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ABSTRACT

***Background*: The burden of malaria is declining globally including Kenya, however a high number of patients continue to be treated for malaria in our set up. Adopting correct diagnosis and appropriate treatment is cost effective, prevents resistance to anti-malarial and has been shown to save lives.**
***Objective*: To determine the clinicians' anti-malarial prescription practices in the management of children with negative microscopy results.**
***Design*:A prospective observational study.**
***Setting*: General Paediatric wards of Moi Teaching and Referral Hospital, Kenya.**
***Subjects*:A total of 250 children, aged one month to forteen years, admitted with a negative microscopy results for malaria parasites were enrolled from December 2012 to June 2013.**
***Main Outcomes*: Anti-malarial prescription and duration of stay in hospital.**
***Results*: The median age of the participants was 19.5 months (IQR10, 36) with 150 (60%) being male. Forty one (16%) of the participants had travelled to malaria endemic regions in the preceding four weeks while 30 (12%) had used anti-malarial prior to admission. Those treated with anti-malarial with negative microscopy results were 34 (13.6%). Increased sleepiness, history of headache and prior anti-malarial use were independent clinical characteristics associated with treatment. The mean duration of hospital stay was 3.53 days for those on anti-malarial versus 3.75 days for those not treated (P =0.61). One participant died in the group not on anti-malarial.**
***Conclusion*: There was a substantial proportion of children treated for malaria with negative microscopy results. No difference was noted in duration of hospital stay in comparison with the group not treated with anti-malarial.**

INTRODUCTION

Malaria remains an important cause of morbidity and mortality in the world. In 2013 there were estimated 198 million people affected by malaria worldwide with 584,000 deaths. Kenya had nine million suspected cases reported but only 2.6 million were confirmed with diagnostic tests. Seventeen percent of them were aged less than five years (1).

The diagnosis of malaria nowadays requires confirmation with a blood slide for malaria parasites. Previously, the diagnosis advocated mainly by integrated management of childhood illnesses (IMCI) guidelines put a lot of emphasis on presence of fever especially in those children aged less than five years. Fever in itself could be caused by several conditions including pneumonia, otitis media, pharyngitis, urinary tract infection and human immunodeficiency virus (HIV) infection. This meant even what may not have been malaria may have been treated as malaria (2). This has since changed. The current guidelines both by World Health Organization (WHO) and the Kenyan Ministry of Health require parasitological diagnosis for all patients irrespective of age unless it is not available (3,4).

The shift in policy guidelines has been informed by evidence which indicates over reliance on clinical diagnosis of malaria has many problems including likelihood of increased drug resistance, misdiagnosis and wastage of health resources thus increasing cost

of health services (5,6,7,8).

The percentage of patients having a parasitological test improved from 37% in 2010 to 62% in 2013. However, millions of people suspected to have malaria still did not receive a diagnostic test, this despite WHO having recommended tests for all people, irrespective of age, before starting them on anti-malarial(1). Further though the blood slides for malaria parasites are requested in Africa, many clinicians do not seem to use them. Many excuses have been given including unreliable laboratory results (9).

Moi Teaching and Referral Hospital (MTRH) being a tertiary institution is expected to be at the forefront in adhering to these policy guidelines since availability of diagnostic tools is not a problem as may occur with level 2 and 3 facilities in the community. Further, the validity of routine blood slide for malaria parasites at this hospital was recently shown to be high, which is, sensitivity of 75% and specificity of 84.8% when compared to polymerase chain reaction (PCR) (10). Adherence to this policy at such a level is likely to prevent the problems associated with over diagnosis of malaria and decrease the burden on resources. Moreover being a teaching hospital, the culture imparted to both under graduates and post graduate students, is key in ensuring that Kenya adheres to this policy.

This study evaluated whether clinicians in a national referral hospital adhered to test results when making a diagnosis of malaria in children in an inpatient set up.

