

Journal of Advances in Medicine and Medical Research

34(21): 62-73, 2022; Article no.JAMMR.89751
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Risk Factors for *Plasmodium falciparum* Recurrence in Artemether Lumefantrine Treated Population from Bushenyi District, Uganda

Josephat Nyabayo Maniga [a,b,c*], Mfitundinda Wilberforce [d,e], Katabazi Aziz [c], Kaweesa Simon Peter [d,e,f], Odoki Martin [b,c,g], Onchoke Vera Bella [h], Jacqueline Njeri Muchiri [d], Ochweri Albert [d], Saheed Adekunle Akinola [b,i], Ismail Abiola Adebayo [b,i] and Odda John [d,j]

[a] Department of Biological Sciences, Kisii University, Kenya.
[b] Department of Microbiology and Immunology, Kampala International University Western Campus, Bushenyi, Uganda.
[c] Department of Microbiology and Immunology, School of Medicine, King Caesor University, Kampala, Uganda.
[d] School of Pharmacy, Kampala International University Western Campus, Bushenyi, Uganda.
[e] Department of Pharmacology and Toxicology, School of Medicine, King Caesor University, Kampala, Uganda.
[f] Department of Biomedical Sciences and Technology, School of Public and Community Health, Maseno University, Kenya.
[g] Department of Applied Sciences, School of Sciences, Nkumba University, Entebbe, Uganda.
[h] Department of Internal Medicine, Kampala International University Western Campus, Bushenyi, Uganda.
[I] Department of Clinical Biology, School of Medicine and Health Sciences, University of Rwanda, Huye Campus, Rwanda.
[j] Department of Pharmacology and Therapeutics, Makerere University, Kampala, Uganda.

Authors' contributions

This work was carried out in collaboration among all authors. Authors JNM, OJ, and IAA designed the study, managed literature review, performed the statistical analysis, and wrote the protocol. Authors JNM, OM, OVB, MV, KSP, KA, SAA and OA wrote the first draft of the manuscript and proof reading of the final draft. All Authors managed the analyses of the study, proof read the first draft of the manuscript and performed the statistical analysis. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2022/v34i2131524

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/89751

Original Research Article

Received 22 May 2022
Accepted 29 July 2022
Published 09 August 2022

**Corresponding author: E-mail: josnyabayo@yahoo.com;*

ABSTRACT

Background: Malaria remains a major Public health problem. In 2019, it was reported that Uganda accounts for 5 % of the total global cases of malaria related deaths after Nigeria and Democratic Republic of Congo.Various risk factors may be responsible for poor treatment outcomes. Thus the main aim of this study was to evaluate the Risk factors for *Plasmodium falciparum* recurrence in Artemether-lumefantrine treated population from Bushenyi district, Uganda.

M**ethods:** A descriptive cross-sectional study was conducted in four selected health centers of Bushenyi district, Uganda by using questionnaire, direct observations and laboratory based studies. Data analysis was done using statistical package for social sciences (SPSS version 23 windows) for descriptive statistics. Logistic regression analysis was done to evaluate the association between *Plasmodium falciparum* recurrence and associated risk factors.

Results: Statistically independent predictor risk factors for *Plasmodium falciparum* recurrence at $p<0.05$ were; Previous Diagnosis used before the current artemether lumefantrine **(**AL) treatment (OR=11.864; 95% CI: 1.477-95.280; $p=0.020$), Sleeping with animals (OR=0.193; 95% CI: 0.075-0.894; $P=00.032$), Age (OR=1.435; 95% CI: 0.0825-0.975; $p=0.040$), Travelling outside the study area (OR=2.324; 95% CI: 0.050-0.699; $p= 0.012$), Weight (OR =1.543; 95% CI: 0.085-0.987; $p= 0.002$), Gametocytes on day 0 (OR =0.284; 95% CI: 0.0625-0.735; $p= 0.032$)9

Conclusions: Monitoring of transmission potentiality after Artemisinin combined therapies (ACTs) treatment is vital in the fight against malaria infection.

Keywords: Risk factors; Plasmodium falciparum; recurrence; Uganda.

1. INTRODUCTION

Malaria remains the major parasitic infection in the world especially in pediatrics and pregnant women. According to World Health Organization (WHO) [1], 216 million cases of malaria were registered worldwide in 2018. According to the World malaria report, approximately 3.4 billion of the world population reside in the geographical regions which are vulnerable to malaria transmission [1]. Mortality resulting from malaria has been reduced through the use of artemisinin based combination therapies (ACTs). Reduced *P. falciparum* sensitivity to ACTs has been reported in South East Asia and this scenario may also affect the African continent where majority of the countries have adopted the use of ACTs in the treatment of uncomplicated malaria.

