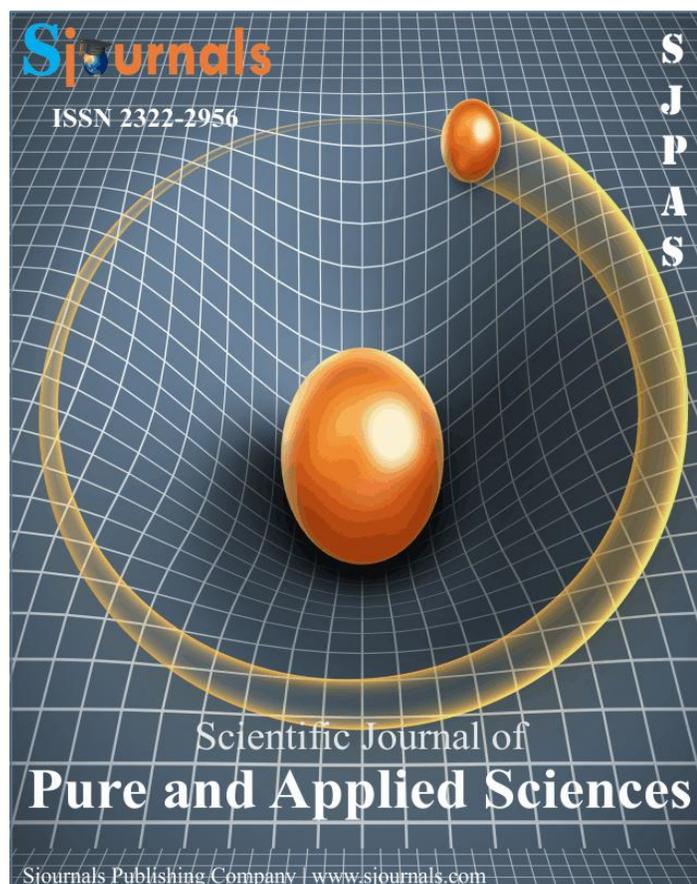


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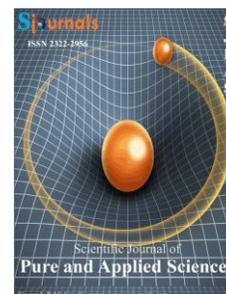
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Original article

Histidine rich protein 2 performance in determining the prevalence of Malaria among patients presenting with clinical symptoms of Malaria

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ABSTRACT

Malaria rapid diagnostic test (RDT) is an antigen capture assay that enables rapid diagnosis of malaria without the need for electricity or highly skilled technicians. Though potentially useful, its adoption needs to be guided by local test sensitivity. This study evaluated the diagnostic performance of a commercially available RDT among 200 febrile patients (aged 2months to 72 years) in Ellison, Ogun State Nigeria. It was a prospective observational study conducted at the Babcock Teaching Hospital (BUTH) between February and June, 2015. Finger prick blood samples were collected from each of the patients (day 0) and immediately tested for *P. falciparum* malaria by both Giemsa microscopy and rapid diagnostic test (RDT). The prevalence of malaria among the study cohort was 15.0% by microscopy and 17.0% by RDT. The RDT had a sensitivity of 83.3% and specificity of 94.7%; with positive and negative predictive values of 73.5% and 96.9% respectively. The diagnostic performance of the RDT in this study was good. Hence, it is recommended as an alternative method for diagnosis of malaria, especially when microscopy is not feasible.

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1. Introduction

Malaria is one of the major health problems in sub-Saharan Africa with approximately 174 million cases and 655,000 deaths per year, which is >80% of cases and >90% of malaria deaths worldwide (WHO, 2011). In 2013, malaria caused an estimated 584 000 deaths (with an uncertainty range of 367 000 to 755 000), mostly among African children where a child dies every minute from malaria (WHO, 2013). Malaria transmission and morbidity has been reported to have declined in areas of East Africa, which is assumed to be at least partly a result of the up-scaling of interventions (e.g., availability of artemisinin combination therapy (ACT) and distribution of insecticide-treated bed nets (ITNs) (O'Meara et al., 2008; Mmbando et al., 2010; Karema et al., 2012). With regard to West Africa, this trend is not well documented with the exception of few hospital-based studies (Ceesay et al., 2010), which have their own limitations (Rowe et al., 2009). World Health Organization recommends prompt parasite-based diagnosis by microscopy or malaria Rapid Diagnostic Test in all patients suspected of malaria before antimalarial treatment is administered.

