Assessment of Factors Influencing Adherence to Malaria Microscopy Diagnosis in the Treatment of Out-patients at Kisumu County Referral Hospital in Kenya

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Authors' contributions

This work was carried out in collaboration among all authors. Author FO conceived and designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors FO and SN managed the analyses of the study. Authors HA and DS coordinated the study and managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Aim: This study sought to assess factors that influence adherence to malaria microscopy diagnosis in the treatment of out-patients in the hospital.
Methods: From April to June 2018, a cross-sectional study was conducted. Semi-structured questionnaires were administered on clinicians and microscopists, while prescription practices of pharmacy personnel and clinicians were observed. To determine microscopy performance, systematically sampled thick blood smears, which had been used to diagnose malaria in out-patients were re-examined for presence or absence of malaria parasites by independent expert microscopists. Each thick blood smear was re-examined by two independent expert microscopists, and in case of discordant results a tie-breaker expert provided reference results for performance

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measures. Test validity and reliability were determined using Graph Pad Prism v5.01.

Results: Three (30%) clinicians strictly (100%) adhered to malaria microscopy diagnosis during treatment of out-patients, had refresher training on malaria case management and were aware that the laboratory participates in national quality assurance (QA) scheme. At the pharmacy-level adherence to microscopy results during treatment was generally 100% and >98% for clinicians. However, 13 (11%) malaria false-positive participants still received Artemether-Lumefantrine. Of 375 selected blood slides, 118(31.5%) were read as positive at the health facility, while 105 (28%) were read as positive by the experts, (P <0.01). Overall, 96% of test results were concordant with expert reference. The overall inter-reader agreement between hospital diagnosis and experts microscopists was κ=0.91 (95% CI: 0.87-0.96). Sensitivity was; 99.1% (95% CI: 94.9-100), specificity; 95.2% (95% CI: 91.9-97.4), Positive Predictive Value; 89% (95% CI: 81.9-94) and Negative Predictive Value; 99.6 (95% CI: 97.9-100).

Conclusion: Our results show commendable adherence to malaria microscopy during treatment of out-patients in Kisumu County Referral Hospital. Refresher training on malaria case management for clinician and awareness by clinicians that the hospital laboratory participates in national QA scheme had positive influence on the adherence to malaria microscopy during treatment of out-patients. Malaria microscopy test validity and reliability were commendable

1. BACKGROUND

Globally, approximately 212 million cases and 584,000 deaths of malaria were reported, with 90% of the deaths occurring in Africa in 2015 [1]. Kenya had an estimated malaria mortality rate of 27.7 per 100,000 persons in 2012 [2]. During this time, malaria accounted for approximately 9 million out-patient visits and 21% of out-patient consultations annually [3]. Kisumu County Referral Hospital (KCRH) is the largest level 4 public-sector hospitals in Kisumu County, hence hospitalizes substantial number of malaria patients and handles many others at its out-patient unit. In 2017, the hospital recorded in the laboratory register approximately 40 thousand malaria microscopy tests, with about 15% malaria microscopy positivity rate.

The National Malaria Control Programme (NMCP) recommends both microscopy and malaria rapid diagnostic test (mRDT) for malaria diagnosis [4,5]. This is in line with the World Health Organization's (WHO's) 'test, treat and track' strategy, which recommends parasitological diagnosis for all patients in whom malaria is suspected [6]. Microscopy is the 'gold' standard for malaria diagnosis [7]. For a while, 50% of health facilities in Kenya have been providing malaria microscopy services, which according to the Kenya National Malaria Strategy 2009-2017 is the primary method for malaria diagnosis in hospitals [8]. It's indeed the primary method for malaria diagnosis in Kisumu County Referral Hospital (KCRH). Malaria RDTs on the other hand are prioritized in dispensaries where