The association between parasite clearances after treatment is not clear and parasite transmissibility is also unknown and it's regarded as the major question behind the successful prevention of evolution and spread of drug resistance. Uganda has made some positive progress in combating the burden of malaria; however, it has still remained high. Recurrence after treatment may influence the occurrence of new clinical infections with a risk of complications on the patient [2]. Thus, understanding on the factors making malaria to remain a persistent crisis even after employing treatment is vital for developing elimination tools in sub-Saharan Africa and Uganda inclusive. The distribution and transmission mechanism is multifaceted in nature affected by environmental factors, parasitic factors, vector factors, and host factors. Thus determining the association between malaria infections and host factors is vital in developing standard interventions in malaria endemic areas.

Biological factors have been implicated in influencing the clinical outcomes of malaria infections. Major biological factors include, but not limited to Age, immunity and health status of human host [3]. Previous studies have reported that acquired immunity reduced the severity of malaria infections. Consequently Health status of human population has been implicated as one of the vital factor influencing the outcomes of malaria infection coupled with malnutrition increased the mortalities and morbidities due to malaria infections. Consequently immunosuppression of the population can increase malaria incidences [4].

A previous meta-analysis has indicated that drug usage, parasitic factors, transmission intensity and host factors were the major factors influencing drug responses by malaria parasites [5]. These factors basically increases the ability of bulky numbers of parasites to be exposed to drug concentration that are inadequate to eradicate the parasites, hence increasing the multiplication and survival of the parasites. Human behavior has also been reported as a

major factor influencing the evolution of poor drug responses. A previous report from Southeast Asia has indicated that treatment failure is majorly concentrated to forested places which are close to migration borders which harbors mostly immigrants of young age who are more prone to malaria. Moreover self-medication without proper diagnosis and using substandard drugs coupled with poor dosage admiration are some of the factors implicated in increasing chances of poor drug responses in the Asia continent, an epicenter of drug resistance (Kumar et al., 2019).

Despite the fact that ACTs drugs are recommended as the first line drugs for the treatment of uncomplicated malaria in Uganda, different treatment outcomes have been reported which might be influenced by both intrinsic such as age, sex, weight and extrinsic factors such as drug use. Robust information about risk factors influencing the treatment outcomes in Uganda is insufficient. Previous ACTs therapeutic efficacy studies have reported occurrences of malaria parasites in patients treated and followed for 28 days despite lack of molecular markers for resistance. A study conducted in Brazil showed that relapse episodes mostly occurred between the day 28 and 90 after initiating treatment [6]. However, such studies have not evaluated the possible risk factors influencing the treatment outcomes. This study forms part of a broader study in the same area having used the same study participants who reported poor responses to ACTs [7], despite lacking sufficient resistant molecular markers in circulation [7]. Uganda has not developed a standard health operating protocols to be followed by malaria patients after undergoing treatment. This can be achieved by first identifying the risk factors which might be influencing the treatment outcomes. Therefore, this study was conducted to establish the risk factors which might be influencing the ACTs treatment outcomes among patients with uncomplicated malaria. The findings from this study are significant to a proposal by the Ministry of Health of Uganda in eliminating malaria infection by the year 2030.

2. MATERIALS AND METHODS

2.1 Study Area Description

This study was carried out in Bushenyi District, which is located in South Western of Uganda. The District is composed of eleven sub-counties namely; Bushenyi-ishaka, Ibaare, Kyamuhunga, Bitooma, Bumbaire, Kyabugimbi, Nyabubare, Nyakabirizi, Kyeizoba, Kakanju, Ruhumuro, 76 parishes, and 529 villages. The total population stands at 235,621 as in the latest census carried out in 2014.The district covers an area of 905 km² with the population Density of 274.3/km². The district is located approximately 380 kilometers from the capital city, Kampala. It lies on latitude: 0° 28' 22.8" (0.473°) South**,** longitude: 30° 16' 8.4" (30.269°) East**.** The average elevation is about 1,649 meters (5,410 feet).The district is a cosmopolitan in nature with majority of the inhabitants being the local Ankole ethnic group. The district experiences seasonal movement of people from other countries such as Rwanda and Democratic Republic of Congo (DRC) who may be a source of imported malaria parasites. Moreover, the district is a hub of many foreign students and foreign health workers who may also be a source of imported malaria. The economic activities of the district include daily farming, fish farming, banana farming and tea farming. The district houses the third largest referral hospital in the country (KIUTRH), but is also served by several government and private health facilities. In the rural setting, the district has local village health heads that coordinate public health issues at the community level. The map showing study area is indicated in Fig. 1.

2.2 Study Design and Sample Size

This was a cross-sectional study. The study employed the usage of laboratory based procedures and questionnaires. Participants were followed up for a period of 28 days after recruitment to the study.
The sample size (n) for this study was determined by using a formula below

Sample size (N) = $(Z^2 \times P \times (1\text{-}P)\ D) / E^2$ (Suresh, 2012)

$= (1.96^2 \times 0.19 \times (1\text{-}0.19)) / 0.05^2$

Total participants =236 participants

Where

D=margin of error of setting a significance level of 0.05 (i.e.5%).
P= Prevalence of malaria in Uganda is 19% (Uganda malaria indicator survey, 2014).
Z=Level of significance (1.96) for confidence interval of 95% confidence
E =The Precision (or margin of error)
D = the design effect reflects the sampling design used in the survey type

Of study = 1.

