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Research Article

Comparative Study between Rapid Diagnostic Tests and Microscopy for Diagnosis of Malaria in Seme, Kisumu County, Kenya

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Malaria infection is a global problem accounting for a 25% mortality rate annually, management and control of malaria involves accurate diagnosis and treatment. The study compared the performance of rapid diagnostic tests and microscopy as used for the diagnosis of malaria in Seme Sub County, Kisumu County. The cross sectional study was conducted in three purposively selected health facilities. A total of 230 participants were randomly selected to participate in the study. Blood samples were collected by a trained phlebotomist from the participants who had given consent to participate. The samples were screened for malaria using both microscopy as a gold standard and two Rapid diagnostic tests (Histidine Rich Protein (HRP2), and Combined HRP2 and parasite lactate dehydrogenase (PLDH) to determine the performance of RDTs. The results revealed that, the sensitivity, specificity, positive predictive values and negative predictive values using microscopy was found to be 94.44%, 85.71%, 80.95%, 96.00% for HRP2 and 94.44%, 85.00%,80.19% ,95.9% for pLDH RDT respectively. There was a significant level of agreement between microscopy and HRP2 RDTs of 89.13% (p-value <0.001) and between microscopy and pLDH RDTs of 88.70% (p-value <0.001). The low sensitivity below the WHO recommendation of ≥95% indicates the need to improve the sensitivity of the mRDTs kits in malaria management, where trained microscopists for malaria diagnosis are not available .The findings are important in informing the ministry of Health and the malaria control unit to improve on the malaria diagnosis techniques. Assist policymakers in post market surveillance of the mRDTs currently in use.

Keywords: *malaria diagnosis, rapid diagnostic test, sensitivity, specificity, predictive values.*

INTRODUCTION

Malaria is a parasitic infection caused by protozoan from the genus *Plasmodium* and transmitted by female *Anopheles* mosquitoes. It is the highest contributor to morbidity and mortality in the developing part of the world (Nonvignon *et al.*, 2016).In order to reduce morbidity and mortality rate resulting from malaria infection, it's important to ascertain that the diagnostic techniques being used are accurate. Malaria is typically diagnosed using microscopy, and this is accepted and regarded as the reference method "gold standard"(Endeshaw *et al.*, 2008). Microscopy is important because within a few hours of collecting the blood, the test can provide valuable information. First and foremost it can determine that malaria parasites are present in the patient's blood. Once the diagnosis is established, usually by detecting parasites in the thick smear, the medical laboratory officer can examine the thin smear to determine the malaria species and the parasitemia, or the percentage of the patient's red blood cells that are infected with malaria parasites. The thin and thick smears are able to provide all the three vital pieces of information to the doctor to guide the initial treatment decisions that need to be made acutely. Different types of RDTs kits have been developed for the diagnosis of malaria infection in both malaria non-endemic and endemic zone due to challenges of availability of skilled, laboratory personnel and logistics to microscopy in several endemic countries, as part of malaria management and

control program (Maltha *et al.*, 2013). However, they are not able to give parasite species and even detect other types of parasites other than *P.falciparum*. Malaria RDTs have supplanted conventional light microscopy in many endemic areas as standard practice, accounting in 2017 for 75% of all diagnostic tests done in sub-Saharan Africa, where most RDTs are distributed (66%) (Martiáñez-Vendrell *et al.*, 2020). The utilization rate of RDTs is about 76% in Seme Sub County, hence the need to determine the performance of these kits to give accurate results by evaluating their application performance, methodological performance, and test efficacy.

