66.7%) had vomiting, and 30/75 (40%) were passing dark urine. Tachycardia was present in 64/75 (85.3%), 09/75 (12%) had respiratory distress, and 10/75 (13.3%) had a weak pulse. LDH was elevated in 63/75(84%) participants, 37/75 (50.7%) had leukocytosis, 24/75(33.3%) thrombocytopenia and bilirubin was elevated in 33/75 (49.3%).

Haemoglobinuria (dark urine/ tea coloured urine / black water fever)

Haemoglobinuria was observed in 62/137(45.3%) participants. Majority of whom were males 39/62(62.9%) and those 5 years or more were 37/62(59.7%). A sizeable number 52/62(83.9%) had reported abdominal pain and 49/62(79.0%) vomiting. More than half 32/62(51.6%) had two (2) or more admissions in the previous year. In this group with haemoglobinuria, 52/62(83.9%) had jaundice, 36/62(58.1%) severe anemia and 49/62 (94.2%) had elevated LDH.

Multiple convulsions

This was observed in 28/137 (20.4%) participants and majority 25/28 (89.3%) were less than 5 years old. More than half 18/28 (64.3%) were febrile and 15/28(53.6%) had impaired consciousness while 4/28(14.3%) had respiratory distress. LDH was elevated in 24/28(85.7%) of the participants, 5/28 (17.9%) had hyperlactaemia and 2/28(7.1%) hypoglycaemia.

Impaired consciousness

This was found in 26/137 (19.0 %) participants. More than half 16/26 (61.5%) had reported vomiting, 11/26(42.3%) convulsions. A number of these patients had the following laboratory features: leukocytosis 14/26 (53.8%), hyperlactataemia 11/26(42.3%), hyperglycaemia 05/26 (19.2%), hypoglycaemia 3/26 (11.5%), and hyperpyrexia was in 4/26 (15.4%).

Acidosis (lactic acidosis)

Was observed in 15/137 (10.9%) participants. Majority 13/15(86.7%) had severe pallor and 10/15(66.7%) jaundice. Leukocytosis was observed in 10/15 (66.7%) and 12/15 (80%) had elevated lactic dehydrogenase (LDH).

Hyperparasitaemia

Was observed in 14/137 (10.2%) participants, 12/14 (85.7%) were below 5years of age. All participants 14/14 (100%) presented with fever. Almost all 13/14 (92.9%) had tachycardia on clinical exam.

Cerebral malaria

This was recorded in 10/137 (7.3%) participants. Eight 8/10 (80%) of participants with cerebral malaria were below 5 years. Five (5/10 and 50%) had convulsions and 5/10 (50%) had jaundice. Half of the participants with cerebral malaria 5/10 (50%) had hyperlactataemia and thrombocytopenia. Only one (1/10) was hypoglycaemic. However, we did not carry out lumbar punctures to rule out any other causes of coma.

Respiratory distress

This was a finding in 9/137 (6.6%) participants. Eight out of nine 8/9 (88.9%) had hyperlactataemia, 6/9(66.7%) had impaired consciousness and hypoxaemia was observed in 3/9(33.3%). Only one patient had a pneumonia as a co-infection.

Hypoglycaemia (Random Blood sugar <2.2mmol/L)

This was an uncommon feature in our study observed in only 5/137 (3.6%). Four of these were males with only one above 5 years. Out the five (5) participants, only one had convulsions and /or hyperlactataemia.

Spontaneous bleeding

Only 4/137 (2.9%) participants had reported spontaneous bleeding. All these participants had normal lactate, blood sugar levels and none had thrombocytopenia. Only one out of four had raised creatinine, elevated liver enzymes and presence of respiratory distress. The bleeding episodes included epistaxis (2/4), haematemesis in one participant and melaena in the other. None had prolonged bleeding from injection sites.

Renal failure (impairment)

Impaired renal function was observed in 4/137 (2.9%) participants. Two out of four (2/4) were passing dark urine. Jaundice, severe pallor and profound anaemia were present in all four participants. All had elevated BUN>20mg/dl and raised creatinine levels on laboratory evaluation. Two out four 2/4 (50%) had hyperlactataemia, respiratory distress and hypoxaemia. However all recovered without progression to full blown renal failure.

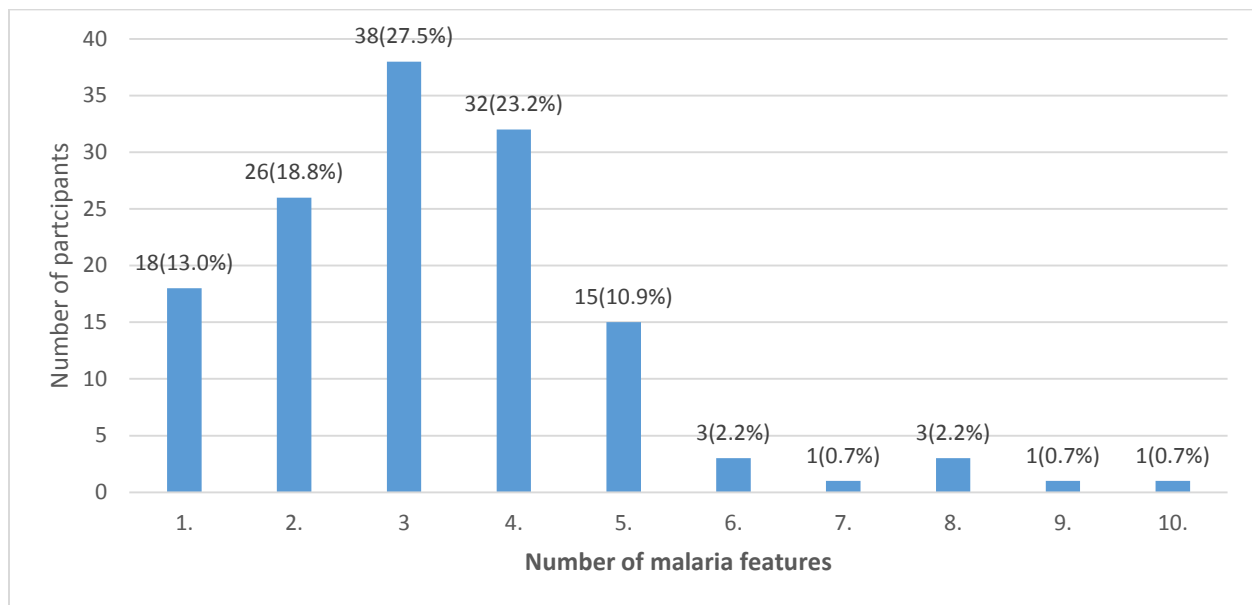
Hypovolemic shock

Hypovolemic shock was in only two 2/137(1.5%) participants. This was the least common of all features. Both had jaundice with severe conjunctival pallor, temperature gradient, tachycardia and capillary refill time > 3 seconds. Laboratory parameters indicated severe malaria anaemia, leukocytosis, and normal platelet count with elevated LDH and bilirubin levels.

Multiple severe malaria features

Figure 8 shows a number of patients presented with more than one severe malaria features. Twenty six- 26/138(18.8%) presented with two, 38/138(27.5%) three, 32/138(23.2%) four and 15(10.9%) five.

Figure 7: Combination of severe malaria features



4.3 POST THERAPEUTIC MALARIA PARASITAEMIA

Out of 138, data for 93 participants who reported for follow up visit was reviewed for this objective. The overall follow up rate was 93/138 (67.4%). Fifteen 15/138 (10.9%) only had telephone visits, 24/138 (17.4%) were lost to follow and 6/138 had died. Overall 31/93 (33.3%) had a positive malaria parasitaemia at follow up, more in males 18/31 (58.1%). Twenty-one 21/31 (67.7 %) were below 5 years. They all received artesunate at admission as initial antimalarial treatment. A bigger proportion of those who had parasitaemia at follow-up 27/31(87.1%) had been admitted for less than 5 days and only 4/31(12.9%) were admitted for 5 days or more. There was no marked difference in post therapeutic parasitaemia between those who got coartem (Artemether / Lumafentrine) 13/31 (41.9%) and DHA-PP (Dihydroartemesinin /piperaquine) 15/31 (48.4%) as an oral antimalarial after the parenteral artesunate (**Table 2**).

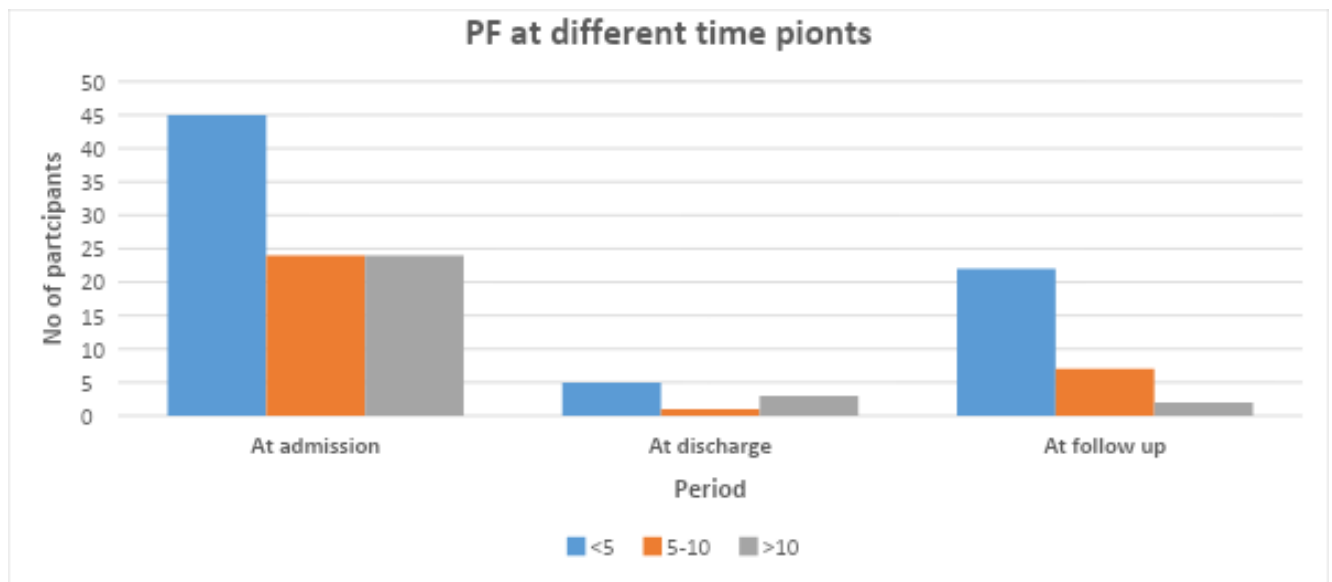
The distribution of malaria parasitaemia at admission was highest at <5% with 45/93(48.4%), both 5-10% and >10% parasitaemia were in equal proportions 24/93(25.8%) each. At discharge, parasitaemia positivity was only 9/93(9.7%). A big proportion 22/31(71.0%) of those with parasitaemia at follow up had <5% malaria parasitaemia and only 2/31(6.5%) had parasitaemia >10% at follow up (**Figure 9**).