MATERIALS AND METHODS

A prospective observational study was carried out at the general paediatrics wards of the Moi Teaching and Referral Hospital between December 2012 and June 2013. MTRH is a national referral hospital serving the Western part of Kenya with a catchment population of approximately 15 million. Uasin Gishu County (where MTRH is situated) has an altitude of between 2100 and 2700 M above sea level. There is low transmission rate for malaria in this area with epidemics likely to occur during the rainy seasons. Other surrounding areas especially the counties in the former Western and Nyanza provinces have high malaria transmission. It is not uncommon for patients seen at MTRH to have had history of travel to these regions.

MTRH has a bed capacity of 800 with the general paediatric wards having 80 beds and admit an average of 4500 patients per year. The general paediatric wards usually admit children aged between one month and 14 years.

Children admitted to the paediatrics wards normally have blood slide for malaria parasite done at the sick child clinic in the outpatient department. Routinely thick films are prepared usingGiemsa stain. The laboratory personnel, including technicians, technologists and parasitologists, then examine blood slides for malaria parasites. These results are normally available to the clinicians from 30 minutes of the slides being taken to the laboratory.

The study population were those children aged between one month and fourteen years with negative microscopy results for malaria parasites admitted to the general paediatrics wards with acute onset of clinical features suggestive of malaria. We excluded those children with known chronic illnesses as well as those with microscopy results for malaria parasites from elsewhere other than MTRH.

The sample size was calculated using Fisher's formulae at 95% confidence interval and a standard error of 5% as well as adjusting for finite population for six months. We estimated proportion of children treated for malaria with a negative BS for MPsat 23.8%(10).

Every second participant who met the inclusion criteria on study days was enrolled into the study. In case they did not meet the inclusion criteria, the next individual was included.

The primary outcome measure was proportion of children put on anti-malarial treatment with a negative microscopy results for malaria parasites.We defined treatment as that child who at 24 hours was on anti-malarial having been started within the hospital, either at the sick child clinic or in the wards on the day of admission. The secondary outcome measures included: duration of hospital stay, discharge home and death among the study participants.

A standard pre-tested questionnaire was used to collect data from inpatient children and their parents/guardian. Initial data were collected at admission and thereafter the participants were reviewed after 24 hours of admission and the current treatment recorded including noting whether anti-malarial had been stopped. Research assistants monitored the study participants on a daily basis and informed the Principal Investigator of the death or discharge of each participant. Upon which the duration of hospital stay, and the treatment at this point were noted.

STATA version 10 statistical software was used for analysis. Measures of central tendency were used for continuous data with frequency listings being used for categorical data. Chi-square test and logistic regression were used to test for association among qualitative variables. Kruskal-Wallis test was used to compare continuous variables among groups. All analysis were carried out at 95% level of significance.

Ethical approval was sought from Institutional Research and Ethics Committee (IREC) of Moi University/MTRH, and permission to conduct the study from the MTRH administration. A written informed consent was obtained from the parents/guardian with verbal assent being sought from the

children aged seven years and above. Confidentiality was maintained and participant information de-identified. No coercion or inducements were used to have participants join the study.

RESULTS

A total of 250 participants were enrolled. The median age of the participants was 19.5 (IQR: 10, 36) months, while the male were 150 (60%) thus a male to female ratio of 1.5:1. Majority of the participants, 225 (90%) were from the Uasin Gishu County. Sixteen percent had history of travel to malaria endemic regions in the preceding four weeks. Abnormal respiratory system (RS) examination findings were noted in 34% of the participants as shown in Table 1.

