Effect of Malaria Rapid Diagnostic Tests on the Management of Uncomplicated Malaria with Artemether-Lumefantrine in Kenya: A Cluster Randomized Trial

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Abstract. Shortly after Kenya introduced artemether-lumefantrine (AL) for first-line treatment of uncomplicated malaria, we conducted a pre-post cluster randomized controlled trial to assess the effect of providing malaria rapid diagnostic tests (RDTs) on recommended treatment (patients with malaria prescribed AL) and overtreatment (patients without malaria prescribed AL) in outpatients ≥ 5 years old. Sixty health facilities were randomized to receive either RDTs plus training, guidelines, and supervision (TGS) or TGS alone. Of 1,540 patients included in the analysis, 7% had uncomplicated malaria. The provision of RDTs coupled with TGS emphasizing AL use only after laboratory confirmation of malaria reduced recommended treatment by 63%-points (*P* = 0.04), because diagnostic test use did not change (−2%-points), but health workers significantly reduced presumptive treatment with AL for patients with a clinical diagnosis of malaria who did not undergo testing (−36%-points; *P* = 0.03). Health workers generally adhered to RDT results when prescribing AL: 88% of RDT-positive and 9% of RDT-negative patients were treated with AL, respectively. Overtreatment was low in both arms and was not significantly reduced by the provision of RDTs (−12%-points, *P* = 0.30). RDTs could potentially improve malaria case management, but we urgently need to develop more effective strategies for implementing guidelines before large scale implementation.

INTRODUCTION

Prompt and effective treatment of patients with malaria parasitemia is a cornerstone of global control efforts to reduce malaria morbidity and mortality.[1] In many malaria-endemic countries in sub-Saharan Africa, malaria is treated presumptively based on a history of fever without an apparent alternative cause. This approach is limited by the poor specificity of clinical symptoms and signs for malaria[2–4] and leads to substantial overdiagnosis of febrile illness as malaria and overtreatment of non-malarial illness with antimalarial drugs.[5–9] As many countries in sub-Saharan Africa are introducing relatively expensive artemisinin-based combination therapies (ACTs) for first-line treatment of uncomplicated malaria into the formal health system,[10] program managers and donors are interested in improving diagnosis of malaria to reduce overtreatment and costs. However, few rigorous trials have assessed whether increasing diagnostic capacity will reduce overtreatment of non-malarial illness with ACT while ensuring that patients with malaria are appropriately treated with ACT.

In June 2006, Kenya introduced artemether-lumefantrine (AL) as recommended first-line treatment of uncomplicated malaria,[11] supported by revised national malaria treatment guidelines prompting presumptive treatment of children < 5 years old and a new diagnostic algorithm for patients ≥ 5 years old.[12] For the latter population, the guidelines recommend 1) if diagnostic testing with microscopy or malaria rapid diagnostic test (RDT) is available, obtain either test on all patients with fever and no apparent alternative cause of fever, and treat with AL according to test results, or 2) if diagnostic

testing is unavailable, treat patients with fever and no apparent alternative cause of fever (i.e., clinical diagnosis of malaria) with AL. Given limited capacity for microscopic diagnosis and concerns regarding the quality of routine microscopy,[6,8] RDTs were being considered as a means to expand diagnostic capacity and improve malaria diagnosis.[13,14] RDTs use immunochromatographic methods to detect malaria parasite-specific antigens, and several commercially available RDTs are relatively inexpensive ($0.70), sensitive (90–95%), specific (> 95%), and stable under operational conditions.[15–21] Moreover, RDTs are relatively simple to use, making them appropriate for use at peripheral health facilities with limited resources and staffing.

We conducted a cluster randomized controlled trial to determine whether the provision of RDTs would reduce overtreatment with AL without decreasing recommended treatment with AL in outpatients ≥ 5 years old.