Table 2: Characteristics of participants with parasitaemia at follow up

Variable	Follow up		
	N=93	Negative n=62	Positive n=31
Male	50(53.8)	32(51.6)	18(58.1)
Female	43(46.2)	30(48.4)	13(41.9)
<5years	59(63.4)	38(61.3)	21(67.7)
≥5 years	34(36.6)	24(38.7)	10(32.3)
COARTEM	40(43.0)	27(43.5)	13(41.9)
DHA-PP	41(44.1)	26(41.9)	15(48.4)
No oral ACT	12(12.9)	9(14.5)	3(9.7)
Hospital stay			
<5 days	73(78.5)	46(74.2)	27(87.1)
≥ 5 days	20(21.55)	16(26.8)	4(12.9)
Parasitaemia at Admission	93(100.0)	62(100.0)	31(100.0)
<5	45(48.4)	28(45.2)	17(54.8)
5-10	24(25.8)	17(27.4)	7(22.6)
>10	24(25.8)	17(27.4)	7(22.6)

COARTEM (artemether /Lumafentrine), DHA-PP (dihydroartemesinin/ piperaquine)

Figure 8: A bar graph showing the variation of parasitaemia at different time points



Overall fever was present in 92/93(98.9%) at admission and in 13/31(41.9%) at follow up of those who had parasitaemia at follow up. Abdominal pain was present in 64/93 (68.8%) at admission compared to a small proportion 9/31(29.0%) at follow up. The clinical features of children with a parasitaemia at follow up included; headache 8/31(25.8%), abdominal pain 9/31(29.0%), loss of appetite 4/31(13.3%), vomiting 2/31(6.5%), fever 13/31(41.9%), cough 6/31(19.4%), general body weakness 2/31(6.5%) and yellow eyes 1/31(3.2%) (**Table 3**).

Severe malaria features that were associated with parasitaemia at follow up included; jaundice 15/31(48.4%), haemoglobinuria 15/31(48.4%), severe malaria anaemia 17/31(54.8%) and prostration 23/31 (74.2%) **Table 4**.

Table 3: Table showing a comparison of the clinical features at admission and at follow up

Variable	Symptoms at admission					Symptoms at day 28				
	Total n=93	PF		COR(CI)	P-value	Total n=93	PF		COR(CI)	P-value
		Negative n=62	Positive n=31				Negative n=62	Positive n=31		
Headache	28(30.1)	18(29.0)	10(32.3)	1.2(0.5, 3.2)	0.670	11(11.8)	3(4.8)	8(25.8)	0.1(0.04,0.6)	0.011
Abdominal pain	64(68.8)	43(69.4)	21(67.7)	1.0(0.4, 2.7)	0.363	15(16.1)	6(9.7)	9(29.0)	0.3(0.1,0.8)	0.017
Loss of appetite	87(93.5)	59(95.2)	28(90.3)	0.4(0.1, 2.5)	0.380	11(12.0)	7(11.3)	4(13.3)	0.8(0.2,3.1)	0.777
Vomiting	62(66.7)	41(66.1)	21(67.7)	1.1(0.4, 2.7)	0.876	2(2.2)	0(0.0)	2(6.5)	1.0(-)	0.043
Diarrhea	17(18.3)	13(21.0)	4(12.9)	0.6(0.2, 1.9)	0.347	0(0.0)	0(0.0)	0(0.0)	1.0(-)	-
Fever	92(98.9)	61(98.4)	31(100.0)	-	-	24(25.8)	11(17.7)	13(41.9)	0.3(0.1,0.8)	0.012
Cough	54(58.1)	41(66.1)	13(41.9)	0.4(0.2, 0.9)	0.026	24(25.8)	18(29.0)	6(19.4)	1.7(0.6,4.9)	0.315
Shortness of breathing/ difficulty	8(8.6)	7(11.3)	1(3.2)	0.3(0.03,2.2)	0.220	0(0.0)	0(0.0)	0(0.0)	1.0(-)	-
Convulsions	6(6.5)	4(6.5)	2(6.5)	1.1(0.2, 6.6)	0.922	0	0	0	-	-
Prostration	29(31.2)	23(37.1)	6(19.4)	0.3(0.1, 1.1)	0.077	2	0	2	-	-
Yellow eyes	3(3.2)	3(4.8)	0(0)	-		1	0	1	-	-
Bloody Urine	12(12.9)	5(8.1)	7(22.6)	4.3(1.1, 16.4)	0.031	0	0	0	-	-
Loss of consciousness	2(2.2)	2(3.2)	0(0)	-		0	0	0	-	-

Table 4: Association of post therapeutic malaria parasitaemia and independent severe malaria manifestations

Severe malaria manifestations	Total n=93	Follow up PF		COR(95 CI)	P-value
		Negative n=62	Positive n=31		
Cerebral Malaria	5(5.4)	3(4.8)	2(6.5)	1.4(0.2,8.6)	0.745
Multiple Convulsions	18(19.4)	15(24.2)	3(9.7)	0.3(0.8,1.3)	0.095
Haemoglobinuria	41(44.1)	26(41.9)	15(48.4)	1.3(0.5,3.1)	0.555
Hypovolemic Shock	2(2.2)	2(3.2)	0(0.0)	-	0.312
Severe Malaria Anaemia	49(52.7)	32(51.6)	17(54.8)	1.1(0.5,2.7)	0.769
Prostration	74(79.6)	51(82.3)	23(74.2)	0.6(0.2,1.7)	0.363
Impaired Consciousness	14(15.1)	10(16.1)	4(12.9)	0.8(0.2,2.7)	0.682
Spontaneous Bleeding	3(3.2)	3(4.8)	0(0.0)	-	0.213
Hypoglycaemia	1(1.1)	0(0.0)	1(3.2)	-	0.155
Respiratory Distress	5(5.4)	4(6.5)	1(3.2)	0.5(0.1,4.5)	0.516
Acidosis (lactic acidosis)	6(6.5)	6(9.7)	0(0.0)	1.0(-)	0.073
Renal Failure	2(2.2)	2(3.2)	0(0.0)	1.0(-)	0.312
Jaundice	56(60.2)	41(66.1)	15(48.4)	0.5(0.2,1.2)	0.099
Hyperparasitaemia	8(8.6)	6(9.7)	2(6.5)	0.6(0.1,3.4)	0.601

PF; *P.falciparum* at follow up

4.4 OUTCOMES OF SEVERE MALARIA

Out of 138, 115 (83.3%) stayed up-to discharge and these were analysed for the prolonged hospitalisation. Five-5(3.6%) died during the admission and 18 (13.1%) were self-discharges (runaways)-(Table 5).

Table 5: Table of General in-hospital Outcome

Outcome	Frequency	Percentage (%)
Prolonged hospitalisation	115	83.3
Died	5	3.6
self-discharges(runaway)	18	13.1
Total	138	100

4.4.1 Prolonged hospitalisation

In the bivariate analysis, impaired consciousness OR 9.2 95% CI (2.6, 31.8) p- value 0.001, lactic acidosis, OR 6.1 95% CI (1.4, 25.0) P-value 0.012 and respiratory distress OR 8.2 95%CI (1.8-37.6) p-value=0.002 were significantly associated with prolonged hospitalisation. Hyperlactatemia, hypoxaemia and tachycardia are also associated with prolonged hospitalisation. However, the multivariate logistic regression analysis in Table 6 does not show a strong relationship between these features and prolonged hospitalisation.

Table 6: Multivariate logistic regression for factors associated with prolonged hospitalisation

Variable	COR (95% CI)	AOR(95% CI)	P-value
fever(>37.5° C)	0.9(0.3, 3.1)	1.7(0.3, 9.1)	0.518
Hyperpyrexia(>39.5° C)	2.9(0.7, 11.6)	6.4(0.7, 57.5)	0.098
Tachypnea	3.0(1.0, 8.8)	0.5(0.1, 2.1)	0.332
Liver (>2cm)	2.3(0.9, 6.0)	1.5(0.3, 8.3)	0.592
spleen(>2cm)	2.2(0.8, 5.7)	1.5(0.3, 8.5)	0.670
Cerebral Malaria	3.3(0.7, 15.9)	0.7(0.03, 12.3)	0.779
Impaired Consciousness	4.4(1.5, 12.9)	2.7(0.4, 18.4)	0.307
Respiratory Distress	4.4(0.8, 23.7)	0.5(0.012, 14.0)	0.736
Acidosis	6.1(1.4, 25.0)	6.5(0.6, 71.3)	0.121
Convulsions	2.9(0.9, 9.0)	4.4(0.8, 25.6)	0.098
Hyperlactatemia	5.3(1.6, 17.2)	1.5(0.2, 11.9)	0.682
Neutrophilia	7.6(2.3, 25.0)	5.3(0.8, 35.2)	0.083
Raised creatinine	6.0(1.8, 20.1)	5.4(0.9, 34.2)	0.071

4.4.2 MORTALITY

Data for only 99 participants was evaluated for this outcome. I included six (6) who died and 93 who came for follow-up. Excluded were those who were lost to follow up and those who had only telephone visits.

Overall mortality was (6/137) 4.4%. Mortality might have been higher in this cohort. Many of the children 18/138 (13.1%) were self-discharges (runaways) and many children did not return for follow-up. The practice in our communities is to take away from hospital care patients considered too ill to survive.

Table 7 shows the association between severe malaria manifestations and mortality. Cerebral malaria, impaired consciousness, respiratory distress, acidosis, hypoglycaemia and renal failure are significantly associated with mortality.

Table 7: Bivariate logistic regression of severe malaria manifestations in relation to mortality

Variable	Total n=99	Survival status		Case fatality Rate (%)	OR(95% CI)	P-value
		Survivors n=93(%)	Deaths n=6(%)			
Male	52(52.5)	50(53.8)	2(33.3)	-	1	
Female	47(47.5)	43(46.2)	4(66.7)	-	2.1(0.4,10.3)	0.366
<5years	64(64.7)	59(63.4)	5(83.3)	-	1	
≥5years	35(35.4)	34(36.6)	1(16.7)	-	0.5(0.1,3.0)	0.425
Cerebral Malaria	7(7.1)	5(5.4)	2(33.3)	28.6	8.9(1.5, 52.5)	0.015*
Multiple Convulsions	21(21.2)	18(19.4)	3(50.0)	14.3	4.1(0.9, 19.5)	0.075
Haemoglobinuria	44(44.4)	41(44.1)	3(50.0)	6.8	1.3(0.3, 5.9)	0.778
Hypovolemic Shock	2(2.0)	2(2.2)	0(0.0)	0.0	-	-
Severe Malaria Anaemia	54(54.5)	49(52.7)	5(83.3)	9.3	3.3(0.5, 21.0)	0.206
Prostration	80(80.8)	74(79.6)	6(100.0)	7.5	3.4(0.2, 63.0)	0.411
Impaired Consciousness	19(19.2)	14(15.1)	5(83.3)	26.3	3.0(1.1, 4.9)	0.002*
Spontaneous Bleeding	3(3.0)	3(3.2)	0(0.0)	0.0	-	
Hypoglycaemia	2(2.0)	1(1.1)	1(16.7)	50.0	16.8(1.5, 189.4)	0.022*
Respiratory Distress	8(8.1)	5(5.4)	3(50.0)	37.5	16.1(2.9, 89.3)	0.001*
Acidosis (lactic acidosis)	9(9.1)	6(6.5)	3(50.0)	33.3	13(2.5, 72.3)	0.002*
Renal Failure	3(3.0)	2(2.2)	1(16.7)	33.3	9.9(1.1, 90.0)	0.040*
Jaundice	60(60.6)	56(60.2)	4(66.7)	6.7	1.2(0.2, 5.9)	0.754
Hyperparasitaemia	9(9.1)	8(8.6)	1(16.7)	11.1	2.7(0.4, 19.11)	0.505

Multivariate logistic regression analysis does not demonstrate the strong link between these severe malaria features with mortality (**Table 8**).

