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Economic Evaluation of a Cluster Randomized Trial of Interventions to Improve Health Workers' Practice in Diagnosing and Treating Uncomplicated Malaria in Cameroon

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ABSTRACT

Background: Malaria rapid diagnostic tests (RDTs) are a valid alternative to malaria testing with microscopy and are recommended for the testing of febrile patients before prescribing an antimalarial. There is a need for interventions to support the uptake of RDTs by health workers. **Objective:** To evaluate the cost-effectiveness of introducing RDTs with basic or enhanced training in health facilities in which microscopy was available, compared with current practice. **Methods:** A three-arm cluster randomized trial was conducted in 46 facilities in central and northwest Cameroon. Basic training had a practical session on RDTs and lectures on malaria treatment guidelines. Enhanced training included small-group activities designed to change health workers' practice and reduce the consumption of antimalarials among test-negative patients. The primary outcome was the proportion of febrile patients correctly treated: febrile patients should be tested for malaria, artemisinin combination therapy should be prescribed for confirmed cases, and no antimalarial should be prescribed for patients who are test-negative. Individual patient data were obtained from facility records and an exit survey. Costs were estimated from a societal perspective using project reports and patient exit data. The analysis used bivariate multilevel modeling and adjusted for imbalance in baseline covariates. **Results:** Incremental cost per febrile patient correctly treated was $8.40 for the basic arm and $3.71 for the enhanced arm. On scale-up, it was estimated that RDTs with enhanced training would save $0.75 per additional febrile patient correctly treated. **Conclusions:** Introducing RDTs with enhanced training was more cost-effective than RDTs with basic training when each was compared with current practice.

Key words: Cameroon, cluster-randomized trial, cost-effectiveness analysis, health worker training, malaria, practice.

Introduction

In 2010, the World Health Organization updated malaria treatment guidelines to confirm that rapid diagnostic tests (RDTs) are a valid alternative to testing using microscopy and to recommend parasitological testing in all patients before prescribing an antimalarial [1]. Interest in RDTs has intensified, and governments across sub-Saharan Africa are now deciding how to expand access to malaria testing and whether to introduce RDTs in health facilities that already offer malaria testing using microscopy. These policy decisions will require revisions to national malaria treatment guidelines and supporting interventions that ensure that the policy change is accompanied by a change in health workers' practice.

In malaria-endemic areas, cases of uncomplicated malaria are routinely treated in primary health facilities and hospital outpatient departments, and clinical guidelines advise that in high-transmission settings malaria should be suspected in patients who present with a fever or report having a fever in the past 24 hours [1]. Malaria testing is advised because malaria symptoms are nonspecific and the fever may have other causes. Microscopy, however, requires a laboratory and technicians able to prepare and read blood slides and these are often limited in low-income settings. Consequently, it has become common for health workers to make treatment decisions on the basis of symptoms alone and for antimalarials to be presumptively prescribed to febrile patients.

RDTs offer considerable potential to transform malaria diagnosis and treatment because they do not require a laboratory and

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can be used with minimal training. This potential, however, will be realized only if health workers prescribe treatment on the basis of test result. Evidence from several countries, including Cameroon, suggests that reliance on a presumptive malaria diagnosis has created a mindset among health workers and patients that febrile illness should be treated with an antimalarial and it is not uncommon for antimalarials to be prescribed to patients who tested negative for malaria [2–6].

The economic argument for introducing RDTs critically depends on health workers' practice [7,8]. This assumption has been emphasized in several studies [7,9,10], and the sensitivity of cost-effectiveness results to health workers' practice has been illustrated using trial data from Tanzania [8]. Results were also sensitive to the prevalence of malaria in febrile patients, specificity and sensitivity of the test, cost of testing and medicines, whether nonmalaria febrile illness was a bacterial or self-resolving viral infection, the efficacy of antimalarials and antibiotics taken, and whether patients take medicines as advised [9]. The literature shows that RDTs tend to be more cost-effective than microscopy when compared with a presumptive diagnosis [7,11,12], while the cost-effectiveness of RDTs compared with microscopy depends on the relative cost of the tests, as well as their specificity and sensitivity in routine use [10,13–15].

To improve malaria diagnosis and treatment using RDTs in Cameroon, interventions were designed following formative research with patients and health workers in two regions of Cameroon [3,6,16]. The formative research showed that microscopy was available in most of the public and mission facilities but was underused and less than 50% of the febrile patients were tested for malaria [6]. Malaria was overdiagnosed: 73% of the febrile patients received an antimalarial, yet malaria was present in only 30% of the febrile patients tested by the study team [6]. Moreover, patients often received an antimalarial regardless of the test result: 82% of the patients who reported that they tested negative for malaria were prescribed an antimalarial [6]. Qualitative research also provided an insight into health workers' practice and highlighted both a mistrust of malaria test results and challenges in managing patient expectations [3].

