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Impact of Intervention Practices on Recurrence of Parasitemia among Artemether-Lumefantrine (Al) Treated Patients in Bushenyi District, Uganda

Abstract **–** Malaria remains a major vector borne disease causing both mortalities and morbidities in the world. Uganda, a moderate intensity malaria transmission country has currently scaled out major campaigns to reduce and eliminate the disease using different interventions together with Artemether-Lumefantrine (AL) drug as a drug of choice for treatment. Different sensitivity profiles have been reported in different parts of the world. This might be influenced by different factors. Therefore, this study was aimed at assessing the impact of previous and current interventions among Artemether-Lumefantrine (AL) treated patients of Bushenyi district, Uganda, for sensitivity profiles. This was a descriptive cross-sectional study carried out among a cohort of 184 study participants for a period of one year (August 2017 to August 2018) in four selected health centers in Bushenyi district, Uganda**.** The investigative methods used included a researcher administered questionnaire, direct observations, laboratory, and clinical evaluation of participants. Data analysis was done by using statistical package for social sciences (SPSS version 10 windows) for descriptive statistics. Statistically significant factors for recurrence of parasitemia after treatment at $p \leq 0.05$ were; practicing indoor residual spraying (IRS) at home (P = 0.001; CI), source of previous drug prescription (P = 0.018; CI), previous finishing of drug dosage (P = 0.006; CI), frequency of previous malaria infection (P = 0.028; CI), Frequency of previous antimalarial usage (P = 0.042; CI) and sleeping under insecticide treated nets (ITNs) (P = 0.039; CI), respectively. Indoor residual spraying and insecticide treated nets were found to be the major intervention practice of malaria reduction after treatment with Artemether- Lumefantrine.

Keywords **–** *Recurrence, parasitemia, Artemether-Lumefantrine*

1 INTRODUCTION

Malaria infection remains the most prevalent vector borne disease (1) and is transmitted by the female anopheles mosquito. Each year an estimated 300 to 500 million clinical cases of malaria occur, making it one of the most common infectious diseases worldwide (2). Over 90% of the Ugandan populations are at risk of the infection (2). The economic loss in Uganda as a result of malaria is approximated to be over $500 million annually. In the year 2021, WHO reported an estimated 13 million malaria cases leading to 19,600 estimated deaths in the country (1) (WHO, 2021). In 2020 for instance 1,502,362 of 3,718,588 Ugandans reporting at health facilities and examined for malaria parasite infection were confirmed positive (3). However, several cases occur outside health facilities and treated with unknown outcomes. Nevertheless, malaria burden is projected to increase due to COVID-19

pandemic. Uganda has been ranked 3rd globally with 5% of the total cases after Democratic Republic of Congo (DRC) (12%) and Nigeria (25%) respectively (2). However, bearing in mind the geographical size of Uganda compared to Nigeria and DRC, it shows that the malaria incidence rate in Uganda is much higher compared to other countries in the world. Malaria based practices used to reduce malaria burden include appropriate diagnostic testing, proper treatment of cases by use of ACTs, vector control, intermittent preventive therapy (IPT) in pregnant women and infants. In relation to the Roll Back Malaria Initiative developed from the United National Millennium Development Goals, extensive interventions have greatly reduced malaria by 40% in sub-Saharan Africa. Therefore, malaria intervention methods have been impressive in the world though it remains unclear what overall reduction in transmission is obtainable by using currently available interventions.

Currently the World Health Organization (WHO) recommends artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated malaria in most countries particularly where resistance has developed towards other drugs. Presently there are five ACTs recommended by WHO which can be adopted in different regions of the world: artesunate-amodiaquine, artesunate-sulfadoxine-pyrimethamine (ASSP), artemether-lumefantrine (AL), artesunate-mefloquine, and dihydroartemisinin-piperaquin. More than 70 percent of malaria endemic countries relies on AL for treatment of complicated and uncomplicated malaria caused by *P. falciparum* (4) (UNITAD, 2018). Uganda adopted the use of ALas the drug of choice for treatment of uncomplicated malaria, however the actual implementation started on 2006 (5).

AL contains a combination of 20 mg of artemether and 120 mg of lumefantrine. In Uganda, the substitute first line treatment is Artesunate/Amodiaquine. Additionally, the second line treatment for uncomplicated malaria is Dihydroartemisinin Piperaquine (DHA-PPQ). However Other ACTs that are recommended by the WHO such as artesunate/mefloquine and artesunate/sulfadoxine-pyrimethamine are not used for treatment of uncomplicated malaria in Uganda. However, ACTs presently not been recommended for treatment of uncomplicated malaria among pregnant women in their first trimester (6).

Even though, there is no significant molecular-based evidence, previous studies have reported occurrences of malaria parasites in patients treated with ACTs and followed for 28 days. However, there is insufficient data on the influence of treatment with the recurrence of parasitemia. Moreover, Uganda has not developed a standard health operating procedures to be followed by malaria patients after undergoing treatment. This can be achieved by first evaluating the influence of previous and post-patient malaria treatment practices, which may be influencing recurrence of parasitemia after treatment with recommended drug of choice. 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 & METHODS

2.1 Study Area

This study was carried out in Bushenyi District, Uganda (Figure 1). The district has eleven (11) Sub-counties; 76 parishes and 529 villages. The district is located approximately 380 kilometers from the capital city, Kampala. It lies on latitude: 0° 29' 27.6" (0.491°) South**,** longitude: 30° 10' 58.8" (30.183°) East**.** The district has a total land of 3,949 square kilometers and it lies between 910 and 2,500 meters above the sea level. It is hilly with forest and swampy vegetation and is characterized by seasonal water bodies, networks of streams, stagnant pools, over filled blocked gutters and drainages. The region experiences three wet seasons (April-May, August-September, and November-December) and one dry season (January and February); the temperatures are about 25°C-37°C no wonder the major economic activity of this community is agriculture.

