Use and Limitations of Malaria Rapid Diagnostic Testing in Sub-Saharan Africa: a

Systematic Review & Longitudinal Study in Western Kenya

by

Matthew R. Boyce

Duke Global Health Institute
Duke University

Date:_______________________
Approved:

____
Wendy Prudhomme-O'Meara, Co-Supervisor

____
Randall Kramer, Co-Supervisor

____
Joy Noel Baumgartner

Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Duke Global Health Institute
in the Graduate School of Duke University

2017

ABSTRACT

Use and Limitations of Malaria Rapid Diagnostic Testing in Sub-Saharan Africa: a

Systematic Review & Longitudinal Study in western Kenya

by

Matthew R. Boyce

Duke Global Health Institute
Duke University

Date:_______________________
Approved:

____
Wendy Prudhomme-O'Meara, Co-Supervisor

____
Randall Kramer, Co-Supervisor

____
Joy Noel Baumgartner

An abstract of a thesis submitted in partial
fulfillment of the requirements for the degree
of Master of Science in the Duke Global Health Institute
in the Graduate School of Duke University

2017

Abstract

The World Health Organization recommends parasitological confirmation of malaria prior to treatment. Malaria rapid diagnostic tests (RDTs) represent simple, mobile diagnostic technologies that are used in a variety of contexts to overcome limitations of other techniques. Malaria RDTs increase the availability and feasibility of accurate diagnoses and may result in improved quality of care. Though RDTs are used in a variety of contexts, no studies have compared how well or effectively RDTs are used across different contexts and types of care providers. This report is composed of two related works: a systematic review and a longitudinal study. The systematic review was conducted to describe the diagnostic use of RDTs in formal health facilities, the community, drug shops and schools. A comprehensive search of the Pubmed database was conducted to evaluate RDT execution, test accuracy, or adherence to test results in sub-Saharan Africa. Overall, RDTs were performed safely and effectively by community health workers provided they receive proper training, but analogous information was largely absent for formal health care workers. Tests were generally accurate across contexts, except for in drug shops where lower specificities were observed. Adherence treatment guidelines based on RDT results was higher among drug shop vendors and community health workers, while adherence was more variable among formal health care workers, most notably with negative test results. Malaria RDTs are generally used well, though compliance with recommended treatment based on test results is variable – especially in the formal health care sector. However, their use by community health workers (CHWs) remains in question due concerns about long-term trends relating to blood safety, the interpretation of test results, and adherence to treatment protocols. In addition to the systematic review, a longitudinal study was conducted to determine if CHWs maintained their competency at conducting RDTs over a 12-month timeframe, and if this competency varied with various socio-demographic measures. 103 CHWs in Kenya were recruited into longitudinal study to compare RDT execution at the time of training and 12 months post-training. Community health workers performed RDTs at acceptable levels, with at least 80% of CHWs completing 18 of the 22 steps correctly. Quality of performance did not decrease over the 12 months. Socio-demographic characteristics including being younger than 50 years of age, and previous experiences with malaria RDTs were correlated with better performance over time. Community health workers provided very accurate interpretation of RDT results, especially when considering only strong-positive and negative test results. Training in using Deki reader devices was associated with better performance in interpreting RDT results. In conclusion, CHWs perform RDTs sufficiently, maintain competency for at least 12 months, and better performance can be associated with certain characteristics. The results of both studies hold important implications for health policy and future multidisciplinary research.

Dedication

For my parents – who taught an inquisitive hellion to always try to make the world a better place and preached that you can accomplish anything you devote yourself to. My dreams and well-being would have been neither conceivable nor realized without your support. Thank you.

Contents

List of Tables

List of Figures

Acknowledgements

I am grateful to the many individuals who made this work possible. Thank you to the community health workers, patients, and health center personnel for your participation in the study.

I would thank the staff of the 'Eldoret Malaria Voucher Study' for their support, dedication, and friendship: Adriane Lesser, Edith Nafula, Lillian Nukewa, Jojes Ambani, Lucy Cayth, Joseph Kipkoech, Daniel Aswa, Patel Biwott, Betty Lelei, Mercy Rob, Eunice Memo.

Thanks to the individuals of the DGHI Research Design & Analysis Core for their assistance in study design and data analysis: Joe Egger, Larry Park, Liz Turner, Alyssa Platt. Thank you to Sarah Martin and Lysa MacKeen who are integral to the positive fieldwork experiences enjoyed by MSc students at DGHI.

I would also like to extend my sincere gratitude to Dr. Wendy Prudhomme-O'Meara for all her mentorship, support, and guidance throughout this project. Thank you to Dr. Randall Kramer and Dr. Joy Noel Baumgartner for their critical reading of the manuscript.

This work was funded by the Duke Global Health Institute through an International Field Work Grant for the Masters of Science in Global Health program.

1. Introduction

1.1 Malaria case management

Malaria remains a leading public health problem, causing significant amounts of preventable morbidity and mortality worldwide. This is especially true in sub-Saharan Africa, where an estimated 90% of all malaria deaths occur, and despite recent improvements in diagnosis and treatment, malaria accounts for 10% of under-five mortality and remains a leading cause of death [1].

Previously, malaria case management in sub-Saharan Africa relied on the presumptive treatment of febrile illness with antimalarial drugs, essentially treating suspected cases of malaria with a full course of antimalarial drugs, usually chloroquine (CQ) or sulphadoxine-pyrimethamine (SP) [2,3]. This practice was endorsed by leading health organizations and widely practiced to reduce malaria-attributable morbidity and mortality in regions where a diagnosis was not feasible [4].

However, malaria treatment policy has changed in recent years as presumptive treatment no longer represents a justifiable approach to malaria case management. In 2010, the World Health Organization (WHO) revised their recommendations to require parasitological confirmation of malaria infection prior to treatment with artemisinin-based combination therapy (ACT), also known as the “test-and-treat” strategy [5]. This change was precipitated by a declining prevalence of malaria in sub-Saharan Africa, likely attributable to the use of modern control interventions, including insecticide-treated nets and indoor residual spraying [6-8]; evidence suggesting that malaria only causes a proportion of all febrile illness in malaria endemic regions [9-11]; concerns surrounding antimalarial drug resistance [12,13] and improvements in diagnostic technologies. The confirmation of parasitological infection is also important for the management of other febrile illnesses; as disease burden shifts it is necessary to know the infection status of each febrile patient so that they may receive proper care [3].

1.2 Malaria diagnostic techniques

Three techniques are currently in use for parasitological confirmation of malaria infection: blood smear microscopy, polymerase chain reaction (PCR), and malaria rapid diagnostic tests (RDTs). Microscopic examination of stained blood smears or films represents the oldest laboratory method, and is currently recognized as the gold-standard for malaria diagnosis [14-19]. In addition to confirming the presence of malaria parasites, microscopy can also confirm the type of *Plasmodium* species causing infection, as well as score parasite density and differentiate developmental and sexual stages of the parasite [17]. Because of these features, microscopy is especially helpful in not only diagnosing malaria but also assessing the severity of infection [14]. However, microscopy has a number of notable limitations. Reliable diagnosis requires experienced laboratory technicians with training and technical expertise, high-quality equipment and reagents (e.g. well-maintained microscope, staining reagents, filtered water at the correct pH, etc.), electricity, and it is relatively time-consuming [14-16,20-22]. Indeed, studies have shown that many health facilities in malaria endemic regions lack the capacity to perform clinical microscopy, making accurate diagnosis unfeasible [15,23-27].

PCR is able to identify parasites and infecting species even when parasites are present at very low densities, and some facilities in some developed countries use it as a routine diagnostic method [23,28-30]. Still, the technology is not able to distinguish between different parasite stages (unless reverse transcriptase PCR is used), or between living and dead parasites, and is subject to many of the same limitations as microscopy, including requiring experienced laboratory technicians, high-quality equipment, specialized reagents maintained at low temperature, and electricity [14,28,29,31]. For these reasons, PCR is generally only used in research settings or to confirm other laboratory findings [18].

Malaria RDTs were developed in the early 1990's and welcomed as a method to overcome the shortcomings of these other laboratory diagnostic techniques, especially in field studies [19,31-34]. This diagnostic method utilizes chromatography and antigen-antibody recognition to detect parasite antigens including histidine-rich protein-2 (HRP-2) or lactate dehydrogenase (pLDH) [15,17]. RDTs do not require electricity or specialized equipment and return results in less than 30 minutes [15,17]. The technology also holds considerable cost advantages over other diagnostic approaches. One systematic review that compared the costs and cost-effectiveness of malaria interventions found that RDT were more cost effective than microscopy for malaria diagnosis [35]. Additionally, other work comparing the cost of RDT diagnosis and ACT treatment with presumptive ACT treatment has found RDT diagnosis to be more cost-effective [36], though these results are likely dependent on transmission levels and have limited generalizability [35].

The malaria RDT procedure may be broken into three phases. The first phase includes assembling the necessary materials including: the RDT cassette, a buffer solution, an alcohol swab, a lancet, cotton wool, and a pipette. The second phase involves explaining the procedure to the patient, cleaning the finger, puncturing the skin, collecting a small volume of blood, and loading the blood and buffer into the RDT cassette. The final phase occurs after waiting for twenty minutes and is the reading of test results. Each RDT cassette is marked with a "C" and a "T." After the twenty minutes, all cassettes should display a line at "C." If it does not, or it only displays a marking at "T," the test is invalid. If the cassette displays a marking at "C" but no other marking is visible (i.e., there is no line at "T"), the test is negative and the patient does not have malaria. If a marking is present at "T," the patient has malaria. The darkness of this marking varies with the density of parasite infection, where darker marks correspond to higher parasite burdens.

According to WHO's recommendations, RDTs should provide diagnostic results at least as accurate as those derived from microscopy under standard field conditions [37]. Test sensitivity poses the most pressing concern, as false-negative test results may cause mistreatment of a potentially fatal disease. Subsequently, WHO defines the minimum sensitivity of 95% compared to microscopy, and 100% when parasite density is greater than 100 parasites per μl blood [37]. WHO also defines the minimum specificity of RDTs as 90% when compared to microscopy [37]. A recent systematic review investigating the diagnostic accuracy of RDTs for detecting uncomplicated malaria found that although there was substantial heterogeneity between studies, the sensitivities and specificities of all RDTs tested exceeded WHO's recommendations, and therefore concluded that RDTs are acceptable to replace microscopy for the diagnosis of malaria [38].

Ultimately, limited access to microscopy for parasitological confirmation of malaria has resulted in the overuse of antimalarials and substandard care for febrile illnesses. A compelling need exists to make malaria diagnosis more available which favors the expanded deployment and use of RDTs. The simplicity of these tests eliminates the need for high levels of technical expertise and allows for them to be used by a wide range of personnel including nurses, community health workers (CHWs), teachers, and other laypersons. Perhaps most importantly, the technology has demonstrated acceptable diagnostic sensitivities and specificities [38], showing potential to dramatically reduce the cost of case management and the risk of drug resistance associated with overuse of antimalarial drugs [39-41].

1.3 Thesis organization

The following manuscript combines two related works that focus on the use of RDTs in sub-Saharan Africa. To combine these works, this thesis is divided into the following three chapters: chapter two is a systematic review comparing how well or effectively RDTs are used across the previously mentioned contexts. Chapter three is a quantitative study that sought to determine how well CHWs performed RDTs, if they maintained their competency at conducting RDTs over time, and if their ability to perform test procedures varied with various socio-demographic measures. Chapter four contains the conclusions and recommendations for policy and research from these works.

Chapter two is a systematic review that addresses a relevant global health issue because comparing the use of RDTs in different environments represents a current gap in knowledge regarding the treatment and diagnosis of suspected malaria cases. The work assesses the diagnostic use of RDTs in four different contexts: health facilities, the community, drug shops and schools, examining how well the tests are executed and how RDTs impact the prescription of antimalarial medication. The quality of RDT use across these contexts and implications for malaria case management is then discussed. This section is a modification of a manuscript that was written in collaboration with Wendy Prudhomme-O'Meara.

Chapter three is a quantitative, longitudinal study conducted in western Kenya. This study evaluated the ability of CHWs to conduct RDTs and to what extent they maintained their competency. The overarching goals of this study were to (i) evaluate the ability of CHWs to safely and correctly administer RDTs, and (ii) determine if CHWs maintain a high level of competence in performing RDTs over a period of time. This chapter was part of a study that was supported by Dr. Wendy Prudhomme-O'Meara, members from the Eldoret Malaria Voucher Study, and various staff at Duke Global Health Institute.

Chapter four combines the conclusions from these works, and summarizes the recommendations to improve malaria case management. It also includes suggestions for achieving the proposed recommendations and future research directions.

2. Use of malaria RDTs in various health contexts across sub-Saharan Africa: a systematic review

2.1 Abstract

The World Health Organization recommends parasitological confirmation of malaria prior to treatment. Malaria rapid diagnostic tests (RDTs) represent one diagnostic method that is used in a variety of contexts to overcome limitations of other diagnostic techniques. Malaria RDTs increase the availability and feasibility of accurate diagnosis and may result in improved quality of care. Though RDTs are used in a variety of contexts, no studies have compared how well or effectively RDTs are used across these contexts. This review assesses the diagnostic use of RDTs in four different contexts: health facilities, the community, drug shops and schools. A comprehensive search of the Pubmed database was conducted to evaluate RDT execution, test accuracy, or adherence to test results in sub-Saharan Africa. Original RDT and *Plasmodium falciparum* focused studies conducted in formal health care facilities, drug shops, schools, or by CHWs between the year 2000 and December 2016 were included. Studies were excluded if they were conducted exclusively in a research laboratory setting, studies where staff from the study team conducted RDTs, or in settings outside of sub-Saharan Africa. The literature search identified 757 records. A total of 52 studies were included in the analysis. Overall, RDTs were performed safely and effectively by community health

workers provided they receive proper training, but analogous information was largely absent for formal health care workers. Tests were generally accurate across contexts, except for in drug shops where lower specificities were observed. Adherence to RDT results was higher among drug shop vendors and community health workers, while adherence was more variable among formal health care workers, most notably with negative test results. Malaria RDTs are generally used well, though compliance with test results is variable – especially in the formal health care sector. If low adherence rates are extrapolated, thousands of patients may be incorrectly diagnosed and receive inappropriate treatment resulting in a low quality of care and unnecessary drug use. Multidisciplinary research should continue to explore determinants of good RDT use, and seek to better understand how to support and sustain the correct use of this diagnostic tool.

2.2 Methods

2.1.1 Database search & screening

A systematic search was performed in the Pubmed database. Web of Science was used to search for missed relevant studies in references and citing articles. Synonyms for 'malaria,' 'RDT,' 'hospital,' 'CHW,' and 'drug shop,' were combined to identify all relevant studies. Please see Appendix A for the complete search syntax. The search was limited to publications from 2000 onwards, and the last search was conducted in

December 2016. There was no restriction placed on outcome or study design. To limit bias in geographic scope no restriction was placed on the language of publication. Two individuals (MRB and WPO) collaborated on screening article titles and abstracts for inclusion and exclusion criteria. A second screening was performed on full-text articles. Discrepant results were discussed between the two individuals until a unanimous decision was reached.

2.1.2 Selection of studies

The criteria for inclusion were: original RDT focused studies conducted in formal health care facilities, drug shops, schools, or by CHWs; studies primarily investigating *Plasmodium falciparum* malaria; studies evaluating one or more of the following steps: test performance by health care providers of interest, accuracy of RDT results performed by health care providers of interest, test interpretation, and adherence to test results by health care providers of interest. *P. falciparum* was the focus of this review because it is the most prevalent on the African continent, results in the highest mortality rates. This study considered the formal health care to be environments that included public and private hospitals, health centers, clinics, and dispensaries. The retail sector included private drug shops and pharmacies staffed by licensed pharmacists or informally trained shop vendors. Schools primary or secondary schools. Use by CHWs was defined as RDT use by non-professional health care workers who provided services at the community level. Execution of tests included the performance of all RDT procedure steps from start to finish and is synonymous with test performance or handling. Execution may be described as 'safe' or 'correct' and it is possible to test the 'quality of execution.' Test safety is a subset of these steps and referred to procedure steps that related to the safety of the health worker or patient. Test accuracy referred to the sensitivity and specificity of RDT results relative to a gold-standard measure. Interpretation referred to correctly reading test results (e.g., not interpreting a positive result as negative or invalid). This study defined adherence as prescribing an antimalarial when a patient was RDT-positive, not providing an antimalarial when RDT-negative.

Exclusion criteria were: studies conducted exclusively in a research laboratory setting, studies where staff from the research team conducted RDTs, and studies outside of sub-Saharan Africa. Studies conducted in a research setting or where study staff conducted RDTs were excluded because this systematic review sought to investigate the use of RDTs in clinical settings by health care workers. Sub-Saharan Africa was the location of interest because of the well-documented burden of *P. falciparum* [1].

