

Original Research Article

Presumptive treatment of malaria during a peak transmission season in a malaria endemic setting: a cross-sectional study

Abstract

Aim: We investigated all malaria symptomatic microscopy-negative patients during a peak malaria transmission season to ascertain the need for presumptive treatment of malaria among these patients.

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 patients. A rapid diagnostic test (RDT) was performed on all patients with negative BS results. All smears were later double-read by experienced 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 experienced 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, administration of anti-malarial drugs to 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.

Key words: malaria, blood smear, microscopy, rapid diagnostic test

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), have led to a tremendous decrease in its morbidity and mortality.

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

In spite of the fact that rapid diagnostic tests (RDTs) are highly sensitive [3-6], user friendly [4,6-8] and are better at targeting of anti-malarial treatments for significant reduction in wasteful anti-malarial drug prescriptions [9-12], microscopy which has a low sensitivity [13,14] remains the main diagnostic tool in most of 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 wasteful drug consumption with adverse health and economic outcomes on the affected population [13,15].

Uganda has one of the highest malaria incidence rates in the world. Gulu regional referral hospital (GRRH) located in Northern Uganda is a malaria hyper-endemic region [16] with two peaks during the rainy seasons, from March to May and September to November.

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

Materials and Methods

Study design and population

This was a systematic cross-sectional study conducted between October and November 2012. 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.

Study site

GRRH located in Gulu district serves as a referral hospital for several health centers northern Uganda. Altogether, the hospital serves more than 400,000 people.

Laboratory procedures

Thick blood smears (BS) were stained using Field's stain and examined microscopically as routinely done. 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 experienced 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 experienced microscopy, 200- high power fields were considered before declaring a smear negative by two independent readers.

Data analysis

Data was double 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.

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.

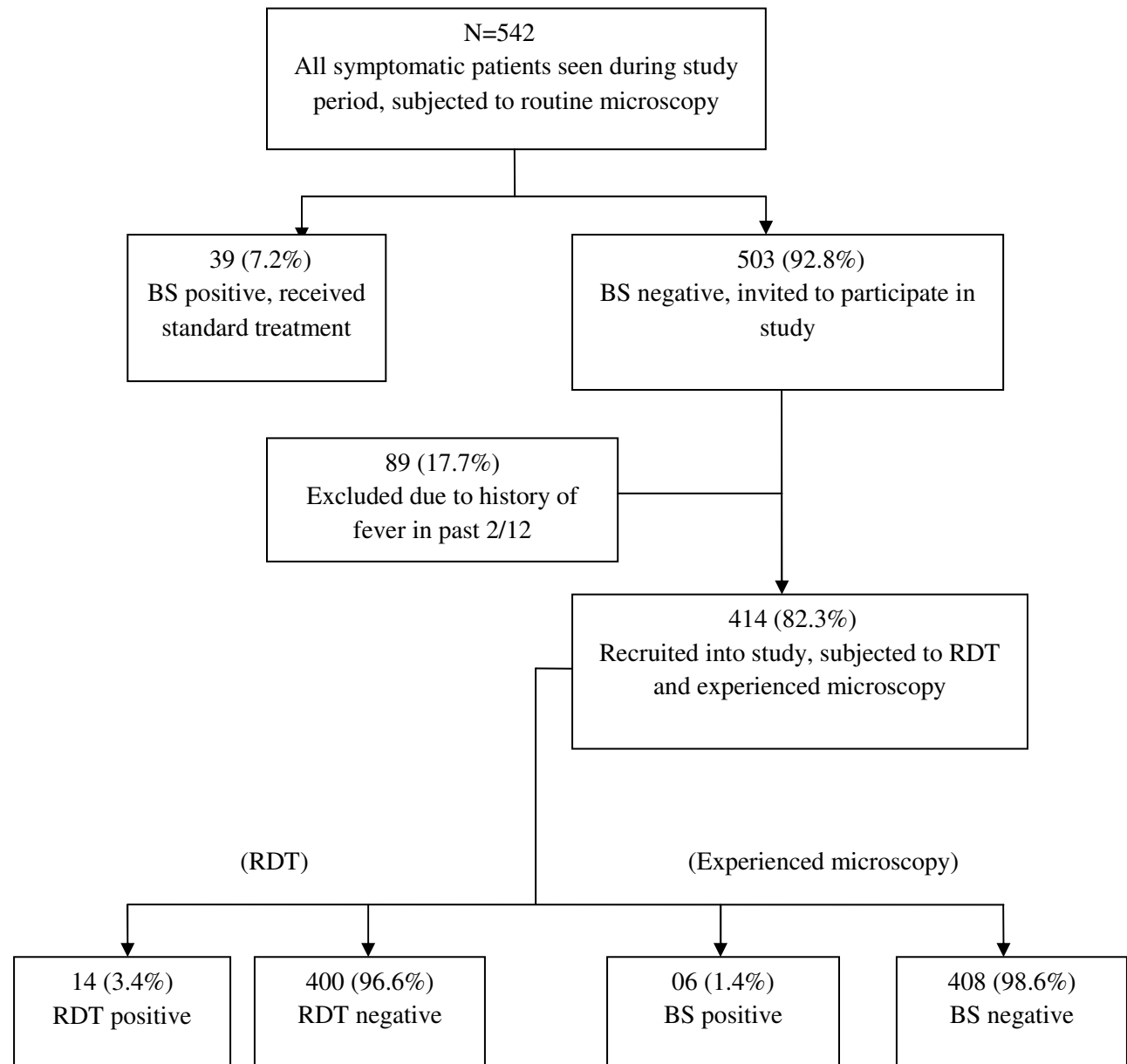
Table 1: Demographic characteristics of study participants (n=414)

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)

Over the two month period, only 53 (9.8%) participants (Figure 1) were confirmed to have malaria by either microscopy or RDT. 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.