In collaboration with the National Malaria Control Programme (NMCP) of Cameroon, training modules were developed to support the introduction of RDTs in public and mission facilities. The basic training was intended to equip health workers with the knowledge and practical skills needed to diagnose and treat uncomplicated malaria, including how to conduct an RDT. Because improving health workers' adherence to the malaria treatment guidelines was a key objective, additional training was designed that used interactive methods and sought to address the gap between health workers' knowledge and practice, and change prescribing behavior.

This article reports the incremental cost per febrile patient correctly treated (according to the malaria treatment guidelines) of each intervention compared with current practice. Cost-effectiveness was assessed from both a provider perspective and a societal perspective. The analysis uses statistical methods suitable for individual patient data on costs and effects obtained from a cluster randomized trial [17,18].

Methods

Trial Design and Intervention

A cluster randomized trial was designed to evaluate the effectiveness and cost-effectiveness of introducing RDTs with basic or enhanced training in facilities in which microscopy was available compared with current practice. The three-arm cluster randomized trial was conducted at 46 public and mission health facilities that offered malaria microscopy testing and were located in central and northwest regions of Cameroon where malaria is endemic. The trial design and interventions are summarized here, and further details are available elsewhere [19,20]. The trial was registered (clinicaltrials.gov: NCT01350752), the study protocol is available [19], and the main trial article has been published [20]. The effect of the interventions on the proportion of febrile patients correctly treated according to the malaria treatment guidelines was measured by surveying febrile patients exiting health facilities.

Facilities were stratified by site, randomly selected, and allocated to one of three arms: control, basic, and enhanced. There was no intervention at facilities in the control arm. Each facility in the two intervention arms was supplied 100 RDTs (SD Bioline Malaria Ag Pf/Pan, Standard Diagnostics, Yongin, South Korea) per month without charge. The brand and number of RDTs supplied was selected on the basis of advice from the NMCP, and the test is reported to have a minimum detection rate of 97.5% for *Plasmodium falciparum* malaria, even at low levels of parasitemia (200 parasites/μl) [21]. Each facility in the basic arm was invited to send three health workers to a 1-day training course that was organized by the study team. The 1-day training had three lectures on the revised malaria clinical guidelines and a practical session on how to use RDTs. The enhanced intervention replicated not only the basic intervention but also contained an additional 2 days of training. The additional training used participatory methods to reinforce material covered in the basic training, while also encouraging health workers to adapt to change, communicate effectively, and support each other. For instance, trainers facilitated small-group work and used problem-solving exercises, a treatment algorithm game, self-developed participatory drama, and role-playing. The training courses were delivered by representatives from the NMCP and members of the study team. Health workers who attended basic and enhanced training courses were encouraged to hold training sessions at their facility (hereafter referred to as in-facility training) and inform their colleagues about RDTs and the revised malaria treatment guidelines. The trial was designed to approximate "real-world" rather than controlled conditions, and it was possible, for example, that a facility encountered stock-outs of RDTs and artemisinin combination therapies (ACTs) during the evaluation.

Effectiveness of Interventions

The effect of the interventions was measured by the proportion of febrile patients attending facilities who were correctly treated according to the revised malaria treatment guidelines. This was a composite measure that required all febrile patients to be tested for malaria using microscopy or RDT, patients to receive an ACT if they have a positive malaria test result, and patients not to receive an antimalarial if they have a negative malaria test result. Patients were invited to participate in an exit survey if they sought treatment for a fever at one of the facilities participating in the trial, were more than 6 months old, were not pregnant, and did not have symptoms of severe malaria. With informed consent, the exit survey was administered by trained fieldworkers to the patient or his or her caregiver. A copy of the malaria test register in each facility was also obtained. Data collection took place between October and December 2011 and commenced 3 months after interventions were implemented. The effectiveness results have been submitted for peer-reviewed publication in an academic journal [20].

Cost Measurement and Valuation

Health care cost for each patient in the exit survey was estimated taking into account direct and indirect costs incurred by the

patient and caregivers to obtain care, net costs to the facility (adjusting for user fees), and the intervention cost. All costs were estimated in 2011 in Central African francs (CFA) and converted to US dollars (US $) at 2011 prices, using a conversion rate of US $1 = CFA 471.87 (the official exchange rate for 2011; http://wdi.worldbank.org/table/4.16 [Accessed August 23, 2013]).

Intervention cost

Financial and economic costs of the training interventions were estimated from project reports and interviews with staff, using an ingredients-based approach (see Table 3 and Appendix A found at http://dx.doi.org/10.1016/j.jval.2014.07.010). Start-up costs were incurred to develop the training materials and to engage national and local stakeholders in the training program and revisions to the malaria treatment guidelines. One-off implementation costs were incurred to train the trainers, administer and implement the training workshops, and hold in-facility training. The base-case scenario assumed that one-off implementation costs would be incurred annually. Many activities to prepare for basic and enhanced training were conducted simultaneously, and the cost that corresponds to each arm has been determined by estimating which costs would have been incurred if the interventions were independent. The cost of the in-facility training was estimated separately for each facility on the basis of the length of the training and the number of health workers attending. RDTs were not included in the cost of the intervention but were captured elsewhere.