expert microscopy is not needed, since severe cases can be referred to higher level health facilities. High quality microscopy is important because it can confirm mRDT diagnosis, perform Plasmodium species identification, quantify parasitaemia and monitor treatment outcome [9]. However, false malaria microscopy results often obtained from clinical laboratories is a serious concern [10]. This technique can be mired with deficiencies in the hands of less proficient laboratory personnel [7,11]. The challenge of microscopic diagnosis of malaria is primarily dependent on the competence of microscopists in morphological identification of parasites [12]. Proper microscopic diagnosis of malaria may therefore require regular malaria microscopy diagnosis refresher training for microscopists or several years of malaria microscopy diagnostic experience and institutionalization of national Quality Assurance (QA) schemes [10]. These also helps in ensuring quality of blood films, quality of staining and condition of microscopes which are known to play key roles in the test accuracy [11].

The national malaria treatment guideline recommends Artemether-lumefantrin (AL) and dihydroartemisinin-piperaquine (DHAP) as first and second line treatments for malaria respectively. Both are Are Artemisinin-based Combination Therapy (ACT). In Vivax malaria, primaquine should also be administered to achieve radical cure and avoid relapses [7]. Presumptive treatment has been reported in certain areas of Kenya and elsewhere [10,13]. This is sometimes blamed on the lack of

functional clinical laboratories [14]. Though, some health workers have reportedly been treating malaria presumptively based on their assessment of signs and symptoms, whose success vary depending on their knowledge and practice, and by the prevalence of other acute febrile illnesses [13]. Moreover, inappropriate treatment is still being reported even in areas with functional laboratories due to inaccurate malaria diagnosis, even by microscopy [10]. It's clear though, that diagnosis of malaria based on symptoms alone can be very inaccurate [7,15]. Hence, accurate parasitological diagnostic testing is a sure way of substantially improving malaria treatment with ACT [16].

The KCRH laboratory recently acquired international repute by attaining ISO 15189:2012 accreditation. Accordingly, it's presumably abreast technologically and has adequate and qualified diagnostic personnel, including expert malaria microscopists. The hospital's catchment population resides within malaria endemic zone [7]. As such individual patients are prone to low Positive Predictive Value (PPV) synonymous with high false negatives during microscopic diagnosis of malaria in such areas [10]. In contrast, overtreatment is reportedly a major problem in such malaria endemic settings [14]. Persons who are misdiagnosed suffer the risk of not being treated effectively, which may lead to increase in morbidity and mortality in the population. Thus, there is need to understand malaria microscopy diagnostic clinical-laboratory interface and adherence to malaria microscopy during patient treatment.

2. METHODS

2.1 Study Design and Area

From April to June 2018, a cross-sectional study was conducted to assess factors influencing adherence to malaria microscopy diagnosis during treatment of out-patients at KCRH. The hospital is located in Kisumu city, which is the major urban setting in Kenya's malaria endemic epidemiological zones [4, 7]. This area has an estimated population-adjusted parasitaemia prevalence of >30% [17].

2.2 Sample Size and Sampling Procedure

A total of 375 out-patients visiting the hospital laboratory with documented request forms from the hospital's out-patient unit with blood smear for malaria diagnosis requests were selected daily from 8.00 AM to 6.00 PM by systematic random sampling to participate in the study. Pregnant patients were excluded. To minimize loss of participants, the hospital management agreed to waive all fees on anti-malarial medicines for all selected patients who couldn't afford to pay for them. After consent was obtained from the hospital management, the laboratory was provided with new slides, slide boxes and then phlebotomists were instructed to label malaria slides appropriately during sample collection. Malaria microscopists were instructed to archive all malaria slides from April to June 2018 in the slide boxes and to record patient results, including age, sex, in-patient /out-patient number and hospital unit where the malaria test was requested. They would also clearly record requesting clinician's name, and sign off each malaria test result with the name of examining microscopist. In the context of this study, the term 'clinician' refers to a clinical officer, while 'microscopist' refers to laboratory personnel examining blood smears using a microscope to detect malaria parasite. All patient records were keyed in the laboratory management information system (LIMS) platform and also backed-up in a log book. All personnel from the participating hospital units were masked to the study objectives. Patients would be selected by systematic random sampling by an independent researcher as they went into the laboratory and their out-patient number relayed to an independent prescription observer stationed at the hospital out-patient unit, who in turn would direct the patient to the pharmacy from where another independent observer captured treatment data. The number of malaria slides collected represented approximately 4% of all malaria slides obtained during the entire study period.