2.2 Results

2.2.1 Study characteristics

A total of 757 titles published from 2000 to present were identified from the database search. Full texts of 152 studies were retrieved, of which 111 were not included as a result of the previously stated exclusion criteria. One study written in French was identified and reviewed by one of the collaborators (WPO), though it was excluded as it did not meet the inclusion criteria. Upon completion of the screening process, 41 studies met the inclusion criteria. Eleven additional studies were identified from the references of other studies and included in the review for a total of 52 included studies (Figure 1). No systematic patterns or similarities were observed in these studies, allowing for confidence in the robustness of the search strategy.

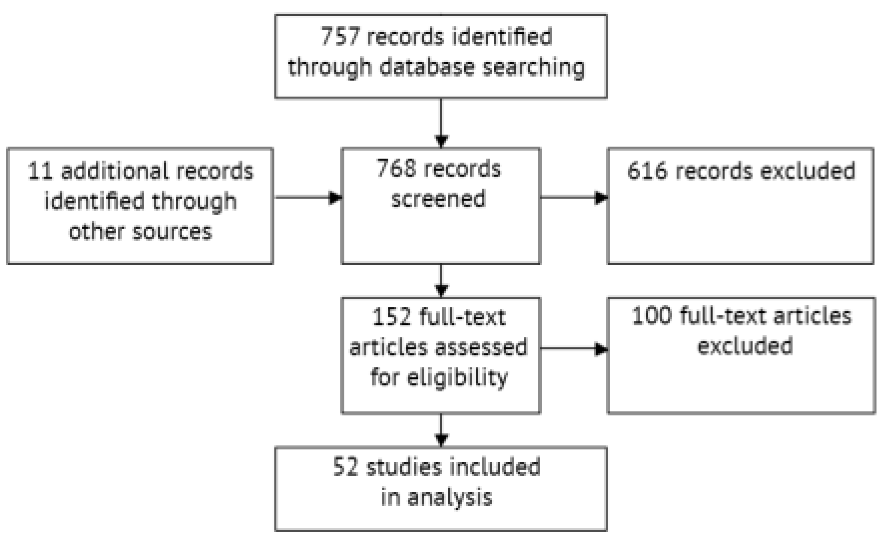

Figure 1: Systematic review study selection flow diagram.

The 11 additional studies may have been excluded because of minor discrepancies between the search strategy and study titles.

2.2.1.1 Geographic characteristics

Geographical restrictions required studies to be conducted in sub-Saharan Africa. Thirteen records were conducted in Tanzania [16,42-53], eight in Uganda [54-61], six in Zambia [22,62-66], three in Burkina Faso [39,67,68], three in Ethiopia [69-71], three in Ghana [72-74], two in Mali [75,76], two in Kenya [77,78], two in Malawi [79,80], two Nigeria [19,81], one in Cameroon [82], one in the Democratic Republic of Congo [83], one in Madagascar [84], one in Mozambique [85], one in Senegal [86], one in Sierra Leone [15], one in South Africa [87], and one in multi-country settings [88].

2.2.1.2 Research context characteristics

The context restrictions allowed for studies to be conducted in four distinct contexts – the formal health care sector, the retail sector, schools, and in the community by CHWs. Thirty of the records reviewed were conducted in the formal health care sector [15,19,22,39,42-48,50-53,55,57,58,67,69,70,73-75,77,78,80,82,85,87]. Nearly all in public or government run hospitals, though a number were conducted in other facilities such as peripheral health centers, outpatient clinics, dispensaries, and community clinics. Of these studies, one contained data regarding RDT performance [87], 20 contained data regarding sensitivity and specificity [15,45-48,50-53,57,58,67,69,70,73-

75,77,80,87], and 14 contained data regarding adherence to results and antimalarial prescription [19,22,39,42-44,50-52,55,79,80,82,85]. Five studies that were included examined the use of RDTs in the retail sector of sub-Saharan Africa [54,56,59,72,81]. Across these studies, one contained data regarding the execution of RDTs [72], two contained data regarding sensitivity and specificity [59,72], and all five contained data regarding adherence to results and antimalarial prescription. Sixteen studies examined the use of RDTs by CHWs at the community level [16,49,60-66,68,71,76,83,84,86,88]. Six of these studies contained data regarding RDT execution [49,63,64,66,71,83], six contained data regarding sensitivity and specificity [16,49,61,68,76,83], and seven contained data regarding adherence to results and antimalarial prescription [49,60,62,64,65,86,88]. Lastly, one study was conducted in a school that investigated RDT execution [79].

2.2.1.3 Research design characteristics

Both experimental and descriptive studies were eligible to be included in this review. Of the 52 records included, two were randomized controlled trials (RCT) [39,51], 12 were cluster randomized trials (CRT) [43,55,56,58,61,64,72,77-79,82,88], one was a randomized cross-over trial [49], two were quasi-experimental studies utilizing a pre-/post-assessment design [42, 54], and 35 were observational studies [15,16,19,22,44-48,50,52,53,57,58,60,62,63,65-71,73-76,81,83-87]. A number of the observational studies were further classified as cross-sectional studies [16,19,22,50,52,60,70,71,74,80,87], longitudinal studies [16,54,63,65], and cohort studies [53,83]. Appendix B shows study characteristics in more detail.

The heterogeneity of study design, context, and outcomes limited the degrees of freedom, making quantitative methods such as meta-analysis, infeasible and inappropriate. Studies are therefore described and reported in the following narrative.

2.2.2 Formal health care sector

Only one of the studies directly investigated the execution of RDTs in the formal health care setting [87]. This study demonstrated that nurses and nursing assistants were not proficient in the safe execution of RDTs, only correctly performing between 8% and 84% of the 14 procedure steps. The reporting of these data made it impossible to determine if any health worker completed all 14 steps correctly, but eight of the 14 steps were completed by at least 70% of the workers. Of importance, less than 80% of the health workers put on a new pair of gloves, checked the test expiration date, used a sterile lancet to prick the patient's finger, properly disposed of the used lancet, dispensed the buffer correctly, waited the correct amount of time to read results, and correctly interpreted results. One additional study that included interviews with health care workers also presented results about self-reported RDT performance [19]. The researchers found that of the 32 nurses interviewed, 6.3% (n=2) practiced unsafe handling or disposal of sharps, 31.3% (n=10) had difficulty drawing and collecting blood samples, 25% (n=8) had difficulty transferring blood to the test device, and 15.6% (n=5) read results too soon (defined before 15 minutes had elapsed).

Sensitivity and specificity of RDT results from these clinical settings were variable (Table 1). Most the studies used microscopy as the gold-standard comparator and demonstrated sensitivities ranging from 64.8% - 100%, whereas specificities ranged from 39% - 99.7%. However, most studies reported sensitivities of at least 90% and specificities of at least 80%. Two studies used PCR as the gold-standard and reported sensitivities and specificities within the same range of values [50,52].

Fourteen of the 30 studies conducted in this context investigated the appropriateness of treatment following RDT diagnosis, defined as the prescription of antimalarial medication in the event of a positive RDT, and withholding antimalarials in the event of a negative RDT. These studies found that adherence to RDT results was generally good, and improved over time as RDT use became more widespread (Figure 2). Appropriate treatment ranged from 54.4% [51] to 99.9% [52]. Four of these studies [19,42,52,55] showed that all patients who tested positive for malaria using an RDT received appropriate antimalarial medication; several other studies reported similar results, with greater than 95% of all RDT-positive patients receiving antimalarials

Table 1: Reported RDT sensitivity and specificity data for included studies. [1]

Author	Year	Sensitivity (95% CI)	Specificity (95% CI)
Formal Health Care Sector			
Ashton	2010	85.6%	92.4-92.7%
Baiden	2012	100%	73.0% (67– 78)
Chinkhumba	2010	90-97%	39-68%
Diarra	2012	89.6% (88.1-90.9)	81.1% (78.8-83.2)
Gerstl [a]	2010	99.4% (96.8-100.0)	96.0% (91.9-98.4)
Gerstl [b]	2010	98.8% (95.8-99.8)	74.7% (67.6-81.0)
Guthmann	2002	97%	88%
Hopkins [a]	2007	85%	99.8%
Hopkins [b]	2007	92%	93%
McMorrow	2008	64.8%	87.8%
McMorrow	2010	90.7%	73.5%
Moonasar	2009	85%	96%
Morankar	2011	93%	99.4%
Msellem	2009	94%	88%
Mtove	2011	97.5% (96.9–98.0)	65.3% (63.8–66.9)
Nicastri [p]	2009	69.2%	100%
Osei-Kwakye	2013	97.7% (95.8–99.0)	58.1% (53.8–62.3)
Ouattara	2011	97.2%	95.4%
Shakley	2013	78.6% (70.8–85.1)	99.7% (99.5–99.9)
Shakley [p]	2013	76.5% (69.0– 83.9)	99.9% (99.7– 100)
Shekalaghe	2013	94.7% (89.8-97.3)	95.6% (94.2-96.6)
Retail Sector			
Ansah [c]	2015	98-100%	30-98%
Mbonye	2015	91.7%	63.1%
Community Health Workers			
Ishengoma [c]	2011	88.6%	88.2%
Ishengoma [d]	2011	63.4%	94.3%
Mubi	2011	85.3%	59.8%
Ndyomugyenyi [e]	2016	72.1%	83.3%
Ndyomugyenyi [f]	2016	20.8%	98.1%
Ratsimbasoa [e]	2012	90.2% (81.7-95.7)	87.2% (78.3-93.4)
Ratsimbasoa [f]	2012	93.7% (69.8-99.4)	83.3% (35.9-99.6)
Tiono	2013	97.9% (96.3-98.8)	53.4% (49.1-57.7)
Willcox	2009	82.9% (78.0-87.1)	78.9% (63.9-89.7)

[22,39,44,51,80,85]. Only three studies showed less than 90% of RDT-positive patients receiving appropriate antimalarial medication [43,50,82].

Though the results for inappropriate treatment – defined as the proportion of patients inappropriately receiving antimalarials following a negative RDT result – were much more variable, generally, the proportion of RDT-negative patients not receiving antimalarials increased over time (Figure 2). Studies showed that the percentages of patients receiving antimalarials inappropriately ranged from 0.1% [52] to 81% [39], although most studies reported significant percentages of patients receiving inappropriate antimalarial treatment. Ten of the 14 studies reported at least 10% of RDT-negative patients receiving antimalarial drugs [19,22,39,42,50,51,55,78,80,82].

---

[1] Most studies used microscopy as a gold-standard, those that used PCR are denoted with a *p*. Two studies [15,58] used two different types of RDTs and calculated separate sensitivities and specificities for each; RDT sensitivity and specificity using a pLDH RDT is denoted with an *a*; RDT sensitivity and specificity using a HRP-2 RDT is denoted with a *b*. Another study [16] included sensitivity and specificity data from a cross-sectional study nested in a larger longitudinal study; RDT sensitivities and specificities from the longitudinal study are denoted with an *c*; RDT sensitivities and specificities from the cross-sectional study are denoted with a *d*. Two studies [61,84] included sensitivity and specificity data from different transmission seasons; RDT sensitivities and specificities from higher-transmission seasons are denoted with an *e*; RDT sensitivities and specificities from lower-transmission seasons are denoted with a *f*. Ansah et al. reported sensitivities and specificities of individual drug shops, but not an overall value for either measure [72]. As such, a range of sensitivities and specificities is reported. Confidence intervals were included if reported in the original study.

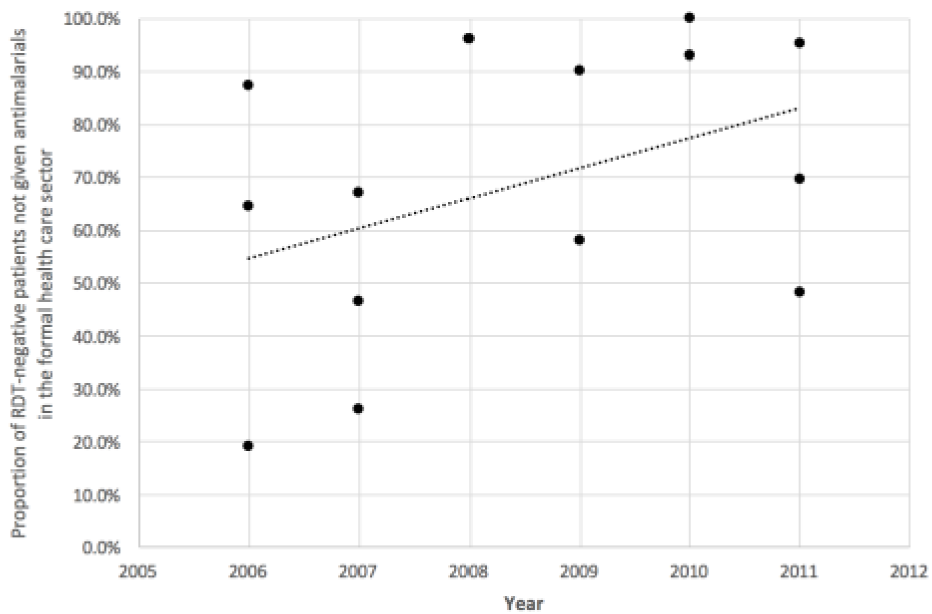

Figure 2: Temporal trend in the proportion of RDT-negative patients not treated given antimalarials in studies conducted in the formal health care sector.

2.2.3 Retail sector

The studies conducted in the retail sector most often focused on evaluating the impact of RDTs on antimalarial drug prescription, drug shop vendor (DSV) adherence to RDT results, referral practices, and overall appropriateness of treatment. One study produced results with data about the execution of RDTs [72]. Ansah and colleagues directly observed testing in the shops and reported that medicine retailers adhered largely to safety instructions. The vendors performed well across all 18 safety indicators assessed in the study, ranging from 87.2% to 100% of steps completed correctly [72].

Results for the accuracy of RDTs in the retail sector suggested that sensitivity was high, ranging from 91.7% to 100% when using microscopy as a gold-standard (Table 1) [59,72]. Specificity results were much more variable. One study reported that in the 28 shops using RDTs, most had specificities between 73% and 98% [72]. However, 3 of the shops reported low specificities of 30%, 31%, and 52% [72]. The other study yielded similar results where researchers re-read tests that were stored and found a low specificity of 63.1%, with a high number of false-positive tests [59]. In this study, over one-third of RDT-positive clients were parasite negative by expert microscopy [59].

Studies investigating prescription of antimalarials following an RDT showed that DSVs generally provided treatment in accordance with the RDT results (Table 2). Results from these five studies show that appropriate treatment based on RDT result was as low as 55.4% in a study conducted in Nigeria [81], to 98.8% [59]. The remaining studies all showed that drug shops supplied appropriate treatment to at least 80% of tested patients. It should also be noted that the low end of this range was produced by a study involving only 1 intervention-drug shop. Furthermore, one of these studies was conducted in Ghana where the sale of antibiotics over the counter is not permitted by law [72]. In other contexts, where antibiotics are readily available over-the-counter, a shift to the prescription of antibiotics instead of antimalarials is probable.

Table 2: Appropriate treatment overall, RDT-positive and RDT-negative results. [2]

Author	Year	Appropriate Treatment (%)	Positives Treated (%)	Negatives Not Treated (%)
Formal Health Care Sector				
Bastiaens	2011	90.4%	100.0%	90.0%
Batwala	2011	88.5%	100.0%	76.6%
Bisoffi	2009	60.7%	97.7%	19.0%
Bottieau	2013	93.4%	95.1%	92.8%
Chinkhumba	2010	86.9%	98.0%	57.9%
Cundill	2015	91.4%	80.3%	95.1%
Hamer	2007	78.7%	96.6%	64.5%
Mansanja	2010	95.9%	95.8%	96.0%
Mbacham [a]	2014	56.1%	72.1%	48.1%
Mbacham [b]	2014	70.8%	72.9%	69.4%
Nicastri	2009	66.4%	55.6%	67.0%
Reyburn	2007	54.4%	98.9%	46.3%
Shakely	2013	99.9%	100.0%	99.9%
Skarbinski	2009	88.0%	92.9%	87.2%
Uzochukwu	2011	60.0%	100.0%	25.9%
Retail Sector				
Ansah	2015	97.7%	99.5%	93.8%
Awor	2015	91.1%	93.5%	82.8%
Cohen	2015	80.0%	83.3%	56.3%
Ikwuobe	2013	55.4%	100.0%	48.4%
Mbonye	2015	98.8%	99.0%	98.5%
Community Health Workers				
Chanda	2011	98.4%	98.4%	98.4%
Hamainza	2014	83.2%	61.6%	98.0%
Hamer	2012	99.3%	98.5%	99.6%
Mubi	2011	96.8%	99.7%	93.9%
Mukanga	2011	96.7%	96.5%	97.5%
Mukanga	2012	99.1%	99.9%	95.1%
Thiam	2012	-	96.6%	-

Similar to the formal health care sector, results from these studies showed that inappropriate treatment of RDT-negative patients with antimalarials was more variable than appropriate treatment of RDT-positive clients. Two studies suggested that over 90% of RDT-negative individuals did not receive antimalarials [59,72], while other studies showed that nearly half of all RDT-negative individuals inappropriately received antimalarials [56,81].