Table 1
The clinical characteristics of the study participants

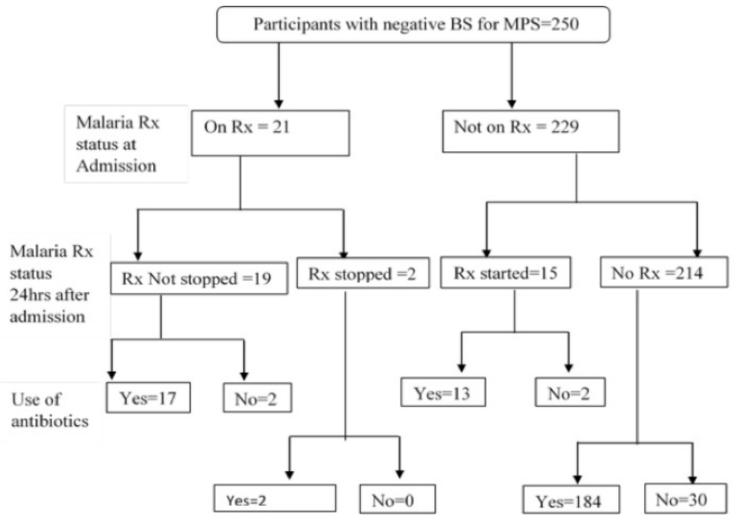
Variable	Frequency n=250	Percentage (% of n)
History of Travel: Yes	41	16.4
No	209	83.6
Prior medication with+: Anti-malarial	30	12.0
Anti-biotics	60	24.0
Anti-pyretics	135	54.0
General Condition: Fair	170	68.0
Ill	80	32.0
Level of Consciousness: Alert	249	99.6
Not Alert<A(V,P,U)	1	0.4
Abnormal Systemic Examination*: CNS	20	8.0
Systemic RS	85	34.0
Examination ENT	30	12.0
	Median (Interquartile Range)	
Temp (ºC)	38.10(37.6,38.1)	
Pulse Rate (per minute)	146(136,159)	
Respiratory Rate (per minute)	30(28,38)	
Duration of Hospital stay (days)	3(3,4)	

#=History of travel to malaria endemic regions.+= Participants having used these drugs prior to coming to MTRH on the day of admission; *Abnormal CNS examination findings included: altered level of consciousness, irritability, confusion and neck stiffness; Ear, Nose and Throat abnormal examination findings included inflamed throat/tonsils. Abnormal RS examination findings were mainly respiratory distress and added sounds on auscultation.

Blood slides were requested in outpatient for 244 (96.7%) of the participants. Five (2%) of the participants with negative blood slides had a repeat of the test during their stay in the wards. Of the 250 participants with negative results, 34 (13.6%, [95%CI 9.6, 18.5]) were treated for malaria. This was based on our preset criteria that anti-malarial treatment was to constitute those on anti-malarial at 24 hours post admissionas defined in the methods above. The distribution of the participants enrolled and their treatment is shown in flow chart in figure 1.

Thirty (88.2%) of these participants had the anti-malarial started in the wards. In 19/34 (55.9%) anti-malarial prescription occurred at admission. Parenteral anti-malarial medication were given in 20/21(95.2%) at admission while 28/34 (82.4%) were still on parenteral anti-malarial medication after 24 hours. Of all the participants treated with anti-malarial with negative BS for MPS, 14 (41.18%) completed their anti-malarial treatment while in the wards.

Figure 1
Flow chart of the participants enrolled and the treatment they received



Rx- Treatment; **At Admission= refers those put on anti-malarials on the day of admission

Univariate analysis was done to determine the demographic and clinical characteristics of the participants associated with treatment with a test negative microscopy results for malaria parasites. History of travel to a malaria endemic region and prior use of anti-malarial were found to be significantly associated with treatment for malaria among the participants (P-Value =0.000). Table 2.

Table 2
Socio-demographic and clinical characteristics association with malaria treatment status

Variable*	Negative- Rx n=34(%)	Negative Not-Rx n=216(%)	P-Value+
County of Res: UG vs. Others	28(82.4)	192(88.9)	0.645
History of Travel**	13(38.2)	28(13.0)	0.000
Age: <6mo	1(3.0)	22(10.2)	
6mo-5yrs	22(66.7)	162(75.3)	
>5yrs	10(30.3)	31(14.4)	0.044
Sex: M vs. F	17(50.0)	133(61.6)	0.200
History of Fever	33(97.1)	197(91.2)	0.242
History of Inability to feed	11(32.4)	83(38.4)	0.497
History of Vomiting	22(64.7)	107(49.5)	0.100
History of Headache	10(29.4)	12(5.6)	0.000
Hx of Increased Sleepiness	16(47.1)	30(13.9)	0.000
Hx of Diarrhoea / Abd. Pains	18(52.9)	91(42.1)	0.237
Hx of Difficulty in Breathing	4(11.8)	49(22.7)	0.148
History of Cough	9(26.5)	112(51.9)	0.006
History of Convulsions	10(29.4)	31(14.4)	0.027
History of Prior use of : Anti-malarial	13(38.2)	16(7.41)	0.000
Anti-biotics	5(14.7)	0.188	
Anti-pyretics	21(61.8)	114(52.8)	0.327