The total annual economic cost of the intervention was estimated for each facility. Start-up costs of the training interventions were annualized over 4 years using a 3% discount rate on the basis of the assumption that the training materials would remain relevant for a minimum of 4 years [22]. The economic costing also incorporated the time health workers spent at the in-facility training, for which there was no financial cost. The cost of the intervention per febrile patient was estimated by apportioning the total annual economic cost across all febrile patients who attend the facility each year on the basis of an estimate obtained from facility records.

Cost of febrile illness

Costs incurred by patients to diagnose and treat febrile illness were estimated for each individual participating in the exit survey, and the mean cost per febrile patient was calculated. Exit survey respondents described the care received during the facility visit and reported direct costs incurred for the consultation, tests undertaken and medicines received, direct cost of travel and other out-of-pocket expenses, and the time spent at the facility and for travel. The time of patients and caregivers was valued at the wage of an unskilled worker (CFA 1200/d).

The costs incurred by facilities to diagnose and treat each febrile patient were also estimated. The facility cost was estimated for each febrile patient using patient-reported information on the consultation, such as the cadre of health worker, malaria tests conducted (by microscopy or RDT), and medicines prescribed and dispensed. These data were combined with detailed unit cost data collected at selected facilities on the average health worker time and resource use per activity plus portion of overhead costs. The net facility cost per febrile patient was estimated by deducting the amount paid by the patient. In some cases, the amount paid by the patient exceeded the cost to the facility (i.e., net facility cost was zero), though in other cases (often when the patient was younger than 5 years) the cost to the facility exceeded the fees paid.

Cost-Effectiveness Analysis

Incremental cost-effectiveness ratios (ICERs) for basic and enhanced interventions, with each intervention compared with control, were calculated for the primary outcome (correctly treated according to guidelines) in an intention-to-treat analysis from both a provider perspective and a societal perspective. The ICERs represent the incremental cost for each additional febrile patient correctly treated.

The cost-effectiveness analysis used individual patient-level data on costs and effects from the cluster randomized trial according to the latest methods [17,18,23]. An initial examination of the data found a correlation between costs and effects at the individual level and the cluster level and an intracluster correlation in both costs and effects. In addition, although randomization of clusters to trial arms should negate the need to include individual-level and cluster-level covariates, there was imbalance in selected baseline characteristics across the three arms. The incremental costs and effects were estimated using a bivariate multilevel model with covariates. This method simultaneously estimates the multilevel model for cost, c_{ij}, and the multilevel model for effect, e_{ij}:

$$c_{ij} = \beta_0^c + \beta_1^c a_j + \beta_2^c x_{ij} + \beta_3^c z_j + u_j^c + \varepsilon_{ij}^c \qquad \begin{pmatrix} \varepsilon_{ij}^c \\ \varepsilon_{ij}^e \end{pmatrix} \sim BVN\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{matrix} \sigma_c^2 & \rho\sigma_c\sigma_e \\ & \sigma_e^2 \end{matrix}\right)$$

$$e_{ij} = \beta_0^e + \beta_1^e a_j + \beta_2^e x_{ij} + \beta_3^e z_j + u_j^e + \varepsilon_{ij}^e \qquad \begin{pmatrix} u_{ij}^c \\ u_{ij}^e \end{pmatrix} \sim BVN\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{matrix} \tau_c^2 & \varphi\tau_c\tau_e \\ & \tau_e^2 \end{matrix}\right)$$

where a_j is the arm of the trial, x_{ij} are the individual-level covariates, z_j are the cluster-level covariates, β_1, β_2, and β_3 are the corresponding parameter for these variables, β_0 is the constant, and e_{ij} and u_j capture the individual-level and cluster-level variation. The assumption of normality was investigated for costs and effects. The distribution of costs was close to a normal distribution. We assumed a normal distribution for effects having considered the alternative specifications, and having confirmed that the predicted probabilities from the linear probability model lay within the 0 to 1 interval, and were similar to those from a logit model [24,25]. Statistical analysis was completed by running MLwiN 2.28 from Stata 12.1 [26].

Confidence intervals for the ICERs cannot be interpreted because there were some observations with worse outcomes and higher costs and some with better outcomes and lower costs, and hence these are not reported. Cost-effectiveness acceptability curves (CEACs) were generated by bootstrapping the residuals from the bivariate multilevel model with covariates [17,27]. The CEACs illustrate the probability that each intervention was optimal for a range of willingness-to-pay values, where the willingness to pay is the value placed on an additional person treated according to the malaria treatment guidelines [28].

The base-case analysis estimated the cost-effectiveness of the interventions compared with current practice as implemented for the trial. The base case included all start-up costs and implementation costs, assuming that the training materials would remain useful for 4 years and the training would be held annually. The cost-effectiveness of the interventions was also considered in a "scale-up scenario" in which the start-up costs were excluded because they were a sunk cost, and it was assumed that the training would be held every 2 years. These estimates should be useful for the Cameroon government in deciding whether to scale-up the introduction of RDTs with health worker training.