RDTs are principally based on the detection of malaria antigens (Histidine Rich Protein (HRP2), parasite lactate dehydrogenase (pLDH) Aldolase enzyme) (Murray *et al.*, 2008). From peripheral blood using monoclonal antibodies prepared against this malaria antigen target and conjugated to either a liposome containing selenium dye or gold particles in a mobile phase. A second or third capture monoclonal antibody applied to a strip of nitrocellulose acts as the immobile phase. The strip enables the labeled antigen to be captured by the monoclonal antibody of the mobile phase, thus providing a visible colored thick line. Incorporation of a labeled goat anti- mouse antibody capture ensures that the system is controlled by migration. Though the principle of the test is similar, there are variations among malaria RDT products. The most common RDTs used in the field consist of a nitrocellulose strip secured in a plastic 'cassette'. Some formats include the 'strip' without any casing, while some are secured to a cardboard plate such a card. Cassettes and cards tend to be more expensive but more easy to use. Different RDTs may be hybrids of these designs. Rapid diagnostic tests detect different antigens. The table (Zhao *et al.*, 2012) below gives the different commercially available RDTs and the particular antigen produced by each (table 2.1).

Table 2.1: Parasite Species and target antigen of some commercially available RDTs

Species of parasites detected	HRP2	PLDH	ALDOLASE
P. Falciparum specific	Yes	Yes	-
P.vivax specific	-	Yes	-
Pan specific (all species)	-	Yes	Yes
Specific to some other species	-	Yes	-

HRP2-Histidine rich protein, PLDH-(Parasite Lactate Dehydrogenase) (Malaria diagnosis, a guide for selecting RDTs kits, 2007).

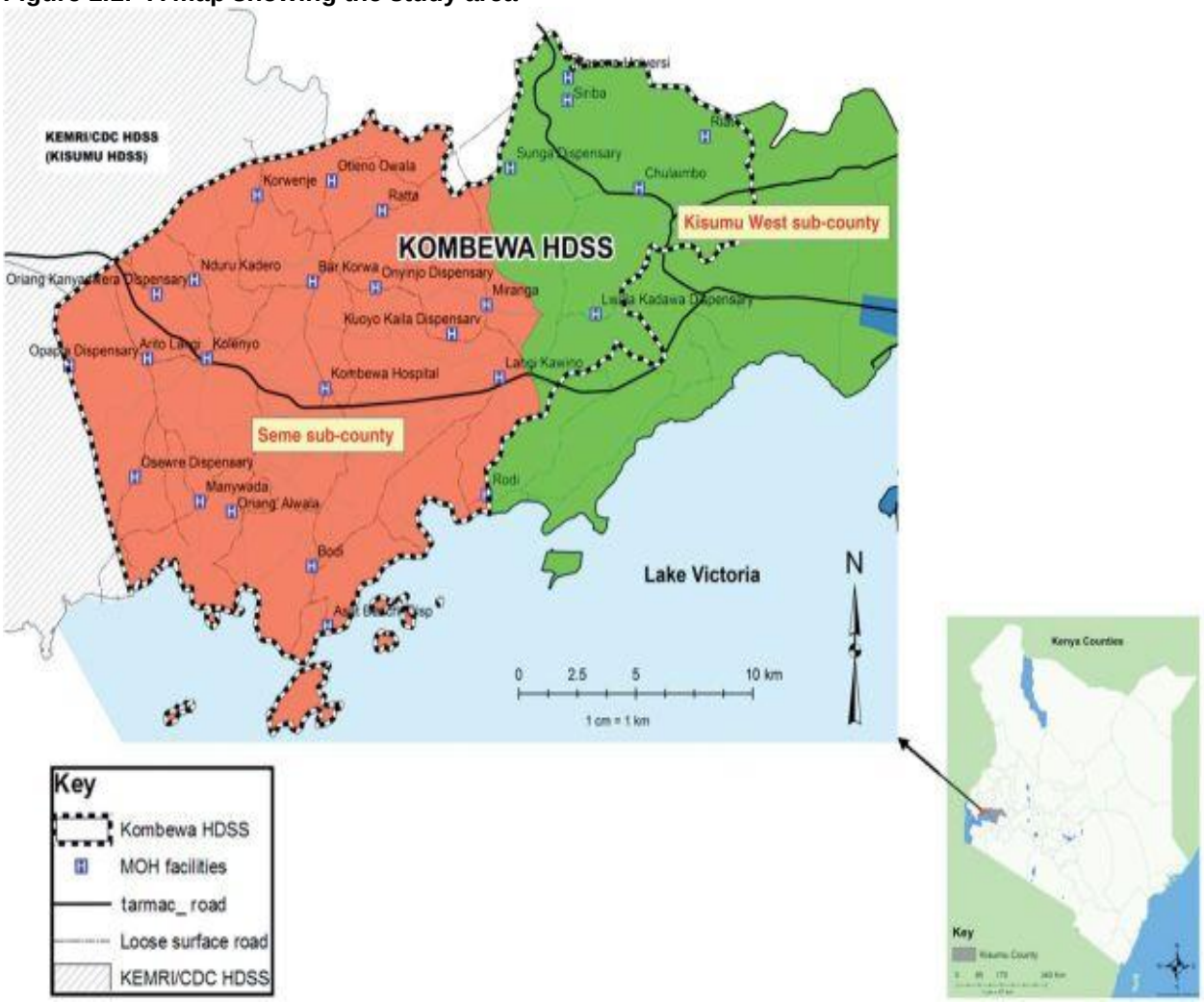
Microscopy is the reference/gold standard for the laboratory diagnosis of malaria parasite but its turnaround time is much more than that of RDTs and it requires adequate training. RDTs are alternative diagnostic methods because they are quick and easy to carry out, they also require little or no training to perform. This study aimed to compare the performance of rapid diagnostic test with microscopy in diagnosis of malaria in patients in Seme Sub County, Kisumu County, Kenya.