The communities reside mainly in semi-permanent and mud-thatched houses. It has overgrown bushes and fields of bananas around residential homes which favors the survival and multiplication of mosquitoes. The land under cultivation consists of 2,215 square kilometers and wetlands covers 183 square kilometers. This study was conducted at the four selected health centers, namely, Kampala International University teaching hospital, Ishaka Adventist hospital, Kyamuhunga health center and Kyeizooba health Centre. The study area has an entomological inoculation rate (EIR) of 100 per annum and *Anopheles gambiae* and *Anopheles funestus* are the main malaria vectors in the region. The control methods which have been scaled up by the government in this

region to prevent malaria infection include proper case management with antimalaria drugs such as ACTs, intermittent prophylaxis during pregnancy (IPTp), use of mosquito nets and indoor residual spraying (IRS) (7).

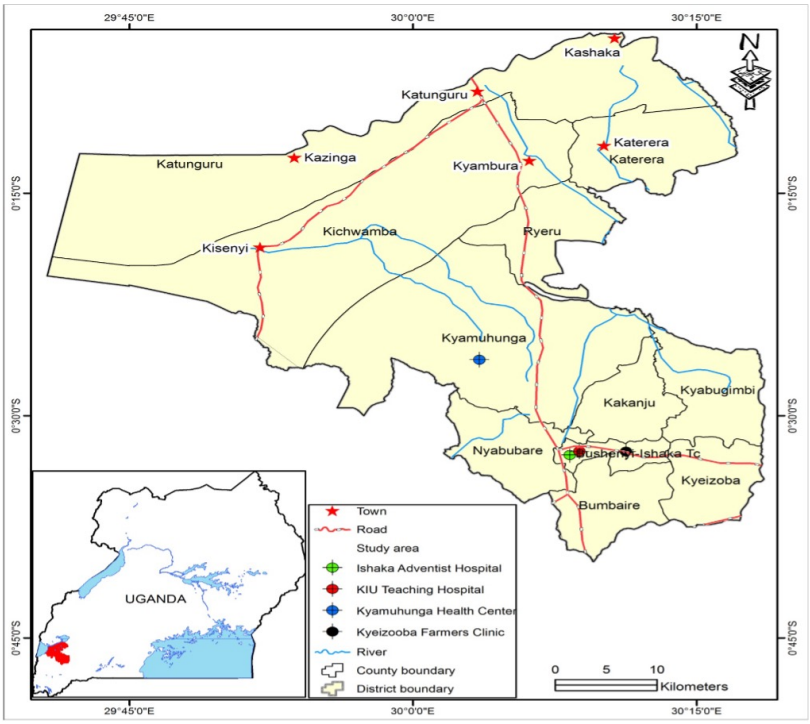

Figure 1. Inset - Map of Uganda showing Bushenyi district (shaded) and the map of Bushenyi district showing the study sites

2.2 Study Design and Study Population

This was a descriptive cross-sectional study carried out to assess the influence of previous and post patient malaria treatment practices which may be influencing recurrence of parasitemia after treatment with recommended drug of choice in Bushenyi district, Uganda**.** The investigative methods included questionnaire, observational study, laboratory and clinical evaluations. The study participants were recruited from the health facility regardless of the age specifications.

2.3 Inclusion Criteria

All participants were out-patients who were presenting with signs of uncomplicated malaria to the clinician in-charge; those who had resided in Bushenyi district for at least the last six months prior to the commencement of the study, those who confirmed that they were able to comply with the stipulated follow-up visits, and those without severe malnutrition as per the 2015 WHO guidelines. Patients over 6 months of age were included in this study.

2.4 Exclusion Criteria

Those who declined to consent to the study, nomadic patients, intolerant to oral treatment according to modified WHO 2010 criteria, hypersensitivity or allergy to ACTs, Febrile conditions due to other malaria, and those under medications which may have interfered with pharmacokinetics of anti-malarial drugs and those with severe malaria as per the WHO guidelines were excluded.

2.5 Study Setting

All adult patients signed the informed consent form and parents or guardians signed the informed consent on behalf of the patients below 18 years.

Out of the 283 participants recruited to this study, 194 completed the follow up schedules while 89 were withdrawn from the study because they did not adhere to the follow up visits in the first three days.