Ethics Statement

Ethical approval was obtained from the ethics committees of the London School of Hygiene and Tropical Medicine (No. 5429) and

Cameroon National Ethics Committee (No. 030/CNE/DNM/09). Administrative clearance was obtained from the Ministry of Public Health (No. D30-343/AAR/MINSANTE/SG/DROS/CRC/JA). The trial is registered with clinicaltrials.gov (NCT01350752).

Results

The study took place between June and December 2011, and 46 facilities participated in the study. The basic and enhanced training was successfully delivered to 37 facilities in the intervention arms, and in-facility training was held in 34 facilities (15 of 18 in the basic arm and all 19 in the enhanced arm) (see Appendix A found at http://dx.doi.org/10.1016/j.jval.2014.07.010). The implementation and fidelity of the interventions have been described elsewhere [20].

Study Population

The effectiveness and cost-effectiveness of basic and enhanced interventions were evaluated using 3982 eligible patients who completed the exit survey (Table 1). Patient characteristics across the three arms of the trial show some differences in the age distribution of patients, and in the proportion that had previously sought treatment and asked for a blood test. Similarly, although facilities were randomly allocated to the trial arm, there were some differences across the arms in the type of facility, the average number of febrile patients per day, and the percentage of facilities that encountered stock-outs of ACT in the past 4 weeks.

Effects

The proportion of febrile patients who were correctly treated according to the clinical guidelines was 42% in the basic arm and 55% in the enhanced arm, compared with 37% in the control arm (Table 2). This is a composite indicator that requires febrile patients to be tested for malaria and for their treatment to be consistent with the malaria test result. Breaking down this indicator shows that the difference between the arms is largely in the treatment prescribed and received by patients who tested negative for malaria: 47% of the patients in the basic arm and 68% in the enhanced arm were correctly treated compared with 14% in the control arm. There were also some differences in malaria positivity rates across the arms, and the percentage of patients with a positive result was higher when patients were tested using microscopy rather than RDT. It should be noted that all these results are unadjusted, and do not take into account the clustering or the imbalance in the baseline covariates, and more detailed analyses are presented elsewhere [20].

Costs

The financial cost of the basic training was $28,392, and the financial cost of the enhanced training was $63,127. A description of the resources used is provided in Appendix A found at http://dx.doi.org/10.1016/j.jval.2014.07.010. The start-up costs constitute a large proportion of the total financial costs (73% and 74% of the basic and enhanced interventions, respectively), which largely reflects the amount of time staff spent designing, piloting, and refining the training materials.

On the assumption that the training materials would remain useful for 4 years, the total annual economic cost was $14,481 for the basic training and $30,976 for the enhanced training (Table 3).

Table 1 – Patient and facility characteristics.

Characteristic	Current practice (N = 681)	Basic (N = 1632)	Enhanced (N = 1669)
Patient's sex			
Male	45.8	45.0	44.0
Female	54.2	55.0	56.0
Patient's age			
6–12 mo	5.7	7.7	6.8
1–4 y	28.9	29.1	29.8%
5–19 y	28.5	22.7	22.1
20–39 y	19.2	26.4	26.2
40+ y	17.3	14.2	15.2
Previously sought treatment for this illness episode			
Yes	73.1	59.5	64.8
No	26.9	40.5	35.2
Patient or caregiver asked for a blood test			
Yes	36.7	22.4	21.3
No	63.3	77.7	78.7
Type of facility			
Public	85.3	61.3	56.7
Mission	14.7	38.7	43.3
Average number of patients at facility per day			
Mean (range)	20.5 (5–80)	45.1 (6–300)	51.3 (4–200)
Facility had stock-outs of artemisinin combination therapy in past 4 wk			
Yes	14.8	12.3	6.0
No	85.2	87.7	94.0
Study site			
Bamenda, northwest region	58.7	42.8	46.6
Yaoundé, central region	41.3	57.2	53.4

Note. Values are % except where indicated.

Table 2 – Summary of effects.*

Effect	Current practice (N = 681)	Basic (N = 1632)	Enhanced (N = 1669)
Primary outcome			
% of febrile patients who were correctly treated according to malaria guidelines	36.8	42.0	55.0
Components of primary outcome			
% tested for malaria	79.2	76.6	78.6
If malaria test-positive, % with ACT	75.6	74.3	75.8
If malaria test-negative, % without an antimalarial	13.7	46.6	68.2
Malaria test type and result†			
If tested for malaria, % tested using microscopy	100	63.4	57.3
% positive if tested using microscopy	53.2	39.7	46.0
% negative if tested using microscopy	45.9	60.3	54.0
If tested for malaria, % tested using RDT	–	36.6	42.7
% positive if tested using RDT	–	23.2	30.6
% negative if tested using RDT	–	76.9	69.4
Treatment prescribed or received			
Of those not tested	N = 274	N = 385	N = 479
% with any antimalarial	90.4	62.1	55.3
% with an ACT	75.6	48.3	47.8
% with an antibiotic	69.6	56.4	52.8
Of those who tested positive for malaria	N = 235	N = 773	N = 730
% with any antimalarial	96.7	92.5	94.4
% with an ACT	75.6	74.3	75.8
% with an antibiotic	39.1	44.9	42.6
Of those who tested negative for malaria	N = 135	N = 351	N = 320
% with any antimalarial	86.3	53.4	31.8
% with an ACT	81.3	41.9	22.9
% with an antibiotic	71.5	62.5	63.4

ACT, artemisinin combination therapy; RDT, rapid diagnostic test.