MATERIALS AND METHODS

Study area

The study was conducted in Seme Sub County Hospitals (Miranga, Manyuada, and Ratta), which are situated approximately 40km from Kisumu (Lat 0.103661/long 34.518190). Seme Sub County has a total population of 98,805 with an area of 190.20km^{2}and 25 Health Facilities; Miranga (9,864), Manyuada (14,059), and Ratta (10,011) (KHIS Aggregate 2019) are some of the Hospitals in the Sub County. Kisumu West, part of Kisumu central Sub Counties and Rarieda Sub County in Siaya County, borders it. Patients from the neighboring Sub Countries also seek care at the Hospital within the Sub County. The Hospitals are located along the Kisian–Bondo road highway. The Hospitals serve the majority of the Malaria infected patients who are among the top ten diseases causing morbidity and mortality within the region.

Figure 1.1: A map showing the study area



Study design

A cross-sectional study design was used. Where 230 blood samples collected from the study participants were tested for the presence of malaria parasites using two different types of Rdts (RDTs with HRP2 only and RDTs with HRP2 combined with PLDH) and using microscopy as the gold standard. The results were interpreted and documented. An observation checklist was used to assess the factors affecting the performance of malaria rapid diagnostic tests from the health care workers who were purposively chosen.

Study population

The target population included all the patients sent to the laboratory for malaria diagnosis and have given consent or assent to participate in the study. It included all patients suspected to have malaria and consent to take part in the study and the minors with assent to participate in the study. Patients who refused to consent were not allowed to participate in the study, and those who are undergoing malaria treatment did not take part in the study.

Sampling technique

The sub county health facilities were selected purposively. Stratified random sampling technique was used. Clients were grouped into different age groups and gender as they visited the laboratory for malaria testing. The groups were classified as follows, 5-9 years, 10-15 years, 16-20years and ≥21 years old. And purposive sampling design was used to collect data on factors affecting the performance of RDTs where the health care workers performing the test were observed and interviewed on the performance of RDTs.

Sample size determination

Sample size determination was done by the use of Cochran's formula, (Bartlett *et al*., 2001). A total of 230 participants participated in the study.

Ethic statements

Ethical approval was obtained from institutional Ethical review committee of Masinde Muliro University of science

and technology (MMUST). The study permit from National Commission for Science, Technology and innovation (NACOSTI).Written informed consent was obtained from adult participants and assent was obtained from guardians of children participant. The participants were given unique identifiers and documentation records kept under lock and key to enhance confidentiality. A trained phlebotomist was used to collect samples to minimize harm to participants. Participants with critical value results were escorted to the clinicians to ensure they receive treatment immediately. The participants had freedom of choice to join the study and leave at will without coercion.