2.6 Malaria Diagnosis

Malaria diagnosis was conducted as per the Uganda ministry of health guidelines by using Rapid Diagnostic Test, Microscopy and fever determination. This was conducted in all follow up days. RDT was used as a preliminary screening method, while microscopy was used as a confirmatory test for malaria diagnosis. The participants were requested to consent to the study. This was followed by determining the body temperature where auxiliary temperature was measured with a thermometer which had a precision of 0.1 °C. In case the result of the temperature was below 36.0 °C, then this was repeated again for the confirmation. Then 100 µL of venous blood sample was collected from the adult participants and in the case of children under 2 years of age, 100 µL finger prick blood sample was collected. This procedure was repeated during the follow up visits. Consequently 5 µL blood was collected on filter paper (ET31CHR; Whatman Limited, Kent, UK) for future genotypic typing and kept in a dust free lock and key cabinet. Rapid Diagnostic Test (RDT) was conducted by using HRP-II (HRP2 (Pf) (Access Bio, Inc, USA). Briefly 5 µL of blood was added to the test kit well, followed with addition of five drops of assay diluent into the well and results read after 30 min. Blood samples was considered RDT positive for *P. falciparum* if there was appearance of a control line and a test line on the result window and considered as negative when there was only one control line. RDT positive samples were then subjected to microscopy evaluation for *P. falciparum* confirmation. Thick and thin blood smears were prepared and then stained with 2% Giemsa for 30 minutes. For thin smears, they were fixed in methanol solution.

The smears were examined under 100 x magnification objective lens with immersion oil for thick and thin film. Parasitemia was estimated by counting the number of asexual parasites per 200 white blood cells and calculating parasites per micro liter. Smears were read three times before making the conclusions. Smear were considered to be negative if no parasites were observed after examination under 100 high-powered fields. The slides were observed by 2 readers from the study team independently without prior knowledge of the RDT outcomes and the results were recorded as positive when both readers recorded a positive result and the same species. When there was a discrepancy, a third reader assessed the slide. All slides and blood spotted filter papers were labeled well with the participant identification study numbers and transported in a dust free cabinet in the lab for future further studies (8).

2.7 Treatment

Treatment was conducted by the study nurse by following the Uganda ministry of health and Uganda National Malaria control programme guidelines for treatment of uncomplicated malaria (9). The treatment drugs were obtained from the health facilities. These drugs are usually supplied by the government of Uganda under the coordination and regulation of Uganda national drugs agency. The drug used in this study was AL which were tablet formulated in nature containing 20 mg of Artemether and 120 mg of Lumefantine. This was administered as a 6 dose regimen given over a period of 3 days depending on the weight of the participant. Those weighing 15-24 kg took 6 tablets in total. Those weighing 15-24 kg took 12 tablets in total. The weighing 25-34 kg took 18 tablets in total and finally those weighing more than 34 kg took 24 tablets in total. The tablets were consumed together with milk to promote sufficient absorption. The treatment was strictly conducted by using Direct observed therapy (DOT). On day 1 and day 2 the participants were given first dose and second dose of the ant malaria drug. On day 3 *P. falciparum* parasites detection was done and the participants were given the third dose of the AL drug. The first dose was given at the health facilities while the second and third doses were given at the places of residence of the participants by the study nurse. The participants were monitored for 30 minutes after treatment with AL drug for any adverse effects such as vomiting. In case any participant vomited the drug then he/she was treated with the same drug of the same dose. If the same participant vomited again he/she was offered rescue treatment of parenteral treatment and then withdrawn from the study.

2.8 Determination of Malaria Treatment Outcomes

The *P. falciparum* positive participants were treated with AL drug and monitored at day 0, 1, 2 3,7,14 and day 28. The efficacy of the AL treatment was assessed by evaluating clinical and parasitological treatment outcomes as per the

WHO *in-vivo* clinical and parasitological classification criteria for areas of intense malaria transmission (10), which classifies the response as adequate clinical and parasitological response (ACPR) if there is no treatment failure, late parasitological failure (LPF) if *P. falciparum* parasitemia occurs between 4 and 28 days without fever, late clinical failure (LCF) if *P. falciparum* parasitemia occurs between 4 and 28 days with fever and finally as early treatment failure (ETF) if there is development of severe symptoms, or insufficient parasitological response by day three.

2.9 Questionnaires and Direct Observation Setting

The study was conducted by using pre-tested administered questionnaires which were used to determine the demographic patterns and effects of health and patient related practices prior to the study and during the study period on treatment outcomes. For the participants who were unable to write and read, they were assisted by the researchers to do so. The questionnaires were developed from the demographic health survey (DHS). This was adapted to reflect the population and health issues relevant to malaria infection in Uganda (5). The questionnaire was pretested to verify for clarity and administrability. The reliability of the questionnaire was ascertained by calculating the cronbach's alpha value, whereby the alpha value of more than 0.7 was considered an acceptable value. Consequently, questionnaires were translated to the two most common local languages of Luganda and Runyankole by using the linguistic translator.

Information on the following independent variables were collected; socio-demographic parameters (age, sex, number of members in each household, educational level of patient or household head). Concerning malaria, the following were determined; protective facilities from mosquito bite including dwelling unit long-lasting insecticidal nets (LLIN) use, indoor residual spraying (IRS) in the household. Symptoms of malaria experienced, frequency of taking anti-malarial drugs, misuse of ant malarial agents, prescription of drugs, hospital visit for fever management, pattern of febrile illness, and intermittent preventive treatment of pregnant women (IPTp) intake were also assessed. Consequently, direct observations of biological and human related parameters were conducted during different follow up days.

Every participant was allocated a unique recognition code at the time of the questionnaire administration. The names of respondents and households were kept as total confidential information and were not used in the presentation of results or available to anybody.