Clinical method of diagnosis, though practiced in many parts of Africa, is often unreliable due to non-specificity of malaria symptoms (Murray et al., 2008; Uzochukwu et al., 2010; WHO, 2011). This method results in over diagnosis and unnecessary treatment which increases the risk of resistance and adverse drug reactions (Perkins 2006; WHO, 2010). Malaria rapid diagnostic tests have currently been recommended by World Health Organization (WHO) as alternative method for parasitological diagnosis of malaria (WHO, 2011). The use of malaria rapid diagnostic tests has been widely advocated to improve *Plasmodium falciparum* diagnosis, especially in settings where quality microscopy is not available. Rapid diagnostic tests have become an essential tool in the contemporary malaria control and management programmes in the world. Microscopic examination of Giemsa-stained blood smears under a light microscope remains the gold standard method for malaria diagnosis. However, this technique requires a relatively long observation time and well-trained microscopists. Malaria RDTs have become very popular in various endemic settings (Lubell et al., 2007), especially in areas where microscopic expertise is lacking.

They are now an essential tool in malaria management during the malaria elimination/ eradication campaign (Bisoffi et al., 2009). However, the wide variety of RDTs and their different performance under different endemic settings suggest that careful comparison of RDTs is needed before mass deployment for diagnosis. These immunodiagnostic tests detect specific antigens (proteins) produced by malaria parasites (Murray et al., 2008, WHO, 2011). They employ a dipstick or test cassette bearing monoclonal antibodies directed against target malaria parasite antigens, which are present in the blood of infected people. RDTs are designed using antibodies against parasite species-specific or genus-specific antigens, such as *P. falciparum*-specific histidine-rich protein-2 (PfHRP2) and parasite lactate dehydrogenase (pLDH) (Wongsrichanalai et al., 2007; Murray et al., 2008). HRP2 is a water soluble protein produced by asexual stages and young, but not mature, gametocytes of *P.falciparum* (Moody, 2002). The amount released in vitro increases throughout the intra erythrocytic cycle, with large quantities being released during schizont rupture (Moody, 2002). Several formats of HRP2-based RDTs are now commercially available and are increasingly being used in Africa. They are rapid, simple to operate and easy to interpret (Wongsrichanalai et al., 2007); hence useful in rural areas with no electricity or laboratory facilities and skill for microscopy (Nwuba et al., 2001; Ben-Edet et al., 2004). However, the performance of RDTs is easily affected by humidity and extreme temperatures. In addition, persistence of antigens that may remain in the circulation of a patient after treatment may give false positive results (Jiang et al., 2010). Though they are potentially useful, their adoption needs to be guided by local test sensitivity.

This study therefore evaluated the diagnostic performance of one of the commercially available HRP2 based RDTs (SD Bioline Malaria *P.f*), with the aim of determining its sensitivity and specificity using microscopy as gold standard.

2. Materials and methods

The study was conducted at the Outpatient Department (OPD) at Babcock University Teaching Hospital (BUTH), Ilishan-remo, which is a tertiary health care facility located in Ilishan-remo, Ogun state, western part of Nigeria. The climate in this region is characterized by seasonal variation, with a hot dry season that spans from October to April and a rainy season which starts in April and lasts up to October. In the study area, the diagnosis of malaria is based mainly on clinical features supported by microscopy. RDTs are never routinely used; partly due to

the exorbitant cost of the kits for RDT, non-availability and lack of expertise in the usage of this diagnostic method. The study was a prospective observational study conducted over a period of five months, from February to June, 2015. This period coincided with rainy season which is characterized by increased malaria transmission. The study subjects were febrile patient who presented to the OPD of BUTH, Ilisan-remo with fever or history of fever. Those who satisfied the following criteria were included for the study: Presence of fever (defined as axillary temperature of $> 37.5^{\circ}\text{C}$) and informed written or thumb-printed consent by the subjects and/or their parents/guardians. Over the period of study, a total of 200 febrile patients (ages 2months – 72 years) were recruited consecutively as they presented to the OPD. The study was approved by the Ethics and Research Committee of BUTH, Babcock University, Ilisan-remo, Ogun state.