MATERIALS AND METHODS

Setting. The study was conducted in government health facilities (hospitals, health centers, dispensaries) with and without microscopy in three districts in western Kenya with two malaria transmission intensities previously described as intense hyper- to holoendemic transmission in Bondo and Siaya Districts,[22] and low, acutely seasonal transmission in Kericho District.[23] The study began during peak malaria transmission season but continued into lower malaria transmission season (Figure 1). As part of the national implementation of the new antimalarial policy, between April and October 2006, the Kenya Ministry of Health delivered AL to all health facilities and conducted a 3-day training course on the new malaria guidelines and on the use of AL and malaria diagnostic tests (microscopy and RDTs) for at least one health worker per health facility.[11] At the time of our baseline survey, most health
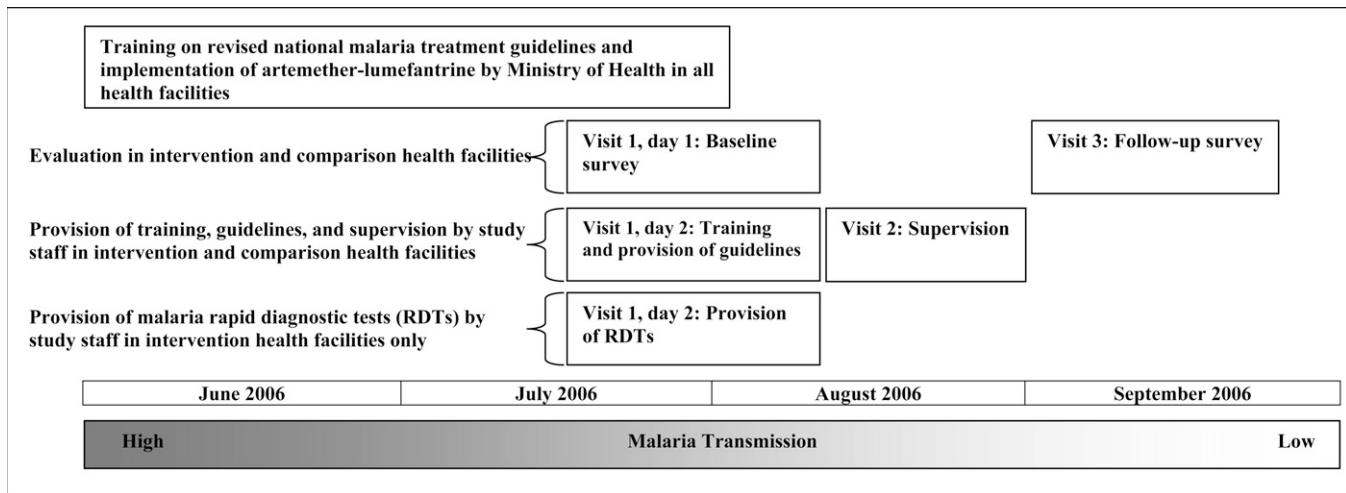
FIGURE 1. Timeline of study activities and key contextual factors. Visit 1: baseline health facility survey on Day 1. In both comparison and intervention health facilities, study staff conduct training on revised national malaria management guidelines and provided all health facility staff with a copy of the guidelines on Day 2. In intervention health facilities only, study staff provided malaria RDTs for routine use on Day 2. Visit 2: supervision visit to assess and provide feedback on correct use of artemether-lumefantrine in all health facilities and RDT use in intervention health facilities. Visit 3: follow-up health facility survey in all health facilities.

facilities in the three study districts had received AL; however, routine in-service training was incomplete.

Study design and interventions. To assess the marginal effect of RDT provision, we conducted a pre-post trial with a randomized comparison group. We used cluster randomization, in which health facilities were clusters. Of a total of 106 eligible health facilities, we selected a probability sample of 60 health facilities using stratified sampling, in which strata were transmission area-health facility type (district hospitals, health centers, dispensaries). After ordering by transmission area-health facility type, systematic sampling was used to randomly assign 30 health facilities to the intervention arm and 30 health facilities to the comparison arm. Health facility surveys were conducted at baseline (Visit 1, Day 1: before any study interventions) and at follow-up (Visit 3: after completion of all study interventions) in all study health facilities (Figure 1), and included all sick outpatients ≥ 5 years old attending the health facility for initial illness consultation on the day of the survey visit.

Both intervention and comparison health facilities received training, a copy of the revised national malaria treatment guidelines, and supervision (TGS). All health facility staff present on the day of training received the half-day on-site training using interactive discussions in small groups (one to five participants) on RDT use, the revised national malaria treatment guidelines for outpatients ≥ 5 years old, the dosing and administration of AL, and management of severe malaria. Study staff who conducted the training were clinical officers or nurses who had undergone a 2-week "train-the-trainers" course led by the primary investigator. All staff were trained to perform RDTs and allowed sufficient practice until they could perform an RDT independently. A copy of the revised national malaria treatment guidelines was provided. Approximately 2 weeks after training, study staff performed a supervisory visit during which they observed at least five health worker–patient consultations and provided feedback using a structured supervision form.

Both intervention and comparison health facilities received TGS, but only intervention health facilities received histidine rich protein 2-based RDTs (Paracheck; Orchid Diagnostics, Mumbai, India) and supplies for safe use and disposal of RDTs for the study period.

Health facility surveys. During each survey, each health facility was visited for 1 day, and all sick patients ≥ 5 years old presenting for an initial consultation were approached for enrollment; written informed consent was obtained from health workers and patients (or their caretakers, if the patient was a child) before enrollment. Clinically trained study staff observed each consultation and collected information on the patient's chief complaint, whether the health worker checked for fever, anemia, danger signs, other common symptoms of illness, pregnancy status, as well as medications and counseling messages given in the consultation room. Study staff did not interfere with the patient–health worker interaction.