* The results are unadjusted and do not take into account the clustering or the imbalance in baseline covariates across the study arms.

† From facility records. Across the three arms, 144 patients were retested by the study team, with 92 patients previously tested using microscopy and 52 tested using RDT. Of the 92 patients previously tested using microscopy, we found that 18 (20%) were true positive, 51 (55%) were true negative, 22 (24%) were false positive, and 1 (1%) was false negative. Of the 52 patients previously tested using RDT, we found that 10 (19%) were true positive, 37 (71%) were true negative, 4 (8%) were false positive, and 1 (2%) was false negative.

The annual economic cost of the training workshops held by the NMCP and the study team (including the training of facilitators) was $5497 for two basic workshops that trained 50 health workers from 18 facilities and was $12,100 for two enhanced workshops that trained 48 health workers from 19 facilities. The economic cost of the in-facility training was on average $190 per facility in the basic arm and $328 per facility in the enhanced arm, and included the value of in-kind items and time of participating health workers. It was estimated that the total annual economic cost of the training interventions in a scale-up scenario would be $4662 for basic and $9585 for enhanced training.

Table 3 – Financial and economic costs of the basic and enhanced training (US $, 2011 prices).

			Annual economic cost			
Financial cost	Financial cost*		Base case†		Scale up‡	
Base case	Basic	Enhanced	Basic	Enhanced	Basic	Enhanced
Start-up						
Develop training (including stakeholder engagement)	20,670	46,970	5,561	12,636	0	0
Training workshop						
Train facilitators and hold workshops	5,497	12,100	5,497	12,100	2,873	6,324
In-facility training						
Health workers train colleagues	2,225	4,057	3,423	6,240	1,789	3,261
Total cost	28,392	63,127	14,481	30,976	4,662	9,585

* Financial costs incurred to design and implement training.

† Start-up costs are treated as investment and annualized over 4 y. Assumes health workers are trained annually. Cost of in-facility training takes into account in-kind items and health workers' time

‡ Excludes start-up costs. Assumes health workers are trained every 2 y; thus, implementation costs are treated as investment and annualized over 2 y. Cost of in-facility training takes into account in-kind items and health workers' time.

Table 4 – Mean cost per febrile patient (US $ 2011 prices).

Cost	Current practice (N = 681)		Basic training (N = 1632)		Enhanced training (N = 1669)	
	Mean	(Min, Max)	Mean	(Min, Max)	Mean	(Min, Max)
Cost of training*						
Base case	–	–	0.52	(0.04, 1.57)	1.12	(0.11, 5.44)
Scale-up scenario	–	–	0.16	(0.01, 0.50)	0.35	(0.04, 1.73)
Cost of febrile illness incurred by patients and caregivers†						
Consultation†	1.10	(0.00, 16.11)	1.14	(0.00, 12.72)	1.55	(0.00, 8.48)
Microscopy†	3.97	(0.00, 20.13)	4.11	(0.00, 19.50)	3.42	(0.00, 20.13)
RDT†	–		3.10	(0.00, 19.50)	2.43	(0.00, 18.65)
Treatment†	3.77	(0.00, 20.66)	4.70	(0.00, 20.98)	4.16	(0.00, 20.98)
Travel†	0.34	(0.00, 12.72)	0.51	(0.00, 10.60)	0.56	(0.00, 10.60)
Other (including food)†	0.20	(0.00, 14.83)	0.32	(0.00, 17.17)	0.23	(0.00, 11.23)
Travel time (return journey)‡	0.35	(0.00, 2.80)	0.30	(0.00, 4.77)	0.36	(0.00, 9.66)
Time at facility‡	1.48	(0.04, 11.44)	2.07	(0.00, 6.48)	2.13	(0.00, 36.62)
Total costs to patient	10.49	(0.51, 41.96	12.18	(0.17, 45.99	11.80	(0.08, 41.07)
Cost of febrile illness incurred by the facility§						
Consultation	1.51	(0.78, 2.48)	1.60	(0.78, 2.48)	1.56	(0.78, 2.48)
Microscopy (if applicable)	1.38	(1.38, 1.38)	1.38	(1.38, 1.38)	1.38	(1.38, 1.38)
RDT (if applicable)	–		1.71	(1.71, 1.71)	1.71	(1.71, 1.71)
Treatment (if received)	2.58	(0.38, 9.92)	2.22	(0.38, 16.91)	2.37	(0.38, 16.17)
Total cost to facility	4.82	(0.88, 12.61)	4.85	(0.78, 21.10)	4.88	(0.78, 19.19)
Net cost to facility‖	0.77	(0.00, 9.11)	0.77	(0.00, 19.65)	0.76	(0.00, 16.86)
Total cost: provider perspective¶						
Base case	0.77	(0.00, 9.11)	1.28	(0.04, 20.62)	1.88	(0.11, 18.68)
Scale-up scenario	0.77	(0.00, 9.11)	0.93	(0.01, 19.96)	1.11	(0.04, 17.36)
Total cost: societal perspective#						
Base case	11.27	(1.89, 41.96)	13.47	(2.32, 46.40)	13.69	(2.01, 44.21)
Scale-up scenario	11.27	(1.89, 41.96)	13.11	(1.78, 46.12)	12.91	(1.81, 43.05)