Figure 1: Study algorithm and results



BS – blood smear, RDT – rapid diagnostic test (for malaria - SD-Bioline Malaria Ag P.f), Experienced microscopy was defined as microscopy done by microscopists with consistently high Kappa scores (as determined by global microscopy experts) over several years but not yet certified by WHO.

RDT showed that 96% of participants (400/414) declared ‘microscopy-negative’ by routine practice were indeed without malaria. 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.

RDT and experienced microscopy were able to detect an additional 14 and 6 malaria cases respectively that were missed by routine microscopy. These figures suggest that RDT is more sensitive than experienced microscopy. Similar findings have been reported by previous studies [3-5]. 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 experienced 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, experienced microscopy as performed by certified experts would require that standard volumes of blood are

used to prepare each smear. The slides examined in this study were certainly far from meeting such a standard. To this extent, experienced microscopy did not reach its full potential.

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.

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. Administration of anti-malarial drugs to BS-negative 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.

Informed consent

All participants gave 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).

References

1. Berkley JA, Maitland K, Mwangi I, Ngetsa C, Mwarumba S, Lowe BS, *et al.* Use of clinical syndromes to target antibiotic prescribing in seriously ill children in malaria endemic area: observational study. *BMJ.* 2005; 330(7498): 995.
2. English M, Berkley J, Mwangi I, Mohammed S, Ahmed M, Osier F, *et al.* Hypothetical performance of syndrome-based management of acute paediatric admissions of children aged more than 60 days in a Kenyan district hospital. *Bull. World Health Organ.* 2003; 81(3): 166-173.
3. Bell D, Go R, Miguel C, Walker J, Cacal L, Saul A. Diagnosis of malaria in a remote area of the Philippines: comparison of techniques and their acceptance by health workers and the community. *Bull. World Health Organ.* 2001; 79(10): 933-941.
4. Kyabayinze DJ, Tibenderana JK, Odong GW, Rwakimari JB, Counihan H. Operational accuracy and comparative persistent antigenicity of HRP2 rapid diagnostic tests for *Plasmodium falciparum* malaria in a hyperendemic region of Uganda. *Malar.J.* 2008; 7: 221.
5. Murray CK, Bell D, Gasser RA, Wongsrichanalai C. Rapid diagnostic testing for malaria. *Trop.Med.Int.Health.* 2003; 8(10): 876-883.
6. Batwala V, Magnussen P, Nuwaha F. Are rapid diagnostic tests more accurate in diagnosis of *plasmodium falciparum* malaria compared to microscopy at rural health centres? *Malar.J.* 2010; 9: 349.
7. Guthmann JP, Ruiz A, Priotto G, Kiguli J, Bonte L, Legros D. Validity, reliability and ease of use in the field of five rapid tests for the diagnosis of *Plasmodium falciparum* malaria in Uganda. *Trans.R.Soc.Trop.Med.Hyg.* 2002; 96(3): 254-257.
8. Lubell Y, Reyburn H, Mbakilwa H, Mwangi R, Chonya K, Whitty CJ, Mills A. The cost-effectiveness of parasitologic diagnosis for malaria-suspected patients in an era of combination therapy. *Am.J.Trop.Med.Hyg.* 2007; 77(6 Suppl): 128-132.

9. Batwala V, Magnussen P, Hansen KS, Nuwaha F. Cost-effectiveness of malaria microscopy and rapid diagnostic tests versus presumptive diagnosis: implications for malaria control in Uganda. *Malar.J.* 2011; 10: 372.
10. Bjorkman A, Martensson A: Risks and benefits of targeted malaria treatment based on rapid diagnostic test results. *Clin.Infect.Dis.* 2010; 51(5): 512-514.
11. Kyabayinze DJ, Asiimwe C, Nakanjako D, Nabakooza J, Counihan H, Tibenderana JK. Use of RDTs to improve malaria diagnosis and fever case management at primary health care facilities in Uganda. *Malar.J.* 2010; 9: 200.
12. Masanja IM, Selemani M, Amuri B, Kajungu D, Khatib R, Kachur SP, Skarbinski J. Increased use of malaria rapid diagnostic tests improves targeting of anti-malarial treatment in rural Tanzania: implications for nationwide rollout of malaria rapid diagnostic tests. *Malar.J.* 2012; 11: 221.
13. Amexo M, Tolhurst R, Barnish G, Bates I: Malaria misdiagnosis: effects on the poor and vulnerable. *Lancet.* 2004; 364(9448): 1896-1898.
14. Moerman F, Lengeler C, Chimumbwa J, Talisuna A, Erhart A, Coosemans M, D'Alessandro U. The contribution of health-care services to a sound and sustainable malaria-control policy. *Lancet Infect.Dis.* 2003; 3(2): 99-102.
15. Reyburn H, Mbakilwa H, Mwangi R, Mwerinde O, Olomi R, Drakeley C, Whitty CJ. Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. *BMJ.* 2007; 334(7590): 403.
16. Okello PE, Van BW, Byaruhanga AM, Correwyn A, Roelants P, Talisuna A, D'Alessandro U, Coosemans M. Variation in malaria transmission intensity in seven sites throughout Uganda. *Am.J.Trop.Med.Hyg.* 2006; 75(2): 219-225.