2.2.4 Community health workers

Sixteen studies examined the use of RDTs by CHWs. The studies included were heterogeneous in study design and highly variable in size, ranging from eight CHWs to 408 CHWs. One of the included studies sought to investigate whether CHWs could prepare and interpret RDTs accurately and safely using manufacturer's instructions alone, or if additional job aids improved performance [66]. These researchers found that CHWs completed 57% of the 16 steps correctly using only the manufacturer's instructions, 80% with a job-aid, and 90% with a job-aid plus training. CHWs using only the manufacturer instructions frequently documented the test incorrectly, forgot to check the test expiry date, frequently did not use gloves, and inappropriately discarded used materials. These errors in use, though still committed by CHWs receiving

---

[2] *'a'* denotes appropriate treatment for clinicians in the basic intervention group of the Mbacham study; *'b'* denotes appropriate treatment for clinicians in the enhanced intervention group of the Mbacham study [82]. Thiam and colleagues did not report the number of negatives not treated, making the calculation of the total amount of appropriate treatment inappropriate [86].

Sixteen studies examined the use of RDTs by CHWs. The studies included were heterogeneous in study design and highly variable in size, ranging from eight CHWs to 408 CHWs. One of the included studies sought to investigate whether CHWs could prepare and interpret RDTs accurately and safely using manufacturer's instructions alone, or if additional job aids improved performance [66]. These researchers found that CHWs completed 57% of the 16 steps correctly using only the manufacturer's instructions, 80% with a job-aid, and 90% with a job-aid plus training. CHWs using only the manufacturer instructions frequently documented the test incorrectly, forgot to check the test expiry date, frequently did not use gloves, and inappropriately discarded used materials. These errors in use, though still committed by CHWs receiving additional training, were much less frequent. This finding was supported by other researchers who evaluated how well CHWs performed RDTs, and found that CHWs who received extended training and supervision significantly out-performed their counterparts with 39.1% (34/87) of these CHWs completing greater than 80% of the steps correctly compared to 21.0% (16/76) of CHWs who did not receive this additional training [71]. Subsequent studies used trained observers to assess CHW performance, with attention to blood- and patient-safety concerns [63,64,83]. These studies showed that between 76% and 100% of CHWs safely completed critical steps in the RDT procedure based on structured, study specific observation checklists, and all reported that CHWs demonstrated the ability to perform RDTs safely and effectively. An additional two studies [49,68] also concluded that adequately trained and appropriately resourced CHWs can perform and interpret RDTs at an acceptable level, but did not explicitly investigate the safety of RDT handling by CHWs.

In a longitudinal study involving 61 CHWs, Counihan and colleagues found that median CHW performance remained steady or improved over time for critical steps, non-critical steps, and RDT interpretation, and that the median percentage of critical RDT steps performed correctly rose from 87.5% at 3 months to 100% at 6 and 12 months [63]. The only measure that did not improve involved the ability to correctly interpret RDT results. Using photographs of 10 different RDT results, CHWs correctly identified 96.5% of positive tests at 3 months and 98.3% at 6 months, but only 90.5% at 12 months. Similarly, CHWs improved from correctly identifying 94.3% of negative results at 3 months to 97.9% at 6 months, but regressed to 94.7% at 12 months. Community health workers' interpretation of invalid test results improved from 90.2% correct at 3 months to 96.7% at 6 months and 96.5% at 12 months. The same pattern held for the interpretation of faint-positive test lines as positive, which improved from 89.7% at 3 months to 96.7% at 6 months, but then declined to 76.7% at 12 months. Taken together, these results indicate acceptable execution of RDTs by CHWs, which is enhanced by training, regular supervision, and feedback, and that these skills are maintained over time, presumably through practice.

Six studies included data on the sensitivity and specificity of RDTs when used by CHWs, all of which used microscopy as the gold-standard. Sensitivities of the tests ranged from 20.8% to 97.9 %, specificities from 53.4 % to 98.1% (Table 1). Five of the six reported sensitivities over 80%, while four of the six reported specificities greater than 75%. The lowest sensitivity was recorded in a trial conducted during a low-transmission season, though the researchers also reported a higher sensitivity in a season with higher rates of malaria transmission [61].

Seven of the 16 studies involving CHWs investigated the appropriateness of treatment and showed that CHWs display high levels of adherence to treatment guidelines (Table 2) [49,60,62,64,65,86,88]. Six of the seven studies showed that greater than 95% of RDT-positive patients received an antimalarial [49,60,62,64,86,88], and only one study [49] showed greater than 5% of RDT-negative patients received an antimalarial.

2.2.5 Schools

One study was conducted by Witek-McManus and colleagues in a primary school [79]. This pre-/post-evaluation involved 107 teachers in southern Malawi and ultimately assessed whether trained teachers executed RDTs correctly, provided appropriate treatment with ACT, and whether this competence was retained up to seven months post-training. Following the final training, teachers completed an average of 93% (19.5/21) of RDT steps correctly. Furthermore, apart from checking the expiry date of the RDT, each step was correctly carried out by ≥80% of teachers. The results of this study showed that teachers could safely perform RDTs and accurately interpret results. Furthermore, this competence was retained over the seven-month timeframe, though some procedural errors did arise over the seven months that have implications for monitoring RDT performance by teachers and future studies involving similar populations.

2.3 Discussion

This review examines how well malaria RDTs are executed and how their use impacts the prescription of antimalarial medication in different contexts – the formal health care sector, in the community, in the retail sector, and in schools. Current knowledge suggests that this is the first study comparing multiple aspects of the use of RDTs (execution, accuracy, and adherence) in these distinct contexts across sub-Saharan Africa.

2.3.1 Formal health care sector

Rapid diagnostic tests are becoming increasingly common in the formal health care sector. Although microscopy has long been the standard of care in clinical settings, it requires technical expertise, a functional microscope, electricity, and specialized reagents [14], which may not be available in a large fraction of lower-level facilities. The use of RDTs also offers considerable cost advantages when compared to microscopy [35]. Furthermore, even when microscopy is available, time and human resource constraints may prevent testing of every suspected malaria fever when patient volume is high. As a result, there is increasing investment in scaling-up the use of RDTs to expand malaria testing coverage.

This review highlights a lack of data pertaining to the execution of RDTs in the formal health care sector. The limited data available in the peer-reviewed literature suggest that RDTs may not be consistently performed in a safe or effective manner [87]. The literature is more robust as it relates to sensitivity and specificity, and the effect of RDT use on antimalarial prescription practices. Most studies reported sensitivities of at least 90% and specificities of at least 80% for RDTs executed by health workers during routine care. Despite adequate accuracy, adherence to RDT results, particularly negative results, is sub-optimal. More than half of the studies reported that at least 30% of RDT-negative clients received an antimalarial. Several studies have emphasized a level of skepticism towards RDT results, both among patients and clinic staff, due to a high rate of negative RDT results, as compared with the expectations of both patients and providers [91,92] which likely contributes to poor adherence. This distrust is heightened when RDT-negative patients later test positive by microscopy, which may be attributed to rare occurrences of other malaria species, HRP-2 deletions, or excess parasite antigens (known as the 'prozone effect') [93], but more likely, are simply due to poor clinical microscopy that results in an incorrect diagnosis. Other work has shown that formal health care workers require experience with positive RDT results before they have high levels of confidence in test results, both negative and positive, which may increase adherence to test result [51,94]. This observation offers one plausible explanation for the increase in adherence to RDT results in the formal health care sector over time.

Patients' expectations may impact health care workers' adherence to RDT results. Patients may expect to be treated for malaria, regardless of test results [91]. Most health care workers acknowledged that this issue was prevalent and problematic, articulating pressures to inappropriately overprescribe antimalarials to RDT-negative patients. This pressure may be amplified when health care workers lack specific guidelines or tools to aid in the diagnosis and treatment of non-malarial febrile illness, especially when presented with a seriously ill patient [92]. This highlights the need for specific guidelines for treating febrile illness, especially with regard as to how health workers should proceed in the event of negative test results.

2.3.2 Retail sector

Though formal health care facilities may see the majority of malaria cases, provide higher quality care, and provide a wider range of services, long wait and travel times often result in patients seeking care elsewhere. In some malaria endemic areas as much as 80% of all suspected malaria cases are treated outside of the formal health care sector. In many cases, retail outlets represent the first and only place of treatment, owing to their accessibility, affordability, and orientation towards satisfying consumer needs [95-99]. Though few of these outlets are staffed by licensed pharmacists – more often staffed by informally trained vendors [100,101] – an estimated 50% of all antimalarial medication is distributed through drug shops [95,96]. As such, it is important to consider the use of RDTs in the retail sector, especially their potential role in improving the quality of care and targeting antimalarials to confirmed malaria cases.

Despite their importance in fever management, we identified only 5 studies of RDTs in retail medicine outlets. Furthermore, only one of these examined the execution of RDTs and two reported sensitivity and specificity data. The results suggest that RDTs are safely executed by DSVs, and that RDTs are highly sensitive in this context, but lack specificity [72]. High rates of false positives may ultimately undermine confidence in RDT results and diminish the perceived importance of testing before taking antimalarials. Reducing these situations is crucial to the wide-spread use of RDTs as they work to undermine confidence in RDT results and the test-and-treat guidelines, ultimately challenging the current treatment recommendations [73]. This raises the concern about how to monitor RDT use in a sector that is often poorly regulated.

Adherence to reported RDT results in the retail sector was high, indicating that RDTs may improve the quality of care and reduce overuse of antimalarial drugs in this context. In 4 of the 5 studies, 80% or greater of the patients received appropriate treatment, while a single study involving only one intervention shop reported substantially lower rates of appropriate treatment [80].

There are a number of additional considerations that must be acknowledged within this specific context. For DSVs, a primary consideration is whether RDTs are viewed as a valuable retail product. As opposed to public health facilities, drug shops, and pharmacies are established for profit. As a result, asking DSVs to restrict the sale of ACT exclusively to RDT-positive clients may present a conflict of interest [72,80]. Furthermore, the provision of RDTs in the retail sector potentially raises a new set of issues and challenges such as the management of severe illnesses, appropriate treatment of RDT-negative fever cases, and referral of patients. Work has shown that within drug shops there is limited awareness of current treatment and diagnosis guidelines, a lack of training in national guidelines, a lack of reference materials, limited record keeping, and weak linkages with the formal health care system [102].

From a patient perspective, it is important to recognize that patients come to the retail sector to purchase a product (i.e., antimalarial medication), as opposed to seeking a diagnosis. Thus, patients have different expectations for the care they will receive in this context [72]. One study suggested that patients may be more inclined to purchase an antimalarial medication, despite RDT-negative status, if it had been recommended by a health professional compared to self-referral, if there was a positive malaria lab test prior to presenting to the drug shop, if the patient had experienced fever in the last 48 hours, and if the patient's educational level was primary school education or less [80]. Another consideration is whether patients trust the RDT results from the retail sector. Isiguzo and colleagues noted that when patients were asked which settings could be trusted to provide RDTs, most individuals indicated formal health care facilities, while diagnostic laboratories and pharmacies received lower marks [103].

Lastly, from a broader policy perspective, it is critical to note that a positive RDT result does not necessarily translate into the purchase of ACT. Individuals who frequent drug shops are more likely to purchase substandard, non-ACT antimalarials [103]. DSVs continue to sell non-ACT antimalarials, perhaps due to client demand. Several studies have shown that retail outlets tend to respond to customer demand, and that DSVs may avoid referring patients for confirmatory blood tests because they fear losing business due to added inconvenience, cost, or both [104]. As a result, client preferences for presumptive treatment and non-recommended drugs may be major factors in seeking care in the retail sector, both of which contradict the intent of using RDTs in this context [105].

2.3.3 Community health workers

Many individuals with suspected malaria in sub-Saharan Africa die without contact with formal medical services, especially in rural and other medically underserved areas [106,107]. For this reason, the World Health Organization has recommended home-based management of malaria (HMM) by CHWs [108] to increase prompt malaria diagnosis and treatment and decrease malaria-related mortality. Through this strategy, lay health persons receive education about the treatment of malaria, the administration of antimalarial drugs, as well as the recognition of severe illness, and are provided medications to distribute to patients [108,109]. Though this approach initially relied upon presumptive treatment, it now abides by the more recent test-and-treat recommendations, relying heavily on the integration of RDTs into HMM programs [110,111].

The services provided in the community by CHWs play an important role in increasing health care coverage and may also reduce workload in the formal sector [112-114]. Therefore, it is important to understand how RDTs are used by CHWs and how their use impacts treatment. The current literature demonstrates that RDTs are performed safely when proper training is provided, that RDTs are generally highly sensitive and specific when executed by CHWs, and that CHWs display high levels of adherence to treatment guidelines. Several of the included studies showed that supplying CHWs with additional training and job aids significantly improved their performance of RDT procedures [64,66,71]. Still, while these results may give cause for optimism, the literature is not as extensive as that in the formal health care sector and some concerns remain. These apprehensions arise from uncertainty in the competence of CHWs due to their education levels and novel, additional responsibilities [62,116]. Most frequent these concerns center around test monitoring as it relates to blood safety, ability to interpret test results correctly, and inappropriate prescription of antimalarial drugs [63,115,116].

Storage conditions represent another crucial aspect that must be given consideration when deploying RDTs at the community level, as their accuracy is directly linked to their storage conditions [16]. One study that examined the storage and long-term stability of RDTs in the community found that they were kept under conditions sufficient for high performance and long-term stability [84], however, strategies for monitoring and enforcing adequate storage conditions in large-scale implementation programs are needed.

2.3.4 Schools

With malaria disproportionately affecting children and increasing levels of enrollment in primary schools throughout sub-Saharan Africa, a practical opportunity to improve timely diagnosis and treatment with antimalarials in schools has been recognized. Building upon the observed successes of training lay-persons as CHWs some researchers have proposed to do the same with school teachers [79]. Though only one study was conducted in this context, it demonstrated teachers could execute RDTs well and accurately interpret results. Additional research is needed to determine how RDT in schools may impact the prescription of antimalarials.

There are some obvious limitations and additional considerations to this approach. On the one hand, children suffering from malaria may not attend school and would not benefit from this strategy. Conversely, parents may decide to send their febrile children to school knowing they can be tested and treated at school, though this may raise concerns pertaining to the well-being of the child. Furthermore, in the case of non-malarial febrile-illnesses (i.e., viral), the presence of a sick child could place other children at risk. Additionally, taking time out from regular duties of teachers to care for sick children could prove problematic; the added responsibility of performing an RDT may result in teachers underperforming in more routine classroom responsibilities. Lastly, in terms of patient care and adherence to RDT results, the key to making this strategy successful would be ensuring adequate communication with the parent regarding test results. This means providing teachers with guidelines for how to advise on appropriate medication and follow-up care.

2.3.5 Comparison across contexts

Results from this review show that data in the peer-reviewed literature describing the safe and correct execution of RDTs is lacking. It is assumed that formal health care workers can safely and properly execute RDTs, though the one study examining this suggested otherwise [87]. Furthermore, interviews with health care workers revealed that some do struggle with the RDT procedures, especially with steps regarding the collecting and transferring of blood samples [19]. Though the retail sector and drug shops have a reputation for delivering lower standards of care [117], the studies reviewed show that DSVs execute RDTs well [72,118]. For laypersons, feedback, supervision, and hands-on experience improved and helped maintain safety skills and adherence to RDT procedures. Across all contexts, the steps most commonly performed incorrectly pertained to the collection and transferring of blood samples, and the documentation of test results. Neither of these steps directly relates to patient safety, though the former could compromise the accuracy of the test results.