Table 8: Multivariate table for predictors of mortality

Variable	COR (95% CI)	AOR(95% CI)
SPO2 (90 %-< 95%)	4.8(0.8, 27.0)	1.0(0.1, 14.7)
Hypoxaemia (SPO2< 90%)	5.0(0.6, 40.1)	0.3(0.03, 30.4)
Cerebral Malaria	8.9(1.5, 52.5)	1.0(0.03, 39.7)
Multiple Convulsions	4.1(0.9, 19.5)	1.7(0.1, 27.5)
Impaired Consciousness	3.0(1.1, 4.9)	7.4(0.5, 114.0)
Respiratory Distress	16.1(2.9, 89.3)	0.6(0.02, 25.5)
Acidosis (lactic acidosis)	13(2.5, 72.3)	17.2(0.4, 784.2)
Renal Failure	9.9(1.1, 90.0)	4.7(0.04, 539.2)

CHAPTER 5: DISCUSSION

This study offers many interesting comparisons with earlier studies done in Uganda and elsewhere.

5.1 SOCIAL DEMOGRAPHIC CHARACTERISTICS

Many of the children were below 5 years 84/138 (60.9%) (**Table 1**), similar to findings in many earlier studies carried out on children with severe malaria. However, our finding was lower than findings by Kalinga of 86% in Tanzania (Kalinga *et al.*, 2012) and 92% in Gabonese children by Dzeing-ella (Dzeing-ella *et al.*, 2005).

Many of our patients were from Budaka (29.7%) and Mbale (24.6%). These two districts consider MRRH as their District and Referral Hospital (**Figure 6**). More than half 76/138 (55.1%) of the participants were males in our study (**Table 1**). This was similar to findings in earlier studies, 57.7% by Olupot *et al.*, (2020), 54.9% by Aloyo and Idro (2004) and 54.5% in Gabon by Gyapong *et al.*, (2009). We have no reasonable explanation for this male predominance.

The average age for our participants was 4.0 years (**Figure 5**). This average age was higher than the findings by Kalinga who found 2.7 years as the average age of the participants (Kalinga *et al.*, 2012). Olupot *et al.*, (2020) reported a median age of 1.5 years. This might suggest that an increasing number of children above five years are now affected by severe malaria.

5.2 CLINICAL SPECTRUM OF SEVERE MALARIA

Fever was reported by a great majority (136/137) 99.3% similar to other studies where fever was above 90% (Olupot *et al.*, 2020; Idro and Aloyo, 2004; Gyapong *et al.*, 2009). Prostration was the commonest severe malaria feature in (109/137) 79.6% (**Figure 7**). This was much higher than the findings of Kalinga in Tanzania who found 29.1% of participants with prostration (Kalinga *et al.*, 2012) and Olupot-Olupot who found only 6.5% with prostration (Olupot *et al.*, 2020). However, it was lower than findings by Gyapong who found that all (100%) participants had prostration (Gyapong *et al.*, 2009). A sizeable proportion 33/137 (24.1%) were afebrile and this was similar to the findings by Olupot-Olupot of 27.9% and Gyapong of 25% (Olupot *et al.*, 2020; Gyapong *et al.*, 2009). This suggests malaria should still be suspected if there is any history of a fever but patient is afebrile.

A big proportion of our patients 89/137(65%) had already been treated with either oral or parental antimalarials. This practice is common in Uganda (Nsabagasani *et al.*, 2007).

Jaundice was the second most common feature in more than half 84/137(61.3%) of the participants. This is significantly higher than findings by Kalinga in Tanzania of 1.2% (Kalinga *et al.*, 2012), Olupot-Olupot in Uganda of 26.7% (Olupot *et al.*, 2020) and 20.1% by Kunuanunua in Congo (Kunuanunua *et al.*, 2015). However, our findings are similar to findings by Paasi *et al.*, (2022) in the same region. This high prevalence could possibly be due to the common undiagnosed haemoglobinopathies such as sickle cell anaemia (SCA) and Thalassemia that predispose to increased hemolysis in Eastern Uganda (Olupot-Olupot, 2014). In this study, only 4 /138 (2.9%) were documented Sickle cell Anaemia. In addition, in the Olupot-Olupot,(2014) study there were other red cell membrane defects found; 11.9% of spherocytosis and 11.9% of elliptocytosis that predispose to hemolysis. These were not screened for. Also the reported increased prevalence of haemoglobinuria in cases of severe malaria in this region might be a key factor. Jaundice was long reported more common in adults than children with severe malaria.

More than half of the children 75/137(54.7%) had severe malaria anaemia in this study. This was higher than findings by Olupot-Olupot who found 25.5% of his patients had severe anaemia in an earlier study conducted in the same area (Olupot *et al.*, 2020). It is also higher than the findings by Kalinga who found 14.2% among his patients in Tanzania (Kalinga *et al.*, 2012) and 41% in the Nigeria study (Ajetunmobi *et al.*, 2012). This finding though was lower than reported in Gabon of 67.8% severe anaemia in children who had severe malaria (Dzeing-ella *et al.*, 2005). In addition, the rising manifestation of passing dark red urine associated with intravascular hemolysis in our community during a malaria episode could be contributing factor (Olupot *et al.*, 2020). Also various severity of malnutrition and worm infestation is common in our community. All the children who died in this study had concurrent severe anaemia.

Haemoglobinuria (dark urine / tea coloured urine /black water fever) was a finding in 62/137 (45.3%) of our participants. This was much higher than findings from several other severe malaria studies across Africa; 25.3% in Congo (Kunuanunua *et al.*, 2015), 19.1% in Nigeria (Ajetunmobi *et al.*, 2012), 14% in Eastern Uganda (Olupot-Olupot, 2014) and 8% in Tanzania (Kalinga *et al.*, 2012). This could be as result of red cell abnormalities probably undiagnosed in this community.

Olupot-Olupot *et al* 2014 had earlier reported prevalences among his patients for HbAS 4.6%, HbSS 4.1%, alpha-thalassaemia homozygous in 3.7% and heterozygous 38.0% and G6PD deficiency in 15.6%. (Olupot-Olupot *et al.*, 2017). We also used visual inspection and did not exclude concomitant myoglobinuria known to occur in severe malaria especially cerebral malaria. I did not assess the possible association between haemoglobinuria and prior antimalarial usage. Like reported in many other studies haemoglobinuria commonly presents with jaundice (83%) and severe anaemia (58%).

Multiple convulsions were recorded in 28/137 (20.4%) of our participants which was higher than findings by Idro and Aloyo of 13.3% (Idro and Aloyo, 2004). It was however, lower than findings in Gabon of 39.2% (Dzeing-ella *et al.*, 2005) and Tanzania of 50.9% by Kalinga (Kalinga *et al.*, 2012). Repeated convulsions may be triggered by high fever, cerebral malaria/ cerebral edema, hypoxaemia, hypoglycaemia and electrolyte imbalance.

Impaired consciousness was a finding in 26/137(19.0%) of our participants. This was higher than findings by Olupot-Olupot of 7.9% who had impaired consciousness (Olupot *et al.*, 2020). Our finding was slightly lower than findings by Seidlien who found 21% of his patients had impaired consciousness (Seidlein *et al.*, 2012) . Impaired consciousness may arise from many events; post convulsion, hypoxaemia, hypoglycaemia and electrolyte imbalance.

Cerebral malaria was found in 10/137(7.3%).This was similar to findings by Olupot-Olupot who reported 7.9% (Olupot *et al.*, 2020) and Idro *et al* 7.2% (Idro and Aloyo,2004) patients with cerebral malaria . However ,it was lower than findings of 24% in Gabon (Dzeing-ella *et al.*, 2005), 30.1% in the Democratic Republic of Congo (Kunuanunua *et al.*, 2015) and Nigeria of 35.4% (Ajetunmobi *et al.*, 2012) children with cerebral malaria. In addition, a higher proportion of children below 5years had cerebral malaria, a finding that does not follow earlier belief of cerebral malaria occurring mainly in older children.

Fourteen – 14/137(10.2%) had hyperparasitaemia in this study. This was much lower than 62.4% finding by Olupot-Olupot of participants with hyperparasitaemia (Olupot *et al.*, 2020). It is slightly higher than findings by Kalinga of 6.1% (Kalinga *et al.*, 2012) and Faith of 1.9% (Access, 2017) participants with hyperparasitaemia. This could be due to prior antimalarial treatment noted in 65% of our patients, which could result in reduction of the parasitaemia before presentation. The

method of hyperparasitaemia determination, percentage parasitisation opposed to absolute count may partly explain the differences.

Respiratory distress was noted in 9/137(6.6%) of our participants. This was similar to findings by Kalinga in Tanzania where only 5.6% had respiratory distress (Kalinga *et al.*, 2012). But much lower than findings by Olupot-Olupot of 83.7% of participants had respiratory distress (Olupot-Olupot, 2014). It was also lower than findings from other studies; 31% in Gabon (Dzeing-ella *et al.*, 2005) and 17.1% in Uganda (Idro and Aloyo, 2004).

Acidosis and hyperlactataemia are major contributors to respiratory distress. Lactic acidosis was recorded in 15/137(10.9%) patients. Kalinga *et al* (2012) did report acidosis in only 3.4 % of his patients. These findings though were lower than 85.2% by Kunuanunua *et al.*,(2015) and 20.3% by Olupot-Olupot *et al.*,(2020).

A few participants 5/137(3.6%) had hypoglycaemia. This was similar to findings by Olupot-Olupot of 3.6% (Olupot-Olupot *et al.*, 2020) but lower than findings by Kunuanunua of 62.2% in the Republic of Congo (Kunuanunua *et al.*, 2015), 11.4% by Idro in Central Uganda (Idro and Aloyo, 2004) and 6.2% by Dzeing-ella in Gabon (Dzeing-ella *et al.*, 2005). Factors that potentiate hypoglycaemia include; not eating for long, diarrhea and vomiting, use of quinine or quinine like drugs, hyperparasitaemia and severe liver derangement. Hypoglycaemia is associated with high mortality.

Features suggestive of renal impairment were found in only 4/137(2.9%). None was reported in the study by Dzeing-ella in Gabonese children (Dzeing-ella *et al.*, 2005). Ajetunmobi *et al* in Nigerian reported that 6.25% of children with severe malaria and haemoglobinuria had acute renal failure (Ajetunmobi *et al.*, 2012). Some of these progressed to severe acute kidney injury (AKI) of which a number of them died and others recovered fully after dialysis. Acute renal failure as a complication of severe malaria is noted more commonly amongst adult patients. Purohit *et al* (2016) reported a prevalence of 36.2 % among his patients (Purohit *et al.*, 2016).

