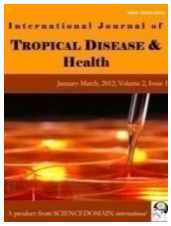

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Microscopy Negative Malaria during a Peak Transmission Season in a Malaria Endemic Setting: Diagnostic Accuracy of RDTs, Expert Microscopy and the Value of Presumptive Treatment

Charles O. Odongo[1], Peter Wambi[1], Jennifer Ajok[1], Ian Musinguzi[1], Samuel Oluka[1], Anita Wanyana[2], Denis Anywar[1], Alfred Andama[3] and Victoria Katawera[4*]

[1]Faculty of Medicine, Gulu University, Gulu, Uganda.
[2]Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda.
[3]School of Medicine, Department of Internal Medicine, Makerere University College of Health Sciences, Kampala, Uganda.
[4]Microbiology Department, Mbarara University of Science and Technology, Mbarara, Uganda.

Authors' contributions

This work was carried out in collaboration between all authors. Authors COO and VK participated in study conception and design, data acquisition, analysis and interpretation, drafting the manuscript and revising it critically for important intellectual content. They have given final approval of the version to be published. Author PW participated in study conception and design, data acquisition, analysis and interpretation, drafting the manuscript. He has given final approval of the version to be published. Authors JA, IM, SO and DA participated in study conception, design, and data acquisition. They have given final approval of the version to be published. Authors AW and AA participated the data acquisition, interpretation and drafting the manuscript. They have given final approval of the version to be published. All authors read and approved the final manuscript.

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**Corresponding author: Email: victoriaktwr32@gmail.com;*

ABSTRACT

Aim: We investigated all malaria symptomatic patients with microscopy-negative results during a peak malaria transmission season to ascertain the need for presumptive treatment of malaria among these patients.
Justification: Due to improved malaria control measures, the administration of anti-malarial drugs to symptomatic patients with negative microscopy results is uncalled for. However, in malaria endemic low resource settings, this practice is upheld especially during peak transmission seasons. There is paucity of data to either support or discourage this practice in these settings.
Study Design: It was a cross-sectional study.
Place and design of study: This study was conducted at Gulu regional referral hospital, Uganda, between October and November 2012.
Methodology: A routine blood smear (BS) was examined for all the 542 malaria symptomatic participants. A rapid diagnostic test (RDT) was performed on all patients with negative BS results. All smears were later read by expert microscopists.
Results: Of the 542 patients seen, 503 (92.8%) had negative routine BS results. Eighty nine (7.2%) were excluded due to history of treated fever in the previous two months. Of the 414 qualifying participants, 14 (3.4%) were positive by RDT and 6 (1.4%) were positive by expert microscopy. Nearly all participants (12/14) with microscopy-negative but RDT-positive results were children less than 5 years.
Conclusion: At a rate of 3.4% true malaria cases, presumptive treatment of all malaria symptomatic cases offers a marginal benefit to children less than five years and is an uncalled-for expense among adults. Prescription practices consistent with these findings could greatly improve rational anti-malarial use and minimize costs, especially in sub-Saharan Africa.

Keywords: Malaria; blood smear; microscopy; rapid diagnostic test; peak transmission.

1. INTRODUCTION

Malaria, a febrile condition, has been endemic in sub-Saharan Africa with high incident rates in the past decades. However, recent interventions like use of insecticide-treated nets, indoor residual spraying (IRS), and availability of highly efficacious antimalarial medicines have led to a tremendous decrease in its morbidity and mortality.

The World Health Organization (WHO) [1] recommends the “test, treat and track” policy where treatment is based on laboratory confirmation of malaria. Unfortunately, malaria usually presents with non-specific symptoms [2] and yet accurate laboratory diagnosis in sub-Saharan Africa is still a challenge.

In spite of the fact that rapid diagnostic tests (RDTs) are highly sensitive [3,4], user friendly [3-5] and are better at targeting anti-malarial treatments for significant reduction in wasteful prescriptions [6-9]. Microscopy is the gold standard, but is cumbersome, requires expertise and has a low sensitivity [4] in sub-Saharan Africa. This limitation of microscopy has often prompted the presumptive treatment of most febrile episodes as malaria even with a negative blood smear (BS) result, especially during peak transmission seasons.

The currently effective artemisinin-based combination therapy (ACT) for malaria is quite costly. The malaria over diagnosis has led to excessive presumptive treatment and hence wasteful drug consumption with adverse health and economic outcomes on the affected population [10].

Uganda has one of the highest malaria incidence rates in the world [11]. Gulu regional referral hospital (GRRH) located in Northern Uganda is a malaria hyper-endemic region [12] with two peaks during the rainy seasons, from March to May and September to November [12].