After the health worker completed the consultation, including ordering and interpreting any diagnostic tests, study staff collected a reference malaria blood slide (i.e., "gold standard") and reference RDT for each patient. Reference blood slides were taken to a central laboratory, stained with Giemsa, and read independently by two experienced microscopists blinded to reference RDT results and study arm. Malaria parasites were counted against 500 white blood cells, and 100 fields were examined before declaring slides negative. Discordant results were resolved based on a reading by a third microscopist.

After observing the consultation and collecting laboratory specimens, study staff conducted a standardized history and physical examination on all patients, referred to as the "gold standard re-examination." Study staff reviewed the patient's clinic card with the results of routine diagnostic tests, diagnoses, and prescriptions as per the health worker and recorded these results. Study staff used the results of the reference RDT to treat patients with malaria parasitemia who had not received AL from the health worker. Additional treatments,

if indicated from the gold standard re-examination, were provided by study staff free of charge.

Study staff recorded the availability of drugs, microscopy, other laboratory supplies, and training materials at the health facility on the day of the survey. Health worker interviews were conducted to assess participation in routine Ministry of Health training on the revised national malaria treatment guidelines and AL, pre-service training, length of service, and previous experience with finger-stick blood collection and RDTs.

Definitions and outcomes. We used revised national malaria treatment guidelines for patients ≥ 5 years old and clinical information from gold standard re-examination to determine when diagnostic testing was indicated, and the same plus gold standard blood slide results to determine when prescription of AL was indicated. Malaria diagnostic testing was indicated for patients with febrile illness (history of fever in the last 48 hours or axillary temperature ≥ 37.5°C) and no apparent alternative cause (defined as soft tissue infection, urinary tract infection, or ear infection), as determined by gold standard re-examination. Uncomplicated malaria was defined as a patient with febrile illness and no alternative cause of fever as determined by gold standard re-examination, and gold standard blood slide positive for malaria parasitemia. Routine diagnostic testing was defined as RDT or blood slide ordered by the health worker and performed at the health facility as part of the health worker-patient consultation. Recommended treatment was defined as patient with uncomplicated malaria prescribed AL. Overtreatment was defined as patient without uncomplicated malaria prescribed

Box 1
Primary and secondary outcome indicators

Primary outcomes*
1) Proportion of patients with uncomplicated malaria prescribed AL (recommended treatment)
2) Proportion of patients without uncomplicated malaria prescribed AL (overtreatment)
Secondary outcomes†
Use of diagnostic tests:
1) Proportion of patients tested with a malaria RDT or blood slide when testing was indicated according to revised national malaria treatment guidelines (recommended testing)
2) Proportion of patients tested with an RDT or blood slide when testing was not indicated according to revised national malaria treatment guidelines (overtesting)
Prescription of AL according to malaria diagnostic test results:
1) Proportion of patients prescribed AL when routine RDT positive
2) Proportion of patients prescribed AL when routine RDT negative
3) Proportion of patients prescribed AL when routine blood slide positive
4) Proportion of patients prescribed AL when routine blood slide negative
5) Proportion of patients prescribed AL when no routine diagnostic test performed and antimalarial treatment indicated by revised national malaria treatment guidelines based on clinical diagnosis (febrile illness without an apparent alternative cause of fever)
6) Proportion of patients prescribed AL when no routine diagnostic test performed and antimalarial treatment not indicated by revised national malaria treatment guidelines based on clinical diagnosis (no febrile illness or febrile illness with an apparent alternative cause of fever)

* Based on "gold standard" re-examination by study staff and gold standard blood slide.
† Based on "gold standard" re-examination by study staff.

AL. Primary and secondary outcome indicators are described in Box 1.

Sample size calculation. At baseline, we assumed a prevalence of recommended treatment and overtreatment to be 85% and 60%, respectively. In the intervention arm follow-up survey, we expected a prevalence of recommended treatment and overtreatment to be 85% and 10%, respectively. We expected no change from baseline in the comparison arm. Assuming that 15% of patients would have uncomplicated malaria in both arms during baseline and follow-up surveys, we needed to enroll 40 patients per health facility survey in each arm (total of 160) to detect a decrease in overtreatment from 60% to 10% with 95% confidence, 90% power, and a design effect of 2. Assuming we recruited 10 patients per health facility and used 30 health facilities per arm, we expected to recruit 300 patients per health facility survey in each arm.