Sample Collection

The demographic information was recorded on a requisition form after which venous blood sample was obtained by a trained phlebotomist from the study participants in to EDTA bottles.

Microscopy examination

This was done using standard procedures as proposed by Chessbrough M, 2009. Briefly, blood samples were collected into EDTA bottles. Thick and thin films were made from the 230 blood samples from which mRDTs tests have been done. 6µl and 2µl of blood samples were used to prepare thick and thin films respectively; the films were stained with 3% Giemsa stain (pH 7.2) for 30 minutes and examined under the microscope (model number: CX21, OLYMPUS) using ×1000 magnification. Positive findings were graded on the thick smear by accounting the parasites against 200 WBCs using a tally counter. The report was done in parasite account/200 WBCs µl of blood.

Rapid diagnostic test

The blood samples from the 230 participants were tested using the Care Start HRP2 kits and CareStart Malaria pf (HRP2/pLDH) Ag RDT which are lateral flow immunochromatographic antigen detection tests kits in a cassette form. The blood samples were put on a sample well using the provided sample collection device, buffer added to the buffer well and the test give 20 minutes according to manufacturer's instructions. Negative result is indicated by the presence of a single line, while a positive result is indicated by two bands in the strip. Three lines can be seen by CareStart Malaria pf (HRP2/pLDH).

Data Analysis

The sensitivity, specificity, and predictive values of each of the two test methods were calculated by comparing it to a gold standard (microscopy). A total of 230 blood samples were subjected to the two different rapid diagnostic tests and the results compared to microscopy to calculate specificity. The distribution of positive samples ranges from 90 with microscopy to 105 and 106 with HRP2 based RDT and HRP2 with pLDH based RDT respectively. This gives the standard 100% hypothetical sensitivity, specificity, and positive and negative predictive values. The sensitivity, specificity, and predictive values of each of the three methods; microscopy by thick blood film, thin blood film, and rapid diagnostic test by CareStart HRP2 based RDTs and Care Start HRP2 /pLDH based RDTs kits were then calculated using a standard formulas. Sensitivity was defined as the probability that a truly infected individual will test positive and specificity is how likely the test to detect the absence of a characteristic in someone without the characteristic.The obtained data was further analyzed for statistical significance using STATA analytical software. 97% of the parasitic disease identified were *plasmodium falciparum* making inference with other parasitic diseases impossible.

RESULTS

Sociodemographic characteristics of the respondents

A total 230 participants were tested using three different types of diagnostic tests and majority of the participants 109(47.39%) were above 20 years old, 33(14.35%) were below 10 years old, 54(23.48%) were between 10 to 15 years old and 34(14.78%) were between 16 to 20 year old. There were more female participants 155(67.39%) than male participants75 (32.61%). Out of 230 participants, 94(40.87%) were tested in Ratta health facility, 67(29.13%) were tested in Miranga health facility and 69(30%) were tested in Manyuada health facility (table 4.1).

Table 4.1: Socio-demographic characteristics of patients

Variables, **N=230**	Frequency (n)	Percentage (%)
Age group		
<10	33	14.35
10 -15	54	23.48
16-20	34	14.78
>20	109	47.39
Gender		
Male	75	32.61
Female	155	67.39

Facility		
Ratta	94	40.87
Miranga	67	29.13
Manyuada	69	30.00

The table below shows that out of 230 sampled respondents, 90(39.13%) were true positive and 140(60.87%) were true negative. However, 105(45.65%) tested positive and 125(54.35%) tested negative by HRP2-RDT while 106(46.09%) tested positive and 124(53.91%) tested negative by pLDH-RDT

Table 4.2: Clinical demographic

Test kits	Frequency (n)	Percentage (%)
Microscopy results		
Positive	90	39.13
Negative	140	60.87
HRP2-RDT		
Positive	105	45.65
Negative	125	54.35
pLDH-RDT		
Positive	106	46.09
Negative	124	53.91

Sensitivity, Specificity, and Predictive values of HRP2 based RDT and HRP2 with pLDH based RDTs compared to microscopy as a gold standard.