Accurate diagnosis is critical in the management and treatment of malaria. The results of this review showed that the diagnostic accuracy of RDTs for *P. falciparum* can be high in all the considered contexts. Sensitivities as high as 100% [73], 100% [72], and 97.7% [68], and specificities as high as 100% [50], 98% [72], and 94.3% [16] were observed in the formal health care sector, retail sector, and community level respectively. However, several studies conducted also reported low sensitivities and specificities, which could lead to the incorrect management of febrile illness. Low sensitivities may be caused by a variety of reasons such as user errors (e.g., collecting inadequate amounts of blood, misinterpreting RDT results, etc.), comparing RDT results against an imperfect gold-standard [45], and low parasite densities. Comparing RDTs to PCR results may also result in lower apparent sensitivities, as PCR can detect parasite DNA remaining in a patient's blood after an infection has been cleared, or detect very low-density (submicroscopic) infections that are possibly not a relevant comparison for RDT performance [119]. Specificity may also be impacted by user errors and comparing RDT results against imperfect gold-standards, but recent malaria infections, and patient factors – such as rheumatoid factor positivity [90] – may also contribute to low specificities.

When comparing adherence to RDT results across contexts, the results of this review indicate that DSVs and CHWs generally have the highest adherence to test results and appropriately prescribe antimalarials most frequently, while adherence to RDT results is more variable in the formal health care sector. A recent systematic review conducted by Kabaghe and colleagues found similar results [120]. They concluded that RDTs have a high diagnostic accuracy, and that overall compliance to test results is fair, though lower cadres of health workers (I.e., CHWs and DSVs) displayed higher rates of adherence. The overall appropriate treatment in the formal health care sector is commonly affected by high percentages of RDT-negative patients still receiving antimalarial medications [19,39,51,82].

Another important factor to consider is how RDTs change the actual and perceived roles of those performing RDTs. For example, introducing RDTs in formal health facilities likely does not substantially change the role of the health care provider or expectation of the patient. But, when examining how RDTs impact the roles of CHWs and DSVs, they fundamentally alter what services can be offered to clients. For the former, RDTs greatly expand CHW services and modifies their role from providing predominantly health promotion to curative services. For the DSVs, it is more complicated. As previously discussed, individuals generally do not go to shops for a disease diagnosis – they go to purchase a specific drug or commodity. Thus, if a patient is seeking a diagnosis, offering RDTs represent additional services that not all drug shops may offer, making some businesses more attractive to customers. Conversely, RDTs may be a low volume commodity if customers do not necessarily want a diagnosis at a drug shop, but would prefer to exclusively purchase medication instead [56]. Still, if shops are expected to treat positive clients and refer negative clients to health facilities, DSVs may be placed in a position in which they must choose between making a profit or following guidelines. Furthermore, if an RDT-negative client already suspects that their illness is malaria but are refused antimalarial medication by the shop owner, they may seek antimalarial drugs at another shop that does not test or is known to stray from treatment guidelines.

Several concerns transcend the various contexts, perhaps most notably quality assurance and long-term sustainability of RDT use. These are especially challenging when considering wide-scale implementation at the community level and in the retail sector. Predicting how RDTs will be used outside of a closely monitored research context is difficult. Far more experience has accumulated from RDT implementation in the formal health sector than other contexts. In all contexts, but particularly the community, continuous supervision and maintaining consistent supplies of RDTs are costly and logistically challenging [121]. Additionally, in the retail sector, drug shops often have no explicit link to the formal health care sector, and monitoring RDT use could require formalizing this connection or increasing regulation.

Successful introduction and scale-up of new health technologies should be supported by policy and implementation frameworks that promote correct RDT use [89] by addressing common implementation issues such as training, supplies distribution, clinical guidelines, and supervision. Inconsistent or ambiguous frameworks may lead to inappropriate use of diagnostic technologies, which could directly impact their effectiveness. In addition, use of RDTs in public health programming requires sustained financial mechanisms to protect against RDT and antimalarial stock-outs [10,89]. In all sectors, problems with erratic availability of RDTs and antimalarials have been reported. Indeed, five of the studies noted RDT or antimalarial stock-outs affecting the care provided by formal health care facilities [42-44,55,82], and several studies involving CHWs also noted RDT or medication stock-outs [62,63,88].

2.3.6 Limitations

This review is not without limitations. First, the risk of bias was not assessed for the studies included. Consequently, we have not taken into account quality of evidence in these studies. Secondly, very few studies have been conducted in schools and the retail sector. Additionally, this review did not include gray literature. This may have limited the data included in this review. For example, only one of the identified studies in the formal health care sector investigated the safety of RDT use, though relevant information may appear in unpublished reports conducted by ministries of health or non-governmental organizations. Studies were also included regardless of sampling strategy or sample size. Small studies are likely to have lower external validity than studies with larger enrollment or stronger design. Lastly, some outcomes lacked standardized criteria. Sensitivity and specificity outcomes are highly dependent on the gold-standard used as a comparison method. Typically, this was microscopy, the quality of which almost certainly varied between studies. Therefore, comparisons of sensitivity and specificity between studies may be confounded by these differences. Other outcomes lacking standardized criteria included checklists evaluating RDT safety and appropriate treatment

2.4 Conclusion

RDTs are used safely and effectively by CHWs, though additional research should be conducted to make the same conclusions for RDT use in the formal health care sector and retail sector. RDTs have a high diagnostic accuracy across contexts, although a worrying trend of lower specificity in the retail sector needs to be examined. Adherence to RDT results is generally high, though compliance with results tends to be lower amongst RDT-negative patients treated in the formal health care sector.

The ultimate impact of RDTs on malaria case management varies between the contexts in which care is sought, but may be linked to the nature of the client-provider interaction. Multidisciplinary research should continue to explore long-term trends and strategies to maintain safety and quality of RDT use during scale-up, especially in the retail sector and community, with an appreciation for the factors that may differ in individual contexts.

3. Evaluation of RDT use by community health workers: a longitudinal study in western Kenya

3.1 Abstract

Malaria rapid diagnostic tests (RDTs) are a simple, mobile technology that hold the potential to dramatically improve the diagnosis and subsequent treatment of malaria. Though they are becoming an increasingly common diagnostic tool, their use by community health workers (CHWs) remains in question due concerns about long-term trends relating to blood safety, the interpretation of test results, and adherence to treatment protocols. This study assessed if CHWs maintained their competency at conducting RDTs over a 12-month timeframe, and if this competency varied with specific socio-demographic measures. 271 Kenyan CHWs were trained, and 103 were recruited for follow-up assessments 12 months later. Community health workers performed RDTs at acceptable levels, with at least 80% of CHWs completing 18 of the 22 steps correctly. Performance as it related to the completion of all steps, safety steps, accuracy steps, and critical steps did not decrease over the 12 months. Socio-demographic characteristics including being younger than 50 years of age, and prior experiences conducting RDTs were found to be associated with better performance over time. Community health workers interpreted RDTs accurately, especially when considering only strong-positive and negative test results. Training in using Deki reader devices was associated with better performance in interpreting RDT results. These

results provide evidence that CHWs perform RDTs safely, that they maintain competency for at least 12 months, and that certain factors may be associated with better performance.

3.2 Introduction

While coordinated efforts to control malaria have resulted in a decline in the burden of disease in many sub-Saharan African countries, including Kenya, malaria remains a common disease diagnosis, especially in children under five years of age who remain most at risk of frequent and severe malaria episodes with high mortality.

Previous studies have demonstrated that CHWs can safely and accurately use RDTs after receiving training and instruction [63,66,123,124]. Still, as previously referenced, concerns remain pertaining to the long-term use of RDTs by CHWs due to gaps in knowledge regarding the monitoring of the quality of testing. Concerns that have been most commonly noted in literature relate to blood safety, the ability to correctly interpret test results, and adherence to treatment protocols [60,63,83,116,124]. Furthermore, concerns have been raised about test performance when RDTs are performed by persons belonging to certain socio-demographic categories, such those with limited formal education [124].

As such, the following work was completed to determine if CHWs maintain their competency at conducting RDTs over time and if this ability varies with various socio-demographic measures. The overarching goals of this study was to (i) evaluate the ability of CHWs to safely and correctly administer RDTs 12-months post training, (ii) examine which, if any, steps are frequently performed incorrectly; (iii) determine if ability varies with socio-demographic characteristics; (iv) determine if CHWs maintain a high level of competence in performing RDTs over a period of time from training; and (v) evaluate if CHWs demonstrate high levels of competence in interpreting malaria RDT results 12-months after training.

3.3 Methods

3.3.1 Study site and context

This study ran from June 2015 to July 2016 in sixteen communities in Bungoma East sub-county and Kiminini sub-county in western Kenya. Bungoma East sub-county is part of Bungoma County, located in western Kenya roughly 50km east of the Ugandan border [125]. Kiminini sub-county is located in Trans-Nzoia County, which is directly northeast of Bungoma County. Most Inhabitants of the counties live below the poverty line and are farmers that grow cash crops such as sugar cane, tobacco, onions, and tomatoes [125,126]. Malaria transmission is moderate to high in each location, with a seasonal peak following the rainy season from March to May [125,126].

3.3.2 Community health worker training

Volunteer CHWs from the intervention arm of a larger cluster-randomization trial were invited to participate in this study. Community health workers were officially affiliated with the Kenyan government and part of the government community health strategy. Between June to September of 2015, 271 CHWs were trained using a validated 3-day curriculum derived from materials from the Kenyan Ministry of Health, in conjunction with practical, skills-oriented training sessions. Training personnel included members of the study team, nurses, public health officers, members of the sub-county health management team and peer mentors with extensive experience administering RDTs during previous studies. The CHWs who successfully completed the training were equipped with bags containing a 3-month supply of RDTs (CareStart Malaria HRP2 (Pf); AccessBio Inc., USA), assay buffer, lancets, bulb type pipettes, gloves, alcohol swabs, cotton wool, a sharps disposal container, a non-sharps disposal bag, a place mat and vouchers for subsidized antimalarial drugs to give to patients in the event of a positive malaria RDT result.

Several of these CHWs received additional training on how to use a small, automated, battery-operated device known as a Deki Reader (Fio Corporation, Toronto, Canada) [53]. These devices were developed to improve the interpretation of RDTs through image analysis software. They used the Deki reader during routine use of RDTs for a period of approximately one month between July 2015 and April 2016.

3.3.3 Baseline data collection

Baseline data was collected using a standardized checklist. The checklist divided the rapid diagnostic test procedure into 22 steps (Table 3). Observers watched CHWs conduct the RDT procedure, noting whether the CHW performed each step correctly, incorrectly, or not at all. Socio-demographic measures including: gender, age, highest education level attained, time employed as a CHW, prior training in malaria case management, and prior experiences with RDTs were collected at this time. Several CHWs reported completing 'Other Certificate Programs.' In these instances, CHWs were recorded as having completed primary school.

3.3.4 Recruitment of participants for follow-up observation

In June of 2016, CHWs who had completed training were recruited for a follow-up assessment. Based on previous work, test quality, defined as a relative percent change in completion of a step, may be expected to change from between 4 and 20% over a 12-month period [63]. Assuming that at completion of their training CHWs performed all 22 steps correctly (SD=1), a minimum of 90 CHWs were required to detect a 10% reduction in test quality, defined as a 10% reduction in average number of steps completed correctly, with 80% power and the probability of committing a Type I error equal to 5%.

Table 3: Checklist of steps required to correctly and safely prepare and perform a malaria rapid diagnostic test. [1]

No.	Task	Task Category
1.	Assembles RDT packet, buffer, swab, lancet, pipette, & cotton wool on a clean surface or place mat	
2.	Read RDT expiration date	Accuracy
3.	Remove contents of test packet	
4.	Write patient's name on cassette	
5.	Identify patient's details and date on the RDT cassette	
6.	Explain procedure to patient	
7.	Wear gloves	Safety *
8.	Select 4th finger from the thumb of the left hand for blood collection	
9.	Clean finger with alcohol swab and allow it to dry	Safety *
10.	Prick finger firmly with sterile lancet	Safety *
11.	Discard lancet in sharps bin immediately after pricking finger	Safety *
12.	Do not squeeze finger excessively	
13.	Collect an adequate volume of blood with pipette	Accuracy
14.	Dispense blood in correct well	Accuracy
15.	Discards the pipette in the sharps box	Safety *
16.	Dispose of gloves & cotton wool in non-sharps container	
17.	Dispense correct volume of buffer	Accuracy
18.	Wait for twenty (20) minutes	Accuracy *
19.	Read results correctly	Accuracy *
20.	Verify internal test control	Accuracy
21.	Records test results, date and time correctly on encounter form	Treatment
22.	Explain to the patient the results and what they mean	Treatment *

[1] Critical steps in the RDT procedure are denoted with an '*'.

The previously trained CHWs were randomly selected to participate in this study using the "randbetween" function in Microsoft Excel (Redmond, WA), set to randomly generate a number between one and ten thousand. The CHWs were then sorted according to the randomly assigned number and invited to participate in the study. A total of 105 CHWs were invited to participate, and 103 CHWs were observed. One CHW did not participate as she had recently given birth and was on maternity leave; the other CHW was recently deceased.

3.3.5 Observation

Observers received one day of training in observation techniques including instruction on how to minimize observer-induced bias. Observers used a standardized checklist identical to that used in the CHWs' 3-day training curriculum. Just as in baseline measurements, observers watched CHWs conduct the RDT procedure, noting whether the CHW performed each step correctly, incorrectly, or not at all. Steps were divided into four broad categories: those critical to test safety, those critical to test accuracy, those critical to treatment, and crucial steps that were defined as those that were related to test safety or accuracy and easily correctable during the RDT procedure (Table 3). Safe use was defined as the completion of steps 7, 8, 9, 10, 11, and 15; those relating to blood safety and disposal of biological hazards. Accurate use was defined as the correct completion of steps 13, 14, 17, 18, and 19; those necessary to arrive at a correct diagnosis. Correct treatment was defined as the correct completion of steps 21 and 22; those relating to the recording and delivery of test results. Crucial steps were considered to be steps 7, 9, 10, 11, 15, 18, and 19. Nine situations were deemed severe enough to require immediate observer intervention: not wearing gloves, failing to properly clean the patient finger, failing to prick with a sterile lancet, attempting to reuse a lancet, failing to properly dispose of a lancet, failing to dispose of a used pipette in the sharps disposal container, failing to wait for the full 20 minutes, incorrectly interpreting results, and failing to explain results to the patient. These nine situations correspond to eight steps in the RDT procedure categorized as critical steps.

Following the testing procedure, CHWs were then requested to participate in a knowledge assessment. This assessment involved the interpretation of ten RDTs that were previously conducted and collected by the study team. The RDTs were laid out in a standardized order and CHWs were requested to read the results as positive, negative, or invalid result to assess CHW their ability to read RDTs accurately. The gold-standard for this assessment was the interpretation of the research team.

Observation took place in locations near to where the CHWs worked, and within the catchment area of nine rural health facilities. Because the study was designed to assess CHW performance in as close as possible to real-life conditions, the study team communicated with the clinical officers and other health facility staff to request that febrile patients be sent to the CHWs at the health facility for malaria testing, rather than to the clinical laboratory. Following testing, CHWs referred patients back to the clinician with an encounter form where the date, patient's name, age, temperature at the time of testing, and malaria RDT result were recorded to allow the patient to receive appropriate follow-up treatment. Patients were excluded from the study and referred back to the health facility staff if they were under one year of age or pregnant. There were some instances in which no febrile patient was available for testing. In these instances, non-febrile volunteers from the research team were recruited, asked to provide informed verbal consent, and used to assess CHWs' RDT performance.

3.3.6 Data analysis

Results of the evaluation checklists and knowledge assessments were collected on paper forms and inputted into Microsoft Excel. Data were then analyzed using Stata (College Station, TX).

The percentage of steps performed correctly at baseline and 12 months later, counts of total steps, safety steps, accuracy steps, and critical steps completed corrected were calculated for both observation cycles. The Wilcoxon sign rank test was used to determine whether time resulted in significant differences between the count distribution for baseline observations and those 12 months later. Univariate and multivariate regressions were fit to test for associations between error count data and demographic covariates. More specifically, selected covariates included sex, age, education level, time employed as a CHW, prior training in malaria case management, prior experiences with RDTs, and Deki reader experience.

Generalized estimating equations (GEE) regression models were fit using a Poisson distribution and an exchangeable correlation matrix to account for clustering between longitudinal data [122]. These models were fit to identify factors associated with correct RDT performance including age, education level, prior experience as a CHW, prior training in malaria case management, prior experience with RDTs, and Deki reader experience. GEE models were also fit to test for relevant interactions between time and relevant covariates such as prior experience as a CHW, prior training in malaria case management, and prior experience with RDTs.

Sensitivities and specificities were calculated for all tests, and then excluding tests with faint-positive results. Linear multivariate regressions were run using count data for the number of RDTs correctly interpreted and all collected socio-demographic characteristics. Statistical significance for all analyses conducted was defined as $p < 0.05$.