In order to assess the magnitude of routine BS negative malaria and therefore the need for continuing presumptive treatment for cost-effective management of malaria, we investigated all suspected malaria cases with routine BS negative results at GRRH during a peak transmission season in a hyper-endemic setting.

2. MATERIALS AND METHODS

2.1 Study Design and Population

This was a cross-sectional study conducted between October and November 2012, a peak transmission season in this region [12]. It involved all patients presenting with a history of unexplained fever in the previous 24 hours and no history of fever in the past two months.

2.2 Study Site

Uganda has one of the highest malaria incidence rates in the world [11]. Gulu regional referral hospital (GRRH) is a referral hospital located in Northern Uganda, a region where malaria is hyper-endemic [12] with two transmission peaks during the rainy seasons, from March to May and September to November [12]. The hospital serves more than 400,000 people.

2.3 Laboratory Procedures

Thick blood smears (BS) were stained using Field's stain and examined microscopically. All patients whose BS were negative were re-tested using an RDT detecting *Plasmodium falciparum* histidine rich protein-2, (SD-Bioline Malaria Ag P.f) (*Standard Diagnostics Inc*. *Kyonggi, Republic of Korea*) and the BS was preserved for expert microscopy. Results were reported as positive (malaria parasites seen) or negative (no malaria parasites seen). Routine microscopy and RDT results were shared with the clinicians for patient management. For expert microscopy, 200- high power fields were considered in accordance with WHO recommendations [13], before declaring a smear negative by two, independent readers.

2.4 Data Analysis

Data was entered into MS Excel program (Microsoft Corporation, Seattle, USA), validated and later exported to Stata version 12.0 (College Station, Texas, USA) for statistical analysis. Results are presented as proportions with 95% confidence intervals.

3. RESULTS AND DISCUSSION

Of the 542 patients subjected to routine BS, 503 (92.8%) had negative results and these were considered for inclusion into the study. However, 89 of these were excluded from the study because of a positive history of undiagnosed fever in the preceding two months. The remaining 414 participants were re-tested using RDT. Children formed the bulk of participants recruited in the study (Table 1) possibly due to a higher vulnerability to malaria.

The study reported a low malaria incidence rate with only 9.8% cases of fever diagnosed to suffer with malaria either by microscopy or RDT (Fig. 1). These findings suggest a low malaria incidence rate and are consistent with Gulu hospital records that show a 43% decline in malaria burden since 2007. This change may be attributed to effective malaria prevention strategies introduced.

Ninety six percent (400/414) of the participants with negative BS results had negative RDT results. This finding appears to suggest that challenges notwithstanding, routine microscopy may still be an effective malaria diagnostic tool in a resource limited setting. We however do not think this to be the case. Instead, this apparent high negative predictive value of routine microscopy might have been influenced by the overall reduction of malaria burden in this setting.

Table 1. Demographic characteristics of study participants (n=414)

Characteristic	No. of participants	Proportion (95% C I)
Gender		
Male	152	36.7 (32.1- 41.3)
Female	262	63.3 (58.7- 67.9)
Age range (yrs)		
0-5	154	37.2 (32.6 - 41.7)
>5-15	129	31.2 (26.8 – 35.7)
>15-20	39	9.4 (6.6 - 12.2)
>20	92	22.2 (18.2- 26.2)

RDT and expert microscopy were able to detect an additional 14 and 6 (with low parasitaemia, <150 parasites/µl) malaria cases respectively that were missed by routine microscopy. These figures suggest that RDT is more sensitive than expert microscopy. Similar findings have been reported by previous studies [3]. Exclusion of

patients who had a history of fever in the preceding two months prevented cases where residual *falciparum* antigenemia would increase occurrences of false-positive RDT results. We are therefore confident that the additional 14 (3.4%) cases detected by RDT were from patients with active malaria infections.

The type of RDT (SD-Bioline Malaria Ag P.f) used detects only *P. falciparum,* the most prevalent and aggressive species in sub-Saharan Africa. There is, however, a minimal chance that other species could have been missed especially if the parasitemia was too low to be detected by microscopy.

Having both routine and expert microscopy done on the same slide preparation meant that results obtained were more likely a reflection of the level of technical skill rather than differences originating from quality of materials used. From this perspective, the findings show that RDT may be more sensitive than experienced microscopy. On the other hand, expert microscopy entails the use of standardized volumes of blood for smear preparation. However, our study did not use standard volumes but rather estimates, therefore, expert microscopy did not reach its full potential.