2.10 Data Analysis

Data was entered in excel spread sheet 2007, by considering different parameters against the study participants. Data retrieved was analyzed using statistical package for social sciences (SPSS version 10 windows). Descriptive statistics were done using tables showing frequencies and percentage distributions. Factors that were statistically significant ($p \leq 0.05$) at bivariate analysis were included in the multivariate analysis. The model was checked for best fit of data and then used to compute adjusted odds ratios of factors that were associated with malaria treatment outcomes. Statistical significance was considered at 95% level of confidence. Interaction and confounding factors were assessed, and values of $p \leq 0.05$ were regarded as statistically significant relationships.

3 RESULTS

3.1 Baseline Characteristics of the Participants

The study recruited 283 respondents; 194 (68.6%) participants completed the follow up schedules while 89 (31.4%) were withdrawn from the study due to different reasons as provided in Figure 2. The participants were grouped in relation to their social demographic patterns such as age, gender and weight as presented in Table 1. By considering the age, participants with 0-5 years represented the least number of 3 (1.5%) in relation to those having 18 years and above who were the majority with 115 (59.3%). 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%).

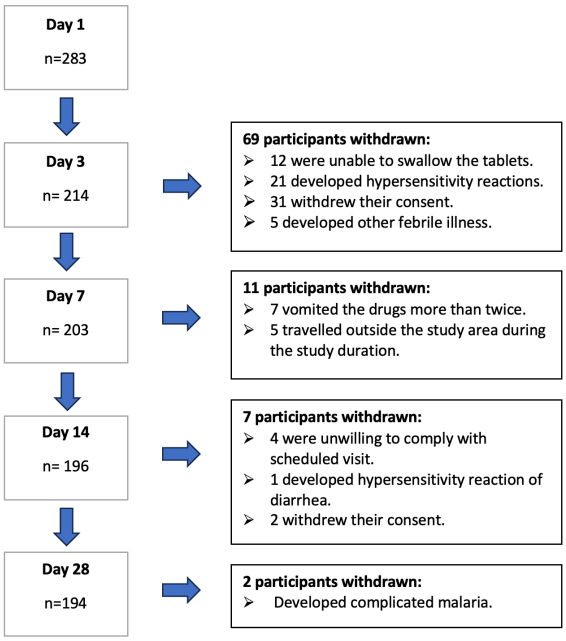

Figure 2. Showing the retention rate and reasons for withdrawing from the study

Table 1. Socio-demographic baseline characteristics of participants

Variable	Number of participants (n, %)
Age (years)	
0-5	3 (1.5)
6-18	76 (39.2)
>18	115 (59.3)
Gender	
Female	104 (53.6)
Male	90 (46.4)
Weight (kg)	
0-10	1 (0.5)
11-20	5 (2.6)
21-30	21 (10.8)
≥31	167 (86.1)
Marital status	
Single	104 (53.6)
Married	90 (46.4)
Education level	
None	4 (2.1)
Primary	107 (55.2)
Secondary	50 (25.8)
University/college	7 (33)
Occupation	
None	3 (1.5)
Student/pupil	84 (43.3)
Casual worker	14 (7.2
Business	23 (11.9
Peasant farmer	53 (27.3
House wife	5 (2.6)
Formal employment	10 (5.2)
Others	2 (1.0)
Number of house holds	
< 5	43 (22.2)
5-10	139 (71.6)
>10	12 (6.2)
Hospital attended	
Kyamuhunga HC III	42 (21.6)
KIUTeaching Hospital	71 (36.6)
Kyeizooba HC III	71 (36.6)
Ishaka Adventist Hospital	10 (5.2)

3.2 Previous Treatment Practices Associated with ACTs Treatment Outcomes

After evaluating the previous treatment practices of the patients by using filled in questionnaires, the study found that the majority of participants used ACTs at a rate of 164 (84.5%). For those who were previously prescribed to ACTs, the study recorded an Adequate Clinical and Parasitological Response (ACPR) of 50 (30.5 %), Late Clinical Failure (LCF) of 19 (11.6 %), Late Parasitological Failure (LPF) of 39 (23.8 %) and Earlier Treatment Failure (ETF) of 56 (34.1). Quinine was the second most used drug of choice prior to the study with a preference rate of 27 (13.9 %). The study recorded an ACPR of 3 (11.1%), LCF of 3 (11.1%), LPF of 4 (14.8%) and ETF of 17 (63%) for the participants who were previously prescribed to Quinine as a treatment drug. Fansidar was the least previously prescribed antimalarial drug with a preference rate of 3 (1.5%). Finally, the study recorded an ACPR of 0 (0%), LCF of 1(33.3%), LPF of 0 (0%) and ETF of 2 (66.7%), respectively for the participants who were treated by using Fansidar (Table 2).

Majority of the participants (n = 100; 51.5%) had previously received the recommendations on the type of drug to use by a medical doctor while 57 (29.4%) received recommendation from the nurse. Self-medication was previously practiced by less percentage of participants at 37 (19.1%). In relation to treatment responses, those who were recommended by a doctor experienced more ACPR at 32 (32%) while those whose recommendation was from a nurse the ACPR was 14 (24.6%) and second most ETF at 9 (24.3%). Moreover, those who practiced self-medication experienced the least ACPR at 7 (18.9%).

The study indicated that those who received the drugs as a result of the doctor's recommendation had the highest ETF at 42 (42%) and those who

practiced self-medication had the lowest ETF at 9 (24.5%), which was statistically significant at p= 0.018 in determining the treatment outcomes (Table 2). Majority of the participants reported that they had previously purchased the drugs from a health care facility at 119 (61.3%) followed by chemist (drug-shop) at 39 (20.1%) and pharmacy shop at 35 (18%).