3.3.7 Ethical approval

Verbal informed consent was obtained from both CHWs and patients, or caregivers in the event of a patient under the age of eight. Verbal consent was also obtained from caregivers for patients under the age of eighteen if they were present at the time of testing. All participants were informed of the aims and study methods and had the opportunity to discuss the study with a study team member. The study protocol was approved by the Duke University Institutional Review Board (Durham, NC) and the Moi University Institutional Research and Ethics Committee (Eldoret, Kenya) as an amendment to an existing protocol (PRO00063384).

3.4 Results

3.4.1 Participant demographics

Sociodemographic characteristics of the 103 participating CHWs are presented in Table 4. Most CHWs (68.9%) were women, most (82.5%) were married, and a majority (58.3%) had completed secondary school or higher education. Community health workers were on average 43.6 years of age, roughly half (51.5%) had prior experience working as a CHW, and roughly one-third (32.2%) had received prior training in malaria case management. A minority (15.5%) of the CHWs were formally employed, defined as occupation outside of self-employment, and several had prior experiences with malaria RDTs (17.5%).

Table 4: Characteristics of participating community health workers. (n=103)

Characteristic	n (% or range)
Sex	
Male	32 (31.1)
Female	71 (68.9)
Mean Age (Years)	43.6 (20-69)
Education (highest level attained)	
Primary or less	43 (41.7)
Secondary or greater	60 (58.3)
Married	85 (82.5)
Formally Employed	16 (15.5)
Prior CHW Work Experience	53 (51.5)
Mean Work Experience (Years)	4.1 (0-6)
Prior Malaria Training	33 (32.2)
Prior Malaria RDT Experience	18 (17.5)

3.4.2 Overall test performance

Median CHW performance improved for total steps completed and critical steps completed, and remained steady for safety, and accuracy steps (Figure 3). The median score for total steps completed increased from 19 steps at baseline, to 20 steps 12 months later; and for critical steps, from 7 steps at baseline, to 8 steps 12 months later, though these results were not statistically significant.

When analyzing step-by-step performance, the results show that CHWs generally adhered well to the testing protocol. Except for step two (reading the expiration date), step 6 (explaining the procedure to the patient), step 16 (disposing of gloves and cotton wool in the correct waste container), and step 22 (explaining test

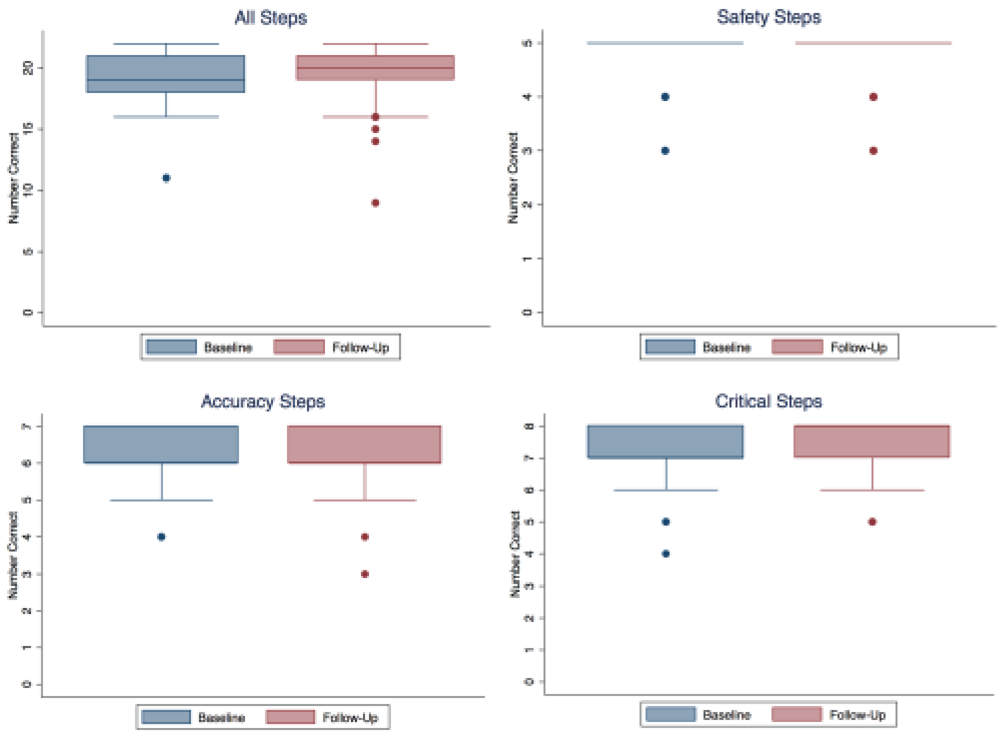

Figure 3: Count of rapid diagnostic test (RDT) steps completed correctly at baseline and 12 months post-training.

results to the patient), each step was correctly carried out by at least 80 % of CHWs (Table 5). When compared to baseline observations, a higher percentage of CHWs were observed to correctly complete step 5 (identify the patient's details on the RDT cassette), step 6 (explain the procedure to the patient), step 13 (collect an adequate volume of blood), and step 19 (read results correctly). A lower percentage of CHWs correctly completed step 8 (select correct finger), step 9 (clean finger with alcohol swab and allow it to dry), step 15 (discard pipette in sharps box), step 16 (dispose of gloves and cotton

Table 5: Step-by-step performance: percent of CHWs who completed each step correctly. [2]

No.		Task	% completing step correctly	
			Baseline	12 Mo.
1.		Assembles necessary materials	92.2	89.3
2.	A	Read RDT expiration date	53.3	52.4
3.		Remove contents of test packet	98.9	99.0
4.		Write patient's name on cassette	92.2	94.2
5.		Identify patient's details and date on the RDT cassette	87.8	92.2
6.		Explain procedure to patient	66.7	73.8
7.	S*	Wear gloves	97.8	95.2
8.		Select 4th finger from the thumb of the left hand for blood collection	93.3	86.4
9.	S*	Clean finger with alcohol swab and allow it to dry	95.6	89.3
10.	S*	Prick finger firmly with sterile lancet	96.7	94.2
11.	S*	Discard lancet in sharps bin immediately after pricking finger	95.6	95.2
12.		Do not squeeze finger excessively *	84.1	88.3
13.	A	Collect an adequate volume of blood with pipette	78.9	87.4
14.	A	Dispense blood in correct well *	97.8	98.1
15.	S*	Discards the pipette in the sharps box *	98.8	92.2
16.		Dispose of gloves & cotton wool in non-sharps container	94.4	70.9
17.	A	Dispense correct volume of buffer *	97.8	97.1
18.	A*	Wait for twenty (20) minutes *	96.6	96.1
19.	A*	Read results correctly *	90.4	99.0
20.	A	Verify internal test control *	97.6	88.4
21.	T	Records test results, date and time correctly on encounter form	--	94.2
22.	T*	Explain to the patient the results and what they mean	--	78.6

[2] Steps denoted with an S relate to test safety, steps with an A relate to test accuracy, and steps with a T steps relate to treatment. Steps 21 and 22 were omitted from the final training, as RDTs were performed on non-febrile volunteers. Baseline checklists for 13 CHWs were unable to be located, and were not included in data analysis. For additional information on incomplete data, please see Appendix C. Critical steps in the RDT procedure are denoted with an '*'.

wool in non-sharps container), and step 22 (verify internal test control).

Poisson regressions modeling the outcome of error count showed that prior training in malaria case management and prior experience using RDTs were associated with overall CHW test performance (Table 6). In univariate analysis, being male was negatively correlated with errors (-0.30, p = 0.037), as was prior RDT training (-0.55, p = 0.007). Older age was positively correlated with errors (0.02, p = 0.000) However, these associations changed when adjusting for all variables in a multivariate regression (Table 6). Being male was no longer negatively associated with error count at a significant level, though a new positive correlation between prior experiences in malaria case management was observed (0.35, p = 0.038). Older age was still positively correlated with error count (0.03, p = 0.000), while prior RDT training was still negatively correlated with error count

(-0.74, p = 0.002).

Results from both the Wilcoxon sign rank test and GEE modeling demonstrated that time did not significantly impact the performance of RDTs by the CHWs. The count distribution for correctly completed total steps, safety steps, accuracy steps, and critical steps did not differ significantly between baseline observations and those 12 months later ($p > 0.05$).

Table 6: Characteristics associated with error count data using multivariate Poisson regression methods. (n=103) [3]

Variable	Coeff.	95% CI	P Value
Male	-0.30	-0.61 – 0.02	0.064
Age	0.03	0.01 – 0.04	0.000*
Education	-0.10	-0.32 – 0.13	0.400
Married	-0.17	-0.50 – 0.16	0.315
Formal Employment	0.03	-0.34 – 0.41	0.858
CHW Experience	-0.16	-0.42 – 0.09	0.214
Malaria Experience	0.35	0.02 – 0.68	0.038*
RDT Experience	-0.74	-1.20 – -0.26	0.002*
Deki Reader Experience	-0.18	-0.46 – 0.09	0.185

Compared to CHWs 39 years of age or younger, the mean number of total, safety, accuracy, and critical errors for CHWs who were between 40 and 49 did not differ significantly at follow-up compared to baseline (Table 7). Compared to CHWs 39 years or younger, the mean number of total errors for CHWs 50 years of age or older was 39% (p=0.025) higher at follow-up than at baseline, the mean number of safety errors was 258% (p=0.001) higher, and the mean number of critical errors 79% higher (p=0.009) (Table 7). Significant interactions between time and prior RDT training were observed. For CHWs with prior RDT training, mean number of total errors was 59%

[3] Statistically significant test results are denoted with a with an '*'.

Table 7: Factors associated with error count data using generalized estimating equation (GEE) models. [4]

	Total Errors		Safety Errors		Accuracy Errors		Critical Errors	
	MER (95% CI)	P Value	MER (95% CI)	P Value	MER (95% CI)	P Value	MER (95% CI)	P Value
Time								
Baseline	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Follow Up	0.88 (0.72–1.07)	0.208	1.65 (0.96–2.82)	0.066	0.51 (0.40–0.63)	0.000	0.76 (0.54–1.08)	0.126
Age								
≤ 39 years	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
40-49 years	0.91 (0.71–1.18)	0.486	1.37 (0.61–3.07)	0.440	0.87 (0.71–1.12)	0.308	0.92 (0.59–1.42)	0.716
≥ 50 years	1.39 (1.04–1.87)	0.025*	3.58 (1.64–7.81)	0.001*	1.24 (0.93–1.65)	0.144	1.79 (1.15–2.79)	0.009*
Education								
Primary or less	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Secondary or greater	1.09 (0.86-1.37)	0.475	1.17 (0.64–2.17)	0.599	1.21 (0.97–1.52)	0.097	1.13 (0.77–1.64)	0.532
CHW Experience								
None	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Experience	0.94 (0.75–1.17)	0.584	0.75 (0.41–1.37)	0.349	1.01 (0.82–1.26)	0.910	0.84 (0.56–1.21)	0.350
Malaria Experience								
None	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Experience	1.10 (0.87–1.40)	0.424	1.30 (0.66–2.53)	0.442	1.21 (0.95–1.53)	0.121	1.34 (0.93–1.95)	0.120
RDT Experience								
None	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Experience	0.95 (0.67–1.36)	0.787	1.21 (0.51–2.87)	0.660	1.14 (0.79–1.63)	0.488	1.36 (0.84–2.20)	0.211
Deki Experience								
None	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Experience	0.91 (0.71–1.16)	0.450	1.36 (0.75–2.46)	0.318	1.07 (0.85–1.36)	0.537	0.73 (0.47–1.12)	0.298

[4] Statistically significant test results are denoted with a with an '*'.

lower (p = 0.003), the mean number of safety errors 68% lower (p = 0.044), the mean number of accuracy errors 57% lower (p = 0.015), and the mean number of critical errors 59% lower (p = 0.02) at follow-up compared to baseline for CHWs without prior RDT training (Table 8).

3.4.3 Test safety

In general, CHWs adhered to appropriate safety measures. Greater than 95% of CHWs, wore gloves at baseline observations and at 12 months. At 12-month observations, 89.3% of CHWs correctly cleaned patients' fingers. The most common error pertaining to cleaning a patient's finger was excessive wiping or scrubbing. One CHW attempted to conduct the RDT procedure without cleaning the patient's finger with alcohol (i.e., wiping it with cotton wool instead). Lancet use by CHWs was satisfactory, with 94.2% of CHWs pricking correctly, and 95.2% of CHWs properly discarding the used lancet. On four occasions at 12-month observations, CHWs opened the lancet and placed it down before pricking the patient's finger, potentially compromising the cleanliness of the tool. Only once did a CHW not prick a patient's finger well during these observations. The most common error regarding the disposal of used lancets was placing it near or around the sharps box, not in it. Only once did a CHW dispose of a used lancet in the non-sharps container. These errors were corrected immediately during the observation and discussed with CHWs following the activities.

Table 8: Interaction terms for the effects of time and selected socio-demographic characteristics on error count data using generalized estimating equation (GEE) models. [5]

	Total Errors		Safety Errors		Accuracy Errors		Critical Errors	
	MER (95% CI)	P Value	MER (95% CI)	P Value	MER (95% CI)	P Value	MER (95% CI)	P Value
CHW Experience								
None	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Experience	0.68 (0.46 –1.00)	0.052	0.65 (0.22 – 1.91)	0.437	0.82 (0.53 – 1.27)	0.375	0.65 (0.33 – 1.29)	0.217
Malaria Experience								
None	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Experience	0.79 (0.51 – 1.23)	0.302	0.42 (0.15 – 1.19)	0.103	1.04 (0.64 – 1.70)	0.863	0.68 (0.34 – 1.32)	0.249
RDT Experience								
None	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Experience	0.41 (0.23 – 0.75)	0.003*	0.32 (0.11 – 0.97)	0.044*	0.43 (.22 – 0.85)	0.015*	0.41 (0.19 – 0.87)	0.020*

[5] Statistically significant test results are denoted with a with an '*'.

3.4.4 Test accuracy

Community health workers generally completed the steps relating to accuracy at sufficient levels. At the 12-month observations, greater than 90% of CHWs completed step 14 (dispense blood in correct well), step 17 (dispense correct volume of buffer), step 18 (wait for twenty minutes), and step 19 (read results correctly). One CHW was observed dispensing too much buffer in the appropriate well, and another was observed dispensing too little buffer in the well. On one occasion a CHW dispensed collected blood in the buffer well. Of the accuracy steps, the step most frequently performed incorrectly was step two (read RDT expiration date), which was completed correctly in 52.4% of the observations. The other two frequently missed steps were step 13 (collect an adequate volume of blood) that was completed correctly 87.4% of the time, and step 20 (verify the internal test control) that was completed correctly 88.4% of the time. As with the safety steps, these errors were corrected and discussed with CHWs following observation.

3.4.5 Interpretation of RDT results

Overall, the CHWs interpretation of RDTs yielded high sensitivities and specificities. The overall sensitivity at 12-month observations was 92.04% and the overall specificity was 97.33% (Table 9). The knowledge assessment also included one invalid test cassette, which all (*n*=103) CHWs correctly interpreted. The test cassettes most

Table 9: Correct interpretation of RDT results (percent read correctly 12 months post-training). [6]

All Test Results		
	True Positive	True Negative
CHW Positive	474	11
CHW Negative	41	401
	Sensitivity	Specificity
	92.04	97.33

Strong-Positive Only		
	True Positive	True Negative
CHW Positive	306	11
CHW Negative	3	401
	Sensitivity	Specificity
	99.03	97.33

(*n*=92) correctly interpreted at least one test cassette correctly, and 73.8% (*n*=76) of CHWs correctly interpreted both test cassettes. When these tests were excluded from sensitivity and specificity calculations (i.e., only comparing strong-positive results to negative results), the observed sensitivity was 99.03% and specificity remained at 97.33%.

Multivariate regressions demonstrated that CHWs who had experience working with Deki Readers performed significantly better (*p*=0.01) on the knowledge assessment than those without Deki Reader experience (Table 9). No other covariates were found to have significant impacts on the interpretation of test results.