Four-4/137(2.9%) reported spontaneous /abnormal bleeding. These might have had a disseminated intravascular coagulopathy and or severe liver dysfunction. A small proportion of our participants 2/137(1.5%) had shock. This was much lower than findings by Olupot-Olupot of 62% (Olupot-

Olupot, 2014) and Kalinga of 30.6% (Kalinga *et al.*, 2012) prevalences for shock. Gyapong in Central Africa did not report any patient with shock (Gyapong *et al.*, 2009).

Lastly, there were many participants with multiple features of severe malaria (**Figure 8**). One hundred twenty-120/138 (87%) patients presented with two or more manifestations of severe malaria. Occurrence of a combination of severe malaria manifestations is associated with high mortality. Only one child in this study was confirmed having HIV/AIDS and had multiple features of severe malaria.

5.3 OUTCOMES OF SEVERE MALARIA

The outcome of *P.falciparum* severe malaria is highly dependent on the quality of care provided before and during admission depending on the available medical resources (Idro and Aloyo, 2004). Poor outcomes include mortality and prolonged hospitalisation.

5.3.1 Prolonged hospitalisation

On average hospital stay in Mbale RRH is 3 days .Twenty three-23/115(20%) of our participants had prolonged hospitalisation of greater or equal to 5 days. This was similar to findings by Saravu who found 21.8% of his cases had prolonged hospitalisation (Saravu, Rishikesh and Kamath, 2014). Presence impaired consciousness were 9.2 times more likely to have prolonged hospitalisation with a p-value= 0.001. Those with acidosis were 6.1 more likely to have prolonged hospitalisation, this was significant with a p-value =0.012). Hypoxaemia (p-0.002) was also significantly associated with prolonged hospitalisation. Prolonged hospitalisation was observed in half (7/14) of the participants with hyperlactataemia, more than half 8/13(61.5%) with impaired consciousness and 5/8 (62.5%) of those who had respiratory distress.

Haemoglobinuria, renal failure and leukocytosis were found to be associated with prolonged hospital stay by Saravu (Saravu, Rishikesh and Kamath, 2014). Paasi et al (2022) found abdominal tenderness, body pains (including foot, chest and hand pain) and fever to be associated with prolonged hospitalisation in a group of children with haemoglobinuria (Paasi *et al.*, 2022). Generally, few studies have reported on prolonged hospitalisation in severe malaria among children.

5.3.2 Post-therapeutic parasitaemia

Follow up at day 28 was low, only 93/137(67.9%) turned up. Thirty one-31/93 (33.3%) had post therapeutic parasitaemia at follow up. This was higher than findings by Duong of 19.2% (Duong, abstract) parasitaemia after day 28 and Kefas of 8.6 % parasitaemia in Western Uganda (Mugittu *et al.*, 2007). However, this was lower than the findings by Byakika who found 63.3% of participants with post therapeutic parasitaemia (Byakika-Kibwika *et al.*, 2017). Parasitaemia at day 28 could have been a new infection, re-infection or parasitological failure. Molecular studies such as polymerase chain reaction (PCR) would differentiated the three. The children were treated with intravenous artesunate followed by either A/L (artemether-lumefantrine) or DHA-PP (dihydroartemisinin /piperaquine).The administration of oral medication dosing and adherence was not studied. However, the presence of post therapeutic parasitaemia at follow up was not different among participants who had A/L vs DHA-PP. The presence of 9/93 (9.7%) parasitaemia at discharge could suggest persistent or resistant strains that later multiplied in some of the individuals giving rise to 28 day parasitaemia. The prevalence of a fever of 41.9% was similar to findings by Olliaro of 42.4% with fever and post therapeutic parasitaemia (Olliaro *et al.*, 2008)

5.3.3 Mortality

The overall mortality was 4.4%, which was higher than 3.1% reported by Aloyo and Idro in Central Uganda (Idro and Aloyo, 2004). However, this mortality was lower than the reports from multiple studies across Africa; 4.6% in Tanzania by Kalinga(Kalinga *et al.*, 2012),8% in Nigeria (Ajetunmobi *et al.*, 2012), 8.9% in Gabon (Dzeing-ella *et al.*, 2005),9.5% by Olupot-Olupot (Olupot-Olupot, 2014) and 9.8% by Seidlein (Seidlein *et al.*, 2012). Interestingly no mortality was recorded in a study carried out in Ghana (Gyapong *et al.*, 2009). Our mortality in this study could actually have been higher. There were many runaways and lost to follow up. In this study respiratory distress (p-0.001), acidosis (p-0.002), impaired consciousness (p-0.002), cerebral malaria (p-0.015) and renal failure (p-0.04) were significantly associated with mortality. In Tanzania severe acidosis and symptomatic severe anaemia were major predictors of death(Kalinga *et al.*, 2012). In Central Uganda, Idro and Aloyo found impaired consciousness, multiple convulsions , jaundice and respiratory distress were significantly associated with death (Idro and Aloyo, 2004). In a multicenter study across 9 countries, acidosis, impaired consciousness, cerebral

malaria ,increased Blood Urea Nitrogen(BUN) and underlying chronic illness were significantly associated with mortality (Seidlein *et al.*, 2012). Olupot-Olupot found that severe anaemia , hyperlactataemia , hypoxaemia and hepatomegaly were associated with high mortality (Olupot *et al.*, 2020). Cserti-gazdewich also found that cerebral malaria, hypoxia, severe thrombocytopenia, leukocytosis and lactic acidosis were associated with high mortality (Cserti-gazdewich *et al.*, 2013).

5.4 STUDY STRENGTHS AND LIMITATIONS

This is one study describing the incidence of post therapeutic parasitaemia in children with severe malaria in Eastern Uganda over the last five years. The following were the possible strengths of the study;

- Eastern Region (Mbale) has a high malaria transmission throughout the year with possible Entomological inoculation Rate (EIR) of 100 or more.
- This was a prospective study with real time case management and investigations.
- Organized follow up for patients.

However, there were some limitations in this study and these included;

- Short duration of the study
- Small sample size
- Lumbar puncture / CSF studies and blood cultures were not done. This is because the children with possible cerebral malaria were deeply comatose.
- PCR/molecular studies were not possible and therefore not done.
- Low follow up rate at day 28.
- The adherence to antimalarial therapy could not be closely tracked due to the inadequate staffing to capture and administer antimalarial.
- Neurological sequelae of severe malaria were not looked for and documented.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 CONCLUSIONS

- i) The average age of children with severe malaria was 4.0 years, higher than the 1.5 years in literature from earlier studies. This suggests that an increasing number of older children are now affected by severe malaria, which was uncommon in the past decades.
- ii) In this study, the clinical spectrum of severe malaria shows a change with more prostration, jaundice and not severe malaria anaemia, respiratory distress or shock, which were reported in earlier studies. This probably, supports the reported epidemiological transition in malaria transmission and disease.
- iii) With the current management of severe malaria with intravenous artesunate the post therapeutic parasitaemia after 28 days was 33.3% amongst our participants. This could be recrudescence, new infection, or resistance. Molecular studies are needed to distinguish the three possibilities.
- iv) Prolonged hospitalisation of greater or equal to 5 days in 20% of our patients calls for more studies on this aspect.
- v) Overall mortality of 4.4% shows a reduction from those documented in earlier studies. This is probably due to the improving severe malaria case management. This mortality though is not yet good enough for the National Malaria Control Program (NMCP) target of 2%.

6.2 RECOMMENDATIONS

- i) In view of the high malaria prevalence, there need to strengthen malaria control measures in the region.
- ii) Enhancing close monitoring and treatment of severe malaria cases in order to improve outcomes.
- iii) Locally to start a regular severe malaria follow up clinic.
- iv) Since many of the deaths had severe malaria anaemia (SMA), there is need to improve availability of blood and related supplies in hospitals.
- v) Further documentation of the clinical spectrum of severe malaria at regular intervals and in different geographical locations.

Recommendations for further research

- i) Molecular studies to differentiate new infection, resistance and recrudescence in malaria infection.
- ii) Further studies investigating the immunological aspects resulting into severe malaria manifestations with low parasitaemia.
- iii) Prolonged hospitalisation as an outcome should be studied in a bigger cohort.

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APPENDICES

APPENDIX A-1: ETHICAL APPROVAL

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Type: Initial Review



17/09/2021

Re: MRRH-2021-76: CLINICAL PRESENTATION, PARASITE RECRUDESCENCE AND OUTCOMES OF SEVERE MALARIA IN EASTERN UGANDA: A PROSPECTIVE STUDY., Version 1.0 , 2021-05-25

I am pleased to inform you that the Mbale Regional Referral Hospital REC, through expedited review held on 13/08/2021 approved the above referenced study.

Approval of the research is for the period of 17/09/2021 to 17/09/2022.

As Principal Investigator of the research, you are responsible for fulfilling the following requirements of approval:

1. All co-investigators must be kept informed of the status of the research.
2. Changes, amendments, and addenda to the protocol or the consent form must be submitted to the REC for re-review and approval prior to the activation of the changes.
3. Reports of unanticipated problems involving risks to participants or any new information which could change the risk benefit: ratio must be submitted to the REC.
4. Only approved consent forms are to be used in the enrollment of participants. All consent forms signed by participants and/or witnesses should be retained on file. The REC may conduct audits of all study records, and consent documentation may be part of such audits.
5. Continuing review application must be submitted to the REC **eight weeks** prior to the expiration date of **17/09/2022** in order to continue the study beyond the approved period. Failure to submit a continuing review application in a timely fashion may result in suspension or termination of the study.
6. The REC application number assigned to the research should be cited in any correspondence with the REC of record.
7. You are required to register the research protocol with the Uganda National Council for Science and Technology (UNCST) for final clearance to undertake the study in Uganda.

The following is the list of all documents approved in this application by Mbale Regional Referral Hospital REC:

No.	Document Title	Language	Version Number	Version Date
1	supervisor APPROVAL	ENGLISH	VERSION 1.0	2021-09-14
2	STORAGE CONSENT	ENGLISH	VERSION 1.0	2021-08-15
3	Informed consent for caretakers(parents/ guardians)	ENGLISH	VERSION 1.0	2021-08-15
4	CHILD ASSENT FOR CHILDREN OF 8-12 YEARS	ENGLISH	VERSION 1.0	2021-08-15
5	RISK MANAGEMENT PLAN	ENGLISH	VERSION 1.0	2021-08-26
6	CIRRICULUM VITAE	ENGLISH	VERSION 1.0	2021-08-26
7	VERBAL CONSENT	ENGLISH	VERSION 1.0	2021-08-25
8	ANTIPLAGARISM REPORT	ENGLISH	1.0	2021-09-06
9	Screening log	English	Version 1.0	2021-05-25
10	Case Report Forms	English	Version 1.0	2021-05-25
11	Protocol	English	Version 1.0	2021-05-25

Yours Sincerely,



Fred Bulamini

For: Mbale Regional Referral Hospital REC

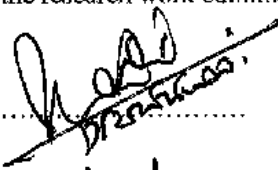


APPENDIX A-2: APPROVALS

Version 1.0 (25/MAY/2021)

SUPERVISORS' APPROVAL

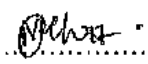
We approve that the research work culminating from this proposal has been developed under our guidance and supervision.