An additional 20 % is added to account for participant withdrawers (Stepniewska, 2006)

20% of 236 = 47 participants

Total sample size =236+47

=283 participants

2.3 Laboratory Protocols

The recruitment of study participants from the health facility was conducted irrespective of their individual ages. These consisted of out-patients presenting with signs of uncomplicated malaria to the responsible medical practitioner. Informed consents were obtained from all participants as adult patients willingly tendered their signatures on the informed consent forms while minors below 18 years, gave their consents through their parents or guardians. Therapy was given using AL for 28 days and the patients were followed throughout the treatment period to determine the presence of parasites using Rapid Diagnostic Test (RDT) and microscopy technique. Blood sample was collected by obtaining 1 ml of venous blood for the adult participants. In the case of children who were under 2 years of age, 100 µL figure prick blood sample was collected. This procedure was repeated during the subsequent follow up visits. Rapid Diagnostic Test (RDT) analysis was done by using HRP-II (HRP2 (Pf) (Access Bio, Inc, USA), and for the positive samples was subjected to microscopy studies for *P. falciparum* confirmation. For microscopy, thick and thin blood smears were prepared by following standard procedures. Thick and thin blood smears were stained with 10% Giemsa stain for 10 min. Slides were considered negative if after examination of thick smears, there was no parasite detected in 100 high power fields. For thin smears, they were fixed in methanol solution [7].



Fig. 1. Map of Bushenyi district showing the study area (Uganda Bureau of Statistics, UBOS, 2015). Copyright © 1998-2018: Copyrights reserved to United Nations Office for the coordination of humanitarian affairs, based on OCHA/relief web

2.4 Questionnaire Administration

The demographic health survey (UDHS, 2015), served as a guide in developing the questionnaires used for this study. This approach was necessary as it availed the researchers with the correct and accurate information regarding the health complications associated with malaria in the Ugandan population. There were three subsections in the questionnaire. Section 1 consisted of socio-demographic characteristics such as marital status, Educational level, Age, Gender, Annual income, Employment status and Agricultural practices. Section 2 contained various modes of exposure to bites by the vector such as nocturnal activities, having extremely close contacts with animals, visits to areas other than the study sites, extreme closeness to mosquito breeding areas. Section 3 involved a study carried out on the final follow up day that observed housing and other environmental factors.

2.5 Data Analysis

Filled questionnaires were serially coded. Data was entered and cross checked for errors using Microsoft Excel version 2013 prior to analysis. Data analysis was done by descriptive statistics and regression using IBM SPSS version 23. Descriptive statistics was used to obtain the 28 day parasitemia frequency and the mean age. Bivariate regression analysis between human related variables and 28 day parasitological outcome as well as bivariate analysis between health and patient practices in relation to parasitological outcome was carried out and all the variables with a *p* value of 0.005 or less were entered into stepwise forward multiple logistic regression model. Interaction and confounding were assessed and values of P≤0.05 were regarded as statistically significant relationships. Chi-Square test was used to determine possible associations between categorical variables.

3. RESULTS

3.1 Baseline Characteristics of the Participants

A total of 283 human participants were recruited into this current study after qualifying for inclusion criteria stated above. Out of the 283 participants recruited to this study 194 (68.6**%**) participants completed the follow up schedules while 89 (31.4**%)** were withdrawn from the study. The participants were withdrawn because they did not adhere to the follow up visits in the first three days. The recruited patients were classified according to the follow up days. On day 3, 214 participants were followed up with a retention rate of 75.6**%**.On day 7, 203 participants were followed up with a retention rate of 71.7**%.** On day 14, 196 participants were followed up with a retention rate of 69.3**%.** And on day 28, 194 participants were followed up with a retention rate of 68.6**%.** The participants were classified in relation to the social demographic patterns via; age, gender and weight. In relation to age, participants with 0-5 years represented the lowest number of 3 (1.5%) compared with those having 18 years and above who were the majority with 115(59.3%) respectively. The median age of the study participants was 22.5 years with the median range 1-108 years and Interquartile range (IQR) = 14-36 years. In relation to the weight of the participants majority of the study participants were weighing more than 31 kg with 167 (86.1%) participants. The Median weight was 52.5 kg, median Range was 8.5-82 and interquartile range (IQR) was 38-62 Kg respectively. In relation to the occupation of the participants, students/ pupils represented the highest number with 84 (43.3%). Detailed information has been published elsewhere (Maniga et al., 2018)

3.2 28 Days Follow Up Parasitemia Recurrence

After a 28 days follow up, 194 participants attending different health facilities in Bushenyi district for malaria treatment were considered for this study. Low parasitemia after day 28 follow up was observed in 17/194 (8.7%). The prevalence of parasitemia was highest in age group 20-29 with 8/17 (53.3%) as compared to the lowest value of 0/17 (0%) in the 50-59 and 60 and above age groups respectively (Table 1).