Diagnostic results with each method

Diagnostic results from a total of 230 samples tested by microscopy, HRP2 based RDT and HRP2 with pLDH based RDTs are summarized in Table 4.3 below. The distribution of positive samples ranges from 90(39.13%) (95%CI=0.32 – 0.45) with microscopy to 105(45.65%) (95%CI=0.39 – 0.52) and 106(46.09%) (95%CI=0.40 – 0.53) with HRP2 based RDT and HRP2 with pLDH based RDT respectively. It was not possible to determine parasite species by with HRP2 based RDT and HRP2 with pLDH based RDTs. However, microscopy test was able to show the species. Out of 90 positive species diagnosed with microscopy, 87(96.67%) samples had *Plasmodium falciparum*, 2(2.22%) had *Plasmodium malariae* and 1(1.11%) had *Plasmodium ovale* species.

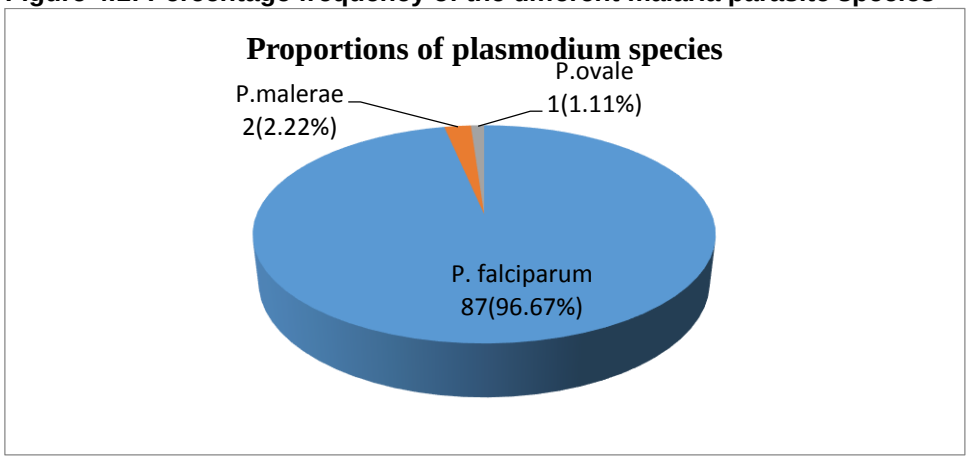
Table 4.3: Test result with Microscopy and RTDs rapid diagnostic tests

	Microscopy		HRP2-mRDTs		HRP2-pLDH	
	n(%)	95%CI	n(%)	95%CI	n(%)	95%CI
Positive samples	90(39.13)	0.32 - 0.45	105(45.65)	0. 39 - 0.52	106(46.09)	0.40 - 0.53
Negative Samples	140(60.87)	0.54 - 0.67	125(54.35)	0.48 - 0.61	124(53.91)	0.47 - 0.60

Proportions of Plasmodium species

Figure below shows that out to 90 respondents who tested positive of malaria, majority 87(96.67%) had P.falciparum, while only 2(2.22%) and 1(1.11%) had *P.malerae* and *P.ovale* respectively.

Figure 4.1: Percentage frequency of the different malaria parasite species



Accuracy of diagnostics for detection of Malaria with HRP2 and pLDH RDTs based

HRP2 RDT and pLDH RDT kits had the same sensitivity of 94.44% (95%CI=0.87 – 0.98). There was no significant difference in the Specificity of the two RDTs kits against microscopy which was at 85.71% and 85.00% for HRP2 RDT and pLDH respectively. HRP2-mRDT had a positive predictive value of 80.95% (95%CI=0.72 - 0.87) and pLDH-RDT had a positive predictive value of 80.19% (95%CI=0.71 – 0.87). Negative predictive value for HRP2-mRDT was found to be 96.00% (95%CI=0.91 – 0.98) where as that of pLDH RDT was found to be 95.97% (95%CI=0.91 – 0.98) (Table 4.2).