[6] All Test Results excludes one invalid test cassette, which 100% of CHWs (n=103) correctly interpreted. Strong-Positive Only Results exclude two faint positive test cassettes, where 73.8% (76/103) of CHWs correctly interpreted both test cassettes, and 89.3% (92/103) correctly interpreted at least one test cassette.

frequently misinterpreted were faint-positive test cassettes. Of these cassettes, 89.3%

Table 9: Characteristics associated with the number RDTs correctly interpreted using multivariate linear regression methods. (n=103) [7]

Variable	Coeff.	95% CI	P Value
Male	0.17	-0.24 – 0.59	0.408
Age	-0.01	-0.03 – 0.01	0.206
Education	0.35	-0.04 – 0.73	0.078
Married	0.04	-0.48 – 0.55	0.852
Formal Employment	-0.08	-0.61 – 0.45	0.765
CHW Experience	0.26	-0.11 – 0.63	0.160
Malaria Experience	-0.27	-0.78 – 0.24	0.294
RDT Experience	0.04	-0.58 – 0.65	0.904
Deki Reader Experience	0.40	0.02 – 0.79	0.039*

3.5 Discussion

Results of this study demonstrate that CHWs can prepare and interpret malaria RDTs correctly 12-months after a receiving a validated 3-day training. Though CHWs were able to correctly perform a majority of the steps required to complete an RDT, this study revealed several specific aspects – explaining the procedure and results to the patient, interpreting faint positive test results, and other steps relating to accuracy – that hold implications for monitoring future RDT use by CHWs. This study adds to the growing body of evidence [49,63,64,66,68,83,124] that CHWs perform RDTs at an acceptable level, and that these skills are maintained over time [63].

[7] Statistically significant test results are denoted with a with an '*'.

Overall the performance of CHWs in conducting the RDT procedures was sufficient. As they pertain to safety, future training should emphasize the importance of properly cleaning the patient's finger, keeping lancets clean, and correctly disposing of used lancets. On several occasions in this study CHWs were observed to excessively scrub a patient's finger, place the lancet down after opening it, and placing used lancets and pipettes down after using them in the test procedure. These actions have not been noted in other CHW studies, but could compromise the safety of the test for the patient, CHW, or others.

Another related concern relates to the collection of blood. While this study did not directly measure the blood volume collected and transferred, observers noted that CHWs did collect too little or too much blood on occasion. Insufficient volumes of blood for testing is an area of concern, as inadequate blood volumes can reduce test sensitivity, while excessive blood volumes can result in staining and obscuring test lines [127]. As opposed to other studies that have noted difficulties with blood collection apparatus [63,66], the most frequently observed error was inadequate amounts of blood resulting from the puncturing technique. Harvey and colleagues have raised concerns about puncturing technique, noting that CHWs may set the lancet on the patient's fingertip and attempt to push it in, rather than using a stabbing motion [66]. This action was not observed in this study, as CHWs were only observed to improperly puncture once, though the insufficient volumes suggest that technique could be improved.

Future trainings should also emphasize the importance of validating tests though checking expiry dates and checking internal controls. In this study, CHWs were frequently observed to conduct RDTs without checking the expiry date. This observation may be explained by fact that RDTs were distributed to the CHWs by the study team before prior to testing. Thus, the CHWs may functioned under the assumption that the RDTs provided to them were not expired. Regardless, it is good practice to verify the expiry date of RDTs irrelevant of the supplier, as the validity of a test result from an expired RDT may be questioned.

Other studies have also noted that reading RDT results early is a frequently observed error in the testing procedure [66,123,126]. This error was also observed in this study, though not at alarming levels. Beisel and colleagues offer a time-savings practice as one potential explanation for this practice [126]. Though training manuals from the manufacturer and in-person trainings recommend waiting at least 20 minutes before readings results, CHWs may read results early, as this can save a considerable amount of time. Still, this action can lead to invalid results, most frequently a false-negative diagnosis, and as such, is an area of concern that should be emphasized in future trainings.

Results demonstrated that CHWs maintained their competency in conducting the RDT testing procedure over the 12-month timeframe. Previous work has noted that the maintenance of testing skills may also be related to regular supervision [63,126]. This study cannot separate adequate training from supervision conducted by study staff.

Certain socio-demographic characteristics such as prior training in malaria case management and experiences with RDTs were found to be correlated with RDT performance. Prior experiences using RDTs were found to be significantly associated with committing fewer errors at 12-month observations. Other work has demonstrated that practicing RDT procedures is associated with improved performance [66]. If prior experiences conducting RDTs is viewed as a form of practice, the improved performance of these CHWs is expected. The association between higher error counts and prior experiences with malaria case management is more surprising. Though the nature and content of these trainings is unknown, one plausible explanation is that these trainings emphasized different testing procedures or steps that may have differed from those used in this study. These discrepancies may have resulted in higher error counts for these CHWs with training in malaria case management.

Both Poisson regressions and GEE models showed that older age was positively associated with a greater number of errors committed in the testing procedure. More specifically, CHWs 50 years of age or older committed more total errors, safety errors, and critical errors over time compared to a reference group of CHWs 39 years of age or younger. Taken together, these results support the assertion that CHWs younger than 50 years of age, and those with prior experiences with RDTs performed the at the highest level over 12 months.

Other work has suggested that CHWs with higher education levels may possess improved arithmetic, literacy comprehension, and knowledge retention skills that would aid in the testing process [126]. The results of this study do not support these conclusions, as CHWs with higher education levels did not perform significantly better at 12-month observations, nor did they retain skills at a significantly better level.

Community health workers performed excellently when asked to interpret test results, achieving at least a sensitivity of 92% and a specificity of 97%. The gold-standard in this study was the interpretation of scientists on the study team. When considering only strong-positive test results, the sensitivity rose to 99%, suggesting that CHWs are competent in interpreting tests results when dealing with strong-positive results. These results are higher than those reported in most studies [16,49,61,68,76,83].

Other studies have also noted difficulties in the reading of faint-positive test lines [60,63,66]. Researchers have suggested that CHW vision should be assessed to ensure that those with impaired vision, possibly due to natural aging, may receive appropriate vision assistance [60]. It should also be encouraged that the CHW conduct RDTs in a well-lit environment to facilitate the reading of test results. The association between training in using Deki readers and better interpretation should provide grounds for incorporating these devices into the training of CHWs in the future.

Although CHWs may correctly perform RDTs and interpret results, it is critical to note that these actions do not guarantee good outcomes for patients. The eventual impact of RDT and targeted ACT on patient outcomes depends on the adherence to test results. This study did not investigate CHW adherence to test results, but results from works included in the systematic review and other reviews suggest that adherence levels among CHWs are high [49,60,62,64,65,86,88,120]. This action is fundamental to providing quality care for patients as it relates to caring for both RDT-positive and RDT-negative patients.

This study had several notable strengths including a relatively large sample size for a study involving CHWs, the longitudinal study design, employing the same observers throughout follow-up observations, which acted to standardize scoring, and conducting the observations in well-lit environments. Still, limitations do exist that may have influenced study results. Perhaps most significant of these concerns is missing baseline data for 13 of the CHWs. These missing data resulted from irretrievable or incomplete baseline checklists. Although sufficient numbers were maintained for adequate study power, and the population missing data did not differ significantly from the rest of the study population for relevant socio-demographic characteristics, this may have still skewed the magnitude of study findings in a non-significant fashion.

Second, the presence of observers may have impacted CHW performance. Some CHWs were visibly uncomfortable performing the testing procedure in front of observers. Researchers have discussed how anxiety regarding evaluation may affect the quality of performance [63,128]. Though actions were taken to mitigate these potential consequences, it is impossible to be certain that the evaluation process did not affect CHW performance.

There were also instances where volunteers from the research team were used in place of febrile patients. These volunteers were often other observers present, that knew the CHWs. This recruitment of a non-febrile patient in front of the CHW that they might have known may have relaxed the formality of testing procedures and deemphasized the importance of certain steps (e.g., step 22: explaining the results to the patient). This could result in artificially low testing scores, whereas had a febrile patient been recruited, the testing procedure would have been more rigid and formal.

3.6 Conclusion

With proper training, CHWs can carry out malaria RDTs safely and accurately. Community health workers retain competency for at least 12 months post-training, and performance could improve over time. Higher testing procedure performance is associated with certain socio-demographic characteristics including younger age and previous experiences with RDTs. Better interpretation of test results is associated with CHW experiences using Deki Readers. The results of this study offer evidence that the use of RDTs by CHWs is a safe and reliable strategy for the diagnosis of malaria.

Further investigation should seek to determine if CHW based interventions are effective in the diagnosis and treatment of other infectious disease, the role and impact of automated technologies in malaria diagnosis, and the motivations for engaging in health work.

4. Conclusions

This work sought to characterize the use of malaria RDTs in sub-Saharan Africa. A systematic review found that RDTs are used safely and effectively by CHWs, though additional research was required to make the same conclusions for the formal health care and retail sectors. RDTs generally have a high diagnostic accuracy, though use in the retail sector is marked by low specificity. Adherence to RDT results is high, but tends to be lower amongst RDT-negative patients treated in the formal health care sector. This work identified long-term trends and strategies relating to RDT safety and quality as an area requiring further research.

Motivated by this study, an additional study was conducted involving CHWs in western Kenya. Findings indicate that, given proper training, most CHWs can conduct and interpret RDTs at an acceptable level. Most CHWs retain these skills for up to 12 months post-training. Testing performance improves with certain socio-demographic characteristics including younger age and previous experiences with malaria RDTs.

4.1 Implications for policy and practice

The results of this work hold a range of implications for health policies pertaining to malaria. First, RDT use in a variety of contexts appears to be safe and accurate. Acknowledging this finding, and given the limitations of other diagnostic techniques, replacing the current gold-standard of microscopy with this more versatile technology may be advisable.

Second, adherence to RDT test results is crucial for reducing the over-prescription of antimalarial medications and for positive health outcomes. This is especially true for RDT-negative patients. If the current trend of declines in the burden of malaria continue, and low adherence rates are extrapolated to all of sub-Saharan Africa, thousands of individuals may be incorrectly diagnosed and receive inappropriate treatment with antimalarials. This action would lead to unnecessary drug use, an increased risk of antimalarial drug resistance, and potentially dangerous situations arising due improperly treating infection (e.g., treating pneumonia with antimalarials).

Lastly, CHWs have a clear role in achieving international health goals. Given the high-quality use of RDTs, retention of skill over time, and adherence to test results and other protocols demonstrated in this work, expanding the roles that CHWs play in malaria diagnosis is recommended to reduce the burden posed by malaria. Doing so will act to help achieve several of the ambitious objectives outlined in the United Nations' Sustainable Development Goals [129]. Most directly, the safe and accurate diagnosis of malaria by CHWs will facilitate Goal 3.3: ending malaria epidemics by 2030. Community health workers' use of RDTs can also help to achieve Goal 1 – ending poverty – as responses to reduce malaria actively improves the health of the poorest, enabling these vulnerable populations to end the vicious cycle of disease and disease-related poverty. The prompt diagnosis of malaria by CHWs could also help to achieve the quality education standards outlined in Goal 4 because reducing malaria will enable children to learn more effectively by increasing attendance in school. Other goals, such as ensuring universal access to malaria prevention, diagnosis and treatment for all populations at risk, as proposed in the Roll Back Malaria Partnership's Action and Investment to Defeat Malaria plan, will require health systems to function more effectively, and efficiently respond to health security threats [130].

4.2 Implications for future research

To build upon the results of this work, future multidisciplinary research should be conducted to promote strategies to maintain safety and quality of RDT use. These studies should focus on these important concepts during the scale-up of interventions, especially in the retail sector and at the community level.

Focus group discussion and in-depth interviews involving workers in the formal health care sector should be conducted to better understand the reasons for low rates of adherence to RDT results and how to improve compliance with diagnostic and treatment guidelines. These qualitative studies should be followed with rigorous testing interventions to better understand adherence trends.

It is imperative that additional studies in the retail sector be conducted. To date, there has been an alarming lack of research conducted in this context, resulting in little knowledge about the safety or accuracy of RDT use in drug shops. These future studies should seek to investigate the motivations for stocking and conducting RDTs, the use of RDTs by drug shop vendors, and adherence to treatment protocols.

Researchers may also wish to further investigate the viability of the novel approach proposed by Witek-McManus [79]. An alternate strategy may be adapting the intervention to fit within existing school health programming that may or may not be administered by teachers. Though it seems unlikely that the use of RDTs in educational setting may replace their use in more traditional health care settings, the availability and use of RDTs in schools represents a new strategy for improving diagnostic coverage at the community level. Future studies should seek to replicate this study in other education environments, investigate the long-term sustainability of this approach, and conduct interviews to understand how this additional responsibility impacts the overall work of teachers.

Lastly, work should continue to explore CHWs roles in diagnosing and treating malaria, in addition to other diseases. The results of this study demonstrate that when provided training, CHWs can safely and accurately diagnose malaria. Given their success in this endeavor, it is recommended that they be trained in the diagnosis and treatment of other infectious diseases. Future studies should also be conducted to identify the effects of automated technologies, such as Deki readers, on the quality of CHWs testing. Work should also be conducted to better understand CHWs' motivations and perceptions of health work to determine the long-term sustainability of CHW focused strategies.

Appendix A

Project: Systemic Review for Context of Use of Malaria RDTs

Purpose: Search Syntax

Date: December 12, 2016

Database	Search syntax
Medline http://www.ncbi.nlm.nih..gov/pubmed/ **Literature Search Restricted From Years:** 2000 - Present	(malaria[mesh] OR malaria [tiab] OR plasmodium falciparum[tiab] OR p falciparum[tiab]) **AND** (mass screening[mesh] OR rdt[tiab] OR rapid diagnos*[tiab] OR rapid antigen test*[tiab] OR screen*[tiab]) **AND** ("barefoot doctor"[tiab] OR community assistants[tiab] OR community based[tiab] OR community case management[tiab] OR CCM[tiab] OR community directed[tiab] OR community drug distributor[tiab] OR community health[tiab] OR "community health workers"[mesh] OR community malaria volunteer*[tiab] OR community management[tiab] OR community owned resource person*[tiab] OR "drug shop"[tiab] OR emergenc*[tiab] OR formal health workers[tiab] OR

	health community worker*[tiab] OR health extension worker*[tiab] OR hmm[tiab] OR home based[tiab] OR home based management of malaria[tiab] OR home health aides[tiab] OR HMM[tiab] OR home management[tiab] OR home health worker*[tiab] OR home case management[tiab] OR hospitaliz*[tiab] OR hospitalis*[tiab] OR home health aides[mesh] OR hospital*[tiab] OR hospital[mesh] OR hospitalization [mesh] OR integrated community case management[tiab] OR iCCM[tiab] OR malaria control assistant*[tiab] OR mobile health units[mesh] OR pharmacy*[tiab] OR physician*[tiab] OR primary care[tiab] OR primary health care[tiab] OR private sector[tiab] OR “retail providers”[tiab] OR “retail shop”[tiab] OR village health worker*[tiab] OR village malaria worker[tiab])

Appendix B

Author	Year	Country	Study Design	Context	# Health Care Workers/Shops	Personnel Cadre	RDT
Chanda	2011	Zambia	Observational	CHW	16	CHWs	NR
Counihan	2012	Zambia	Longitudinal	CHW	59	CHWs	ICT malaria Pf
Hamainza	2014	Zambia	Longitudinal	CHW	NR	CHWs	ICT malaria Pf
Hamer	2012	Zambia	Cluster Randomized Trial	CHW	18	CHWs	ICT malaria Pf
Harvey	2008	Zambia	Observational	CHW	47	CHWs	Paracheck Pf
Hawkes	2009	DRC	Prospective Cohort	CHW	12	CHWs	Paracheck Pf
Ishengoma	2011	Tanzania	Longitudinal	CHW	NR	CHWs	Paracheck Pf
Ishengoma	2011	Tanzania	Cross-sectional	CHW	NR	CHWs	ParaHIT
Mubi	2011	Tanzania	Randomized Cross-Over	CHW	22	CHWs	Paracheck Pf
Mukanga	2011	Uganda	Cross-sectional	CHW	14	CHWs	NR
Mukanga	2012	Ghana; Uganda; Burkina Faso	Cluster Randomized Trial	CHW	44	CHWs	ICT malaria Pf; Paracheck Pf
Ndyomugyenyi	2016	Uganda	Cluster Randomized Trial	CHW	85	CHWs	First Response
Ratsimbasoa	2012	Madagascar	Observational	CHW	8	CHWs	NR
Thiam	2012	Senegal	Observational	CHW	408	CHWs	SD Bioline