3.3 Biological Factors Associated 28 Days Follow Up Occurrence of Parasitemia

Weight and level of parasitemia before treatment was statistically significant at influencing the reoccurrence of the parasites after treatment at *p*=0.001. However gender was not found to be influencing the treatment outcomes (Table 2).

Table 1. Age-specific parasitemia after day 28 follow up

	Parasitological Outcome		Total, n (%)
Age range	**Positive, n (%)**	**Negative, n (%)**	
1-9	1 (6.7)	16 (9.0)	17 (8.9)
10-19	4 (13.3)	64 (36.2)	68 (34.4)
20-29	8 (53.3)	31(17.5)	39 (20.3)
30-39	3 (20.0)	31 (17.5)	34 (17.7)
40-49	1 (6.7)	21 (11.9)	22 (11.5)
50-59	0 (0.0)	9 (5.1)	9 (4.7)
60 and above	0 (0.0)	5 (2.8)	5 (2.6)
Total	17 (100)	177 (100)	194 (100)

Table 2. Analysis of biological characteristics and 28 day parasitemia recurrence

	Hospital				
Variables	**Kyamuhunga HC III n (%) (n=42)**	**KIUTH n (%) (n=71)**	**Kyeizooba HC III n (%) (n=71)**	**Ishaka Adventist Hospital n (%)(n=10)**	***P* value**
Weight (kg), mean (SD)	54.8±6.1	49.9±10.5	56.4±8.7	48.4±9.5	0.002*
Gender (male), n (%)	18 (42.8)	42 (59.1)	47 (66.1)	6 (60.0)	0.38
Gender (female), n (%)	24 (57.2)	29 (40.9)	24 (33.9)	4 (40.0)	0.51
Body temperature on day 0, °C, mean (SD)	37.7 °C ± 1.1	37.5 °C ± 1.1	37.9 °C ± 1.1	37.4°C ± 1.1	0.42
Gametocytes (µl) on day 0* (95% CI)	10,4801 (8,257–11,785)	13,623 (9,242–14,570)	13,540 (9,300–16,620)	9,221 (7,308–11,252)	0.032*
Median age in years (males)	31.5	28.5	32.5	31.5	0.153
Age range in years (males)	(5–72)	(3–82)	(6–69)	(2–65)	0.245
Median age in years (females)	21.5	38.5	31.5	30.5	0.85
Age range in years (females)	(4–63)	(2–65)	(4–70)	(3–62)	0.235

°C: degree Celsius; Temperature of ≥37.5°C or history of fever during the previous 24 hours. Parasitemia: geometric mean parasite density (asexual parasites/µl); n: number of patients; SD: standard deviation; 95% CI: 95% confidence interval; *p < 0.05, the mean was significantly different*

3.4 Human Related Factors Associated 28 Days Follow Up Occurrence of parasitemia

When the predictor variables for occurrence of parasitemia were subjected to bivariate analysis, they had the following logistic regression values: Utilization of mosquito nets (OR=0.253; 95% CI: 0.083-0.774*;* p<0.05), sleeping with animals (OR=0.420; 95% CI: 0.053-3.337; p<0.05), outdoor activities (OR=0.249; 95% CI: 0.092-0.678; p<0.05), travelling outside the study area (OR=0.342; 95% CI: 0.042-2.534; p<0.05). Whereas, presence of stagnant water near the homestead, type of house owned and presence of vegetation in homestead were found to have no significant association with occurrence of parasitemia after 28 days follow up (Table 3).

3.5 Health and Patient Practices Associated 28 Days Follow Up Occurrence of Parasitemia

When the predictor variables for occurrence of parasitemia were subjected to bivariate analysis, they had the following logistic regression values: Previous Diagnosis used (OR=13.213; 95% CI: 1.7-102.697; p<0.05), frequency of infection (OR=3.519; 95% CI: 1.141-10.847; p<0.05), indiscriminate use of drugs (OR=0.090; 95% CI: 0.011-0.738; p<0.05) (Table 4 and Table 5).

3.6 Risk Factors Associated with 28 Days Parasitological Outcome Using Stepwise Forward Multiple Logistic Regression Analysis

When the predictor risk factors were subjected to stepwise multiple logistic regression analysis, they had the following regressions values: Previous Diagnosis used (OR=11.864; 95% CI: 1.477-95.280; p<0.05), sleeping with animals (OR= 0.193; 95% CI: 0.075-0.894; p<0.05), Age (OR=1.435; 95% CI: 0.0825-0.975; p<0.05), travelling outside the study area (OR=2.32495% CI: 0.050-0.699; p<0.05) (Table 5).