Table 4. 2: Sensitivity, Specificity, and Predictive values of HRP2 based RDT and HRP2 with pLDH based RDTs compared to microscopy as a gold standard

	HRP2-mRDTs			HRP2-pLDH	
	Value (%)	95%CI		Value (%)	95%CI
Sensitivity	94.44	0.87 - 0.98		94.44	0.87 - 0.98
Specificity	85.71	0.79 - 0.91		85.00	0.78 - 0.90
Positive predictive value	80.95	0.72 - 0.87		80.19	0.71 - 0.87
Negative predictive value	96.00	0.91 - 0.98		95.97	0.91 - 0.98

Agreement between microscopy test and RDTs test

The results reveal that there was a significant perfect agreement between microscopy test and HRP2 RDT test (89.13%) and perfect agreement of 88.70% between microscopy and pLDH RDT tests (p-value<0.001),(Table 4.3).

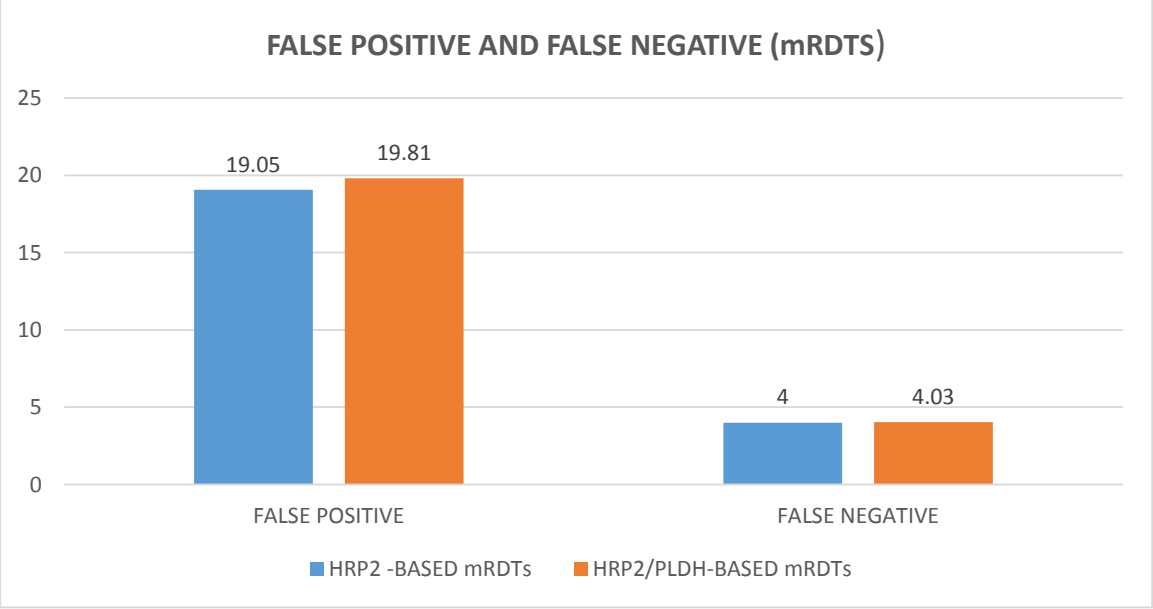
Table 4. 3: Kappa test showing the level of agreement between microscopy and RDTs (HRP2 and pLDH)

	Agreement	Expected agreement	Kappa	Std. Err.	Z	p-value
HRP2 RDT	89.13%	50.95%	0.7784	0.0654	11.91	<0.001
pLDH RDT	88.70%	50.85%	0.77	0.0653	11.8	<0.001

False positive and false negative

Out of 230 patients tested using HRP2-RDT, 20(19.05%) were false positive and 5(4.00%) were false negative using microscopy test as gold standard. It also reveal that 21 out of 230 (19.81%) were false positive for pLDH-RDT test and 5(4.03%) were false negative for pLDH-RDT against microscopy as gold standard (Figure 4.2).