2.1. Pre- assessment and evaluation

Relevant demographic information and clinical history including age, gender, presenting symptoms, duration of fever, clinical diagnosis, and history of treatment in the preceding 2 weeks were obtained from the patients or their parents/guardians and then recorded into a predesigned study proforma data sheet or a case report form. All the patients had complete physical examination, with measurements of their auxiliary temperatures and body weights. Prior to commencement of the study, the laboratory scientists were trained on the use of RDT and on the technique of staining and microscopic examination of blood films by a WHO trained malaria microscopist at the Malaria diagnosis unit, Department of Medical Microbiology and Parasitology Benjamin Carson School of Medicine Babcock University Ilisan-remo, Ogun state.

2.2. Rapid diagnostic test (SD-Bioline Malaria P. Falciparum Rapid Device)

The rapid diagnostic test for malaria was performed using Malaria *P.f* Rapid device (Standard Diagnostic International, Korea). It has a shelf life of two years at the time of usage. The lot number is (05AD15015), while the expiring date is 09/09/2016. Each kit has 30 individual pouches, with each pouch containing a blue-coloured desiccant and a 5 μl blood dropper. The kit also contains a clearing buffer, sterile lancet, alcohol swab and an instruction manual.

2.3. Test principle

The SD- Bioline Malaria pf Rapid Device is an in-vitro immunochromatographic test which detects circulating *P.falciparum* Histidine-Rich Protein 2 (HRP2) antigen in whole blood. When blood is added into the sample well, followed by addition of buffer in the well. The buffer enables the blood to flow along the strip embedded in the cassette. If malaria parasite antigen (HRP2) is present, a control and a positive test bands are formed. In the absence of the antigen, only the control band is seen only.

2.4. Quality control measures

As part of quality control measures, all the RDT test kits were stored within the recommended temperature range of 4-40 $^{\circ}\text{C}$ using an air conditioned room and the integrity of the kits was ascertained before commencement of the test by checking for the blue colour of the desiccant. A colour change indicates exposure to moisture which might affect RDT sensitivity. In addition, quality control (QC) testing of each of the RDT pack was done using positive and negative control samples at different parasitaemia dilutions (200p/ μl and 2000p/ μl) which were prepared by the laboratory Scientist.

2.5. Test technique

For each patient that was enrolled for the study, finger prick blood sample, which is ideal for detection of malaria parasites, was collected. The sample was used for testing by both the RDT and the Giemsa microscopy methods. The rapid diagnostic test was performed according to manufacturer's instruction. Results were read blindly and independently by both the investigator and the laboratory scientist at the pediatrics side laboratory, within 15 minutes as recommended. RDT was considered positive for *P. falciparum* when pink coloured bands appeared in both the control window 'C' and test window 'T'. The test was recorded as negative for *p. falciparum* when only one pink coloured band was seen in the control window 'C'. However, it was considered invalid when no band appeared on the device or when the control line was absent, the test would be repeated.

2.6. Giemsa stained Malaria microscopy test

Thick and thin blood films were prepared and stained according to standard guidelines as described by Cheesbrough (1998) and by Warhaust and Williams et al., (1996). Blood films were examined by the investigator blindly, without having prior knowledge of the corresponding RDT result. The examination was done at the BUTH laboratory with a

Light microscope, using 40x and 100x objectives. A positive test is when asexual and sexual forms of *P.falciparum* are seen. A slide is considered negative only after 200 High Power Fields (HPF) were examined without seeing any human malaria parasite (WHO, 2005). Discordant results (between the RDT and microscopy tests) were rechecked independently by two experienced laboratory scientist, at the BUTH main Microbiology Laboratory. They were first blinded to the clinical status of the patient, the result of the RDT and that of initial microscopy. Results obtained by the two independent Laboratory scientists were regarded as final. Parasite density was determined from thick film by counting the number of parasites against 200 leucocytes and assuming that each subject has 6000 leucocytes / μ l of blood as described by other workers (Warhaust and Williams, 1996). Therefore, parasite count = (number of parasite x 6,000)/200.