Gen. Condition: ill Vs. Fair	11(32.4)	69(31.9)	0.976
Presence of Pallor Vs. None	7(20.6)	10(4.6)	0.001
Abnormal CNS Exam	7(20.6)	13(6.0)	0.004
Abnormal RS Exam	8(23.5)	77(35.6)	0.166
Abnormal ENT Exam	6(17.6)	24(11.1)	0.276
	Median (IQR)	P Value#	
Mean Resp Rate	34.08(8.44)	0.534	
Mean Pulse Rate	143.26(23.27)	0.511	
Mean Temperature	38.21(1.15)	0.977	

+= P-value based on Pearson Chi-Square, #=P-value based on Kruskal-Wallis, *Hx-History; **History of travel to malaria endemic regions.

Amultiple logistic regression on these factors showed that history of prior anti-malarial use, history of headache and increased sleepiness were still significant factors independently. No collinearity exist on these factors. Table 3.

Table 3

Multiple logistic regressions on clinical characteristics significant on Univariate analysis

Clinical Characteristic	Odds	[95%Conf.	Interval]	P-value
Sex	0.66	0.26	1.66	0.379
History of Travel*	2.10	0.73	6.08	0.171
Age Category	0.92	0.36	2.32	0.854
History of Headache	4.36	1.17	16.20	0.028
History of Increased Sleepiness	4.45	1.66	11.94	0.003
History of Cough	0.52	0.19	1.40	0.193
History of Convulsions	1.96	0.67	5.67	0.217
Prior Anti-malarial use	7.68	2.73	21.62	0.000
Presence of pallor	1.75	0.43	7.15	0.436
Abnormal CNS Exam	1.93	0.54	6.94	0.312

*History of travel to malaria endemic regions.

The mean duration of hospital stay was 3.53 (2.57) days for those treated while negative versus 3.75 (2.21) days for those negative but not treated (P-value=0.61).The mortality rate among study participants was 0.4% (1 participant) who was not on anti-malarial.

DISCUSSION

The rate of treatment with anti-malarial for children testing negative for BS for MPs, was substantial at 13.6%. In comparison to other available studies this was however relatively low. Previous studies in East Africa have shown higher values, in 2010, Juma and Zurovac showed that 56.6% of children in Kenya were put on anti-malarial with negative blood slides (11). In Tanzania, Reyburn H *et.al* in various studies has shown least value of 48% (12,13). However, these studies looked at outpatient set up and mainly lower level facilities. These studies had more of a nationwide coverage with both low and high endemicity sites. No studies from inpatient set up were retrievable. The lower value may be attributable to the different set up although other factors may play a role. There is documented decreasing prevalence of fever attributable to malaria in various countries including Kenya and this may have influenced clinicians' decisions (1,14,15). Instructively, most anti-malarial were started in the wards and this may mean that only a select subjects with certain factors were being put on anti-malarial.On the other hand, even in similar set ups there has been a decrease in presumptive treatment (15,16). Changes in policy and treatment guidelines may be responsible for some of these changes. Currently all children should be started only on anti-malarial medication if they test positive for malaria (3,4). Adherence to test results has been shown to be a reason for low prescription of anti-malarial in those with test negative results as

demonstrated in a clinical trial in Tanzania (17). This may have played a role too.