HW, health worker; RDT, rapid diagnostic test.

* Total cost of intervention per facility (obtained from project reports and interviews with staff) divided by the number of febrile patients per facility per year (estimated from facility records).

† From patient exit survey. Patients reported the amount, including zero costs if the category was applicable.

‡ Time of patient (and caregiver if applicable). Amount of time, as reported in exit survey. Time valued at wage of an unskilled worker (Central African franc 1200/d or US $2.54).

§ From facility costing undertaken at nine facilities. Facility unit cost per activity was estimated taking into account the use of HW time, equipment, and supplies. Cost to facility per febrile patient was estimated from exit survey data on resource use (e.g., if tested, type of test, medicines received) and average unit costs from facility costing. Cost per-patient takes into account the cadre of HW (as reported by the patient) for each activity, where possible.

‖ Total cost to facility less amount patient reported for consultation, test, and treatment.

¶ Sum of training cost and net cost to facility.

Sum of training cost, patient cost, and net cost to facility.

The mean cost per febrile patient was estimated from both the provider and societal perspectives, and presented by study arm for both the base-case and scale-up scenarios (Table 4). The mean cost of training per febrile patient in the base-case scenario was $0.52 in the basic arm and $1.12 in the enhanced arm (and falls to $0.16 and $0.35, respectively, for the scale-up scenario). In the base-case scenario, the total cost per febrile patient in the base-case scenario was $1.28 in the basic arm and $1.88 in the enhanced arm from a provider perspective and $13.47 in the basic arm and $13.69 in the enhanced arm from a societal perspective. The substantial difference between provider and societal costs arises because patients pay user fees to access health care, which vary by facility and depend on the care received. The average out-of-pocket cost relating to the consultation, tests conducted, and treatment received was reported to be $8 to $10 per febrile patient.

Cost-Effectiveness

In the base-case scenario, the interventions were not only more costly but also more effective than current practice. From a provider perspective, the incremental cost per patient correctly treated was $10.13 for the basic intervention and $6.70 for the enhanced intervention (Table 5). From a societal perspective, which includes any costs incurred by patients, the incremental cost per patient correctly treated was $8.40 for the basic intervention and $3.71 for the enhanced intervention. Thus, it was more cost-effective to introduce RDTs with enhanced training, than basic training, when each intervention was compared with current practice.

The cost of the intervention is reduced in the scale-up scenario, and the interventions become more cost-effective. From a provider perspective, incremental cost per patient correctly treated was $4.39 for the basic arm and $2.45 for the enhanced arm. From a societal perspective, incremental cost was $2.46 per patient correctly treated in the basic arm, while the enhanced arm had a net saving of $0.75 per additional patient correctly treated.

The probabilities that each intervention was cost-effective at different levels of the cost-effectiveness threshold compared with current practice are illustrated using CEACs (Fig. 1). These graphs show that the basic intervention has the lowest probability of being cost-effective at all values from both a provider

Table 5 – Incremental costs and effects.*

Cost	Basic vs. current practice	Enhanced vs. current practice
Incremental effect (difference in % correctly treated)	0.10 (0.03–0.32)	0.25 (0.17–0.47)
Provider perspective		
Incremental cost (US $ 2011 prices)		
Base case	1.06 (0.67–2.08)	1.67 (1.24–2.74)
Scale-up	0.46 (0.10–1.36)	0.56 (0.22–1.43)
Incremental cost per febrile patient correctly treated (US $ 2011 prices)†		
Base case	10.13	6.70
Scale-up	4.39	2.25
Societal perspective		
Incremental cost (US $ 2011 prices)		
Base case	0.85 (−0.12 to 3.62)	0.92 (0.17–3.89)
Scale-up	0.25 (0.77–2.90)	−0.19 (−1.31 to 2.40)
Incremental cost per febrile patient correctly treated (US $ 2011 prices)†		
Base case	8.40	3.71
Scale-up	2.46	−0.75

ICER, incremental cost-effectiveness ratio.