2.7. Data analysis

Data was entered and analyzed using Epi info version 332, statistical software and also with the help of Graph Pad in Stat version 3.05 Software. Nominal data was summarized using proportions and frequency tables were used to illustrate quantitative data. Chi square (χ^2) with Yates correction was used to compare proportions. But where more than 20% of expected frequencies are less than 5, Fisher's exact probability test was used. Test of significance was determined at $p < 0.05$. The following variables were determined using microscopy as gold standard: number of true positive (TP), false positive (FP), true negative (TN), and false negative (FN). Test performance indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and test accuracy were also calculated. Furthermore, sensitivity of the RDT was determined in relation to parasite densities and to other variables including gender, duration of fever and type of concomitant illnesses at presentation.

3. Results

3.1. Demographic and baseline characteristics of the study population

A total of 200 malaria suspected patients participated in the study at OPD of BUTH, Ilesha Remo. Their baseline characteristics are summarized in Table 1. The study population comprised of more of females 125(62.5%) than male 75(37.5%), giving a female to male ratio of 1.7:1. Mean age of the subjects was 23.6 years (range 2 months to 72 years). The age distribution of the patients is depicted in Table 1. The age range of 0 - 5 had the highest population of 48 (24.0%) followed by 16-20 age range 20(10.0%) and least was age group 56-60 1(0.5%) (Table 2). The mean axillary temperature and mean duration of fever of the subjects at presentation were 36.9°C +0.8°C (range- 36.5°C to 40.8°C) (table 1). Patients with temperature of <37.4 were more 178(89.0%) while those with temperature \geq 37.5 22 (11.0%). The major drug taken by participant at home before coming to the health care center was PCM 87(43.5%) followed by Agbo 35 (17.5%) and ACTs 28 (14.1%). The least drug used at home was Antibiotics 10 (5.0%) (table 1).

Table 3 shows the clinical signs recorded in percentage of study participants. Among the study population, some of the clinical signs and symptoms were irrelevant due to the insignificant population size and therefore, did not show any significant relationship with participants age. But few of the clinical signs and symptoms like body weakness, headache, fever and joint ache showed significant difference when compared with age of the study population. Fever showed the highest frequency 102 (51.0%), followed by yellow urine 85(42.6%), body weakness 72(36.0%) and headache 70 (35.0%), while insomnia showed the least frequency 6(3.0%).

3.2. Laboratory diagnosis of malaria: comparison of RDT with gold standard microscopy

The prevalence of uncomplicated malaria among febrile patients was 15.0% by microscopy and 17.0% by the RDT. Table four shows the results of microscopy against RDTs. Out of the 200 study participants used in this study, 30 participants were positive by microscopy technique, while, 34 participants were positive by RDTs. Overall, 25 patients had a matching positive microscopy and RDT results (true positive tests), whereas 161 patients were

negative by both diagnostic test methods (true negative tests). There were 9 false positive and 5 false negative results (Table 4).

Table five shows the sensitivity and specificity of the RDT as 83.3% and 94.7% respectively. Both positive and negative predictive values were 73.5% and 96.9% respectively. Using Kappa statistics, a Kappa value (K) of +0.86 was obtained which showed good degree of agreement (concordance) between Giemsa microscopy and the RDT.

3.3. Parasite density

The study participants showed parasite density ranging from 14.77 to 445,544 parasites / μl . Table 6 shows the distribution of positive RDT results and the corresponding sensitivities stratified by parasite density. When parasite count was less than 200 / μl , the RDT failed to detect all the positive slides. However, the sensitivity of the RDT increased consistently from 62% at parasite density range of 1-500p/ μl to 100% at >2000p / μl . It is of note that 70.0% (21/30) of patients with positive slides had parasite density less than 1000p/ μl which is the level above which RDT achieved sensitivity of 62.0%.

Table 1

Baseline characteristics of the study participants.

Character	N (%)
No of Participants	200
Sex	
Female	125(62.5)
Male	75(37.5)
Temperature ($^{\circ}\text{C}$)	
Mean \pm SD	36.9 \pm 0.8
<37.5	178(89.0)
\geq 37.5	22(11.00)
Home treatment drugs	
ACTs	28(14.0)
Agbo	35(17.5)
Paracetamol	87(43.5)
SP	24(12.0)
Chloroquine	16(8.0)
Antibiotics	10(5.0)

Table 2

Age Distribution of study Participants.

Age (years)	Frequency (n)	Percentage (%)
0-5	48	24
6-10	14	7
11-15	16	8
16-20	20	10
21-25	14	7
26-30	13	6.5
31-35	12	6
36-40	12	6
41-45	19	9.5
46-50	11	5.5
51-55	10	5
56-60	1	0.5
>60	10	5
Total	200	100

Table 3

Frequency of Clinical symptoms among Study Participants.