Signature.....

Date.....14/09/2021

Professor Peter Olupot-Olupot

MB.Ch.B, MPLI, PhD, SRF, FUNAS

Signature.....

Date.....14/SEP/2021

Dr. Chebet Martin

MB.Ch.B, MMed (Paeds)

CLEARANCE FROM THE HIGHER DEGREES COMMITTEE



P.O. Box 236, Tororo, Uganda
Gen: +256 - 45 444 8838
Fax: +256 - 45 4436517
Email: info@adm.busitema.ac.ug
www.busitema.ac.ug

August 13, 2021

To the Candidates who Defended their Dissertation Research Proposals cc. Dean

cc. Deputy Dean

cc. HoD Public Health cc. HoD

Paediatrics cc. SAR cc. Mbale

RRH-REC

Dear Candidates

SINo.	CANDIDATE	REGISTRATION NO.	RESEARCH TOPIC
1	Mugasha Edgar	BU/GSI 91MPH/21	A Prevalence and Factors Associated with Iron Deficiency Anemia Among School Going Adolescents in Mbale City, Eastern Uganda
2	Eudu James	BU/GS19/MPH/14	Characteristics And Treatment Outcomes of COVID-19 Patients Under Home Based Care Management
3	Apolot Consiliate	BU/GS19/MPH/5	Prevalence and Factors Associated with Herbal Medicine and Conventional Medicine Use: A Comparative Study
4	Omara Godfrey	BU/GS19/MPH/32	Predicting Treatment Outcomes Among HIV/TB Co-Infected Patients in Uganda: A Retrospective Cohort Stud
5	V',fenani Daniel	BU/GS19/MPH/41	Neonatal Skin Care Practices in Eastern Uganda: A Mixed Methods Stud
6	Etolu William	BU/GSI 9/ IPH/14	Assessing Efficiency of Implementation of Tuberculosis Diagnostic Approaches in Children (0-14 Years) at Lower Level Health Facilities of Serere District
7	Ouni Patrick Diox	BU/GSI 9/MPH/36	Assessment Of COVIO-19 Vaccine Hesitancy Amongst Health Care Workers in Dokolo District
8	Tuwa Ally Hassan	BU/GS19/MPH/44	Prevalence and Factors Influencing Isoniazid Preventive Therapy Uptake Among Children Living with HIV Aged Below d O Years in Mwanza Re ion
9	Alunyo Jimmy Patrick	BU/GS19/MPH/3	Prevalence, Risk Factors and Outcomes of in School Teenage Pregnancy During COVID-19 In Pakwach District, Uganda
10	Abeso Angella	BU/GS19/MPH/d	Community Assessment Of Household Dietary Practices and Nutrition Status of Children 6-59 Months in Namatala
11	Onyango Jagire	BU/GS19/MPH/34	Enablers For and Post-Vaccination Experiences with

			COVID-19 Vaccine in Tororo, District, Eastern Uganda
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RE: OUTCOME OF RESEARCH PROPOSAL ASSESSMENT HELD ON AUGUST 13 2021.

I am pleased to provide a report on the above activity as follows

There were 14 eligible candidates (11 from the Department of Public Health and 3 from the Department of Paediatrics & Child Health). The candidates listed (MPH) on page 2 and MPC on page 3 have been recommended to as follows:

1. Include hypotheses in your research proposals.
2. Proceed to the Research Ethics Committee to complete procedures and obtain letter of clearance before commencement of data collection.
3. Work with their respective supervisors to address issues that were raised at review (please contact your HoD the week of 16 August 2021 for the specific comments).

Yours sincerely,

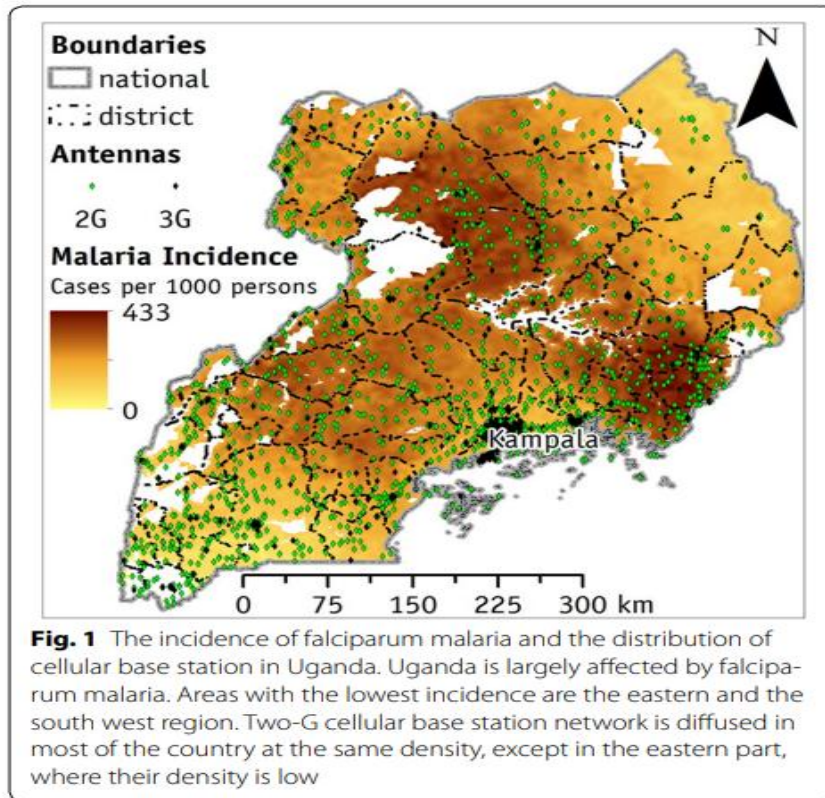


Professor (Dr) Peter Olupot-Olupot, MB.ChB, MPH, PhD & FUNAS
CHAIR I-IDC BUSITEMA UNIVERSITY FACULTY OF HEALTH SCIENCES

MPC CANDIDATES

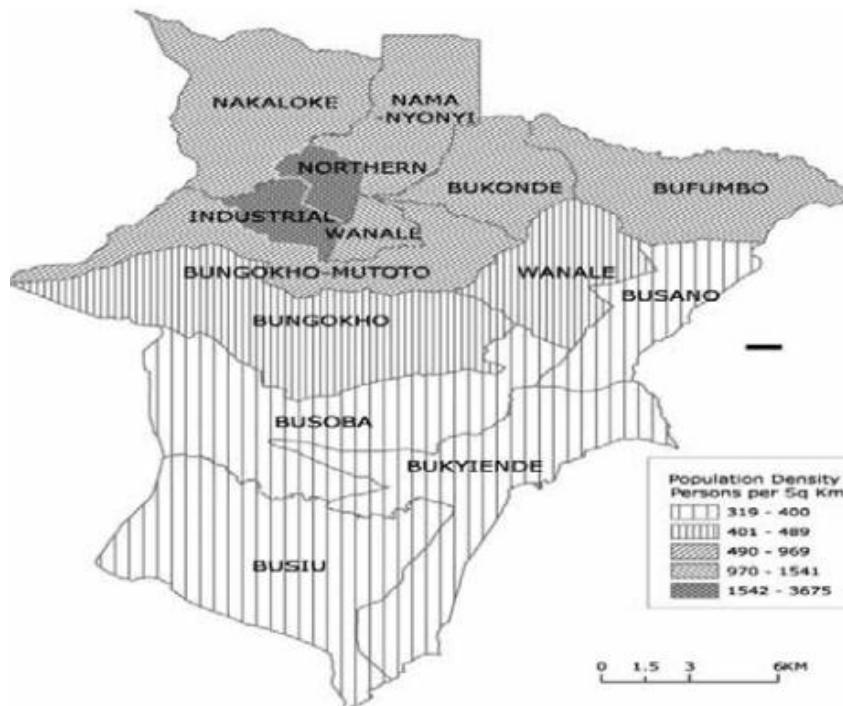
<u>REGISTRATION</u>		<u>RESEARCH</u>	
SIN10.	CANDIDATE	<u>REGISTRATION</u> NO	RESEARCH TOPIC
1	Egiru Emma Isaiah Eregu	BU/GS18/MPC/2	Malaria Parasite Density and Patient Outcomes Among Children Admitted with Severe Malaria in Mbale Hospital; A Cross Sectional Study
2	Namayanja Cate	BU/GS18/MPC/4	Severe Malaria Presentation, Malaria Parasite Recrudescence and Outcomes Among Children in Eastern Uganda: A Prospective Study
3	Naizuli Ketty	BWGS18/MPC/3	Prevalence and Risk Factors Associated with Renal Dysfunction and its Contribution To Morbidity Among Children With Sickle Cell Anaemia At Mbale Regional Referral Hospital In Eastern Uganda: A Prospective Study

APPENDIX A-3: MAPS



Source (Larocca, Moro Visconti and Marconi, 2016)

MAP OF MBALE SHOWING ADMINISTRATIVE BOUNDARIES

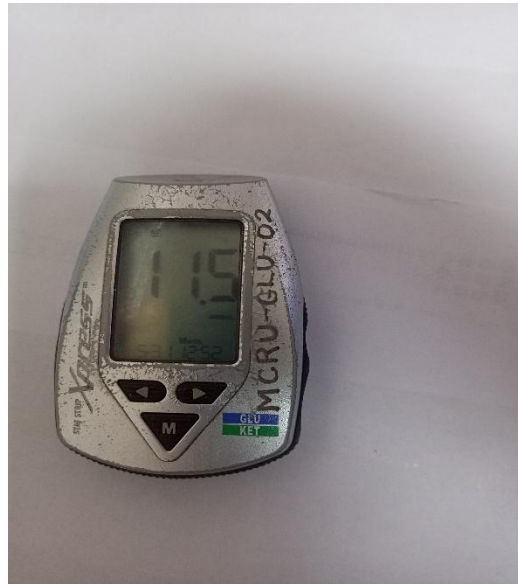


Source: Municipal Council Records

APPENDIX A-4:PHOTOS



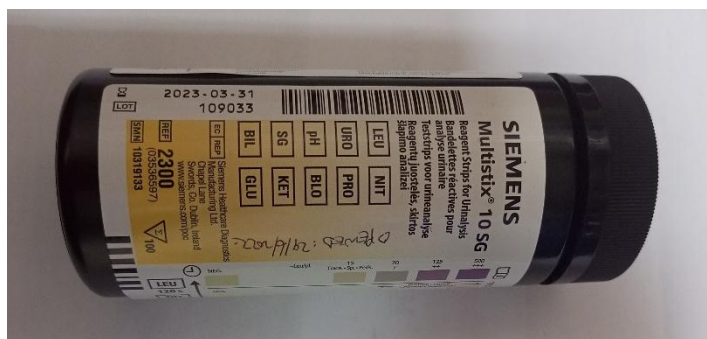
LACTOMETER



GLUCOMETER



HAEMOCUE



URINE DIPSTICKS

Photos continued



DxH500 HEAMATOLOGY MACHINE



MALARIA RDT



i-STAT

APPENDIX A- 5: WORK PLAN

Periodical activity	MAY-21 JUN-21	JULY 2021	AUG 2021	SEP 2021	OCT-21- JAN-22	FEB 2022	MAR 2022	APR 2022
Periodical activity								
Concept development								
Concept presentation								
Proposal development								
Proposal presentation								
Ethical approval								
Data collection								
Data entry And analysis								
Report writing								
final report submission								