4. DISCUSSIONS

Malaria infection has been documented as the major killer disease, in the East African country of Uganda. More than 90% of the population is at risk of the infection. Currently, Uganda is ranked fourth in the countries with malaria burden, accounting for 50% of outpatient visits, 20% of mortalities and up to 15–20% of admissions [1]. Among all control measures that are used against the spread of malaria, chemotherapeutic agents seem to contribute largely to the strategy of combating malaria mortality in the world. However, different treatment outcomes have been reported all over the world [8,9,10,11,12], thus raising the question of therapeutic efficacy

Table 3. Bivariate regression analysis between human related variables and 28 day parasitemia

Variables	Categories	Unadjusted Odds ratio	95% CI	*p*-value	χ2 value
Presence of stagnant water near the homestead	Present	0.926	0.322-2.668	0.887	0.9
	Absent	1			
Type of house owned	Permanent	0.535	0.182-1.568	0.254	0.3
	Local	1			
Sleeping with animals	Yes	0.420	0.053-3.337	0.0412*	4.1
	No	1			
Presence of vegetation in homesteads	Present	1.543	0.332-7.7.172	0.580	0.4
	Absent	1			
Materials for house roof	Iron sheets	0.398	0.050-3.161	0.384	0.3
	Grass	1			
Outdoor activities	Yes	0.249	0.092-0.678	0.018*	3.8
	No	1			
Travelling outside the study area	Yes	0.342	0.042-2.534	0.012*	3.2
	No	1			

*Footnote: CI= confidence interval, p= probability, *statistically significant factors (p <0.05) under logistic regression*

Table 4. Bivariate analysis between health and patient practices in relation to parasitological outcome

Variables	Categories	Unadjusted Odds ratio	95% CI	*p*-value	χ2 value
Fever at admission	Present	4.031	1.362-11.928	**0.012***	6.1
	Absent	1			
Previous Diagnosis used	Standard diagnosis	13.213	1.7-102.697	0.014*	5.3
	Presumptive treatment	1			
Frequency of infection	Once in a year	3.519	1.141-10.847	0.029*	4.0
	More than once	1			
Indiscriminate use of drugs	Yes	0.090	0.011-0.738	0.025*	3.7
	No	1			

*Footnote: CI= confidence interval, p= probability, p≤0.05 value is * statistically significant under logistic regression*

Table 5. Stepwise forward multiple logistic regression analysis

Variables	Categories	Adjusted Odds ratio	95% CI	*p*-value	χ2 value
Previous Diagnosis used	Standard diagnosis	11.864	1.477-95.280	0.020*	1.5
	Presumptive treatment	1			
Sleeping with animals	Yes	0.193	0.075-0.894	0.032*	1.3
	No	1			
Age	Less than 18 years	1.435	0.0825-0.975	0.040*	1.4
	More than 18 years	1			
Travelling outside the study area	Yes	2.324	0.050-0.699	0.012*	1.2
	No	1			
Weight	Less than 10 Kg	1.543	0.085-0.987	0.002*	1.8
	More than 10 Kg	1			
Gametocytes on day 0	Yes	0.284	0.0625-0.735	0.032*	1.7
	No	1			

*Footnote: CI= confidence interval, p= probability, p≤0.05 value is * statistically significant under stepwise forward multiple logistic regression analysis*

of different chemotherapeutic drugs used against malaria. A previous study on the same study area of Bushenyi district using the same human participants reported early treatment failure (ETF) among 75 (38.7%) participants [7]. Moreover, a follow up molecular study which was evaluating the presence of ACTs resistant markers in the study area did not find sufficient evidence of resistance emergence in the study area (unpublished data). Several studies have evaluated different risk factors associated with occurrence and transmission of malaria in Uganda and the rest of the world; however, there are insufficient reports in relation to risk factors influencing the occurrences of parasites after treatment of patients with drugs. Different factors have been implicated previously in eliminating parasites after treatment from the bloodstream, hence determining the treatment outcomes [13]. Recurrent malaria parasites may occur as a result of relapses, recrudescence or new infections. Malaria is generally influenced by intrinsic factors such as parasite, human, mosquito and extrinsic factors such as environmental, social, behavioral, political, economic conditions and malaria intervention strategies [14]. Therefore, this study was aimed to establishing the risk factors which might be influencing the ACTs treatment outcomes among patients treated for uncomplicated malaria in the study area.

The association between slow parasite clearance and gametocyte carriage reported in our study

may be attributed to the ongoing gametocyte production by persisting asexual parasites after treatment. This is because parasite clearance dynamics shortly after initiation of ACTs influences malaria transmission potentiality after 1 week treatment [15]. Our results is in agreement with previous studies which postulated that elevated gametocyte production is associated with slow clearance of parasites after treatment with ACTs [16,17,18]. Moreover our results are in agreements with reports from Thailand– Myanmar border, an epicenter of drug resistance, where slow parasite clearance was related with a higher period of gametocyte carriage after mefloquine-artesunate treatment [19]. Parasitaemia is associated with the degree of malaria severity, thus serving as a vital indicator of decision making in relation to the type of treatment. Additionally it serves as epidemiological indicator since it can give a clue on the level of transmission intensity.