* Estimates from bivariate multilevel model, having adjusted for clustering, correlation between costs and effects, and imbalance in baseline characteristics.

† Confidence intervals for the ICERs were not reported because there were some observations with worse outcomes and higher costs and some with better outcomes and lower costs and they cannot be interpreted.

perspective and a societal perspective. Current practice has the highest probability of being cost-effective at very low threshold levels (<$5), though as the threshold increases so does the probability that the enhanced intervention is cost-effective. The CEACs for the scale-up scenario lie to the left of the base-case scenario, and in the scale-up scenario from a societal perspective the enhanced intervention has the highest probability of being cost-effective at all threshold values.

Discussion

The cluster randomized trial evaluated the introduction of RDTs with either basic or enhanced training in health facilities in which microscopy was available. The interventions had a positive effect on health workers' practice in the diagnosis and treatment of febrile illness, though were also more costly than current practice. The enhanced intervention was more cost-effective than the basic intervention when each intervention was compared with current practice, which indicates that the additional 2 days of training represent good value for money. Because there is no established cost-effectiveness threshold in Cameroon, however, the question of whether it is cost-effective to introduce RDTs (with training) in health facilities in which microscopy is already available will depend on the government's willingness to pay for improvements in the diagnosis and treatment of febrile patients. The incremental cost of introducing RDTs with enhanced training for the trial was $3.71 per patient correctly treated from a societal perspective (2011 prices). Similar ICERs have been reported elsewhere [7,10,11,13,29]. For instance, the incremental cost per patient correctly treated by replacing microscopy with RDTs in public health facilities was $3.6 in Ghana (2009 prices) [13], $1.78 in low malaria transmission areas in Uganda, and $8.9 in high malaria transmission areas in Uganda (2011 prices) [11].

Differences in study design should be noted, however, when comparing results, and our study was distinctive for several reasons. First, RDTs were introduced to complement rather than replace malaria microscopy because existing laboratory services were expected to continue in Cameroon. Second, we included the costs of training health workers and distributing revised guidelines because the NMCP indicated that changes in policy would need to be disseminated. The need for interventions that improve health workers' adherence to clinical guidelines was also identified in formative research and highlighted in the cost-effectiveness literature [3,6,8]. Third, the study used individual patient-level data collected in a real-world setting, which meant that the availability, use, and quality of malaria testing was not controlled and there was variation among febrile patients in whether they were tested for malaria, the type of test used, the treatment prescribed, and the prices charged. Finally, the analysis applied statistical methods that took into account the cluster randomized design, correlation between costs and effects, and imbalance between arms in baseline characteristics [17,18].

Several aspects of the study design should be noted when interpreting effectiveness and cost-effectiveness results. The NMCP considered training as integral to the introduction of RDTs, and the evaluation was designed to focus on whether health workers adhered to the malaria treatment guidelines. As a result, it is not possible to distinguish the effect of introducing RDTs from the effect of training, though the observed differences between the basic and enhanced arms suggest that training alone can change health workers' practice. Moreover, the study was not designed to assess the specificity and sensitivity of the tests conducted and the primary outcome was measured using the test result recorded by health workers. Disaggregating this outcome indicated that there were similar results across the study arms in the proportion of febrile patients tested for malaria. This countered our expectations because we had expected that the interventions would encourage malaria testing but we also noted that there had been a substantial increase in the use of testing since 2009 [6].

The decision to focus on the treatment supplied in a single consultation, rather than the health outcome of the illness episode, also has limitations for the cost-effectiveness analysis and it would not have been possible to estimate the number of deaths (or disability-adjusted life-years) averted without making several assumptions about the specificity and sensitivity of each diagnostic method, causes of nonmalaria febrile illness, patient adherence to medication, or the costs and effects of subsequent