APPENDIX A- 6: CONSENT FORMS

V 1.0

ICF for caretaker

15/AUG/2021

INFORMED CONSENT FOR CARE TAKERS (GUARDIANS /PARENTS)

STUDY TITLE: Clinical presentation , parasite recrudescence and outcomes of severe malaria among children in Eastern Uganda: a prospective study

Investigator : NAMAYANJA CATE , BUSITEMA UNIVERSITY TEL:+256771430347

email :catenamayanja@gmail.com

Background and rationale for the study:

Severe malaria is a major health problem in Uganda and very common in Eastern Uganda. It is one of leading cause of illness and death in children below 12 years of age. Severe malaria is highly due to *p.falciparum* species. The complications include severe anemia, respiratory distress, convulsions, passing of dark urine, bleeding, kidney failure and changing of mental state. There are many readmissions and febrile illnesses one of the causes being following a severe malaria episode in Eastern Uganda. These could be due reactivation of the malaria parasite that could have responsible for the first episode of severe malaria in a red blood cell (recrudescence). This normally occurs after 28 days from the first episode but not known among children in Mbale. The study will be conducted in Mbale Regional Referral Hospital in the paediatric unit for the next 6 months after commencement. It will be conducted among children with severe malaria ages 2 months to less than 12 years. We are to recruit and follow up a total of 301 participants will be in this study.

Study purpose: In this study we are trying to understand the burden and rate of reactivation of malaria in children who have had severe malaria that present in Acute Care Unit of Mbale Regional Referral Hospital (MRRH). It also aims at describing the factors that are related to the this reactivation. This will also inform clinicians on the patterns of recurrence and probably pave way for improved care in susceptible individuals and future

Procedures: At admission, a quick assessment will be carried out including taking vital signs (heart rate, oxygen saturation, respiratory rate, temperature, and blood pressure), conscious level, rapid diagnostic test (RDT) for malaria and a structured questionnaire will be completed in view of the clinical symptoms for severe malaria. Your child will have the usual daily assessments including vital signs . We shall carry out blood tests including blood slide for malaria parasites



(*p.falciparum* malaria) on admission day(0)and follow up (28). Rapid diagnostic test (RDT)for malaria will be used in screening . In addition, clinical history and vitals will be taken on all these visits. Additional genetic tests will be carried out on the samples for pair positive malaria test on day 0 and 28 (follow up). A total volume of blood to be taken off during the entire study period will be approximately 4 mls (about 1½ teaspoonful) of venous blood .

Who will participate in the study? The study is targeting children between 2 months and 12 years having a positive blood slide malaria caused by *p.falciparum* species with clinical symptoms or laboratory findings of severe malaria. The study will continue for 4 weeks (28 days), with admission as the starting day. However, we will ask you to return your child to return after 28 days (after 4 weeks from the initial days) visit after admission. This will be a follow up , some tests will be carried out and simple checklist will be carried out concerning the child's health ,this will last one hour approximately.

Risks/Discomforts: For this study, the primary risk will be minimal pain during sampling for the blood. However, no other risks will be encountered as the no other interventions will be carried out on the participants and all care will be as per the hospital standards of care.

Benefits: Your child will not benefit directly from the study. However, the benefits will be to the society because of knowledge about malaria recrudescence (reactivation of malaria in those declared cured) in children with severe malaria enhancing proper case management in the future.

Alternatives: it is not compulsory for your child to participate in the study. Your child will receive medical care as per the national guidelines even when they participate in study or not.

Cost: during the conduct of the study as far as the participation is concerned you will not incur any costs. The sponsor of the study EDCTP will incur the bills for the tests.

Compensation/Reimbursement for participation in the study:

It will not cost you any money to take part in this study. Transport refund of ten thousand (10,000/=) Uganda shillings will be provided when you come for your next appointment.

Questions: You are free to ask questions any time, you may contact the researcher using a phone Tel :(+256 771430347 or the research assistants when are interacting with you.

Questions about participant's rights:

In case you have questions / concerns it is your right as participant to have them addressed .The study has been reviewed by Mbale Regional Referral Hospital REC and they can contact the



chairperson on mobile 0793197393 or the office on 0393280584. You are free to withdraw from the study any time during the study period. Your participation in this study is voluntary and you can opt out any time. However, your failure to participate will not affect the medical care of your child in any way.

Confidentiality:

The results of this study will be kept strictly confidential and used only for research purposes. Your identity will be concealed in as far as the law allows. Your name will not appear anywhere on the coded forms with the information. Paper and computer records will be kept under lock and key and with password protection respectively. For any further questions, you may contact Cate Namayanja Cate Tel :(+256 771430347 or the chairperson MRRH-REC Dr. Fred Bulamba Telephone number +256793197393 (MRRH-REC-IRB) 0414671162 / or Uganda National Council of Sciences and Technology. Tel: (+256) 772-404970 or (+256)-41-250431

STATEMENT OF CONSENT/ASSENT

..... has described to me what is going to be done, the risks, the benefits involved and my rights regarding this study. I understand that my decision to participate in this study will not alter my usual medical care. In the use of this information, my identity will be concealed. I am aware that I may withdraw at any time. I understand that by signing this form, I do not waive any of my legal rights but merely indicate that I have been informed about the research study in which I am voluntarily agreeing to participate. A copy of this form will be provided to me.

Name of parent/guardian..... Signature of parent/guardian
Date

Name of witness.....Signature of witness.....
Date

Name of staff.....Signature of staff
Date.....



CHILD ASSENT (FOR CHILDREN AGED 8-12 YEARS)

STUDY TITLE: Clinical presentation , parasite recrudescence and outcomes of severe malaria among children in Eastern Uganda: a prospective study

Investigator : NAMAYANJA CATE , BUSITEMA UNIVERSITY TEL:+256771430347

email :catenamayanja@gmail.com

Background and rationale for the study:

Severe malaria is a major health problem in Uganda and very common in Eastern Uganda. It is one of leading cause of illness and death in children below 12 years of age. Severe malaria is highly due to *p.falciparum* species. The complications include severe anemia, respiratory distress, convulsions, passing of dark urine, bleeding, kidney failure and changing of mental state. There are many readmissions and febrile illnesses one of the causes being following a severe malaria episode in Eastern Uganda. These could be due reactivation of the malaria parasite that could have responsible for the first episode of severe malaria in a red blood cell (recrudescence). This normally occurs after 28 days from the first episode but not known among children in Mbale. The study will be conducted in Mbale Regional Referral Hospital in the paediatric unit for the next 6 months after commencement of the study. It will be conducted among children with severe malaria ages 2 months to less than 12 years. We are to recruit and follow up a total of 301 participants will be in this study.

Study purpose: In this study we are trying to understand the burden and rate of reactivation of malaria in children who have had severe malaria that present in Acute Care Unit of Mbale Regional Referral Hospital (MRRH). It also aims at describing the factors that are related to the this reactivation. This will also inform clinicians on the patterns of recurrence and probably pave way for improved care in susceptible individuals and future care.

Procedures: At admission, there will be a quick assessment including vital signs (heart rate, oxygen saturation, respiratory rate, temperature, and blood pressure); conscious level, rapid diagnostic test (RDT) for malaria and a structured questionnaire completed in view of the clinical symptoms for severe malaria. You will have the usual daily assessments including vital signs. We shall carry out blood tests including blood slide for malaria parasites (*p.falciparum* malaria) on



admission day(0)and follow up (28). Rapid diagnostic test (RDT)for malaria will be used in screening . In addition, clinical history and vitals will be taken on all these visits. Additional genetic tests will be carried out on the samples for pair positive malaria test on day 0 and 28(follow up). A total volume of blood to be taken off during the entire study period will approximatley 4 mls (about 1½ teaspoonful) of venous blood .

Who will participate in the study? The study is targeting children between 2 months and 12 years having a positive blood slide malaria caused by *p.falciparum* species with clinical symptoms or laboratory findings of severe malaria .The study will continue for 4weeks (28 days), with admission as the starting day . We shall ask your parents to bring you back for day 28 appointment (after 4 weeks from the initial days) visit after admission. This will be a follow up , some tests will be carried out and simple checklist will be carried out concerning your health ,this will last one hour approximately.

Risks/Discomforts: For this study, the primary risk will be minimal pain during sampling for the blood. However, no other risks will be encountered as the no other interventions will be carried out on the participants and all care will be as per the hospital standards of care.

Benefits: You will not benefit directly from the study. However, the benefits will be to the society because of knowledge about malaria recrudescence (reactivation of malaria in those declared cured) in children with severe malaria enhancing proper case management in the future.

Alternatives: it is not compulsory for you to participate in the study. You receive medical care as per the national guidelines even when they participate in study or not.

Cost: during the conduct of the study as far as the participation is concerned you will not incur any costs. The sponsor of the study EDCTP will incur the costs for the tests carried out.

Compensation/Reimbursement for participation in the study:

Transport refund of ten thousand (10,000/=) Uganda shillings will be provided when you come for your appointment.

Questions: You are free to ask questions any time, you may contact the researcher using a phone Tel :(+256 771430347 or the research assistants when are interacting with you.

Questions about participant's rights:

In case you have questions / concerns it is your right as participant to have them addressed .The study t has been reviewed by Mbale Regional Referral Hospital REC and they can contact the



CONSENT FORM FOR THE STORAGE OF RESEARCH STUDY SAMPLES

STUDY TITLE: Clinical presentation , parasite recrudescence and outcomes of severe malaria among children in Eastern Uganda: a prospective study

Investigator : NAMAYANJA CATE , BUSITEMA UNIVERSITY TEL:+256771430347

email :catenamayanja@gmail.com

Background and rationale for the study:

Severe malaria is a major health problem in Uganda and very common in Eastern Uganda. It is one of leading cause of illness and death in children below 12 years of age. Severe malaria is highly due to *p.falciparum* species. The complications include severe anemia, respiratory distress, convulsions, passing of dark urine, bleeding, kidney failure and changing of mental state. There are many readmissions and febrile illnesses one of the causes being following a severe malaria episode in Eastern Uganda. These could be due reactivation of the malaria parasite that could have responsible for the first episode of severe malaria in a red blood cell (recrudescence). This normally occurs after 28 days from the first episode but not known among children in Mbale. The study will be conducted in Mbale Regional Referral Hospital in the paediatric unit for the next 6 months after commencement. It will be conducted among children with severe malaria ages 2 months to less than 12 years. We are to recruit and follow up a total of 301 participants will be in this study.

Purpose: In this study we are trying to understand the burden and rate of reactivation of malaria in children who have had severe malaria that present in Acute Care Unit of Mbale Regional Referral Hospital (MRRH). It also aims at describing the factors that are related to the this reactivation. This will also inform clinicians on the patterns of recurrence and probably pave way for improved care in susceptible individuals and future.