Figure 4.2: False positive and false negative with mRDTs



DISCUSSION

The sensitivity for both the rapid diagnostic tests in this study was 94.44% and the specificity was at 85.71% for HRP2 based mRDTs and 85.00% HRP2/pLDH based mRDTs. This means that the mRDTs kit used in the study is capable of detecting correctly (giving positive results) only with 217 out of 230 participants with malaria infection and will give negative result in 196 out of the 230 participants without malaria infection. A good diagnostic test is required to have 100% sensitivity and 100% specificity rate to ensure that true positive and true negative results are given to the patients. Therefore, the sensitivity recorded in this study is against the WHO recommendations of ≥95%(Boateng, 2013), this can be explained by the false negative of 5.56% of mRDTs as compared to the microscopy. The low sensitivity that was observed can also be linked to low parasite density below the threshold of mRDTs positivity (<100 asexual parasites/µl or <0.002% of red blood cells infected (Mouatcho *et al.*, 2013). Other similar studies by Tahar *et al*., showed some degree of false negative results for mRDTs because of hyperparasiteamia,(Tahar *et al.*, 2013), deletion or mutation of HRP2 gene and the prozone effect which is define as false negative or false positive results in immunological reactions because of excess of either antigens or antibodies, which has a direct effect on the sensitivity of the test (Gillet *et al.*, 2009). In this study, false positive and false negative results can also be attributed to failure to adhere to standard operative procedure and inadequate training of the health care workers.

The different RDTs tested herein had relatively low specificity (85.71 and 85.00% for HRP2 and HRP2/pLDH) in comparison to the study done in Ethiopia which had a specificity of 98.6% (Feleke *et al.*, 2017).The loss in specificity could be attributed to the detection of HRP2 circulating antigens, which may persist in the blood for several weeks after malarial treatment and failure to wait for the recommended test incubation time . Similar studies in Nigeria, reported a sensitivity and specificity of 80% and 93.8% respectively .(Ezeudu *et al.*, 2015). The sensitivity obtained by this research was higher than for this study done in Nigeria. This is possible because standard operative procedures and job aids were provided to the health care workers. Mentorship and on job training was also be done during the process to ensure patients get the correct results. Nyanmar endemic border in China also found that the HRP2 based rapid diagnostic test had a sensitivity of 89.68% and specificity of 98.26% compared to the gold standard microscopy method for the detection of malaria (Xiaodong *et al.*, 2013). Variation in sensitivity between the different studies may be attributed to different in the types of RDTs used or test methodology and skills of the microscopist.

The findings from this study also indicated that 15 out of 230 participants whose microscopy results were negative were positive with rapid diagnostic test (false positive). This may be as a result of persistent antigen of malaria parasite in the blood even after parasite clearance following adequate antimalarial treatment of the index cases. The persistent antigenaemia may have contributed to high specificity recorded in the study. This agreed with Batwala *et al.,* 2010.The percentage agreement of positive results of mRDTs and microscopy was at perfect agreement of 89.13% for HRP2 based mRDTs and 88.70% for HRP2/pLDH base mRDTs. The expected agreement rate was 50.95% and 50.85% respectively. The explanation for this may be because this is a high endemic area hence the parasiteamia density is high that can be detected by both mRDTs and microscopy.