Tiono	2012	Burkina Faso	Observational	CHW	13	CHWs	FirstSign Pf
Willcox	2009	Mali	Observational	CHW	NR	CHWs	Paracheck Pf
Wogi	2014	Ethiopia	Cross-sectional	CHW	170	CHWs	NR
Gerstl	2010	Sierra Leone	Observational	Formal Health Care Sector (Private)	NR	Lab technicians	CareStart
Ashton	2010	Ethiopia	Observational	Formal Health Care Sector (Public)	NR	Nurses & Health Extension Worker	CareStart, ParaScreen, & ICT Combo
Baiden	2012	Ghana	Observational	Formal Health Care Sector (Public)	NR	Clinicians	CareStart
Bastiaens	2011	Tanzania	Pre-/Post Study	Formal Health Care Sector (Public)	NR	Clinical Officers	ICT malaria Pf; Paracheck Pf
Batwala	2011	Uganda	Cluster Randomized Trial	Formal Health Care Sector (Public)	30	Clinical Officers & nurses	Paracheck Pf
Bisoffi	2009	Burkina Faso	Randomized Control Trial	Formal Health Care Sector (Public)	NR	Nurses	Paracheck Pf
Bottieau	2013	Mozambique	Observational	Formal Health Care Sector (Public)	NR	Clinicians	Paracheck Pf; ICT Malaria Pf; SD Malaria Antigen Pf
Chinkhumba	2010	Malawi	Cross-sectional	Formal Health Care Sector (Public)	NR	Clinicians & nurses	ICT malaria pf; SD Bioline; Paracheck Pf; First Response
Cundill	2015	Tanzania	Cluster Randomized Trial	Formal Health Care Sector (Public)	36	Health workers	NR

de Oliveira	2009	Kenya	Cluster Randomized Trial	Formal Health Care Sector (Public)	30	Health workers	Paracheck Pf
Diarra	2012	Burkina Faso	Observational	Formal Health Care Sector (Public)	14	Clinic health workers	OptiMAL
Guthmann	2002	Uganda	Observational	Formal Health Care Sector (Public)	NR	Nurses	Paracheck Pf, ParaHIT, Malaria Rapid, & BIO P.F.
Hamer	2007	Zambia	Cross-sectional	Formal Health Care Sector (Public)	NR	Lab technicians & Health workers	Paracheck Pf
Hopkins	2007	Uganda	Longitudinal	Formal Health Care Sector (Public)	NR	Clinicians	Paracheck Pf; Parabank
Mansanja	2010	Tanzania	Observational	Formal Health Care Sector (Public)	99	Health workers & health volunteers	ParaHIT
Mbacham (*Basic*)	2014	Cameroon	Cluster Randomized Trial	Formal Health Care Sector (Public)	95	Clinicians	SD Bioline
Mbacham (*Enhanced*)	2014	Cameroon	Cluster Randomized Trial	Formal Health Care Sector (Public)	103	Clinicians	SD Bioline
McMorrow	2008	Tanzania	Observational	Formal Health Care Sector (Public)	105	Health workers	Paracheck Pf
McMorrow	2010	Tanzania	Observational	Formal Health Care Sector (Public)	99	Health workers & health volunteers	Paracheck Pf
Moonasar	2009	South Africa	Observational	Formal Health Care Sector (Public)	25	Nurses & Nursing Assistants	NR
Morankar	2011	Ethiopia	Cross-sectional	Formal Health Care Sector (Public)	NR	Lab technicians	NR

Msellem	2009	Tanzania	Observational	Formal Health Care Sector (Public)	NR	Nurses	Paracheck Pf
Mtove	2011	Tanzania	Observational	Formal Health Care Sector (Public)	NR	Clinical Officers	Paracheck Pf
Nicastri	2009	Tanzania	Cross-sectional	Formal Health Care Sector (Public)	NR	Lab technicians	ParaHIT
Osei-Kwakye	2013	Ghana	Cross-sectional	Formal Health Care Sector (Public)	NR	Lab technicians	Parascreen
Ouattara	2011	Mali	Observational	Formal Health Care Sector (Public)	NR	Health workers	OptiMAL
Reyburn	2007	Tanzania	Randomized Control Trial	Formal Health Care Sector (Public)	NR	Clinicians	Paracheck Pf
Shakely	2013	Tanzania	Cross-sectional	Formal Health Care Sector (Public)	33	Clinicians & nurses	Paracheck Pf
Shekalaghe	2013	Tanzania	Prospective Cohort	Formal Health Care Sector (Public)	NR	Clinician	SD Bioline
Skarbinski	2009	Kenya	Cluster Randomized Trial	Formal Health Care Sector (Public)	NR	Clinical Officers & nurses	Paracheck Pf
Uzochukwu	2011	Nigeria	Cross-sectional	Formal Health Care Sector (Public)	32	Clinicians, nurses, & CHWs	ICT malaria Pf
Ansah	2015	Ghana	Cluster Randomized Trial	Retail Sector	24	Drug Shop Vendors	CareStart
Awor	2015	Uganda	Pre-/Post Study	Retail Sector	44	Drug Shop Vendors	NR

Cohen	2015	Uganda	Cluster Randomized Trial	Retail Sector	92	Drug Shop Vendors	CareStart
Ikwuobe	2013	Nigeria	Observational	Retail Sector	1	Drug Shop Vendors	SD Bioline
Mbonye	2015	Uganda	Cluster Randomized Trial	Retail Sector	10	Drug Shop Vendors	First Response
Witek-McManus	2015	Mali	Cluster Randomized Trial	School	92	Teacher	NR

Appendix C

Baseline Checklist	Number of Observations (*n*)
Step 1	90
Step 2	90
Step 3	90
Step 4	90
Step 5	90
Step 6	90
Step 7	90
Step 8	90
Step 9	90
Step 10	90
Step 11	90
Step 12	88
Step 13	90
Step 14	89
Step 15	86
Step 16	90
Step 17	89
Step 18	87
Step 19	83
Step 20	83
Step 21	--
Step 22	--

Follow-Up Checklist	Number of Observations (*n*)
Step 1	103
Step 2	103
Step 3	103
Step 4	103
Step 5	103
Step 6	103
Step 7	103
Step 8	103
Step 9	103
Step 10	103
Step 11	103
Step 12	103
Step 13	103
Step 14	103
Step 15	103
Step 16	103
Step 17	103
Step 18	103
Step 19	103
Step 20	103
Step 21	103
Step 22	103

References

1. World Health Organization (WHO). (2015). World Malaria Report. Geneva, Switzerland: WHO.

2. Mugittu K., Abdulla S., Falk N., et al. (2005). Efficacy of sulfadoxine-pyrimethamine in Tanzania after two years as first-line drug for uncomplicated malaria: assessment protocol and implication for treatment policy strategies. *Malar. J.*; 4:55.

3. Yukich JO., Bennett A., Albertini A., et al. (2012). Reductions in artemisinin-based combination therapy after the nationwide scale up of routine malaria rapid diagnostic testing in Zambia. *Am. J. Trop. Med. Hyg*.; 87:437-46.

4. World Health Organization (WHO). (2006). Guidelines for the treatment of malaria. Geneva, Switzerland: WHO.

5. World Health Organization (WHO). (2010). Guidelines for the Treatment of Malaria, 2nd ed. Geneva, Switzerland: WHO.

6. O'Meara WP., Mangeni JN., Steketee R., et al. (2010). Changes in the burden of malaria in sub-Saharan Africa. *Lancet Infect Dis.*; 10:545-55.

7. Bhattarai A., Ali AS., Kachur SP., et al. (2007). Impact of artemisinin-based combination therapy and insecticide treated nets on malaria burden in Zanzibar. *PLoS Med*.; 4:e309.

8. Sharp BL., Kleinschmidt I., Streat E., et al. (2007). Seven years of regional malaria control collaboration–Mozambique, South Africa, and Swaziland. *Am. J. Trop. Med. Hyg*.; 76:42-47.

9. Reyburn H., Mbatia R., Drakeley C., et al. (2004). Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. *BMJ*; 329:1212.

10. D'Acremont V., Kilowoko M., Kyungu E., et al. (2014). Beyond malaria—causes of fever in outpatient Tanzanian children. *N. Engl. J. Med*.; 370: 809-17.

11. Okiro EA., Hay SI., Gikandi PW., et al. (2007). The decline in paediatric malaria admissions on the coast of Kenya. *Malar. J.*; 6:151.

12. Wellems TE., Plowe CV. (2001). Chloroquine-resistant malaria. *J. Infect. Dis*.; 184:770-76.

13. Parija SC., Praharaj I. (2011). Drug resistance in malaria. *Indian J. Med. Microbiol.*; 29:243-48.

14. Adesanmi T., Okafor HU., Okoro AB., et al. (2011). Diagnosis of malaria parasitemia in children using a rapid diagnostic test. *Niger. J. Clin. Pract.*; 14:195-200.

15. Gerstl S., Dunkley S., Mukhtar A., et al. (2010). Assessment of two malaria rapid diagnostic tests in children under five years of age, with follow-up of false-positive pLDH test results, in a hyperendemic falciparum malaria area, Sierra Leone. *Malar. J.;* 9:28.

16. Ishengoma DS., Francis F., Mmbando BP., et al. (2011). Accuracy of malaria rapid diagnostic tests in community studies and their impact on treatment of malaria in an area with declining malaria burden in north-eastern Tanzania. *Malar. J.;* 10:176.

17. Maltha J., Gillet P., Jacobs J. (2013). Malaria rapid diagnostic tests in endemic settings. *Clin. Microbiol. & Infection.*; 19:399-407.

18. Strøm GE., Haanshuus CG., Fataki M., et al. (2013). Challenges in diagnosing paediatric malaria in Dar es Salaam, Tanzania. *Malar. J.*; 12:1.

19. Uzochukwu BSC., Onwujekwe E., Ezuma NN., et al. (2011). Improving rational treatment of malaria: perceptions and influence of RDTs on prescribing behaviour of health workers in Southeast Nigeria. *PLoS ONE*; 6:e14627.

20. Derua YA., Ishengoma DR., Rwegoshora RT., et al. (2011). Users' and health service providers' perception on quality of laboratory malaria diagnosis in Tanzania. *Malar. J.;* 10:78.

21. Bell D., Peeling RW. (2006). Evaluation of rapid diagnostic tests: malaria. *Nature Rev. Microbiol.*; 4:S7-20.

22. Hamer DH., Ndhlovu M., Zurovac D., et al. (2007). Improved diagnostic testing and malaria treatment practices in Zambia. *JAMA*; 297:2227-31.

23. McKenzie FE., Sirichaisinthop J., Miller RS., et al. (2003). Dependence of malaria detection and species diagnosis by microscopy on parasite density. *Am. J. Trop. Med. Hyg.*; 69:372-76.

24. Bates I., Maitland K. (2006). Are laboratory services coming of age in sub-Saharan Africa? *Clin. Infect. Dis.*; 42:383-84.

25. Petti CA., Polage CR., Quinn TC., et al. (2006). Laboratory medicine in Africa: a barrier to effective health care. *Clin. Infect. Dis*.; 42:377-82.

26. Bronzan RN., McMorrow ML., Kachur SP. (2008). Diagnosis of malaria. *Mol. Diagn. & Ther.;* 12:299-306.

27. Wafula R., Sang E., Cheruiyot O., et al. (2014). High sensitivity and specificity of clinical microscopy in rural health facilities in Western Kenya under an external quality assurance program. *Am. J. Trop. Med. Hyg*.; 91:481-85.

28. World Bank. (1993). World Development Report. New York: Oxford University Press.

29. Gilles HM. (1993). Diagnostic methods in malaria. In: Gilles HM, Warrell DA eds. Bruce-Chwatt's Essential Malariology, 3rd ed. New York, Oxford University Press; p.78-95.

30. Morassin B., Fabre R., Berry A., et al. (2002). One year's experience with the polymerase chain reaction as a routine method for the diagnosis of imported malaria. *Am. J. Trop. Med. Hyg*.; 66:503-08.

31. Moody AH. (2002). Rapid diagnostic tests for malaria parasites. *Clin. Microb. Rev*.; 15:66-78.

32. Iqbal J., Siddique A., Jameel M., et al. (2004). Persistent Histidine-Rich Protein 2, Parasite Lactate Dehydrogenase, and pan malarial antigen reactivity after clearance of Plasmodium falciparum monoinfection. *J. Clin. Microbiol*.; 42:4237-41.

33. Fryauff DJ., Purnomo MA., Sutamihardja IRS., et al. (2000). Performance of the Optimal assay for detection and identification of malaria infections in asymptomatic residents of Irian Jaya, Indonesia. *Am. J. Trop. Med. Hyg*.; 63:139-45.

34. Laurent A., Schellenberg J., Shirima K., et al. (2010). Performance of HRP-2 based rapid diagnostic test for malaria and its variation with age in an area of intense malaria transmission in southern Tanzania. *Malar. J.;* 9:294.

35. White MT., Conteh L., Cibulskis R., et al. (2011). Costs and cost-effectiveness of malaria control interventions - a systematic review. *Malar. J.*; 10:337.

36. Lemma H., San Sebastian M., Lofgren C., et al. (2011). Cost-effectiveness of three malaria treatment strategies in rural Tigray, Ethiopia where both Plasmodium falciparum and Plasmodium vivax co-dominate. *Cost effectiveness and resource allocation*; 9:2.

37. World Health Organization (WHO). (2000). Manual of Integrated Management of Childhood illnesses on management of the child with a serious infection or severe malnutrition: Guidelines for care at the first referral level in developing countries. Geneva, Switzerland: WHO.

38. Abba K., Deeks JJ., Olliaro PL., et al. (2011). Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. *Cochrane Database of Systematic Reviews*; (7) Art. No.: CD008122.

39. Bisoffi Z., Sirima BS., Angheben A., et al. (2010). Rapid malaria diagnostic tests vs. clinical management of malaria in rural Burkina Faso: safety and effect on clinical decisions. A randomized trial. *Trop. Med. & Intl. Health*; 14(5):491-98.

40. O'Brien C., Henrich PP., Passi N., et al. (2011). Recent clinical and molecular insights into emerging artemisinin resistance in Plasmodium falciparum. *Curr. Opin. Infect. Dis.*; 24:570-77.

41. World Health Organization (WHO). (2000). New Perspectives: Malaria Diagnosis. Geneva, Switzerland: WHO.

42. Bastiaens GJH., Schaftenaar E., Ndaro A., et al. (2011). Malaria diagnostic testing and treatment practices in three different Plasmodium falciparum transmission settings in Tanzania: before and after a government policy change. *Malar. J.;* 10:76.

43. Cundill B., Mbakilwa H., Chandler CI., et al. (2015). Prescriber and patient-oriented behavioural interventions to improve use of malaria rapid diagnostic tests in Tanzania: facility-based cluster randomised trial. *BMC Med.*; 13:118.

44. Masanja MI., McMorrow M., Kahigwa E., et al. (2010). Health workers' use of malaria rapid diagnostic tests (RDTs) to guide clinical decision making in rural dispensaries, Tanzania. *Am. J. Trop. Med. Hyg.*; 83:1238-41.

45. McMorrow ML., Masanja MI., Abdulla SM., et al. (2008). Challenges in routine implementation and quality control of rapid diagnostic tests for malaria–Rufiji District, Tanzania. *Am. J. Trop. Med. Hyg.*; 79:385-90.

46. McMorrow ML., Masanja MI., Kahigwa E., et al. (2010). Quality assurance of rapid diagnostic tests for malaria in routine patient care in rural Tanzania. *Am. J. Trop. Med. Hyg.*; 82:151-55.

47. Msellem MI., Mårtensson A., Rotllant G., et al. (2009). Influence of rapid malaria diagnostic tests on treatment and health outcome in fever patients, Zanzibar: a crossover validation study. *PLoS Med*.; 6:e1000070.

48. Mtove G., Nadjm B., Amos B., et al. (2011). Use of an HRP-2-based rapid diagnostic test to guide treatment of children admitted to hospital in a malaria-endemic area of north-east Tanzania. *Trop. Med. & Intl. Health*; 16:545-50.

49. Mubi M., Janson A., Warsame M., et al. (2011). Malaria rapid testing by community health workers is effective and safe for targeting malaria treatment: randomised cross-over trial in Tanzania. *PLoS ONE*; 6:e19753.

50. Nicastri E., Bevilacqua N., Schepisi MS., et al. (2009). Accuracy of malaria diagnosis by microscopy, rapid diagnostic test, and PCR methods and evidence of antimalarial overprescription in non-severe febrile patients in two Tanzanian hospitals. *Am. J. Trop. Med. Hyg*.; 80:712-17.

51. Reyburn H., Mbakilwa H., Mwangi R., et al. (2007). Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: Randomised Trial. *BMJ*; 334:403.

52. Shakely D., Elfving K., Aydin-Schmidt B., et al. (2013). The usefulness of rapid diagnostic tests in the new context of low malaria rransmission in Zanzibar. *PLoS ONE*; 8:e72912.

53. Shekalaghe S., Cancino M., Mavere C., et al. (2013). Clinical performance of an automated reader in interpreting malaria rapid diagnostic tests in Tanzania. *Malar. J.;* 12:141.

54. Awor P., Wamani H., Tylleskar T., et al. (2015). Drug seller adherence to clinical protocols with integrated management of malaria, pneumonia and diarrhoea at drug shops in Uganda. *Malar. J*.; 14:277.