Symptoms	Frequency	Percent	95% Conf limits	
Fever	102	51.0%	40.8%	66.1%
Yellow urine	85	42.6%	23.9%	49.4%
Joint ache	62	31.0%	20.4%	45.9%
Headache	70	35.0%	12.0%	37.3%
Chills	66	33.0%	10.4%	35.7%
Body weakness	72	36.0%	9.8%	27.6%
Loss of Appetite	26	13.0%	8.3%	19.6%
Stomach ache	38	19.0%	7.3%	17.3%
Cough	16	8.0%	7.1%	17.2%
Vomiting	24	12.0%	6.8%	13.4%
Dizziness	49	24.5%	4.0%	10.1%
Isomnia	6	3.0%	0.9%	5.1%
Nausea	13	6.5%	4.5%	4.6%
Chest pain	11	5.5%	3.6%	3.2%
Diarrhea	17	8.5%	6.7%	2.1%
Itching	12	6.0%	5.7%	2.1%

Table 4

Results of Giemsa stained microscopy against RDT.

Microscopy	RDT		
	Positive	Negative	Total
Positive	TP= 25	FN=5	30
Negative	FP=9	TN=161	170
Total	34	166	200

TP=True positive, TN=True negative, FP=False positive, FN=False negative.

Table 6

Parasite density against RDT sensitivity.

Parasite density (μ L)	No. Positive by microscopy (n=30)	No. Positive by RDT (n=34)	Sensitivity (%)
1-500	16	10	62.5
501-1000	5	3	60
1001-1500	0	0	0
1501-2000	0	0	0
>2000	10	10	100

Table 5

Performance characteristics of Malaria RDTs.

Performance characteristics	RDT method
Sensitivity	83.3%
Specificity	94.7%
Predictive Positive Value	73.5%
Predictive Negative Value	96.9%
Positive Likelihood Ratio	15.71
Negative Likelihood Ratio	0.17