Procedures: the study will involve real time tests and those carried out later during the study period. The tests will be carried out in Mbale Regional Referral Hospital. The later tests will require us to store the blood samples taken off during the two visits (admission and day 28 appointment). The blood sample stored will be part of the total 4mls that will be taken off. The stored samples will be for carrying out genetic testing for malaria (PCR for *P.falciparum* malaria).



chairperson on mobile 0793197393 or the office on 0393280584. You are free to withdraw from the study any time during the study period.

Your participation in this study is voluntary and you can opt out any time. However, your failure to participate will not affect the medical care of your child in any way.

Confidentiality:

The results of this study will be kept strictly confidential and only for research purposes. Your identity will be concealed in as far as the law allows. Your name will not appear anywhere on the coded forms with the information. Paper and computer records will be kept under lock and key and with password protection respectively. For any further questions, you may contact Cate Namayanja Cate Tel :(+256 771430347 or the chairperson MRRH-REC Dr. Fred Bulamba Telephone number +256793197393 (MRRH-REC-IRB) 0414671162 / or Uganda National Council of Sciences and Technology. Tel: (+256) 772-404970 or (+256)-41-250431

STATEMENT OF CONSENT/ASSENT

..... has described to me what is going to be done, the risks, the benefits involved and my rights regarding this study. I understand that my decision to participate in this study will not alter my usual medical care. In the use of this information, my identity will be concealed. I am aware that I may withdraw at any time. I understand that by signing this form, I do not waive any of my legal rights but merely indicate that I have been informed about the research study in which I am voluntarily agreeing to participate. A copy of this form will be provided to me.

Name of child Signature (thumbprint)/initials

Date

Name of staff.....Signature of staff

Date



For participants having a positive malaria slide at day 28, a paired PCR test will be carried out on both the admission and day 28 samples. Presence of appositve PCR on both occasions with similarity in the alleles will confirm the reactivation (recrudescence).

Who will participate in the study? The study is targeting chidren between 2 months and 12 years having a positive blood slide malaria caused by p.falciparum species with clinical symptoms or laboratory findings of severe malaria. The study will continue for 4weeks (28 days), with admission as the starting day. However, we will ask you to return your child to return after 28 days (after 4 weeks from the initial days) visit after admission. This will be a follow up , some tests will be carried out and simple checklist will be carried out concerning the childs health ,this will last one hour approximately.

Risks/Discomforts: For this study, the primary risk will be minimal pain during sampling for the blood. However, no other risks will be encountered as the no other interventions will be carried out on the participants and all care will be as per the hospital standards of care. No extra blood samples will be taken off for storage, all tests will be carried out on the 4mls of blood taken off during the two visits.

Benefits: Your child will not benefit directly from the study. However, the benefits will be to the society because of knowledge about malaria recrudescence (reactivation of malaria in those declared cured) in children with severe malaria enhancing proper case management in the future.

Alternatives: it is not compulsory for your child to participate in the study. Your child will receive medical care as per the national guidelines even when they participate in study or not.

Cost: during the conduct of the study as far as the participation is concerned you will not incur any costs. The sponsor of the study EDCTP will incur the bills for the tests.

Compensation/Reimbursement for participation in the study:

It will not cost you any money to take part in this study. Transport refund of ten thousand (10,000/=) Uganda shillings will be provided when you come for your next appointment.

Questions: You are free to ask questions any time, you may contact the researcher using a phone Tel :(+256 771430347 or the research assistants when are interacting with you.

Questions about participant's rights:

In case you have questions / concerns it is your right as participant to have them addressed .The study t has been reviewed by Mbale Regional Referral Hospital REC and they can contact the



chairperson on mobile 0793197393 or the office on 0393280584. You are free to withdraw from the study any time during the study period. Your participation in this study is voluntary and you can opt out any time. However, your failure to participate will not affect the medical care of your child in any way.

Confidentiality:

The results of this study will be kept strictly confidential and used only for research purposes. Your identity will be concealed in as far as the law allows. Your name will not appear anywhere on the coded forms with the information. Paper and computer records will be kept under lock and key and with password protection respectively. For any further questions, you may contact Cate Namayanja Cate Tel :(+256 771430347 or the chairperson **MRRH-REC Dr. Fred Bulamba Telephone number +256793197393** (MRRH-REC-IRB) 0414671162 / or Uganda National Council of Sciences and Technology. Tel: (+256) 772-404970 or **(+256)-41-250431**

STATEMENT OF CONSENT/ASSENT

..... has described to me what is going to be done, the risks, the benefits involved and my rights regarding this study. I understand that my decision to participate in this study will not alter my usual medical care and a sample of my child's blood will be stored for genetic and further tests. In the use of this information, my identity will be concealed. I am aware that I may withdraw at any time. I understand that by signing this form, I do not waive any of my legal rights but merely indicate that I have been informed about the research study in which I am voluntarily agreeing to participate. A copy of this form will be provided to me.

Name of parent/guardian..... Signature of parent/guardian
Date

Name of witness.....Signature of witness.....
Date

Name of staff.....Signature of staff
Date.....



APPENDIX A-7: DATA COLLECTION TOOLS

Version 1.0 (25/MAY/2021)

CLINICAL PRESENTATION, PARASITE RECRUDESCENCE AND OUTCOMES OF SEVERE
MALARIA IN EASTERN UGANDA; A PROSPECTIVE STUDY.

SM STUDY



CASE REPORT FORM

Version1.0 (10/APR/2021)

Study Number: SM
(E.g. SM 001)

Participant Initials
(e.g. A-B)

1. DEMOGRAPHIC					
Child's initial ____	Clinic/Hospital No: ____				
Sex: Male ☐ Female ☐	Date of Birth: __ / __ /20 __	Age:	Y Y M M		
Admission Date: __ / __ /20 __	SCREENING NUMBER	____			

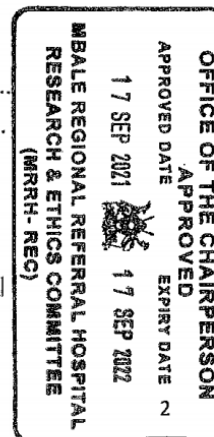
1. Temperature Axillary <u> </u> <u> </u> <u> </u> °C	2. Heart rate <u> </u> <u> </u> <u> </u> bpm
3. Respiratory rate <u> </u> bpm	4. Blood pressure <u> </u> <u> </u> <u> </u> / <u> </u> <u> </u> <u> </u> mmHg (eg. 120/80) (systolic)/(diastolic)
5. capillary refill <u> </u> sec	6. oxygen saturation <u> </u> <u> </u> <u> </u> %

1. Weight	_____.____ kg	2. Height / length	_____.____ cm
3. MUAC	_____.____ cm	4. Head circumference (< 2 years)	_____.____ cm

INCLUSION CRITERIA		YES	NO
1	Age $\geq$ 2 months to 12 years	☐	☐
2	Positive Slide for <i>P.falciparum</i> at admission	☐	☐
3	Any of: haemoglobinuria, impaired consciousness and/or respiratory distress, Severe Anaemia (Hb< 5 g/dl) ,prostration	☐	☐
4	Willingness to consent by guardian/parent	☐	☐
3. EXCLUSION CRITERIA		YES	NO
1	Allergy to ACT or any other contraindication	☐	☐
2	Unwilling to give consent	☐	☐

- Completed by: _____ initial _____

DATE| | | - | | | -20 | |



SEVERE MALARIA	ENROLLMENT & CLINICAL REVIEW	STUDY ID	Study Number
1. POST-enrollment CONSENT			
Was post randomization consent taken and the consent form completed and signed?			
☐ No consented before randomisation ☐ No Died before consent obtained below ☐ No consent declined ☐ Yes please Initial below ☐ No absconded before consent obtained			
Initials of person obtaining consent			
2. HISTORY BEFORE THIS ILLNESS			
	1=Yes	0=No	8=NK
1. Two or more hospital admissions in the last year. If yes specify causes of admission-----	☐	☐	☐
2. Previously received a blood transfusion in the past	☐	☐	☐
If Yes, on how many occasions? 1=0 1-2 2=0 3-4 3=0 ≥ 5 If yes when was the last one 1= <3month ago 2=3 months ago			
3. Received ant helminths in the last 6 months	☐	☐	☐
4. Known to be HIV positive	☐	☐	☐
5. Is the child known to have any chronic illness? If yes specify -----	☐	☐	☐
6. Currently on any medication for pre-existing illness? If Yes, specify -----	☐	☐	☐
3. CURRENT ILLNESS			
When did you/your child's illness start?		_ _ - _ _ -20 _ _ (e.g. 01-JAN-2017)	
	1=Yes	0=No	8=NK
1. Admitted for over 24 hours in a different hospital during current illness	☐	☐	☐
2. Received oral antimalarial medications in the last week If Yes, specify -----	☐	☐	☐
3. Received oral antibiotics in the last week If Yes, specify -----	☐	☐	☐
4. Received traditional medicine in the last week	☐	☐	☐
5. Received a blood transfusion during current illness	☐	☐	☐
6. Received quinine/ Artesunate IV If yes specify -----	☐	☐	☐
7. Other relevant disease If yes specify -----	☐	☐	☐



Version 1.0 (25/MAY/2021)

SEVERE MALARIA				SYMPTOMS QUESTIONNAIRE				Study Number			
DAY 0	YES	NO	NK	Duration (Days)		YES	NO	NK	Duration (Days)		
1. Headache	☐	☐	☐	_ _	9. Hot body/chills	☐	☐	☐	_ _		
2. Fatigue	☐	☐	☐	_ _	10. Cough	☐	☐	☐	_ _		
3. Abdominal Pain	☐	☐	☐	_ _	11. Short of breath/difficulty breathing	☐	☐	☐	_ _		
4. Loss of appetite	☐	☐	☐	_ _	12. Myalgia/ Arthralgia	☐	☐	☐	_ _		
5. Nausea	☐	☐	☐	_ _	13. Other1 _____				_ _		
6. Vomiting	☐	☐	☐	_ _	14. Other2 _____				_ _		
7. Diarrhoea	☐	☐	☐	_ _	15. Other3 _____				_ _		
8. Itching	☐	☐	☐	_ _							

COMPLETED BY (NAME)..... (INITIALS).....