Analysis. Data were entered and verified using Cardiff teleforms software (Cardiff, Vista, CA). Patients with signs and symptoms of severe malaria and pregnant women with uncomplicated malaria were excluded from the analysis, because first-line treatment in Kenya for these patients should be parenteral or oral quinine, respectively, and not AL. In addition, patients seen in health facilities without AL were excluded from the analysis, because our primary outcomes were recommended treatment and overtreatment with AL. Descriptive analyses were done using SAS version 9.13 (SAS Institute, Cary, NC) with the survey analysis tools, which use the Taylor expansion method to account for stratification, cluster sampling, and unequal selection probabilities. Comparisons of proportions were done using the Wald χ^2 test accounting for stratification, clustering, and unequal selection probabilities. Univariate and multivariate logistic regression modeling was performed using SUDAAN version 9.0 (RTI International, Research Triangle Park, NC) with the RLOGIST procedure with an exchangeable working correlation matrix, which uses generalized estimating equations to account for stratification, clustering, and unequal selection probabilities. All analyses were weighted, and weights equaled 1/the exact probability of selection. Statistical significance was defined as $P \leq 0.05$.

We performed intention-to-treat analyses. We used multivariate logistic regression modeling to test for the statistical significance of changes in outcome indicators between the baseline and follow-up surveys and the "difference of differences" (i.e., change in the intervention group between baseline and follow-up surveys – change in the comparison group). Using a model with terms for study arm (intervention versus comparison), time (baseline versus follow-up), and the study arm–time interaction, we assessed the effect of RDT provision by testing the statistical significance of the time–study arm interaction term, and we assessed the effect of TGS by testing the statistical significance of the time term. Because of differences between baseline and follow-up surveys in the intervention and comparison arms in Ministry of Health training on the revised national malaria treatment guidelines, we included this variable in all multivariate models used to estimate adjusted effect size. Because of small sample size, we only assessed our primary outcome of overtreatment with AL for effect modification by patient factors (age, sex), health facility factors (health facility type, presence of microscopy, health facility in low versus high transmission area), and health worker factors (pre-service training,
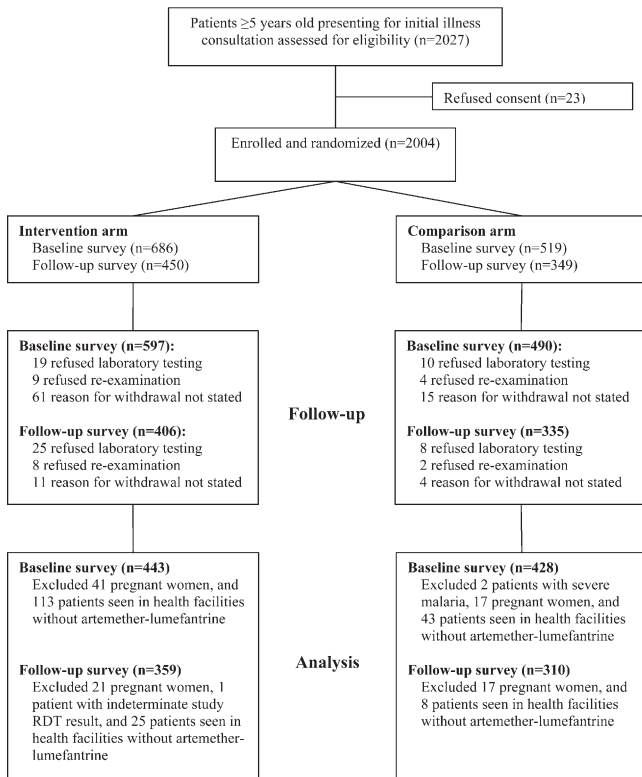
FIGURE 2.   Enrollment of patients in the baseline and follow-up health facility surveys by study arm, Kenya, 2006.

Ministry of Health training on revised national malaria treatment guidelines).

Ethical review. This study was approved by the ethical review committees of the Kenya Medical Research Institute (KEMRI; SSC 1057) and the Centers for Disease Control and Prevention (CDC), Atlanta, GA, and was registered with ClinicalTrials.gov (Identifier: NCT00336388).

Role of funding source. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Enrollment, patient characteristics, and implementation of AL and RDTs. Altogether, we enrolled 2,004 patients and included 1,540 in the analysis (Figure 2). Median time between baseline and follow-up surveys was 32 days (interquartile range, 28–34 days). Baseline demographics, parasitemia prevalence, and health facility type were similar across both arms in both baseline and follow-up surveys (Table 1). However, the Ministry of Health implementation of the new antimalarial policy was not equally distributed between arms; the proportion of patients seen in a health facility with at least one health worker trained on the revised national malaria treatment guidelines by the Ministry of Health increased significantly between baseline and follow-up survey in the intervention arm (34–83%; $P = 0.007$), but did not change in the comparison arm (64–70%). Supply of RDTs in intervention health facilities was adequate, with 100% of patients in the follow-up survey seen in a health facility with RDTs available. However, 25%

of patients in the comparison arm follow-up survey were seen in health facilities where RDTs (from non-study sources) were available. About one half of patients in each arm were seen in health facilities with microscopy. During the follow-up survey, only 60% of patients in the intervention arm and 70% of patients in the comparison arm were seen by a health worker trained by the study staff on RDT use, revised national malaria treatment guidelines, and AL.