Those who obtained the drugs from friends were the least at 1 (0.5%). The study found that those who purchased the drugs from the hospital had the highest percentage of ACPR at (28.6%; n=34) compared with those who purchased from pharmacy at 9 (25.7%) and chemist at 9 (23.1%) (Table 2). The study reported that 130 (67%) of the participants were previously able to finish the recommended dose and those who were unable to finish the dose were 64 (33.0%). Out of those who completed the dose, 60 (46.2%) developed ETF compared to 15 (23.4%) of those who did not complete the dose. Further, out of those who completed the dose, 33 (25.4%) developed ACPR, compared to 20 (31.2%) of those who did not complete the dose. The study revealed that 103 (53.1%) of the participants experienced malaria infections twice a year, 46 (23.7%) once a year, 42 (21.6%) once in three months and 3 (1.5%) of the participants experienced the infection once in a month. The study reported that 32 (31.1%) of the participants who experienced malaria infections twice a year developed ACPR compared to ACPR of 1 (33.3%) for those who experienced malaria infections once in a month (Table 2).

The study revealed that the highest percentage (51%, n = 99) previously used anti-malarial drugs as recommended in the health care facility, 4 (2.1%) used anti-malaria drugs once a while and 91 (46.9%) of the population used anti-malaria drugs any time they felt feverish. It was found out that ACPR was highest (n= 30, 30.3%) among those who used the drugs as recommended in the health care facility compared to 24.2% (n=22) of those who used anti-malaria drugs anytime they felt feverish and 1 (25%) among those who used the drugs once in a while (Table 2).

Table 2: Bivariate analysis of previous malaria treatment practices associated with treatment outcomes

Variable		Treatment Outcomes n (%)					
	Number of participants, N (%)	ACPR (n= 53)	LCF (n= 23)	LPF (n= 43)	ETF (n= 75)	cOR (95% CI)	P-value
Antimalarial used							
ACT	164(84.5)	50(30.5)	19(11.6)	39(23.8)	56(34.1)	0.679 (0.058-7.913)	0.757
Quinine	27(13.9)	3(11.1)	3(11.1)	4(14.8)	17(63.0)	0.353 (0.042-5.231)	0.449
Fansider	3(1.5)	0	1(33.3)	0	2(66.7)	1.000	
Source of antimalarial recommendation							
Doctor	100(51.5)	32(32.0)	10(10.0)	16(16.0)	42(42.0)	0.286 (0.101-0.807)	0.018*
Nurse	57(29.4)	14(24.6)	4(7.0)	15(26.3)	24(42.1)	0.469 (0.159-1.378)	0.169
Self-medication	37(19.1)	7(18.9)	9(24.3)	12(32.4)	9(24.3)	1.000	

Source of antimalarial drugs							
Health care facility	119(61.3)	34(28.6)	8(6.7)	26(21.8)	51(42.9)	0.889 (0.350-2.257)	0.805
Pharmacy shop	35(18.0)	9(25.7)	9(25.7)	4(1.4)	13(37.1)	0.537 (0.135-2.130)	0.376
Chemist	39(20.1)	9(23.1)	6(15.4)	13(33.3)	11(28.2)	-	-
Friends	1(0.5)	1(100)	0	0	0	1.000	
Ability of finishing dose							
Yes	130(67.0)	33(25.4)	13(10.0)	24(18.5)	60(46.2)	0.316 (0.138-0.721)	0.006*
No	64(33.0)	20(31.2)	10(15.6)	19(29.7)	15(23.4)	1.000	
Reasons for stopping prescribed dose							
When I feel healed	66(34.0)	21(31.8)	10(15.2)	20(30.3)	15(22.7)	3.478 (0.170-1.203)	0.003*
When I complete dose	128(66.0)	32(25.0)	13(10.2)	23(18.0)	60(46.9)	1.000	
Frequency of malaria infection per year							
Once in a month	3(1.5)	1(33.3)	0	0	0	-	-
Once in 3 months	42(21.6)	11(26.2)	4(9.5)	8(19.0)	19(45.2)		
Once in a year	46(23.7)	9(19.6)	4(8.7)	8(17.4)	25(54.3)	0.344 (0.133-0.892)	0.028*
Twice a year	103(53.1)	32(31.1)	15(14.6)	27(6.2)	29(28.2)	1.000	
Frequency of antimalarial drug use							
Once in a while	4(2.1)	1(25.0)	1(25.0)	2(50.0)	0	-	-
Anytime I feel feverish	91(46.9)	22(24.2)	16(17.6)	24(26.4)	29(31.9)	2.239 (1.031-4.865)	0.042*
As recommended in health care facility	99(51.0)	30(30.3)	6(6.1)	17(17.2)	46(46.5)	1.000	
Distance to health facility							
< 1 km	48(24.7)	13(27.1)	5(10.4)	15(31.2)	15(31.2)	2.143 (0.921-4.987)	0.077
≥1 km	146(75.3)	40(27.4)	18(12.3)	28(19.2)	60(41.1)	1.000	

*Statistically significant factors (p <0.05) for ACPR treatment outcome were included in multivariate model. ACPR= adequate clinical and parasitological response; ETF= earlier treatment failure; LPF=late parasitological failure; LCF= late clinical failure