The implication of the low sensitivity in this study compared to the WHO set target is that in areas with low malaria parasiteamia, a negative result should be cross checked with microscopy and clinical acumen of clinician to rule out possibilities of false negative with the mRDTs. The specificity of 85% in the study implied that mRDTs may be used in primary healthcare by community health volunteers to rule out the absence of malaria where microscopes are hardly seen or where the required expertise is lacking, however for the health facilities the gold standard method should be used to ensure true positive results are obtained. The false positive rates for HRP2 and HRP2/pLDH based mRDTs was 19.05% and 19.081% respectively and the false negative rates for HRP2 and HRP2/pLDH based mRDTs was 4.00% and 4.03%.The false positive and negative results may be attributed to, low parasite density. According to WHO, false negative results can be caused by any or combination of the following. The procurement and use of poor quality RDTs, poor transport and storage conditions for RDTs with sustained exposure to high temperature operator errors during performance and interpretation of rdts results and finally deletion or mutation of HRP2.However the possibility of the RDTs being able to detect parasites with hrp2 gene deletion needs to be explored. This is because the RDT could not identify the infection that was identified by microscopy in five samples. In these samples it is likely that RDTs failed to identify parasite densities because they had low parasite density since other samples had comparable parasite densities but were correctly identified by the RDTs. A thorough review of HRP2 based RDTs is required given the reports of hrp2 gene deletion infection in Mali (Koita *et al.*, 2012) and potentially in Ghana as suggested by Amoah *et al* 2016 (Amoah *et al.*, 2016).

Positive and negative predictive values of malaria rapid diagnostic test. The positive predictive values on this study for HRP2 and HRP2/pLDH based mRDTs were 80.95% and 80.19% respectively. The negative predictive values were higher than the PPV. For HRP2 it was 96.00% and for HRP2/pLDH based mRDTs was 95.97%. This is slightly different from the findings of Falade *et al, (*2016), who had PPV and NPV of 65.6% and 86.1% respectively.

The positive predictive value of 80.57% means that the kit has the capacity of confirming malaria with a precision of 80.57%. Whilst the negative predictive value of 95.99% means that the mRDTs is good in ruling out malaria, thus giving the clinician the confidence that negative test excluded malaria in about 95.99% of cases.

CONCLUSION

The sensitivity of the HRP2 and HRP2 combined with pLDH based mRDTs compared with microscopy diagnosis of malaria in this study were found to be 94.44%. The specificity of HRP2 based mRDTs and HRP2 combined with pLDH based mRDTs was 85.71% and 85.00% respectively. The low sensitivity below the WHO recommendation of ≥95% indicates the need to improve the sensitivity of the mRDTs kits in malaria management, where trained microscopist for malaria diagnosis are not available. However, where there are trained personnel and all the requirements for microscopy, there should be increased microscopy diagnostic sites because this is the gold standard for malaria diagnosis. The study found out that the positive predictive values for HRP2-mRDTs was 80.95% and the positive predictive values for HRP2 combined with pLDH-mRDTs was 80.19%. The findings reveal that the two different mRDTs can only detect true positive up to 80 %. It is worth to say that mRDTs is easy and rapid test for malaria diagnosis for quick intervention in treatment. The results obtained in the two mRDTs test kits for malaria parasite should be confirmed with tests with high sensitivity hence the need to increase malaria microscopy diagnostic sites. Microscopic examination of malaria parasite is still the method of choice and also the gold standard especially for confirmation of clinical diagnosis. It is therefore recommended that malaria parasite slide microscopy should be emphasized than the use of rapid diagnostic tests (RDTs) as it is more sensitive and more specific as highlighted in this study. More so, feasible implementation of an integrated quality assurance for model for malaria parasite microscopy and RDTs using known positive control wells for RDTs and use of known negative and positive controls for malaria microscopy.

Author Summary

Our study was informed by the observation that Rapid Diagnostic Test kits (RDTs) have become widely used but predominantly in primary health care and level two hospitals. Their use in Seme Sub County is at 76% where only six microscopy sites were present at the time of the study out of the twenty five health facilities. We decided to compare microscopy and RDTs in malaria diagnosis so as to provide a basis for the need to increase microscopy sites in Seme Sub County. We used microscopic examination of thick and thin blood film and rapid diagnostic test kits to detect the presence of malaria parasite in individuals with signs and symptoms for malaria attending the health facilities. We then compared the performance of these diagnostic testing procedures by calculating their sensitivity, specificity and predictive values in order to find out which of them is more sensitive and accurate. Our study indicates that RDT performance is below the WHO target expectation and therefore should not replace microscopy.

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