Our results reported a high parasitemia of 53.3% after 28 day follow up in the age group of 20-29 years. This may be attributed to the social practices which allow most people aged between 20-29 years of the Ugandan population to stay outside in the night hence being exposed to mosquito bites after treatment. Thus, our findings are in contrast with a previous study conducted in Nigeria which reported a high parasitemia recurrence after day 28 treatment in the age group of less than 2 years [20]. Moreover, a study conducted over a period of more than 10 years at Thai-Myanmar border, an epicenter of antimalarial resistance also reported that the age group of less than 2 years had more risk of parasitemia recurrence after treatment [21] Consequently, a study conducted in Nigeria reported a contrasting findings by indicating that poor treatment outcomes increased with the decrease in the age of the participants, with the children of less than 12 months having poor treatment outcomes [22]. Moreover, a recent study conducted in Kenya also reported that age was not a predictor risk factor among the children participants [23].

Proper malaria diagnosis stands out as one of the pillar in malaria elimination. Accurate diagnosis leads to appropriate treatment. Malaria is a febrile disease having clinical symptoms resembling other microorganisms, thus specific diagnostic methods are necessary for differentiation. Moreover, early diagnosis and treatment may halt further progression of the disease. Febrile illness in Africa are commonly treated with drugs which are not properly prescribed by health workers. Our study is in agreement and in contrast with previous study conducted in three countries of Gambia, Zaire and Burkina Faso. In Gambia it was reported that previous presumptive diagnosis increased parasite incidence after treatment. This might be correlated with drug resistance which had been reported in Gambia prior to this report. However, in Zaire and Burkina Faso, they recorded reduction of parasite incidences on those patients who had undergone presumptive diagnosis [24]. Use of antimalarial drugs unnecessary without proper diagnosis may promote drug resistance and may lead to development of severe malaria [25].

Despite the high prevalence of malaria in Uganda, no much reports have implicated human movement as a risk factor for recurrence of parasitemia after treatment. Our current study has clearly indicated that travelling outside the study area after treatment was an independent risk factor for *P. falciparum* recurrence. However, the relationship between travelling and malaria risk is likely to be as a result of many factors other than travelling such as malaria vector abundance and vector protection methods. Interestingly, as far as travelling may be indicated as a risk factor, it is a complicated variable which is retrospectively difficult to measure since the patients may not remember exactly the date of travelling. Our study however is in agreement with a previous study conducted in Ethiopia which reported that, travelling was a major risk factor for *P. falciparum* incidences [26]. Furthermore, our study also corroborates with a recent study conducted in Thailand-Myanmer border, a geographical location considered an epicenter of antimalarial resistance [27].

Integration of zoo prophylaxis which is the usage of animals to prevent the occurrence of malaria parasites in the community has been suggested as the future option, with some studies reporting conflicting protective values. Our study used the relationship between domestic animal possession and occurrence of malaria parasites, however the study did not record the specific domestic animal used. This study, reported that, sleeping with animals was a risk factor for occurrence of malaria after treatment. Our study is in agreement with a recent meta-analysis which has indicated that, staying together or next to animals served as risk factors for malaria incidences [28]. Previous studies conducted in Uganda and outside Uganda reported that

presence of animals around the residential areas reduced high malaria parasitemia [29,30,31].

Our present study reported lack of association of presence of stagnant water near the homesteads, type of house owned, materials for house roof and presence of vegetation in homestead with recurrence of malaria infection. This in in contrast with other studies conducted globally. A recent study conducted in Equatorial Guinea reported that environmental factors such as altitude and distance to rivers and forests served as risk factors of malaria infections [32]. Moreover a recent study conducted Thailand-Myanmar border, an epicenter of drug resistance, reported poor housing condition as a predictor of malaria episode after treatment. Additionally, the study reported that malaria episodes increased with staying with other malaria infected individuals in the same house, age, male sex, young age, forest-related occupation [27].

In contrast with our study, other previous studies have reported other factors which have significant influence on malarial recurrence in patients with uncomplicated malaria. They reported that, the recurrence of malaria after treatment of *Plasmodium* parasites was as a result of many factors such as drug resistance, substandard drugs and poor malarial immunity [25]. Such factors were not considered in our study, thus serving as a major study limitations.

5. CONCLUSIONS

A thorough understanding of the risk factors influencing the treatment outcomes is vital in setting up policy guidelines which may help to eliminate malaria in Uganda. This may be attained by putting in place robust regulations by the Uganda Ministry of Health. Moreover, increased vigilance during and after treatment needs to be strengthened. Consequently, more researches needs to be conducted to gain better understanding on the parasite recurrence after treatment. Despite the fact that causes of *P. falciparum* malaria was not genetically identified, drug resistance and effective drug management needs to be extensively monitored.