Table 3. Bivariate analysis of current malaria control practices on treatment outcomes

Variable	Number of participants n (%)	ACPR (n= 53)	LCF (n= 23)	LPF (n= 43)	ETF (n= 75)	cOR(95% CI)	P-value
Practice indoor residual spraying at home							
Yes	82(42.3)	15(18.3)	10(12.2)	13(15.9)	44(53.7)	0.305 (0.138-0.677)	0.004*
No	112(57.7)	38(33.9)	13(1.6)	30(26.8)	31(27.7)	1.000	
Source of indoor residual spraying							
Government	66(78.6)	13(19.7)	7(10.6)	8(12.1)	38(57.6)	0.253 (0.062-1.035)	0.056
Yourself	4(22.2)	4(2.2)	3(16.7)	5(27.8)	6(33.3)		
Last indoor residual spraying							
< 6 months	19(22.9)	2(10.5)	3(15.8)	3(15.8)	11(57.9)	0.900 (0.209-3.874)	0.887
≥ 6 months	64(77.1)	14(21.9)	7(10.9)	10(15.6)	33(51.6)	1.000	
Sleep under mosquito net							
Yes	162(83.5)	49(30.2)	19(11.7)	29(17.9)	65(40.1)	0.319 (0.127-0.801)	0.015*
No	32(16.5)	4(12.5)	4(12.5)	14(43.8)	10(31.2)	1.00	
Mosquito net treatment							
Yes	73(45.1)	23(31.5)	6(8.2)	7(9.6)	37(50.7)	0.241 (0.090-0.643)	0.004*
No	89(54.9)	26(29.2)	13(14.6)	22(24.7)	28(31.5)	1.000	
Number of mosquito nets owned							
One	92(56.4)	33(35.9)	14(15.4)	16(17.4)	29(31.5)	1.570 (0.652-3.780)	0.314
More than one	70(43.2)	16(22.9)	4(5.7)	13(18.6)	37(52.9)		
Source of mosquito net							
Government facility	90(56.2)	30(33.3)	7(7.7)	11(12.1)	43(47.3)	0.179 (0.056-0.578)	0.004*
Pharmacy shop/open market	43(26.5)	11(25.6)	11(25.6)	7(16.3)	14(32.6)	0.350 (0.093-1.317)	0.120
Malaria campaign	6(3.7)	4(66.7)	0	1(16.7)	1(16.7)	0.700 (0.037-13.179)	0.812
Hawkers	22(13.65)	4(18.2)	1(4.5)	10(45.5)	17(31.8)	1.000	
Have vegetation near homestead							
Yes	159(82.0)	43(27.0)	20(12.6)	35(22.2)	61(38.4)	1.004 (0.383-2.630)	0.993
No	35(18.0)	10(28.6)	3(8.6)	8(22.9)	14(40.0)	1.000	
Have stagnant water near homestead							
Yes	108(55.7)	30(27.8)	15(13.9)	28(25.9)	35(32.4)	2.133 (0.984-4.626)	0.055
No	86(44.3)	23(26.7)	8(9.3)	15(17.4)	40(46.5)	1.000	

*Statistically significant factors (p <0.05) for ACPR treatment outcome were included in multivariate model. ACPR= adequate clinical and parasitological response; ETF= earlier treatment failure; LPF=late parasitological failure; LCF= late clinical failure.

Table 4. Multivariate regression analysis of factors associated with treatment outcomes

Predictor variable	Adjusted Odds ratio	95% C I	P-value
Ability of completing antimalarial dose			
Yes	2.635	0.067-10.307	0.604
No	1.000		
Reasons for stopping prescribed dose			
When I feel healed	6.348	0.170-23.735	0.317
When I complete dose	1.00		
Practice indoor residual spraying at home			
Yes	0.151	0.047-0.479	0.001*
No	1.000		
Frequency of malaria infection per year			
Once in 3 months	0.329	0.072-1.500	0.151
Once in a year	0.133	0.034-0.526	0.004*
Twice a year	1.00		
Is mosquito net treated?			
Yes	0.283	0.085-0.938	0.039*
No	1.000		

*Statistically significant risk factors for ACPR treatment outcome at $p \leq 0.05$.

3.3 Current Malaria Control Practices Associated with Treatment Outcomes

The study revealed that 66 (78.6%) of the participants obtained the indoor spraying from the government compared to 4 (22.2%) who self-sourced. Indoor residual spraying at home was practiced by 82 (42.3%) of the participants was shown to have a statistically significant value (*P*=0.004) in influencing treatment outcomes compared to the 57.7% (n =112) who did not practice indoor spraying. The highest ACPR was recorded at 38 (33.9%) among those who did not practice indoor spraying compared to 10 (18.3%) who practiced indoor spraying. Similarly, the study reported highest ETF of 44 (53.7%) among those who practiced indoor spraying compared to 31 (27.7%) of those who did not. Those who had sprayed their homes not more than 6 months prior to this study represented 19 (22.9%) of the participants compared to 64 (77.1%) participants who had sprayed their homes in more than 6 months prior to this study. Only 2 (10.5%) of the participants who had sprayed their homes in not more than 6 months developed ACPR compared to 14 (21.9%) among the participants who had sprayed their homes in more than 6 months. However, those who sprayed their homes in more than 6 months experienced the lowest percentage of ETF 51.6% compared to 57.9% of those who had sprayed their homes not more than 6 months.