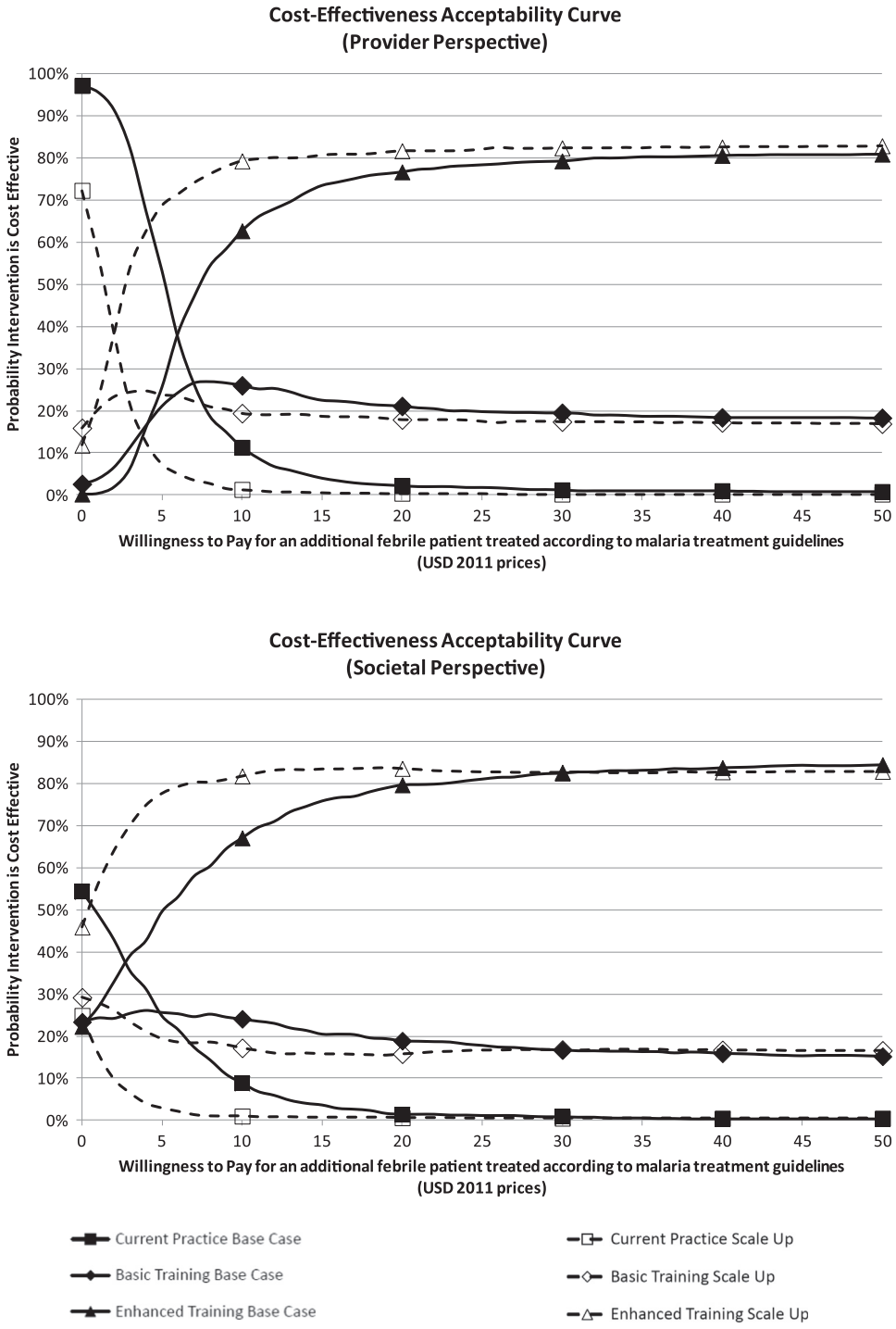

Fig. 1 – Cost-effectiveness acceptability curves.

treatment seeking. There are, however, plans to synthesize findings from this and other cost-effectiveness studies undertaken within the ACT Consortium (www.actconsortium.org), and the synthesis will include data on the accuracy of microscopy and RDT in routine use and data from following up febrile patients.

The study was designed to approximate the real world, though the extent to which this can be achieved in the context of a trial could be questioned. For example, although the number and distribution of RDTs supplied was based on advice from the NMCP and sought to replicate the existing supply management systems, some modifications may be needed for nationwide implementation. The timing of the evaluation is a further consideration. The results reflect the situation 3 months postimplementation, but we do not know whether the effect of the interventions on health workers' practice will be sustained.

We considered a scale-up scenario to facilitate the government's decision on whether to roll out RDTs beyond the study sites. In this analysis, the start-up costs incurred to develop the training were considered a sunk cost. Excluding start-up costs not only substantially reduces the cost of the intervention but also

increases the probability that interventions were cost-effective. Moreover, from a societal perspective, the results indicate that it would be net saving to introduce RDTs with enhanced training, though there is uncertainty surrounding the point estimates.

Finally, the findings highlight two areas for further research. First, differences in the malaria positivity rates by type of test should be explored because data from a limited sample of patients retested by the study team indicated there were more false positives with microscopy than with RDT. The observed differences are unlikely to affect the findings of this study, which assesses whether the treatment prescribed was consistent with the test result recorded by the provider; however, it would be valuable to understand the implications for health outcomes and the incremental cost-effectiveness of each diagnostic method in routine use. Second, the patient cost of testing and treatment warrants further investigation. There was considerable variation in the cost of malaria diagnosis and treatment and the cost reported by patients was often high compared with the amount we estimated it cost health facilities to provide these services. It will be important to understand the extent to which cost is a barrier to treatment seeking.

Conclusions

It was more cost-effective to introduce RDTs with enhanced training than RDTs with basic training when each was compared with current practice. The supplementary training improved health workers practice, especially in terms of reducing the consumption of antimalarials among test-negative patients. Since the trial concluded, the Cameroon government has revised the national malaria treatment guidelines to support the use of RDT and recommend that all febrile patients be tested for malaria using microscopy or RDT. The NMCP has incorporated the enhanced training in its efforts to disseminate the policy change and health worker training commenced in January 2014.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2014.07.010 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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