Participants' characteristics were analysed in an effort to determine whether any clinical features possibly influenced clinicians to start anti-malarial medication in test negative patients. History of travel to malaria endemic regions was significantly associated with treatment with anti-malarial. This may have been influenced by known geographical distribution of malaria in Kenya. Although there is no policy to treat children using clinical algorithms in this hospital, the factors coming out have for long been associated with malaria. In a Gambian study evaluating clinical signs and symptoms predicting malaria, reduced feeding, sleeping and palmar pallor were associated with malaria. Convulsions however were not associated with malaria in that study as were difficulty in breathing, presence of diarrhoea and vomiting. These factors were not different in the group not treated versus that treated with negative results in our study (18). A review of similar clinical features in Kilifi, Kenya at the Coast had only showed pallor and increased sleepiness to be significant in children below five years (19). These studies were done in high malaria transmission areas. Chandra Mohan D *et al*. in India had argued that in low endemic regions, normally fewer factors seem to be associated with malaria clinically (20). Following multiple logistic regression however only prior use of anti-malarial, history of headache and increased sleepiness were associated independently with increased chance of treatment in test negative results participants. Among these increased sleepiness has been shown to be associated with clinical diagnosis of malaria as described in the various studies discussed above. Notable, this is what the Kilifi study (19) had found and was thought to be likely to occur in low malaria endemic region. The catchment area of MTRH is largely low endemic especially where majority of the participants came from.

The sensitivity of using clinical symptoms in algorithm to diagnose malaria is high even up to 100% (6). The problem has been specificity. Some authors have argued previously that physician diagnosis on the basis of clinical features without laboratory support has a sensitivity of as high as 89%. The specificity is low also at 20% (20). The previous study in this same hospital by Odongo, showed clinical diagnosis only correctly identified malaria at 3.61%. On the other hand specificity and sensitivity of microscopy under normal circumstances is not 100%,it has been shown to be 61.5% and 68.6% respectively in Kenya(16). In MTRH it was shown to have 75% sensitivity and 85% specificity. While one may want to believe that this 25% chance of missing a patient with malaria makes clinicians ignore test results, they never do so when results are positive (10,11,16). In a study looking at clinicians view on the utilisation of laboratory results at MTRH, clinicians in these wards acknowledged that they trusted the validity of the results; 72 and 83% of them felt they were reliable and accurate respectively. However, only 50% of these clinicians felt the results influenced their clinical decisions (21). It may therefore be true that clinicians as seen from above followed what appeared to be a logical clinical judgement rather than the test results in starting some participants on anti-malarial. This may have been influenced by previous experience with malaria positive patients. However, most of these factors seemed not to be independent when subjected to further analytical processes.

There was no significant differences in the outcome measured between the groups treated with anti-malarial versus the negative group not treated. This is in terms of duration of hospital stay and death versus discharge home. A larger sample size may be necessary to unmask this or prove the lack of it since we know the policy documents, both nationally and internationally, have advocated treatment of test positive treatment only based on likely worse outcomes when there is indiscriminate use of anti-malarial (6,22).

In general it appears that there are some known clinical factors which may have tipped clinicians to still go ahead and treat test negative patients with anti-malarial. However, most of these factors were not found to be statistically significant on multiple logistic regression. We recognise that since we did not interview the clinicians directly, the information we derived is mainly inferred. On the other hand, this may reflect the true picture as asking the clinicians their practice may have resulted in them telling us the theory of it. We further acknowledge that our data which was not collected throughout the year may be affected by malaria seasonality in the area of study. This was partially addressed by having both dry and rainy months as part of study period.

In conclusion, a substantial proportion of children were treated for malaria while having a negative blood slide for malaria parasites results at Moi Teaching and Referral Hospital. Prior use of anti-malarial, history of headache and being abnormally sleepy were significantly associated with anti-malarial prescription. There was no significant difference in hospital outcomes for those children treated compared with those not treated with anti-malarial while having negative blood slide for malaria parasites.

RECOMMENDATIONS

Efforts need to be made to lower the proportion of children put on anti-malarial with negative microscopy results for malaria parasites. A qualitative study to establish why clinicians do not adhere to test results in the management of children for malaria should be done.

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