2.3 Data Collection

Each clinician who prescribed any medication to the participating patients was interviewed by trained study personnel using a pilot-tested semi-structured questionnaire. Likewise, each microscopist who examined the selected malaria blood smear was interviewed using a similar pilot-tested semi-structured questionnaire. These interviews generated data on demographics, work experiences, refresher trainings, knowledge on diagnosis and treatment guidelines, knowledge on malaria epidemiology, malaria blood smear examination practices, prescription and treatment practices. The expert malaria microscopy readers recorded results in

standardized worksheets. A prescription and treatment form was used to compile each patient's malaria microscopy test results, prescribed anti-malarial medicine and anti-malaria medicine issued for treatment.

The expert microscopists, who had been certified through the WHO External Competency Assessment for Malaria Microscopy scheme, re-examined thick malaria blood smears for presence or absence of parasites. Each slide was cross-checked by two independent expert microscopists, and an independent tie-breaker expert microscopist in case of parasite detection discordance between the first two expert readers. The concordant expert microscopist results, or the tie-breaker results when necessary, would be considered the reference measurements. Each expert microscopist, reading a maximum of 20 slides per day, would each time use new standardized worksheet to record results to have them masked to both the hospital laboratory microscopy results and other expert microscopy results. For each slide, a minimum of 100 fields would be examined using high-power (X100) magnification by the expert microscopists before it would be classified as negative according to the Kenya Ministry of Health and WHO guidance [5,9].

2.4 Data Management and Analysis

Data from the expert microscopy standardized worksheets, clinician and pharmacy-level data from the prescription and treatment forms, and data from the semi-structured questionnaires were all entered into Microsoft Excel [TM] 2010 (Microsoft, Seattle, WA, USA). Using the Excel, characteristics of clinicians and microscopists were obtained by univariate analysis of the data that generated frequencies, proportions, median and range. Adherence to microscopy results was also obtained by running counts and proportions. Clinicians' adherence to malaria diagnosis in the treatment of out-patients was defined as making prescriptions in accordance with the hospital laboratory malaria microscopy test results; which is prescribing 1st line ACT (or AL) or 2nd line DHAP in treatment failure to only out-patients with positive malaria microscopy test results and not prescribing any anti-malarial to out-patients with negative malaria microscopy test results. Likewise, pharmacy-level adherence to malaria microscopy diagnosis in the treatment of out-patients was defined as dispensing anti-malarial in accordance with the hospital laboratory malaria microscopy test results; which is

dispensing 1st line ACT (or AL) or 2nd line DHAP in treatment failure to only out-patients with positive malaria microscopy test results and not dispensing any anti-malarial to out-patients with negative malaria microscopy test result. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the hospital laboratory results were calculated with the expert microscopists results as reference at 95% confidence intervals (CI) using exact method by Graph Pad Prism version 5.01. Inter-reader agreement for the hospital *versus* reference expert readings was expressed as kappa (κ) values with 95% CIs using Graph Pad Prism version 5.01.

3. RESULTS

Of 375 malaria slides collected, 118(31.5%) were read as positive at the hospital laboratory, while 105 (28%) were read as positive by the expert microscopists, (p<0.01). Overall, 96% of test results were concordant with expert reference (Fig. 1). The expert readers disagreed on 2 (<1%) malaria slides requiring a third tie-breaker.