Overall, the influence of sleeping under a mosquito net upon the treatment outcome was statistically significant (*P*=0.015). Consequently, it was reported that out of those who slept under an ITN, 49 (30.2%) developed ACPR compared to 4 (12.5%) among those who did not sleep under the mosquito net. Moreover, those who slept under an ITN developed ETF of 65 (40.1%) compared to 10 (31.2%) for those participants who did not. However, 73(45.1%) slept under ITN while 89 (54.9%) did not sleep under ITN. The study found out that 23 (31.5%) of the participants who slept under ITN developed ACPR compared to 26 (29.2%) for those who did not sleep under ITN. The highest number of the participants obtained the mosquito nets from the government facility at 90 (56.2%), compared to the lowest number of 6 (3.7%) who reported to have obtained the mosquito nets from malaria campaign. On the environmental front, most of the participants reported to have vegetation such as bananas near their homesteads at 159 (82.0%) compared to 35 (18.0%) who didn't have vegetation near their homesteads. In relation to the occurrence of stagnant water near the homesteads, 108 (55.7%) of the participants reported to have stagnant water compared to 86 (44.3%) who didn't have stagnant water (Table 3).

3.4 Multivariate Regression Analysis of Factors Associated with Treatment Outcomes

Multinomial regression model was used in bivariate analysis to obtain crude odds for the strength of association between influencing factors (malaria treatment practices and malaria control interventions) on malaria treatment outcomes. Factors that were statistically significant ($p \leq 0.05$) at bivariate analysis, were included in the multivariate analysis. The model was checked for best fit of data and then used to compute adjusted odds ratios of factors that were associated with malaria treatment outcomes. Statistical significance was considered at 95% level of confidence (Table 4). When the bivariate significant predictor factors for treatment outcomes were subjected to multivariate regression analysis, they had the following logistic regression values: practicing indoor residual spraying at home (OR=0.151; 95% CI: 0.047-0.479; $p<0.05$), previous frequency of malaria infection per year (OR=0.133; 95% CI: 0.034-0.526; $P<0.05$) and mosquito net treatment (OR= 0.283; 95% CI: 0.085-0.938; $P<0.05$). However, ability of previous completion of antimalarial dose (OR=2.635; 95% CI: 0.067-10.307; $P<0.05$) and reasons for previously stopping prescribed dose (OR=6.348; 95% CI: 0.170-23.735; $P<0.05$) were found to have no significant association with determining treatment outcomes.

4 DISCUSSION

Malaria treatment and control practices have been generally implicated in the overall reduction of clinical episodes across the world though the exact reduction rate is unknown. The Ugandan government has currently scaled out different intervention programs to combat malaria infection. Despite the efforts being embraced, there still remains huge percentage of mortalities and morbidities caused by the disease, thus raising the questions on the factors behind this scenario. This may be due to poor practices or inefficient practices put in place. Many studies have been carried across the world and Uganda to determine the usage of different malaria intervention practices on the occurrence of malaria (9, 11 – 12). This study assessed the impact of previous and post patient malaria treatment practices which may be influencing recurrence of parasitemia after treatment with recommended drug of choice, the first study of its kind to be conducted in Bushenyi District in Western Uganda. The development and spread of resistance to previously used anti-malarial drugs (sulfadoxine–pyrimethamine, and chloroquine) has prompted Uganda to adopt a new malaria control policy based on three major interventions: vector control with long lasting insecticide-treated nets (LLINs), the use of artemisinin-based combination therapy (ACTs) for treating uncomplicated malaria; and chemoprophylaxis for pregnant women (12).

Among all control measures that are used against the malaria spread, chemotherapeutic agents seem to contribute largely to the strategy of combating malaria mortality in the world. Quinoline derivatives and antifolates were the first mainstream malaria agents in the world, however, resistance has been reported in some parts of the world (13). Currently they are recommended for use as malaria prophylactic agents in infants and pregnant mothers (2). Presently, the World Health Organization (WHO) recommends artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated malaria in most countries particularly where resistance has developed towards other drugs. Uganda adopted the use of Artemether-Lumefantrine (AL) as the drug of choice for treatment of uncomplicated malaria, however the actual implementation started in 2006 (7).

The current study reported the highest participants adopting ACTs for malaria treatment at 84.5% which is in agreement with other previous studies done in Africa and other parts of the world (14 – 16). This could be attributed to the fact that ACTs are provided free of charge by the governments in the study sites. The high prevalence for ACTs usage might have been because it is the first line therapy for uncomplicated malaria in Uganda. Moreover, it is mostly available in public health facilities. The Low-level use of fansidar observed in this study could be due to the fact that it is recommended by Ministry of Health for prophylaxis majorly to pregnant women and at the same time it is not available in most health facilities.

The present study recorded the highest ACPR (30.5%) among participants who previously used ACTs. This is not surprising since ACTs are currently recommended by WHO and adopted by the Ugandan government as the first line treatment regimen for uncomplicated malaria. This finding is in agreement with a previous study conducted in Gulu district of Northern Uganda (17), which recorded ACPR of 95.2% with all participants being negative for parasites at day 2 of the follow up after treatment with ACTs. The study

conducted in Tororo district of Eastern Uganda reported an ACPR prevalence of 40% among the participants (18). Another study conducted at Tororo district recorded an ACPR prevalence of 50% (19), while similar study conducted at Gulu district of Northern Uganda recorded an ACPR prevalence of 42% among the participants (20).