Treatment of patients with and without uncomplicated malaria. Overall, the prevalence of uncomplicated malaria was low and did not differ between baseline and follow-up in either arm (intervention arm, 12% versus 4%; comparison arm, 6% versus 4%). Provision of recommended treatment was low in both baseline and follow-up surveys in both arms (intervention arm, 59% versus 36%; comparison arm, 7% versus 48%; Table 2). After adjusting for confounders, stratification, clustering, and weighting, we found that the provision of RDTs significantly reduced recommended treatment by 63%-points ($P = 0.04$), and TGS alone significantly increased recommended treatment by 41%-points ($P = 0.05$).

Overtreatment with AL was rare in both baseline and follow-up surveys (intervention arm, 21% versus 11%; comparison arm, 13% versus 14%); neither the provision of RDTs ($P = 0.30$) nor the provision of TGS ($P = 0.89$) had a significant effect (Table 2). We found no significant effect modification of the relationship between RDT provision and overtreatment with AL by patient, health facility, or health worker factors. Many patients without uncomplicated malaria were prescribed non-recommended antimalarials in both baseline and follow-up surveys (intervention arm, 36% versus 24%; comparison arm, 40% versus 30%); neither the provision of RDTs nor the provision of TGS significantly reduced overtreatment with non-recommended antimalarials.

Use of malaria diagnostic tests. The proportion of patients for whom diagnostic testing was indicated by revised national malaria treatment guidelines did not vary significantly between baseline and follow-up surveys in either arm (intervention arm: 45% versus 42%; comparison arm: 47% versus 46%). In the intervention arm, use of RDTs for recommended testing increased from 3% to 46%, whereas the use of blood slides decreased from 38% to 8% (Table 3). Overall use of malaria diagnostic tests (RDT or blood slide) for recommended testing did not change as a result of the provision of RDTs. Health workers frequently ordered either RDTs or blood slides when not indicated in both baseline and follow-up surveys (intervention group, 37% versus 34%; comparison group, 15% versus 17%); overtesting did not change significantly as a result of the provision of RDTs or TGS.

Adherence to malaria diagnostic test results. In the intervention arm follow-up survey, health workers generally adhered to RDT and blood slide results when prescribing AL (Table 4). They often prescribed AL for RDT-positive and blood slide–positive patients (88% and 68%, respectively); all RDT-positive patients and blood slide–positive patients were treated with either AL, a second-line or non-recommended antimalarial. Health workers rarely prescribed AL for RDT-negative and blood slide–negative patients (9% and 2%, respectively), but they often prescribed non-recommended antimalarials for RDT-negative patients and blood slide–negative patients (27% and 48%, respectively). Health workers rarely prescribed AL based on a clinical diagnosis of malaria (i.e., the presence of fever with no apparent alternative cause)

TABLE 1
Characteristics of patients ≥ 5 years old by study arm and survey in Kenya, 2006 (N = 1540)