Version 1.0 (25/MAY/2021)

SEVERE MALARIA		PHYSICAL EXAMINATION		SMI	
1. Jaundice		1= ☐ Yes 0= ☐ No			
2. Severe pallor (conjunctiva)		1= ☐ Yes 0= ☐ No			
3. Signs of malnutrition wasting		1= ☐ Yes 0= ☐ No			
4. Signs of malnutrition bipedal edema		1= ☐ Yes 0= ☐ No			
5. Liver size		_ _ cm			
6. Spleen size		_ _ cm			
Body system	1=Normal	2=Abnormal	Body system	1=Normal	2=Abnormal
1. Mouth	☐	☐	7. Central Nervous System	☐	☐
2. Lymphadenopathy	☐	☐	8. Skin	☐	☐
3. Cardiovascular System	☐	☐	9. Joints	☐	☐
4. Respiratory System	☐	☐	10. Other1 _____		
5. ENT	☐	☐	11. Other2 _____		
6. Gastrointestinal System	☐	☐			
Specify abnormal signs (indicate which number you are referring to):					

Completed by: _____ (Initials)					



SEVERE MALARIA		INITIAL ASSESSMENT		SMI [] [] []
		WORKING DIAGNOSIS (tick all that apply)		Study Number
Respiratory	Infection	CNS		
☐ LRTI/Pneumonia ☐ Bronchiolitis ☐ URTI ☐ Pulmonary TB ☐ Otitis media ☐ Asthma ☐ Aspiration e.g. of feed	☐ Gastroenteritis ☐ Sepsis ☐ Severe Malaria ☐ Extra pulmonary TB ☐ Soft tissue infection ☐ UTI ☐ HIV related illness (Specify)..... ☐ Measles ☐ Varicella ☐ Osteomyelitis ☐ Confirmed enteric fever ☐ Typhoid / paratyphoid ☐ Febrile illness unspecified ☐ Bacterial pathogen(s) isolated (complete microbiology CRF)	☐ Febrile convulsions ☐ Epilepsy ☐ LP confirmed meningitis ☐ Other encephalopathy ☐ Hydrocephalus ☐ Developmental delay unspecified ☐ Cerebral palsy ☐ Congenital syndrome		
General		Other diagnosis		
☐ Severe /profound Anaemia ☐ Sickle cell crisis (specify)..... ☐ Recurrent hemoglobinuria ☐ Nephrotic syndrome ☐ Nephritis ☐ Liver dysfunction ☐ Severe Acute malnutrition ☐ Cardiac disease (confirmed)		☐ Suspected drug / food toxicity ☐ Other 1 ☐ Other 2		
Severe malaria classify	☐ Cerebral malaria ☐ Multiple convulsions ☐ Haemoglobinuria ☐ Hypovolaemic Shock ☐ Severe Malaria Anaemia ☐ Prostration ☐ Impaired consciousness ☐ Spontaneous bleeding (DIC)			
		☐ Hypoglycaemia ☐ Respiratory Distress ☐ Acidosis ☐ Renal Failure ☐ Jaundice ☐ Hyperparasitaemia		
INVESTIGATOR NAME		DATE		



SEVERE MALARIA		OBSERVATION FORM			SM [] [] []	
					Study Number	
	D0	D1	D2	DISCHARGE	D28	D22
Date (dd/mm/yy)						
Heart rate (beats/min)						
Weak pulse	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Blood pressure (mmHg) Systolic / Diastolic	S D	S D	S D	S D	S D	S D
Hypotension (>20mmHg drop in SBP)						
Capillary refill(seconds)						
Temperature gradient	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Temperature(axillary) °c						
Respiratory rate(breath/min)						
Respiratory distress	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Oxygen saturation (%)						
Level of consciousness	AVPU	AVPU	AVPU	AVPU	AVPU	AVPU
Impaired consciousness (P/U)	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
☐ GCS / ☐ BCS						
Oedema	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Passing dark urine	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Observed convulsions	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO	☐ YES ☐ NO
Blood glucose (mmol/l)						
Blood lactate (mmol/l)						
Haemoglobin (g/dl)						
Completed by (Initials)						



Version 1.0 (25/MAY/2021)

SEVERE MALARIA		TREATMENT SHEET		SM [] [] [] [] Study Number
MEDICINE	ROUTE (e.g. oral)	START DATE (dd-MMM-yyyy) (e.g. 01-JAN-2018)	END DATE (dd-MMM-yyyy) (e.g. 01-JAN-2018)	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	
		[]-[]-[]-[]-20[]	[]-[]-[]-[]-20[]	

Completed by: _____ initials

DATE []-[]-[]-[]-20[]



Version 1.0 (25/MAY/2021)

SEVERE MALARIA	FOLLOW UP DAY 28	SM [] [] [] [] Study Number
----------------	---------------------	------------------------------------

visit ☐ Days 28 ☐ Extra – specify ☐ Days DATE [] [] - [] [] [] - 20 [] []
☐ Home visit / community ☐ Telephone visit
☐ Missed visit Date of next visit [] [] - [] [] [] - 20 [] []

DAY 28	yes	no	NK	Duration (DAYS)		YES	NO	NK	Duration (DAYS)
1. Headache	☐	☐	☐	[] [] []	8. Hot body/chills	☐	☐	☐	[] [] []
2. Fatigue	☐	☐	☐	[] [] []	9. Cough	☐	☐	☐	[] [] []
3. Abdominal Pain	☐	☐	☐	[] [] []	10. Short of breath/difficulty breathing	☐	☐	☐	[] [] []
4. Loss of appetite	☐	☐	☐	[] [] []	11. Myalgia/ Arthralgia	☐	☐	☐	[] [] []
5. Nausea	☐	☐	☐	[] [] []	12. Other1 _____				[] [] []
6. Vomiting	☐	☐	☐	[] [] []	13. Other2 _____				[] [] []
7. Diarrhoea	☐	☐	☐	[] [] []	14. Other3 _____				[] [] []

OFFICE OF THE CHAIRPERSON	
APPROVED	
APPROVED DATE	EXPIRY DATE
17 SEP 2021	17 SEP 2022
	
MBALE REGIONAL REFERRAL HOSPITAL RESEARCH & ETHICS COMMITTEE (MRRH- REC)	

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SEVERE MALARIA	EXTRA VISIT	SM: [] [] [] [] Study Number							
Extra ☐ specify Days DATE [] [] [] [] -20[] []									
Date of next visit [] [] [] [] -20[] []									
1. SYMPTOMS QUESTIONNAIRE									
EXTRA VISIT			#Grading	Duration (DAYS)				#Grading	Duration (DAYS)
1. Headache	☐	☐	☐	[] []	8. Hot body/chills	☐	☐	☐	[] []
2. Fatigue	☐	☐	☐	[] []	9. Cough	☐	☐	☐	[] []
3. Abdominal Pain	☐	☐	☐	[] []	10. Short of breath/difficulty breathing	☐	☐	☐	[] []
4. Loss of appetite	☐	☐	☐	[] []	11. Myalgia/ Arthralgia	☐	☐	☐	[] []
5. Nausea	☐	☐	☐	[] []	12. Other1 _____				[] []
6. Vomiting	☐	☐	☐	[] []	13. Other2 _____				[] []
7. Diarrhoea	☐	☐	☐	[] []	14. Other3 _____				[] []
					COMPLETED BY (INITIALS).....				



SEVERE MALARIA		BLOOD SLIDES/PCR RESULTS		SMI	
D0 H0	Date of blood collection _ _ - _ _ -20 _ _ (e.g. 01-JAN-2021)				
0= ☐ Not done	Time of blood collection _ _ : _ _ (hh:mm in 24 hrs)				
PCR ☐ positive ☐ negative ☐ Not done					
Species (more than one allowed)		1= ☐ Negative	1= ☐ PF	1= ☐ PM	1= ☐ PO 1= ☐ Unknown 0= ☐ Not done
Pf. asexual count	_ _ _ _	1= ☐ 0/2000RBC	2= ☐ 0/500WBC	3= ☐ 0/200HPFs	4= ☐ Not Countable
Pf. gametocytes	_ _ _ _	1= ☐ 0/500WBC	2= ☐ Not Countable	Initials: _____	
Discharge	Date of blood collection _ _ - _ _ -20 _ _ (e.g. 01-JAN-2021)				
0= ☐ Not done	Time of blood collection _ _ : _ _ (hh:mm in 24 hrs)				
Species (more than one allowed)					
1= ☐ Negative		1= ☐ PF	1= ☐ PM	1= ☐ PO	1= ☐ Unknown 0= ☐ Not done
Pf. asexual count	_ _ _ _	1= ☐ 0/2000RBC	2= ☐ 0/500WBC	3= ☐ 0/200HPFs	4= ☐ Not Countable
Pf. gametocytes	_ _ _ _	1= ☐ 0/500WBC	2= ☐ Not Countable	Initials: _____	
D28	Date of blood collection _ _ - _ _ -20 _ _ (e.g. 01-JAN-2021)				
0= ☐ Not done	Time of blood collection _ _ : _ _ (hh:mm in 24 hrs)				
PCR ☐ positive ☐ negative ☐ Not done					
Species (more than one allowed)		1= ☐ Negative	1= ☐ PF	1= ☐ PM	1= ☐ PO 1= ☐ Unknown 0= ☐ Not done
Pf. asexual count	_ _ _ _	1= ☐ 0/2000RBC	2= ☐ 0/500WBC	3= ☐ 0/200HPFs	4= ☐ Not Countable
Pf. gametocytes	_ _ _ _	1= ☐ 0/500WBC	2= ☐ Not Countable	Initials: _____	
ETRA DAYS	Date of blood collection _ _ - _ _ -20 _ _ (e.g. 01-JAN-2021)				
0= ☐ Not done	Time of blood collection _ _ : _ _ (hh:mm in 24 hrs)				
PCR ☐ positive ☐ negative ☐ Not done					
Species (more than one allowed)		1= ☐ Negative	1= ☐ PF	1= ☐ PM	1= ☐ PO 1= ☐ Unknown 0= ☐ Not done
Pf. asexual count	_ _ _ _	1= ☐ 0/2000RBC	2= ☐ 0/500WBC	3= ☐ 0/200HPFs	4= ☐ Not Countable
Pf. gametocytes	_ _ _ _	1= ☐ 0/500WBC	2= ☐ Not Countable	Initials: _____	



Version 1.0 (25/MAY/2021)

SEVERE MALARIA	FINAL STATUS	SMI
		Study Number

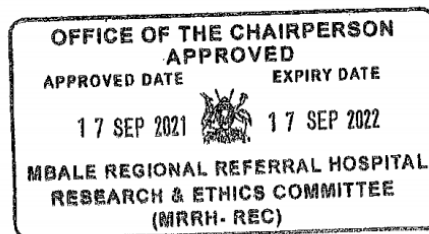
SUBJECT FINAL STATUS	
Did subject complete the study?	
☐ YES, <i>If yes</i>	Date of completion: - - 20 (e.g. 01-JAN-2018)
☐ No, Date of discontinuation	- - 20 (e.g. 01-JAN-2018)
If No, select the reason of not completing the study as planned:	
☐ Death	
☐ Consent Withdrawn	
☐ Ineligibility (either arising during the study or retrospective having been overlooked at screening)	
☐ Significant non-compliance	
☐ Disease Progression (which results in an inability to continue to comply with study procedures)	
☐ Lost to Follow-Up	
☐ Other, specify _____	
Completed by: _____ initial	
DATE - - 20	

INVESTIGATOR'S STATEMENT

I HAVE REVIEWED THE DATA RECORDED IN THIS CRF AND CONFIRM THAT THE DATA ARE COMPLETE AND ACCURATE.

INVESTIGATOR (PRINT FULL NAME) _____

SIGNATURE _____ SIGNATURE DATE | | | | - | | | | - 20 | | | |
(E.g. 01-JAN-2018)



Version 1.0 (25/MAY/2021)

[illegible]

APPROVED DATE EXPIRY DATE

APPROVED DATE

EXPIRY DATE

17 SEP 2022

MBALE REGIONAL REFERRAL HOSPITAL
RESEARCH & ETHICS COMMITTEE
(MRRH- REC)