ETHICAL APPROVAL AND CONSENT

The ethical approval of the study was sought from Mbarara University of Science and Technology (MUST), Institutional Research and Ethics Committee (IREC) on Human Research (Approval no 06/01-17) and Uganda National Council for Science and Technology (Approval no HS2241). All research protocols were performed in accordance with the ethical standards of the committees on human experimentation laid down in the Helsinki declaration of 1975 as revised in 2000. Permission was sought from the community leadership. Written consent was obtained from the participants after clearly explaining the purpose and procedures behind the study. Moreover, privacy and confidentiality of the participants was highly maintained during the entire period of the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Malaria report W. World malaria report 2019. In WHO Regional Office for Africa; 2019.
Available:https://www.who.int/news-room/fact-sheets/detail/malaria
2. WHO. Guidelines for the treatment of malaria. 3rd ed. Geneva: World Health Organization. 2015;316.
3. Protopopoff N, Van Bortel W, Speybroeck N, Van Geertruyden JP, Baza D, D'Alessandro U, Coosemans M. Ranking malaria risk factors to guide malaria control efforts in African highlands. PLoS ONE. 2009;4(11):1–10.
Available:https://doi.org/10.1371/journal.pone.0008022
4. Carrasco-Escobar G, Gamboa D, Castro MC, Bangdiwala SI, Rodriguez H, Contreras-Mancilla J, et al. Micro-epidemiology and spatial heterogeneity of P. vivax parasitaemia in riverine communities of the Peruvian Amazon: A multilevel analysis. Scientific Reports. 2017;7(1):1–17.
Available:https://doi.org/10.1038/s41598-017-07818-0
5. Woodrow CJ, White NJ. The clinical impact of artemisinin resistance in Southeast Asia and the potential for future spread. FEMS Microbiology Reviews. 2017;41(1):34–48.
Available:https://doi.org/10.1093/femsre/fuw037
6. Simoes LR, Alves ER Jr, Ribatski-Silva D, Gomes LT, Nery AF, et al. Factors

associated with recurrent Plasmodium vivax malaria in Porto Velho, Rondonia State, Brazil, 2009. Cad Saude Publica. 2014;30:1403–17.

7. Maniga JN, Aliero AA, Ibrahim N, Okech MA, Mugasa CM. Plasmodium falciparum Malaria Clinical and Parasitological Outcomes after *In- vivo* Artemether-Lumefantrine (AL) Treatment at Bushenyi District Uganda. March; 2018. Available:https://doi.org/10.9734/IJTDH/2018/39642
8. Ocan M, Bwanga F, Okeng A, Katabazi F, Kigozi E, Kyobe S, et al. Prevalence of K13-propeller gene polymorphisms among Plasmodium falciparum parasites isolated from adult symptomatic patients in northern Uganda. BMC Infectious Diseases. 2016;16(1):1–9. Available:https://doi.org/10.1186/s12879-016-1777-7
9. Balikagala B, Mita T, Ikeda M, Sakurai M, Yatsushiro S, Takahashi N, et al. Absence of *in vivo* selection for K13 mutations after artemether-lumefantrine treatment in Uganda. Malaria Journal. 2017;16(1):1–11. Available:https://doi.org/10.1186/s12936-016-1663-1
10. Ouji M, Augereau JM, Paloque L, Benoit-Vical F. Plasmodium falciparum resistance to artemisinin-based combination therapies: A sword of Damocles in the path toward malaria elimination. Parasite. 2018;25. Available:https://doi.org/10.1051/parasite/2018021
11. Siddiqui FA, Boonhok R, Cabrera M, Mbenda HGN, Wang M, Min H, et al. Role of Plasmodium falciparum kelch 13 protein mutations in P. Falciparum populations from northeastern myanmar in mediating artemisinin resistance. MBio. 2020; 11(1):1–19. Available:https://doi.org/10.1128/mBio.01134-19
12. Kassaza K, Long AC, McDaniels JM, Andre M, Fredrickson W, Nyehangane D, et al. Surveillance of Plasmodium falciparum pfcrt haplotypes in southwestern uganda by high-resolution melt analysis. Malaria Journal. 2021; 20(1):1–10. Available:https://doi.org/10.1186/s12936-021-03657-7
13. Kone A, Sissoko S, Fofana B, Sangare CO, Dembele D, Sedhigh A, Diallo N, et al. International Journal of Infectious Diseases Different Plasmodium falciparum clearance times in two Malian villages following artesunate monotherapy. International Journal of Infectious Diseases. 2020;95: 399–405. Available:https://doi.org/10.1016/j.ijid.2020.03.082
14. Breman JG. The ears of the hippopotamus: manifestations, determinants, and estimates of the malaria burden. Am J Trop Med Hyg. 2001;64(1–2 Suppl):1–11. Available:https://doi.org/10.1093/infdis/jiv551
15. Adjalley SH, Johnston GL, Li T, et al. Quantitative assessment of Plasmodium falciparum sexual development reveals potent transmission blocking activity by methylene blue. Proc Natl Acad Sci U S A. 2011;108:E1214–23. Available:https://doi.org/10.1186/s12936-016-1663-1
16. Krishna S, Kremsner PG. Antidogmatic approaches to artemisinin resistance: Reappraisal as treatment failure. 59(8): 5061–5064. Available:https://doi.org/10.1128/AAC.00921-15
17. Fairhurst RM, Nayyar GM, Breman JG, et al. Artemisinin-resistant malaria: Research challenges, opportunities, and public health implications. Am J Trop Med Hyg. 2012;87:231–41.
18. Das D, Price RN, Bethell D, Guerin PJ, Stepniewska K. Early parasitological response following artemisinin-containing regimens: A critical review of the literature. Malar J. 2013;7(1):1–17. Available:https://doi.org/10.1038/s41598-017-07818-0
19. Carrara VI, Zwang J, Ashley EA, et al. Changes in the treatment responses to artesunate-mefloquine on the northwestern border of Thailand during 13 years of continuous deployment. PLoS One. 2009;4:e4551. Available:https://doi.org/10.1128/AAC.03647-14
20. Contoh B, Issa J, Tabares I, Objek PBB, Hasil L, Informasi T, Aradea Ade Yuliana HH, et al. 2019;15(1):1–8. Available:https://doi.org/10.1186/s12936-016-1379-2
21. Vugt V, Douglas NM, Ashley EA, Phaiphun L, Singhasivanon P, White NJ, Price RN. Plasmodium vivax Recurrence Following