All microscopists who had examined study malaria blood smears and all clinicians who prescribed medication to out-patients whose malaria blood smears were selected for study agreed to participate. In total, 10 (83%) out-patient clinicians and 9 (53%) microscopists participated in the study. During interview, all (100%) microscopists effectively described the recommended battlement as their usual method of blood smear examination under microscope for detection of malaria parasites. Four (44%) said they were very motivated, while the rest (56%) were only partially motivated towards malaria microscopy work.

During interviews with clinicians, seven (70%) of them were aware that the hospital laboratory was participating in the national malaria microscopy QA scheme. Six (60%) said that sometimes they had no confidence in malaria microscopy test results from the hospital laboratory, while one (10%) had preference for more experienced microscopists. Similarly, six (60%) of them said they wouldn't request for malaria microscopy test if the patient indicated they couldn't afford to pay for it. Four (40%) would yield to pressure from a patients on their decision to request for malaria test. Seven (70%) said they would prefer microscopy to mRDT as a diagnostic test for malaria. Regarding treatment, all (100%) clinicians during interview correctly pointed out
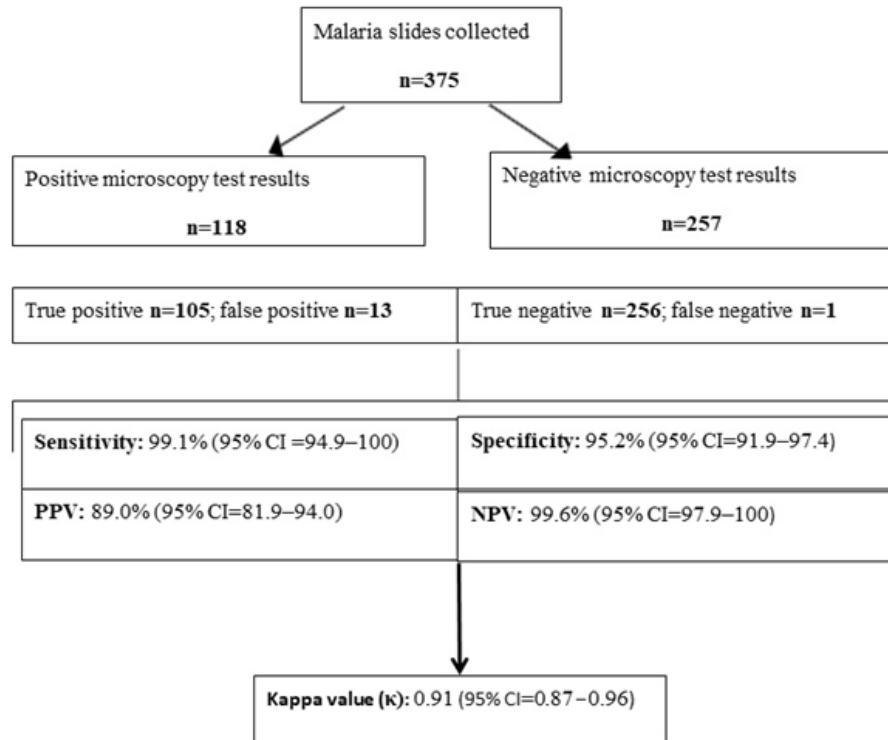
Fig. 1. Validity and reliability of malaria microscopy test in Kisumu County Referral Hospital laboratory, 2018
PPV = Positive predictive value; NPV = Negative predictive value