4. Discussion

The present study shows that the RDT (SD Bioline Malaria pf) had an overall sensitivity of 83.3% and specificity of 94.7% among febrile patients attending BUTH OPD department. The result compares favourably with that of several studies (Singh et al., 1997; Beecham et al., 1999; Nwuba et al., 2000; Ben-Edet et al., 2004; Marx 2007; Oguonu and Okafor, 2007; Khainar 2009; Ansah et al., 2010; Sani et al., 2013), which reported a variable sensitivity of 84.2-100% and specificity of 82.8%-98%. However, the sensitivity in our study was lower than that of Iran (100%) which used an RDT format (Biotec Mal pv/pf rapid device) from a similar manufacturer (Samane et al., 2010). When compared to previous Nigerian studies, the sensitivity obtained by the present study (83.3%) was lower than that of Ibadan, South-western Nigeria (93.1%) (Nwuba et al., 2001), but much higher than what was reported in Lagos (69.9%) (Ben-Edet et al., 2004). Variations in test sensitivity between these studies may be due to differences in the types of RDT formats used or due to variations in epidemiologic characteristics of the study population, level of parasitaemia, test methodology and skill of microscopists (Wongsrichanalai *et al.*, (2007). Nevertheless, the present study like earlier studies in Nigeria (Nwuba et al., 2001; Oguonu, 2007), further confirms the efficacy of the RDT as alternative method for rapid diagnosis of malaria in endemic region. The sensitivity of the RDT decreases at low parasite density. This was evident by the fact that the RDT gave negative results for all the five study patients with parasite density below 200/ μ l; and it reached satisfactory sensitivity of 100% only at density >2000p/ μ l. Fortunately, most of the parasitaemic patients (84%) in our study had parasite count above 800/ μ l, making the RDT still relevant for routine clinical use. Similar observation was made in Ibadan, Nigeria where sensitivity fell to 71% at parasite density less than 519p/ μ l (Nwuba *et al.*, 2001) and in Lagos, Nigeria (Ben-Edet et al., 2004) where it decreased to as low as 14.3% at density below 400p/ μ l. Several other studies have demonstrated variation in RDT sensitivity with parasite density and have emphasized the tendency of the test to misdiagnosed patients with low parasitaemia (Singh et al., 1997; Beecham et al., 1999; Wongsrichanalai et al., 2007). Though 3 of the 5 patients with false negative results in our study had low parasitaemia with density below 1000/ μ l, the remaining two patients with negative results had relatively higher parasitaemia (> 1000/ μ l). Other workers (Beadle et al., 1994; Sani et al., 2013) have similarly observed false negative results in some patients with high parasitaemia, up to 18,000p/ μ l. The explanation for this was not clear, but HRP-2 deletion/ mutation and existence of anti-HRP-2 antibodies or an inhibitor in patient's blood may be responsible (Baker et al., 2005; Lee et al., 2006). HRP-2 antigen is also known to have significant geographic diversity and some variants may escape monoclonal recognition, leading to false negative result (Talman et al., 2007; Mariette et al., 2008, Kumar et al., 2012). Factors such as temperature (Chidionin et al., 2007), duration of fever and prior anti malarial drug therapy can affect the diagnostic performance of the RDT. The study showed that >60% of patients who tested positive by the RDT had temperature above >37.5°C where as only 30.9% of the patients with temperature <37.5°C gave positive RDT result. Hence, patients with higher temperature are significantly more likely to test positive for malaria. This has been attributed to increase release of HRP2 antigens into the blood stream simultaneously with fever-inducing cytokines and other pyrogens at the time of schizont rupture (Ben-Edet et al., 2004). Beside temperature, duration of fever at presentation may have significant effect on RDT result. Therefore, the RDT may be negative despite the presence of parasitaemia. On the other hand, the study showed that patients with longer duration of fever are more likely to have false positive results; as all the 9 patients with false positive tests had fever duration beyond 3days. These facts should be born in mind while interpreting results of the RDT. In our study, malarial parasitaemia was detected in only 37.8% of patients who had preceding antimalarial drug treatment, compared to 49.8% in those who had no prior treatment at presentation. It is known that prior anti malarial drug therapy is associated with significant decrease in the rate of microscopy positive test results (Warhust and Williams, 1996). This is because such treatment can grossly reduce parasitaemia, making it harder to detect by microscopy (Warhust and Williams, 1996). However, for the RDT, prior anti malarial drug treatment was not associated with significant reduction in parasite detection rate. Instead, an increase in the rate of false positive results was observed in patients who had anti malarial treatment before presentation. This finding was similarly highlighted by Singh and Valechi *et al.*, (1997) and by previous Nigerian studies in Ibadan (Nwuba et al., 2001) and Lagos (Ben-Edet et al., 2004; Sheyin and Bigman, 2013). In the latter study, all the two patients with false positive had received treatment with chloroquine and quinine before the tests were conducted. The phenomenon of persistent antigenemia after treatment was studied by several workers, with results suggesting that HRP2 antigens can persist for a variable length of time (Beadle et al., 1994; Humar et al., 1997; Hopkins et al., 2007). Humar et al., (1997) observed antigenemia in 68% of patients by day 7 after treatment; whereas Hopkins and colleagues (2007)

noted that the HRP-2 antigen persisted even beyond 28 days in some of their patients. However, Beadle *et al.* (1994) in Kenya found no evidence of circulating antigenaemia by day 6 post treatment. Another limitation is the inability to do Polymerase chain reaction and ascertain whether such positive RDT test is actually a false result or indeed a truly positive result due to re-infection. The implication of antigenemia persisting well after completion of therapy is that it limits the usefulness of HRP2-based RDT in monitoring drug resistance or treatment failure malaria (Moody, 2002). This is in contrast to rapid test formats that are based on enzyme assays such as plasma parasite lactate dehydrogenase (pLDH). This enzyme, unlike HRP2 antigen, correlates directly with parasitaemia (Moody, 2002; Gersti et al., 2010) and can therefore be used to monitor antimalarial therapy and drug resistant malaria (Hopkins et al., 2007). Compared to Microscopy, the rapid diagnostic method is easier to learn and perform. It is also more rapid as results were ready within 15 minutes in all the study subjects compared to Giemsa microscopy which ranged between 45 and 60 minutes duration. The duration can be much more prolonged in settings with high out patients' case load and erratic power supply. The apparently high cost of the RDT can discourage its widespread use in resource limited, malaria endemic countries. Hence, there is need for increase in subsidy on the RDTs to make them easily available and affordable. This will enhance rapid malaria case diagnosis and management, and play an important role in the fight against malaria infection.

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