Falciparum and MixedSpecies Malaria: Risk Factors and Effect of Antimalarial Kinetics. 2011;52.
Available:https://doi.org/10.1093/cid/ciq249

22. Sangowawa AO, Amodu OK, Olaniyan SA, Amodu FA, Olumese PE, Omotade OO. Factors Associated with a Poor Treatment Outcome among Children Treated for Malaria in Ibadan, Southwest Nigeria. 2014;10–17.
Available:https://doi.org/10.1093/infdis/jiu467.
23. Beshir KB, Sutherland CJ, Sawa P, Drakeley CJ, Okell L, Mweresa CK, et al. Residual Plasmodium falciparum parasitemia in kenyan children after artemisinin-combination therapy is associated with increased transmission to mosquitoes and parasite recurrence. Journal of Infectious Diseases. 2013;208(12):2017–2024.
Available:https://doi.org/10.1093/infdis/jit431
24. Hopkins H, Talisuna A, Whitty CJM, Staedke SG. Impact of home-based management of malaria on health outcomes in Africa: A Systematic Review of the Evidence. 2007;10:1–10.
Available:https://doi.org/10.1186/1475-2875-6-134
25. Mahittikorn A, Masangkay FR, Kotepui KU, De G. The high risk of malarial recurrence in patients with Plasmodium - mixed infection after treatment with antimalarial drugs: A systematic review and meta - analysis. Parasites & Vectors. 202;11–18.
Available:https://doi.org/10.1186/s13071-021-04792-5
26. Yukich JO, Taylor C, Eisele TP, Reithinger R, Nauhassenay H, Berhane Y, Keating J. Travel history and malaria infection risk in a low-transmission setting in Ethiopia: A Case Control Study. 2013;1–9.
Available:https://doi.org/10.4269/ajtmh.16-0889
27. Lawpoolsri, S, Sattabongkot J, Sirichaisinthop J, Cui L, Kiattibutr K. Epidemiological profiles of recurrent malaria episodes in an endemic area along the Thailand - Myanmar border: A prospective cohort study. Malaria Journal. 2019;1–11.
Available:https://doi.org/10.1186/s12936-019-2763-5
28. Asale A, Duchateau L, Devleesschauwer B, Huisman G, Yewhalaw D. Zooprophylaxis as a control strategy for malaria caused by the vector Anopheles arabiensis (Diptera : Culicidae): A Systematic Review. 2017;1–14.
Available:https://doi.org/10.1186/s40249-017-0366-3
29. Bogh C, Clarke SE, Walraven GEL, Lindsay SW. Zoo-prophylaxis, artefact or reality? A paired-cohort study of the effect of passive zoo-prophylaxis on malaria in The Gambia. Trans R Soc Trop Med Hyg. 2002;96:593–6. 33.
Available:https://doi.org/10.1186/s12879-017-2634-z
30. Saul A. Zooprophylaxis or zoopotentiation: The outcome of introducing animals on vector transmission is highly dependent on the mosquito mortality while searching. Malar J. 2003;2(32):1602–1608.
Available:https://doi.org/10.1038/s41591-020-1005-2.
31. Donnelly B, Berrang-Ford L, Labbé J, Twesigomwe S, Lwasa S, Namanya DB, et al. Plasmodium falciparum malaria parasitaemia among indigenous Batwa and non-indigenous communities of Kanungu district, Uganda. Malar J. 2016; 15:254.
Available:https://doi.org/10.1093/infdis/jiv551
32. Gómez-Barroso D, García-Carrasco E, Herrador Z, Ncogo P, Romay-Barja M, Mangue MEO, et al. Spatial clustering and risk factors of malaria infections in Bata district, Equatorial Guinea. Malar J. 2017;16:146.
Available:https://doi.org/10.1371/journal.pone.0117396

© 2022 Maniga et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/89751