that AL is the current recommended 1st line treatment for uncomplicated malaria in the country, although three (30%) noted that AL is sometimes not an effective treatment for uncomplicated malaria. In contrast, two (20%) of them said SP and three (30%) said quinine are also recommended 1st line treatments for uncomplicated malaria in the country. Three (30%) had admittedly ever prescribed AL as a prophylaxis. Regarding 2nd line treatment, during interviews six (60%) clinicians correctly pointed out that DHAP is the current recommended 2nd line treatment for uncomplicated malaria in the country. In contrast, the other four (40%) pointed out Quinine, SP or Artesunate as the recommended 2nd line treatment for uncomplicated malaria in the country. All (100%) clinicians had no idea that Primaquine should be included during treatment of *Plasmodium vivax* malaria infection. Two (20%) agreed that sometimes they yielded to pressure from patients on the type of anti-malarial to prescribe. Similarly, six (60%) agreed that sometimes they prescribe AL to malaria test negative patients when they highly suspected malaria

disease. Four (40%) agreed to ever consulting peers during prescription of anti-malarial.

Only AL was prescribed and issued to participants during the study period. Only clinicians prescribed medicine to participants during the entire study period. Adherence by clinicians to malaria microscopy test results during prescription of medicine to participants with positive malaria microscopy test results was 100% (n = 118). Their adherence level dropped to 98% (n = 257) when prescribing medicine to those with negative malaria microscopy test results. Thirteen (11%) of participants who were issued with AL prescriptions had false positive malaria microscopy results, while 1(1%) false negative participant missed AL prescription. Adherence to malaria microscopy results during treatment at pharmacy-level was generally 100%, since the 118 participants who had positive malaria test results, and had AL prescription from the clinicians, were all issued with AL at the hospital pharmacy. No participant with a negative malaria test result was issued with AL or any other anti-malarial at the

Table 1. Characteristics of study clinicians and microscopists in Kisumu County Referral Hospital in Kenya, 2018

Characteristic	Clinician (N = 10)		Microscopist (N = 9)	
	Number	Percentage	Number	Percentage
Individual level				
≥Diploma-level training	9	90	9	100
Recent refresher training*	2	20	0	0
Earlier refresher training*	2	20	2	22
Worked in malaria low-transmission area	0	0	1	11
Read malaria diagnostic and treatment guideline	5	50	5	56
Knowledge				
Malaria diagnostic and treatment guideline	5	50	1	11
Malaria epidemiology in county	9	90	7	78
Malaria epidemiology in country	7	70	8	89
Community prevalence of malaria	3	30	0	0
Characteristic	**Clinician (N=10)**		**Microscopist (N=9)**	
	Median	Range	Median	Range
Years of experience	6.5	1-15	5	2-18
Age	28	23-40	-	-

*Recent refresher training; malaria case management refresher training for clinician and malaria microscopy refresher training for microscopist within the year prior to the study, *Earlier refresher training; malaria case management refresher training for clinician and malaria microscopy refresher training for microscopist earlier than the year prior to the study*

pharmacy. Thus, 4 (2%) people among those with negative malaria test results, but who had AL prescription from clinicians, were not issued with any anti-malarial at the pharmacy. On the other hand, all the 13 (11%) false positive malaria patients with AL prescriptions from the clinicians were issued with AL at the pharmacy, while 1(1%) false negative malaria participant who was not issued with an AL prescription by a clinician was not issued with AL at the pharmacy.

Participating clinicians who adhered strictly (100%) to malaria microscopy test results in the treatment of the out-patients during this study were 3 (30%). They had a number of similarities. Together they prescribed medicine to a total of 110 (29%) participants. Characteristics that defined these clinicians are described in Table 2. During interviews, all the 3 (100%) clinicians correctly pointed out that AL is the 1st line medicine for treatment of uncomplicated malaria, DHAP for severe malaria. They also all noted that they would never prescribe any monotherapy to uncomplicated and severe malaria patients. They all shared one belief, that AL is an effective uncomplicated malaria medicine. They all expressed no preference for an individual microscopist or even primary parasitological test method (microscopy or mRDT) used in the diagnosis of malaria. They asserted that they would never be influence by pressure from the patients or patient's economic status in prescribing anti-malaria medicines. They expressed that they trusted malaria microscopy test results from the hospital laboratory.