Our study recorded high ACPR among participants who obtained the anti-malaria drugs from the hospital compared with those obtaining from the pharmacy or chemist. This could be because health practitioners in the hospital settings prescribe antimalarial drugs in relation to laboratory results. Furthermore, patients can purchase antimalarial drugs directly from the pharmacies and chemists without any medical prescription. The rate of self-medication practice was found to be 19.1 % which was low compared to other studies. For example, a study conducted in northern Uganda, a geographical area of high malaria transmission intensity reported slightly at a higher prevalence of 36.2% self-medications among the study population (21). Moreover, it has been previously reported in a study done in Apac, northern Uganda that 75.7% of adult (≥18 years) community members accessed and used antimicrobial drugs generally without taking a laboratory test and nor a prescription from health care providers (22).

The probable reason for the reduced self-medication might be because of the current scaling of free malaria treatment offered by the government of Uganda and the availability of many health facilities across the district. The low self-medications reported in the current study area might also be due to the fact that majority of the population have access to health facilities which are located not more than ten kilometers. Another study conducted in Nigeria reported a high percentage of 33.7% for self-medication compared to 17.4% for doctor recommendations and 12.5% for nurse recommendation (23). Anti-malaria drug use pattern influences the development and spread of resistance in the community due to continued sub-optimal use of the drugs. Self-medication uses treatment without any diagnosis and this can lead to anti-malaria resistance. Appropriate use of the correct prescribed dose is an important factor in malaria treatment. From the current study, 31.2% of the participants did not complete their prescribed doses while 67% completed the prescribed anti-malaria doses in the recent malaria illness. These findings are contrary to those from other studies such as one that was carried out in Bangladesh which reported that 68% of the participants did not complete the treatment doses because patients would stop taking medications as soon as they would feel well. Failure to complete treatment doses leads to sub-therapeutic drug levels in patient blood which encourages selection for resistant parasites and treatment failure.

The current study recorded a substantially low usage of indoor residual spraying at 42.3%. Contrary to previous findings by Uganda demographic health survey (3), which found out 67.2% of the population was using IRS. However, it was established that majority of the participants (78.6%) used government to access the IRS. This is because currently the government of Uganda has scaled out nationwide IRS in all households present in the high malaria transmission areas. In 2012, 88 countries in Africa were implementing IRS, and the number of people protected by IRS increased from 5% of those at risk in 2005 to 11% in 2010 but reduced to 8% in 2012. Our study has shown significant reduction by IRS on the occurrence of parasitemia after treatment with anti-malaria drugs (P = 0.001; CI). This is in agreement with other studies conducted elsewhere in Uganda (12, 13, 24), as well as in other studies conducted outside Uganda (25 – 27).

In 2018, WHO recommended universal coverage for ITNs use by all persons in all households (2). The present study found out that 83.5% of the participants slept under mosquito nets. This may be due to the fact that the government of Uganda has distributed free nets in previous years as well as the continued malaria campaigns that have been taking place. But surprisingly only 45.1% of those who owned nets were insecticides treated nets (ITNs). These findings are in contrast to a recent report which has indicated that 54% of African households owned at least one ITN and only 36% of the population slept under ITNs (44). According to the Uganda Demographic Health Survey done in 2018/2019, 83% of the total population was in possession of at least an ITN per household (28) (UDHS, 2019). West Nile region had the highest possession of ITNs at 92%, with Karamoja region at 58% and Ankole region where the current study area is located at 86%. Our findings did not show any significant difference on the protective effect against malaria between ITNs and non-insecticides treated nets. The results however, showed that sleeping under any type of net reduced the rate of malaria occurrence after treatment with anti-malarial agents.

Our findings are in agreement with a study conducted in Uganda from 2009 to 2014 which showed a strong ITNs effect on parasitemia risk reduction (12). Other studies done in Uganda also reported similar trends on usage of ITNs in the reduction of malaria incidences (29-31). In relation to the influence of ITNs on treatment outcomes, our study recorded an ACPR of 30.2% which disagrees with previous studies conducted outside Uganda that recorded lower ACPR. For example, a study conducted in Tanzania among malaria positive pregnant women recorded a 6% prevalence of ACPR (32). The outcomes of treatment in relation to the intervention measures might have been influenced by other factors such as genetic, immunological, and pharmacokinetic factors which are not assessed in this study.

5 CONCLUSION

This study has demonstrated that two major malaria control practices i.e., IRS and ITNs had a positive impact on reducing of parasitemia risk after treatment of patients with antimalaria drugs.

RECOMMENDATION

We hereby recommend that the government of Uganda with other private sectors need to increase the universal ITN and IRS coverage. Uganda Ministry of Health should promote malaria prevention awareness campaigns so as to educate the public about the importance of ITNs and IRS even after being treated with drugs. ITNs and IRS should be integrated together with ACTs in patients under malaria treatment so as to reduce malaria complications and death. However, we also recommend future studies by employing PCR-Corrected treatment outcomes. In addition, we recommend that more studies covering larger geographical regions should be conducted in Uganda.

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DATA AVAILABILITY

Data in tables used to support the findings of this study are included within the article.

AUTHORS' CONTRIBUTIONS

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

COMPETING INTEREST

All authors declare that there are no conflicts of interest existing in regard to this study and publication of the findings.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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.

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