	Intervention arm		Comparison arm	
	Baseline survey (N = 443) [N (%; 95% CI)]*	Follow-up survey (N = 359) [N (%; 95% CI)]*	Baseline survey (N = 428) [N (%; 95% CI)]*	Follow-up survey (N = 310) [N (%; 95% CI)]*
Patient demographics				
Median age in years (Interquartile range)	26 (18–42)[1]	27 (18–44)[2]	24 (16–40)[3]	25 (15–38)[4]
Female	269 (63%; 58–69)[5]	216 (61%; 55–66)	261 (62%; 57–66)[6]	187 (63%; 56–69)
Uncomplicated malaria prevalence	51 (12%; 5–19)	13 (4%; 1–7)	27 (6%; 2–10)	13 (4%; 2–7)
Health facility (HF), health worker (HW), and consultation characteristics				
Seen in hospital outpatient department	93 (13%; 0–27)	91 (15%; 0–31)	78 (11%; 0–25)	54 (10%; 0–23)
Seen in health center	185 (30%; 8–52)	134 (26%; 5–47)	162 (28%; 11–45)	124 (28%; 10–46)
Seen in dispensary	165 (57%; 32–83)	134 (59%; 34–85)	188 (60%; 40–81)	132 (61%; 41–82)
Seen by nurse, clinical officer or physician	397 (91%; 78–100)[7]	301 (90%; 77–100)[8]	343 (74%; 53–95)	268 (86%; 72–100)[9]
Seen by HW who received supervisory visit from district health manager in last 6 months	344 (83%; 67–100)[7]	293 (89%; 76–100)[10]	292 (68%; 47–90)	255 (87%; 72–100)[11]
Median consultation time in minutes (Interquartile range)	4 (2–6)[12]	5 (3–7)[2]	4 (2–5)[13]	4 (3–6)[9]
Implementation of revised national malaria treatment guidelines by Ministry of Health				
Seen in HF with second line or non-recommended antimalarial	443 (100%)	359 (100%)	428 (100%)	310 (100%)
Seen in HF where at least one HW trained on revised national malaria treatment guidelines and artemether-lumefantrine use by Ministry of Health	155 (34%; 8–61)[7]	269 (83%; 63–100)[8]	309 (64%; 44–85)	227 (70%; 47–93)[9]
Availability of malaria diagnostic testing				
Seen in HF with malaria rapid diagnostic tests (RDTs)	35 (5%; 0–13)	359 (100%)	24 (4%; 0–12)	74 (25%; 6–44)
Seen in HF with microscopy	278 (55%; 27–83)	247 (57%; 27–87)	271 (50%; 28–72)	201 (50%; 27–72)
Seen in HF with either RDTs or microscopy	288 (57%; 28–85)	359 (100%)	278 (52%; 30–74)	229 (59%; 36–83)
Training on RDT use, revised national malaria treatment guidelines and AL use by study staff				
Seen by HW trained on RDT use, revised national malaria treatment guidelines and AL use by study staff	0 (0%)[7]	207 (60%; 31–90)[8]	0 (0%)	217 (70%; 49–90)[9]

*Weighted percent and 95% CI adjusted for stratification, clustering, and weighting.
[1] N = 438.
[2] N = 348.
[3] N = 420.
[4] N = 300.
[5] N = 442.
[6] N = 425.
[7] N = 431.
[8] N = 328.
[9] N = 301.
[10] N = 326.
[11] N = 291.
[12] N = 419.
[13] N = 426.

when no test was performed (8%). The provision of RDTs significantly reduced the use of clinical diagnosis of malaria to prescribe AL by 36%-points (P = 0.03).

DISCUSSION

The goal of a malaria case management policy is to treat patients with malaria with an effective antimalarial (recommended treatment) while minimizing treatment of patients without malaria (overtreatment). In the pre-ACT era, presumptively treating fever without an apparent alternative cause resulted in high levels of recommended treatment, but with substantial overtreatment. With the introduction of relatively expensive ACTs, there is a renewed interest in improving malaria diagnosis to reduce overtreatment. We hypothesized that improving malaria diagnosis through the provision of RDTs, after implementing TGS, would reduce overtreatment

without decreasing recommended treatment of uncomplicated malaria. However, we were alarmed to find that providing RDTs significantly reduced recommended treatment without reducing overtreatment.

Improved malaria diagnosis will improve case management if the diagnostic test is used when indicated, the diagnostic test has high sensitivity and specificity, and health workers adhere to test results. Significantly fewer patients with uncomplicated malaria received recommended treatment with AL as a result of the provision of RDTs because of two factors. First, the provision of RDTs did not significantly increase diagnostic test use, because RDT use replaced microscopy. Second, although RDTs performed by health facility staff had adequate sensitivity (92%; 95% CI: 81–100%) and specificity (97%; 95% CI: 93–100%)[24] and health workers generally adhered to RDT results for prescribing AL, the provision of RDTs significantly reduced AL prescriptions for patients who were not tested,

TABLE 2

Treatment of patients ≥ 5 years old with and without uncomplicated malaria by study arm and survey, Kenya, 2006

	Intervention arm		Comparison arm		Effect of training, guidelines, and supervision + malaria rapid diagnostic tests [% change* (P value)]	Effect of training, guidelines, and supervision [% change* (P value)]	Effect of malaria rapid diagnostic tests only [% change* (P value)]
	Baseline survey (%)*	Follow-up survey (%)*	Baseline survey (%)*	Follow-up survey (%)*			
Treatment of patients with uncomplicated malaria	N = 51	N = 13	N = 27	N = 13			
Artemether-lumefantrine (recommended treatment)	59%	36%	7%	48%	−22% (0.18)	+41% (0.05)	−63% (0.04)
Quinine (second-line treatment)	9%	5%	15%	10%	−4% (0.82)	−4% (0.75)	−0% (0.88)
Non-recommended antimalarial†	21%	0%	50%	4%	−21% (< 0.001)	−46% (0.003)	+25% (< 0.001)
Treatment of patients without uncomplicated malaria	N = 392	N = 346	N = 401	N = 297			
Artemether-lumefantrine (overtreatment)	21%	11%	13%	14%	−10% (0.09)	+1% (0.86)	−12% (0.30)
Quinine (second-line treatment)	19%	6%	8%	10%	−13% (0.003)	+2% (0.66)	−15% (0.04)
Non-recommended antimalarial†	36%	24%	40%	30%	−12% (0.24)	−10% (0.30)	−2% (0.81)