4. DISCUSSION

The hospital laboratory malaria microscopy diagnosis was often adhered to during treatment of out-patients. There was commendable adherence noted during prescription and total adherence noted at pharmacy-level during issuance of medicines. The strict adherence expressed at the pharmacy-level could be attributable to the fact that in Kenya, public hospital pharmacy personnel are considerably detached from patients' feelings during issuance of medicines and only interact with written prescriptions from clinicians and laboratory results, which they are often obliged to comply with accordingly. In this hospital, there might have been a consistent program that made only AL available for out-patients, with no alternative routes for prescribing or issuing any other anti-malarial outside official policy of the hospital; hence AL was the only prescribed and issued

anti-malaria during the entire study period. Even as only three, representing 30% of all participating clinicians adhered strictly to malaria microscopy diagnosis during treatment of out-patients per national protocol for the management of uncomplicated malaria. Nevertheless, adherence by clinicians to malaria microscopy diagnosis during prescription of medicine was marginally higher among the positive malaria (100%) compared to negative (98%) malaria out-patients. These findings are consistent with a recent review of malaria data and meta-analysis [18].

There were instances when undeserving participants were treated with AL. This largely arose from false positive malaria microscopy diagnosis. However, some participants correctly categorized by microscopy as negative for malaria were inconceivably issued with AL prescription without any clear criteria. Similarly, one deserving patient was not issued with an anti-malarial prescription by clinicians, certainly because they had falsely been categorized as negative for malaria during microscopy diagnosis. Studies indicate that even county health facilities adjacently located to the study hospital, were rampantly engaged in presumptive treatment for malaria [19]. A recent study in Tanzania realized similar practices, in which anti-malarial medicines were prescribed to all patients

with positive test results and 14% of patients with negative test results [20]. Various other African countries continue to report similar practices [21, 22]. It's an anomaly for clinicians to prescribe anti-malarial to patients with negative malaria test results. They've been shown to veer off from treatment protocol when they feel it's their sole duty to give the best care to patients, when they have alternative ways to acquire anti-malarial medicines, and when they are immersed to patients' predicaments as to consider their physical condition, preferences and economic status during treatment among other factors [23]. Perceptions of treatment failure or undetectable malaria in patients who had taken ACT prior to arriving at the hospital have also been identified by a recent study in neighboring Uganda as a possible reason caregivers issue anti-malarial medicines to patients with negative test results [23].

In this study, two key factors appeared to positively influence clinicians to adhere to malaria microscopy diagnosis during treatment of persons in whom malaria was suspected. They include formal refresher training of clinicians on malaria case management, and awareness by clinicians on the existence of national laboratory QA scheme. This is because all the strictly adhering clinicians exhibited both aspects. A study conducted nearby in

Table 2. Characteristics of clinicians who adhered strictly (100%) to malaria microscopy test results in the treatment of out-patients in Kisumu County Referral Hospital, 2018

Characteristic	Clinician (N = 3)	
	Number	**Percentage**
Individual level		
≤ Diploma-level training	3	100
Recent refresher training*	1	33
Earlier refresher training*	3	100
Worked in malaria low-transmission area	0	0
Read malaria diagnostic and treatment guideline	3	100
Knowledge		
Malaria diagnostic and treatment guideline	3	100
Malaria epidemiology in country	3	100
Community prevalence of malaria	2	67
Laboratory participation in national QA	3	100
	Median	**Range**
Years of experience	9	10-15
Age	30	28-40

*Recent refresher training; malaria case management refresher training within the year prior to the study, *Earlier refresher training; malaria case management*

Ethiopia also show that sustained refresher training of health personnel and other factors not measured in this study are imperative drivers of appropriate malaria case management [24]. Even among microscopists working elsewhere in Kenya, similar refresher trainings was recently found to have strong positive association with accuracy of malaria microscopy diagnosis. This and all other factors that enhance microscopists' performance in diagnosis of malaria often have positive influence on clinicians' trust on laboratory results, which potentially enhances their adherence to treatment protocol [10,12,21, 25,26].