55. Batwala V., Magnussen P., Nuwaha F. (2011). Comparative feasibility of implementing rapid diagnostic test and microscopy for parasitological diagnosis of malaria in Uganda. *Malar. J*.; 10:373.

56. Cohen J., Fink G., Maloney K., et al. (2015). Introducing rapid diagnostic tests for malaria to drug shops in Uganda: a cluster-randomized controlled trial. *Bull. World Health Organ*.; 93:142-51

57. Guthmann JP., Ruiz A., Priotto G., et al. (2002). 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*.; 96:254-57.

58. Hopkins H., Kambale W., Kamya MR., et al. (2007). Comparison of HRP-2 and pLDH-based rapid diagnostic tests for malaria with longitudinal follow-up in Kampala, Uganda. *Am. J. Trop. Med. Hyg*.; 76:1092-97.

59. Mbonye AK., Magnussen P., Lal S., et al. (2015). A cluster randomised trial introducing rapid diagnostic tests into registered drug shops in Uganda: impact on appropriate treatment of malaria. *PLoS ONE*; 10:e0129545.

60. Mukanga D., Babirye R., Peterson S., et al. (2011). Can lay community health workers be trained to use diagnostics to distinguish and treat malaria and pneumonia in children? Lessons from rural Uganda. *Trop. Med. & Intl. Health*.; 16:1234-42.

61. Ndyomugyenyi R., Magnussen P., Lal S., et al. (2016). Appropriate targeting of artemisinin-based combination therapy by community health workers using malaria rapid diagnostic tests: findings from randomized trials in two contrasting areas of high and low malaria transmission in south-western Uganda. *Trop. Med. & Intl. Health*; 21(9):1157-70.

62. Chanda P., Hamainza B., Moonga HB., et al. (2011). Community case management of malaria using ACT and RDT in two districts in Zambia: achieving high adherence to test results using community health workers. *Malar. J*.; 10:158.

63. Counihan H., Harvey SA., Sekeseke-Chinyama M., et al. (2012). Community health workers use malaria rapid diagnostic tests (RDTs) safely and accurately: results of a longitudinal study in Zambia. *Am. J. Trop. Med. Hyg*.; 87:57-63.

64. Hamer DH., Brooks ET., Semrau K., et al. (2012). Quality and safety of integrated community case management of malaria using rapid diagnostic tests and pneumonia by community health workers. *Pathogens & Global Health*; 6: 32-39.

65. Hamainza B., Moonga H., Sikaala CH., et al. (2014). Monitoring, characterization and control of chronic, symptomatic malaria infections in rural Zambia through monthly household visits by paid community health workers. *Malar. J*.; 13:128.

66. Harvey SA., Jennings L., Chinyama M., et al. (2008). Improving community health worker use of malaria rapid diagnostic tests in Zambia: package instructions, job aid and job aid-plus-training. *Malar. J*.; 7:160.

67. Diarra A., Nébié I., Tiono A., et al. (2012). Seasonal performance of a malaria rapid diagnosis test at community health clinics in a malaria-hyperendemic region of Burkina Faso. *Parasites & Vectors*; 5:103.

68. Tiono AB., Diarra A., Sanon S., et al. (2013). Low specificity of a malaria rapid diagnostic test during an integrated community case management trial. *Infect. Dis. and Ther*.; 2:27-36.

69. Ashton RA., Kefyalew T., Tesfaye G., et al. (2010). Performance of three multi-species rapid diagnostic tests for diagnosis of Plasmodium falciparum and Plasmodium vivax malaria in Oromia Regional State, Ethiopia. *Malar. J*.; 9:297.

70. Morankar S., Tegene A., Kassahun W., et al. (2011). Validity and reliability of RDT for diagnosis of malaria among febrile children in Jimma Town: southwest Ethiopia. *Ethiop. Med. J*.; 49:131-38.

71. Wogi A., Teno D., Bulto, T., et al. (2014). Effect of integrated community case management of common childhood illnesses on the quality of malaria case management provided by health extension workers at health posts. *Ethiop. Med. J*.; 52:99-108.

72. Ansah EK., Narh-Bana S., Affran-Bonful H., et al. (2015). The impact of providing rapid diagnostic malaria tests on fever management in the private retail sector in Ghana: a cluster randomized trial. *BMJ*; 350:h1019.

73. Baiden F., Webster J., Tivura M., et al. (2012). Accuracy of rapid tests for malaria and treatment outcomes for malaria and non-malaria cases among under-five children in rural Ghana. *PLoS ONE*; 7:e34073.

74. Osei-Kwakye K., Asante KP., Mahama E., et al. (2013). The benefits or otherwise of managing malaria cases with or without laboratory diagnosis: the experience in a district hospital in Ghana. *PLoS ONE*; 8:e58107.

75. Ouattara A., Doumbo S., Saye R., et al. (2011). Use of a pLDH-based dipstick in the diagnostic and therapeutic follow-up of malaria patients in Mali. *Malar. J.;* 10:345.

76. Willcox ML., Sanogo F., Forster M., et al. (2009). Rapid diagnostic tests for the home-based management of malaria, in a high-transmission area. *Ann. Trop. Med. Parasitol*.; 103:3-16.

77. de Oliveira AM., Skarbinski J., Ouma PO., et al. (2009). Performance of malaria rapid diagnostic tests as part of routine malaria case management in Kenya. *Am. J. Trop. Med. Hyg.*; 80:470-74.

78. Skarbinski J., Ouma PO., Causer LM., et al. (2009). Effect of malaria rapid diagnostic tests on the management of uncomplicated malaria with artemether-lumefantrine in Kenya: a cluster randomized trial. *Am. J. Trop. Med. Hyg.*; 80:919-26.

79. Witek-McManus S., Mathanga DP., Verney A., et al. (2015). Design, implementation and evaluation of a training programme for school teachers in the use of malaria rapid diagnostic tests as part of a basic first aid kit in southern Malawi. *BMC Pub. Health*; 15:904.

80. Chinkhumba J., Skarbinski J., Chilima B., et al. (2010). Comparative field performance and adherence to test results of four malaria rapid diagnostic tests among febrile patients more than five years of age in Blantyre, Malawi. *Malar. J.;* 9:209.

81. Ikwuobe JO., Faragher BE., Alawode G., et al. (2013). The impact of rapid malaria diagnostic tests upon antimalarial sales in community pharmacies in Gwagwalada, Nigeria. *Malar. J.*; 12:380.

82. Mbacham WF., Mangham-Jefferies L., Cundill B., et al. (2014). Basic or enhanced clinician training to improve adherence to malaria treatment guidelines: a cluster-randomised trial in two areas of Cameroon. *Lancet Global Health.;* 2:e346.

83. Hawkes M., Katsuva JP., Masumbuko CK. (2009). Use and limitations of malaria rapid diagnostic testing by community health workers in war-torn Democratic Republic of Congo. *Malar. J.;* 8:308.

84. Ratsimbasoa A., Ravony H., Vonimpaisomihanta JA., et al. (2012). Management of uncomplicated malaria in febrile under five-year-old children by community health workers in Madagascar: reliability of malaria rapid diagnostic tests. *Malar. J.;* 11:85.

85. Bottieau E., Gillet P., De Weggheleire A., et al. (2013). Treatment practices in patients with suspected malaria in provincial hospital of Tete, Mozambique. *Trans. R. Soc. Trop. Med. Hyg.*; 107:176-82.

86. Thiam S., Thwing J., Diallo I., et al. (2012). Scale-up of home-based management of malaria based on rapid diagnostic tests and artemisinin-based combination therapy in a resource-poor country: results in Senegal. *Malar. J.;* 11:334.

87. Moonasar D., Goga AE., Frean J., et al. (2009). Primary health workers' proficiency in using malaria rapid diagnostic tests in Limpopo Province. *S. Afr. Med. J.*; 99(11):798-99.

88. Mukanga D., Tiono AB., Anyorigiya T., et al. (2012). Integrated community case management of fever in children under five using rapid diagnostic tests and respiratory rate counting: a multi-country cluster randomized trial. *Am. J. Trop. Med. Hyg.*; 87:21-29.

89. Asiimwe C., Kyabayinze DJ., Kyalisiima Z., et al. (2012). Early experiences on the feasibility, acceptability, and use of malaria rapid diagnostic tests at peripheral health centres in Uganda-insights into some barriers and facilitators. *Implementation Science*; 7:5.

90. Grobusch MP., Alpermann U., Schwenke S., et al. (1999). False-positive rapid tests for malaria in patients with rheumatoid factor. *Lancet*; 353:297.

91. Diggle E., Asgary R., Gore-Langton G., et al. (2014). Perceptions of malaria and acceptance of rapid diagnostic tests and related treatment practises among community members and health care providers in Greater Garissa, North Eastern Province, Kenya. *Malar. J.*; 13:502

92. Altaras R., Nuwa A., Agaba B., et al. (2016). Why do health workers give anti-malarials to patients with negative rapid test results? A qualitative study at rural health facilities in western Uganda. *Malar. J.;* 15:23.

93. Gillet P., Mori M., Van Esbroeck M., et al. (2009). Assessment of the prozone effect in malaria rapid diagnostic tests. *Malar. J.*; 8:271.

94. Faust C., Zelner J., Brasseur P., et al. (2015). Assessing drivers of full adoption of test and treat policy for malaria in Senegal. *Am. J. Trop. Med. Hyg.;* 93:159-67.

95. Nankabirwa J., Zurovac D., Njogu JN., et al. (2009). Malaria misdiagnosis in Uganda-implications for policy change. *Malar. J.*; 8:66.

96. O'Connell KA., Gatakaa H., Poyer S., et al. (2011). Got ACTs? Availability, price, market share and provider knowledge of antimalarial medicines in public and private sector outlets in six malaria-endemic countries. *Malar. J.*; 10:326.

97. Ndyomugyenyi R., Magnussen P., Clarke S. (2007). Diagnosis and treatment of malaria in peripheral health facilities in Uganda: findings from an area of low transmission in South-Western Uganda. *Malar. J.*; 6:39.

98. Awor P., Wamani H., Tylleskar T., et al. (2014). Increased access to care and appropriateness of treatment at private sector drug shops with integrated management of malaria, pneumonia and diarrhoea: a quasi-experimental study in Uganda. *PLoS ONE*; 9:e115440.

99. Smith N., Obala A., Simiyu C., et al. (2011). Accessibility, availability and affordability of anti-malarials in a rural district in Kenya after implementation of a national subsidy scheme. *Malar. J.;* 10:316.

100. National Population Commission (NPC), National Malaria Control Programme (NMCP), ICF International. Nigeria Malaria Indicator Survey 2010. (2012). Abuja, Nigeria: NPC, NMCP, and ICF International.

101. Oladepo O., Kabiru S., Adeoye BW., et al. (2008). Malaria treatment in Nigeria: the Role of Patent Medicine Vendors. Future Health Systems (FHS), Innovations for equity. *Innovations and Knowledge for Future Health Systems for the Poor*, *Policy Brief*; (1): 1-4.

102. Mbonye AK., Lal S., Cundill B., et al. (2013). Treatment of fevers prior to introducing rapid diagnostic tests for malaria in registered drug shops in Uganda. *Malar. J.*; 12:131.

103. Isiguzo C., Anyanti J., Ujuju C., et al. (2014). Presumptive treatment of malaria from formal and informal drug vendors in Nigeria. *PLoS ONE*; 9:e110361.

104. Onwujekwe O., Onoka C., Uguru N., et al. (2010). Preferences for benefit packages for community-based health insurance: an exploratory study in Nigeria. *BMC Health Services Research*; 10:162.

105. Mangham LJ., Cundill B., Ezeoke O., et al. (2011). Treatment of uncomplicated malaria at public health facilities and medicine retailers in south-eastern Nigeria. *Malar. J.*; 10:155.

106. Rafael ME., Taylor T., Magill A., et al. (2006). Reducing the burden of childhood malaria in Africa: the role of improved diagnostics. *Nature*; 444:39-48.

107. Velema JP., Alihonou EM., Gandaho T., et al. (1991). Childhood mortality among users and non-users of primary health care in a rural west African community. *Intl. J. Epi.*; 20:474-79.

108. World Health Organization (WHO). (2006). Strategy for improving access to treatment through home-based management of malaria. Geneva, Switzerland: WHO.

109. Hopkins H., Talisuna A., Whitty CJM., et al. (2007). Impact of home-based management of malaria on health outcomes in Africa: a systematic review of the evidence. *Malar. J.*; 6:134.

110. Yeboah-Antwi K., Gyapong JO., Asare IK., et al. (2001). Impact of prepackaging antimalarial drugs on cost to patients and compliance with treatment. *Bull. World Health Org.*; 79:394-99.

111. Ansah EK., Gyapong JO., Agyepong IA., et al. (2001). Improving adherence to malaria treatment for children: the use of pre- packed chloroquine tablets vs. chloroquine syrup. *Trop. Med. & Intl. Health*; 6:496-504.

112. Källander K., Tomson G., Nsungwa-Sabiiti J., et al. (2006). Community referral in home management of malaria in western Uganda: A case series study. *BMC Intl. Health Hum. Rights*; 6:2.

113. Tiono AB., Kaboré Y., Traoré A., et al. (2008). Implementation of Home based management of malaria in children reduces the work load for peripheral health facilities in a rural district of Burkina Faso. *Malar. J.*; 7:201.

114. Chinbuah MA., Kager PA., Abbey M., et al. (2012). Impact of community management of fever (using antimalarials with or without antibiotics) on childhood mortality: a cluster-randomized controlled trial in Ghana. *Am. J. Trop. Med. Hyg.*; 87:11-20.

115. Ndiaye Y., Ndiaye J., Cisse B., et al. (2013). Community case management in malaria: review and perspectives after four years of operational experience in Saraya district, southeast Senegal. *Malar. J.;* 12:240.

116. Okello G., Ndegwa S., Halliday K., et al. (2012). Local perceptions of intermittent screening and treatment for malaria in school children on the south coast of Kenya. *Malar. J.;* 11:185.

117. Smith F. (2009). The quality of private pharmacy services in low and middle-income countries: a systematic review. *Pharm. World Sci.*; 31:351-61.

118. Mbonye AK., Clarke SE., Lal S., et al. (2015). Introducing rapid diagnostic tests for malaria into registered drug shops in Uganda: lessons learned and policy implications. *Malar. J.*; 14:448

119. Coleman RE., Sattabongkot J., Promstaporm S., et al. (2006). Comparison of PCR and microscopy for the detection of asymptomatic malaria in a Plasmodium falciparum/vivax endemic area in Thailand. *Malar. J.*; 5:121.

120. Kabaghe A., Visser B., Spijker R., et al. (2016). Health workers' compliance to rapid diagnostic tests (RDTs) to guide malaria treatment: a systematic review and meta-analysis. *Malar. J.*; 15:163.

121. Bennett S., George A., Rodriguez D., et al. (2014). Policy challenges facing integrated community case management in Sub-Saharan Africa. *Trop. Med. & Intl. Health.*; 19:872-82.

122. Seger SL., Liang KY., Albert PS. (1988). Models for longitudinal data: A generalized estimating equation approach. *Biometrics*; 44:1049–60.

123. Rennie W., Phetsouvanh, R., Lupisan S., et al. (2007). Minimising human error in malaria rapid diagnosis: clarity of written instructions and health worker performance. *Trans. R. Soc. Trop. Med. Hyg.*; 101:9-18.

124. Ruizendaal E., Dierickx S., Grietens KP., et al. (2014). Success or failure of critical steps in community case management of malaria with rapid diagnostic tests: a systematic review. *Malar. J.*; 13:229.

125. Ochomo, EO., Bayoh, NM., Walker, ED., et al. (2013). The efficacy of long-lasting nets with declining physical integrity may be compromised in areas with high levels of pyrethroid resistance. *Malar. J.*; 12:368.

126. Beisel U., Umlauf R., Hitchinson E., et al. (2016). The complexities of simple technologies: re-imagining the role of rapid diagnostic tests in malaria control efforts. *Malar. J.*; 15:64.

127. Luchavez J., Lintag ME., Coll-Black M., et al. (2007). An assessment of various blood collection and transfer methods used for malaria rapid diagnostic tests. *Malar. J.*; 6:149.

128. Donaldson SI., Gooler LE., Scriven M. (2002). Evaluation strategies for managing evaluation anxiety: Toward a phsychology of program. *Am. J. Eval.*; 23: 261–73.

129. United Nations (UN). (2015). Transforming our world: the 2030 Agenda for Sustainable Development. New York, NY: United Nations.

130. World Health Organization (WHO). (2015). Action and Investment to defeat Malaria 2016-2030: For a Malaria-Free World. Geneva, Switzerland: WHO.