 *Predicted prevalences using logistic regression model adjusted for confounder (health facility staff trained on revised national malaria treatment guidelines by Ministry of Health) and accounting for stratification, clustering, and weighting. Statistical testing performed using Wald χ^2 test.
 †Primarily sulphadoxine-pyrimethamine alone, amodiaquine alone, or sulphadoxine-pyrimethamine and amodiaquine combination.

but who had a clinical diagnosis of uncomplicated malaria (fever without an apparent alternative cause). Thus, the lack of an increase in recommended diagnostic testing (−2%-points) coupled with a significant reduction in AL prescriptions based on clinical diagnosis (−36%-points) led to a significant reduction in recommended treatment of uncomplicated malaria. This pattern of RDT and AL use might partially be explained by differences in the key messages delivered during our training and supervision. In the intervention arm, health workers received TGS with an emphasis on increasing diagnostic test use according to guidelines and only prescribing AL after laboratory confirmation. In practice, health workers mostly prescribed AL only after laboratory confirmation, but did not increase diagnostic test use sufficiently. In the comparison arm, health workers received TGS with an emphasis on increasing AL use with laboratory confirmation, if available, or based on clinical diagnosis alone. In practice, health workers

increased overall prescribing of AL and especially for patients who had a clinical diagnosis of malaria. Much of the literature on malaria diagnostic testing has focused on health workers' adherence to test results; however, our results showed that we need a better understanding of when and why health workers order diagnostic tests. Health worker supports are needed to improve adherence to guidelines for ordering diagnostic tests not only to increase appropriate diagnostic test use but also to decrease overtesting, which erodes the potential cost savings from RDTs.

Despite the reduction in recommended treatment, the provision of RDTs did not change overtreatment with AL. In our study, we found relatively low levels of overtreatment with AL (11–21%) and relatively high levels of overuse of non-recommended antimalarials (primarily sulphadoxine-pyrimethamine and amodiaquine) in patients without uncomplicated malaria (24–40%). In the pre-ACT era, overuse of

TABLE 3

Use of malaria diagnostic tests (RDT or BS) when indicated and not indicated by revised national malaria treatment guidelines in patients ≥ 5 years old by study arm and survey, Kenya, 2006

	Intervention arm		Comparison arm		Effect of training, guidelines, and supervision + RDTs [% change* (P value)]	Effect of training, guidelines, and supervision [% change* (P value)]	Effect of RDTs only [% change* (P value)]
	Baseline survey (%)*	Follow-up survey (%)*	Baseline survey (%)*	Follow-up survey (%)*			
Diagnostic test used when testing indicated by guidelines (recommended testing)	N = 203	N = 145	N = 206	N = 139			
RDT	3%	46%	0%	11%	+44% (0.002)	+11% (< 0.001)	+33% (< 0.001)
BS	38%	8%	13%	17%	−30% (0.02)	+5 (0.54)	−35% (0.02)
Either RDT or BS	43%	56%	13%	29%	+14% (0.21)	+16% (0.07)	−2% (0.57)
Diagnostic test used when testing not indicated by guidelines (overtesting)	N = 240	N = 214	N = 222	N = 171			
RDT	3%	23%	1%	4%	+21% (0.02)	+3% (0.11)	+18% (0.44)
BS	33%	6%	15%	13%	−26% (0.03)	−1% (0.83)	−25% (0.03)
Either RDT or BS	37%	34%	15%	17%	−2% (0.79)	+2% (0.80)	−4% (0.76)

 *Predicted prevalence using logistic regression model adjusted for confounder (health facility staff trained on revised national malaria treatment guidelines by Ministry of Health) and accounting for stratification, clustering, and weighting. Statistical testing performed using Wald χ^2 test.
 BS = blood slide.