Validity measures, especially the sensitivity, specificity and Negative Predictive Value (NPV) were commendable at over 90%. Such commendable performance might have been supported by laboratory participation in national malaria microscopy QA scheme and other factors not measured in this study, since even refresher training was uncommon among microscopists. These findings on performance measures are consistent with a recent study conducted in an area in the same epidemiological zone [27]. Inter-reader agreement measure of reliability was almost perfect at kappa, κ = 0.9 [28]. In contrast, PPV obtained from this study was commendable but lower compared to NPV. Malaria slides for this study were collected in April to June, which is a peak malaria transmission season in Kenya [29]. Therefore, most patients attending this facility, even if not febrile, were likely to have malaria at the time of the study. Normally, PPV and NPV are dependent on the prevalence of a disease in a given population [10]. As such, PPV increases as NPV decreases with increase in prevalence. The observed swap, where PPV appeared much lower than NPV in a high prevalence setting, might be explained by inter-observer variability in malaria slide examination criteria by various microscopists, given the fact that refresher training, necessary for standardization of procedures and processes was largely lacking among microscopists. However, PPV and NPV obtained in this study were comparable to those obtained in a recent study in Tanzania [30]. In high malaria transmission areas like this study site, the high NPV translates into very low numbers of false negative malaria microscopy results. Persons correctly categorized by a malaria test as having no malaria, have an opportunity of being managed for their actual disease, which reduces morbidity and potentially mortality. On the other hand, high PPV translates

into low numbers of false positive malaria microscopy results, although relatively high numbers of false positive results were obtained in this study. Nonetheless, Persons correctly categorized by a test as having malaria, have an opportunity of promptly and effectively being managed for malaria within the national malaria treatment protocol tenets [7].

This study had some limitations. For instance, analytical test of association was untenable given the design of the study, hence univariate analysis applied herein is limited in the extent to which independent factors of influence to adherence could be identified. Additionally when the health facility consented to participate in the study, phlebotomists and microscopists were sensitized on labeling and archiving slides during the study period. They might have been aware slides would later be retrieved for re-checking. Knowing they were being observed, they might have changed behavior to perform better during this period (i.e., Hawthorne effect), resulting in overestimation of malaria microscopy diagnostic accuracy [31,32]. The arising potential bias would however be minimized by random sampling of slides. Another important limitation was that the malaria slides were selected without regard to parasitaemia density levels. Many malaria positive slides might have had high parasitaemia levels, which is generally easy to detect in thick films. The net effect of this would still be overestimation of the diagnostic test accuracy and incorrect estimation of patient treatment appropriateness. It's expected that the effects of this would as well be minimized by random sampling.

5. CONCLUSIONS

Results show commendable adherence to malaria microscopy during treatment of out-patients in Kisumu County Referral Hospital, at both the pharmacy and clinicians level. Refresher training on malaria case management for clinician and awareness by clinicians that the hospital laboratory participates in national QA scheme had positive influence on the adherence to malaria microscopy during treatment of out-patients. Malaria microscopy test validity and reliability were commendable. Therefore, formal refresher training on diagnosis and treatment of malaria should be implemented among both clinicians and microscopists, and the national QA scheme awareness campaign run among clinicians to improve and sustain accurate

malaria diagnosis and adherence to national malaria treatment protocol.

CONSENT

The medical superintendent of KCRH, each participating microscopist and each participating clinician provided written consent. No personal identifiers were collected from microscopists and clinicians or extracted from laboratory or clinical records.

ETHICAL APPROVAL

The protocol was reviewed and approved by Maseno University Ethics Review Committee (MUERC) through the School of Graduate Studies (SGS) of Maseno University (#MSU/DRPI/MUERC/00448/17) in collaboration with the Ministry of Health.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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