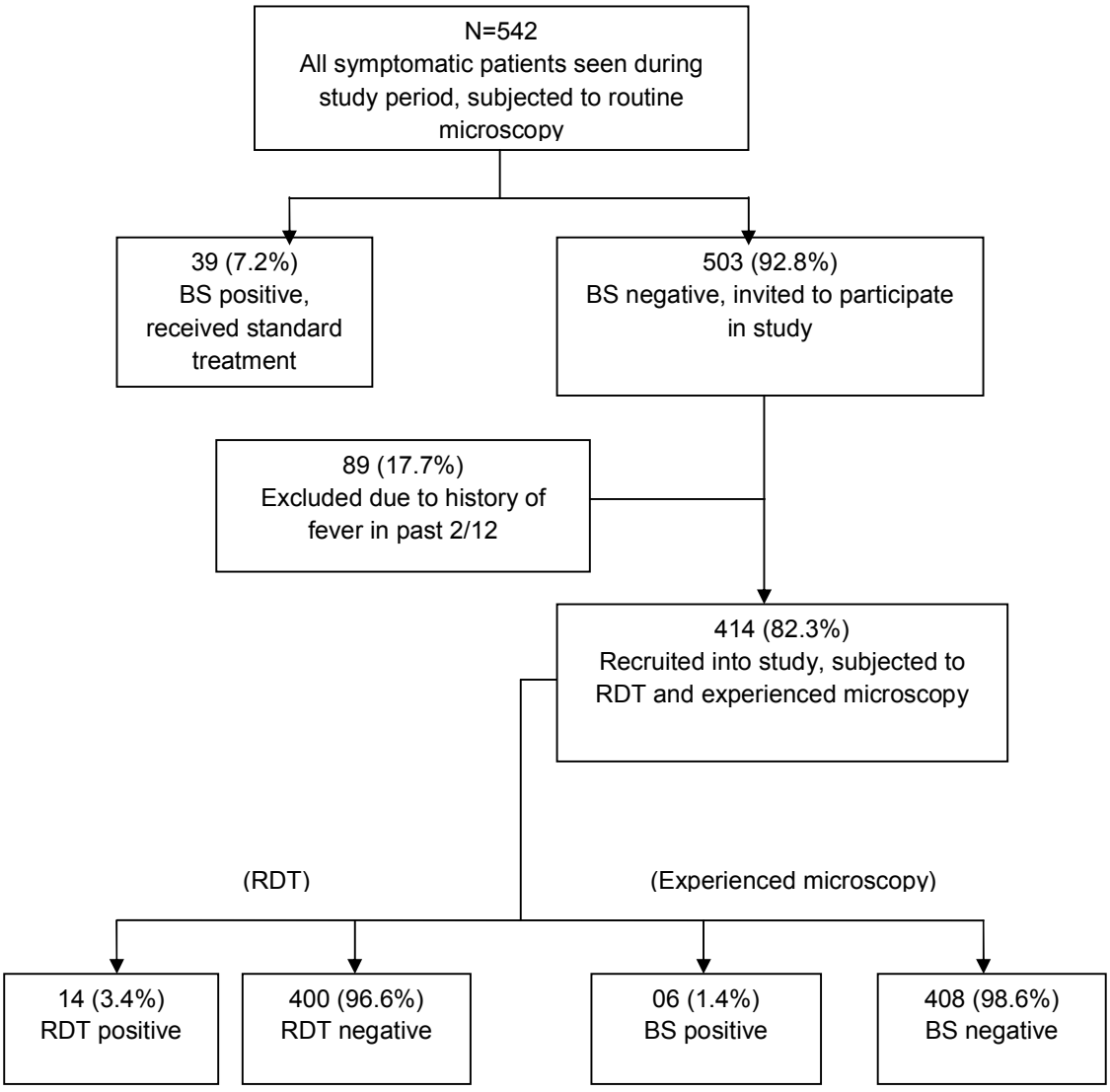

Fig. 1. Study algorithm and results

BS – Blood Smear, RDT – Rapid Diagnostic Test (for malaria - SD-Bioline Malaria Ag P.f)

Besides, there is a high degree of self medication in Uganda, as is the case with most of sub-Saharan Africa, prior to seeking professional care. This introduces the possibility that cases with low parasitemia associated with self-medication were likely to be missed by microscopy.

4. CONCLUSION

Parasite-based malaria diagnosis is currently a global health priority as the malaria burden decreases with increasing malaria control strategies. RDTs appear to provide a more accurate diagnosis in limited resource areas. At 3.4%, the prevalence of microscopy-negative malaria was extremely low in this setting. Presumptive treatment of malaria symptomatic patients may have a marginal benefit among children less than five years and is an uncalled for expense among adults. Prescription practices consistent with these findings will significantly contribute to rational antimicrobial drug use in sub-Saharan Africa.

5. RECOMMENDATION

We recommend the adherence to the treat and test policy as recommended by WHO in resource limited malaria endemic settings during both low and peak transmission seasons.

CONSENT

All participants gave informed consent / ascent to participate in the study.

ETHICAL APPROVAL

The study and its consent form were approved by the Institutional Review Committee of Gulu University (reference no. GU/IRC/10/09/12), and permission to conduct the study was granted by the Uganda National Council for Science and Technology (ref. HS 1277).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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