Table 4

Prescription of artemether-lumefantrine according to routine malaria diagnostic test (RDT or BS) results and clinical diagnosis of malaria* in patients ≥ 5 years old by study arm and survey in Kenya, 2006

	Intervention arm		Comparison arm		Effect of training, guidelines, and supervision + RDTs [% change† (P value)]	Effect of training, guidelines, and supervision [% change† (P value)]	Effect of RDTs only [% change† (P value)]
	Baseline survey [n/N (%†)]	Follow-up survey [n/N (%†)]	Baseline survey [n/N (%†)]	Follow-up survey [n/N (%†)]			
RDT positive‡	1/1 (100%)	13/14 (88%)	0/0 (0%)	0/0 (0%)			
RDT negative‡	0/4 (0%)	11/86 (9%)	0/2 (0%)	1/21 (5%)			
BS positive	30/49 (52%)	12/20 (68%)	11/21 (50%)	9/26 (51%)	+16% (0.80)	+2% (0.95)	+14% (0.70)
BS negative‡	4/106 (3%)	1/49 (2%)	3/71 (4%)	0/54 (0%)			
Clinical diagnosis of malaria and no diagnostic test performed	22/115 (30%)	5/59 (8%)	16/161 (12%)	17/84 (26%)	−21% (0.10)	+15% (0.11)	−36% (0.03)
No clinical diagnosis of malaria and no diagnostic test performed	21/160 (19%)	9/120 (4%)	11/169 (11%)	6/121 (6%)	−15% (0.05)	−5% (0.47)	−10% (0.46)

* Clinical diagnosis of malaria based on presence of fever and no alternative cause in patients who do not receive a malaria diagnostic test.
† Predicted prevalence using logistic regression model adjusted for confounder (health facility staff trained on revised national malaria treatment guidelines by Ministry of Health) and accounting for stratification, clustering, and weighting unless otherwise noted. Statistical testing performed using Wald χ^2 test.
‡ Proportions adjusted for stratification, clustering, and weighting, but no logistic regression modeling or statistical testing performed because of small sample size.
BS = blood slide.

non-ACT antimalarials was well described[5,6,25–28]; similarly, we found health workers commonly treated RDT-negative patients, blood slide–negative patients, and patients who did not undergo diagnostic testing with non-recommended antimalarials. In addition, similar to other studies in the ACT era, we found that health workers underprescribed AL while overprescribing non-recommended antimalarials.[29–32] Qualitative work from Kenya suggests that concerns about the cost of AL, fear of stockouts, confusion about AL prescribing without diagnostic confirmation, and easy availability of non-recommended antimalarials contributed to prescriber confusion and led to low use of AL and overuse of non-recommended antimalarials.[33] Potentially, AL rationing and prescriber confusion could have been minimized by guaranteeing an adequate and stable supply of AL while completely withdrawing non-recommended antimalarials.

This study had several limitations. First, it was conducted while the new malaria treatment policy was being implemented; thus, our findings might not reflect patterns of AL use after the policy has been in place for an extended period. AL use might increase after health workers have had the opportunity to become familiar with the drug. However, reports from Zambia (2 years after AL implementation) and Kenya (6 months after implementation and 5 months after this study was performed) continue to show low AL use.[29,31,32] Although we adjusted for baseline differences in Ministry of Health training between intervention and comparison arms in all of our models, other differences between intervention and comparison arm health facilities in factors that we did not measure might have biased our results. Second, we only measured indicators at two time points and the median time between surveys was only 32 days; thus, we could only assess the immediate impact of our interventions. Future studies should have longer follow-up and use continuous monitoring to assess long-term trends in malaria management. Third, we used direct observation to measure indicators. Health workers might have performed better because of being observed ("Hawthorne effect"), although it seems unlikely that it would have affected study groups differently and thus is unlikely to be an important source of bias.[34] Fourth, our results might be biased towards the null, because some health facilities in the comparison arm had RDTs.

In conclusion, this study rigorously assessed the provision of RDTs in the setting of antimalarial policy change to AL. After implementing TGS, the provision of RDTs reduced recommended treatment with AL without reducing overtreatment. The provision of RDTs did not increase malaria diagnostic test use, because RDTs replaced microscopy. In addition, we noted low levels of recommended testing and high levels of overtesting. Future efforts at RDT implementation should focus on appropriate use of RDTs. Health workers adhered to RDT test results when prescribing AL, but often prescribed non-recommended antimalarials for diagnostic test–negative patients. Our concerns that health workers would ignore negative RDT test results and inappropriately prescribe AL seem to be unfounded. Many countries, like Kenya, are considering large scale implementation of RDTs and the implementation of guidelines that focus on the need for malaria diagnostic testing. Although this strategy has great potential, our findings, if confirmed, suggest that this strategy will waste resources used to purchase RDTs and substantially worsen case management quality for patients who truly have malaria. However, with timely research to understand why health workers make the decisions they do on the use of RDTs, ACTs, and other antimalarials, more effective health worker supports can be developed, helping RDTs realize their potential. We urgently need to develop strategies to improve use of malaria diagnostic tests and prescribing practices before moving forward with large-scale implementation.

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