# DETERMINING COST-EFFECTIVENESS AND COST COMPONENT OF THREE MALARIA DIAGNOSTIC MODELS BEING USED IN REMOTE NON-MICROSCOPE AREAS

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**Abstract.** This cross-sectional experimental study developed a methodology to analyze the cost-effectiveness of three malaria diagnostic models: microscopy; on-site OptiMAL®; and on-site Immunochromatographic Test (on-site ICT), used in remote non-microscope areas in Thailand, from both a public provider and patient perspective. The study covered six areas in two highly malaria-endemic areas of provinces located along the Thai-Myanmar border. The study was conducted between April and October 2000, by purposively recruiting 436 malaria suspected cases attending mobile malaria clinics. Each patient was randomly selected to receive service via the three diagnostic models; their accuracy was 95.17%, 94.48% and 89.04%, respectively. In addition, their true positive rates for all malaria species were 76.19%, 82.61% and 73.83%; for *falciparum* malaria 85.71%, 80.95% and 80.00%, and for *vivax* malaria 57.14%, 100% and 50%, respectively, with the parasitemia ranging from 80 to 58,240 μl of blood. Consequently, their costs were determined by dividing into provider and consumer costs, which were consequently classified into internal and external costs. The internal costs were the costs of the public providers, whereas the external costs were those incurred by the patients. The aggregate costs of these three models were 58,500.35, 36,685.91, and 40,714.01 Baht, respectively, or 339.53, 234.39, and 243.93, in terms of unit costs per actual case. In the case of microscopy, if all suspected malaria cases incurred forgone opportunity costs of waiting for treatment, the aggregate cost and unit cost per actual case were up to 188,110.89 and 944.03 Baht, respectively. Accordingly, the cost-effectiveness for all malaria species, using their true positive rates as the effectiveness indicator, was 446.75, 282.40, and 343.56 respectively, whereas for *falciparum* malaria it was 394.80, 289.37 and 304.91, and for *vivax* malaria 595.67, 234.39 and 487.86, respectively. This study revealed that the on-site OptiMAL® was the most cost-effective. It could be used to supplement or even replace microscopy for this criteria in general. This study would be of benefit to malaria control program policy makers to consider using RDT technology to supplement microscopy in remote non-microscope areas.

## INTRODUCTION

Malaria is recognized as a serious health problem in tropical and subtropical regions of the world and one that has far-reaching medical, social and economic consequences for the countries in which it is found. There are many factors that require vigilance of malaria to be sustained such as drug-resistant malaria, unsuccessful vector control activities, and the migration of non-immune persons to malaria sensitive areas (Anonymous, 1995). In Thailand, malaria is confined mostly to remote areas along the border (Malaria Division, 2000). Although the geographical areas affected by malaria have been reduced over the past decade, control is becoming more difficult. Routine malaria diagnosis by microscopy is the time-

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honored method of laboratory confirmation of the parasite, but it is not immediately accessible in those areas. Delay in the detection and treatment of malaria cases may result in malaria outbreaks and incur considerable expense to control them (Indaratna and Kidson, 1995). If early diagnosis and prompt treatment can be improved, by rapid diagnostic tests (RDTs), such outbreaks/epidemics can be prevented and controlled and the public expenditure on special malaria control activities will be reduced (Indaratna and Kidson, 1995). Therefore, early diagnosis and prompt treatment has been recommended. Nowadays, malaria rapid diagnostic tests or dipsticks are of considerable interest. The test can be performed within a few minutes by individuals with minimal training. It requires no electricity and no special equipment. The product of dipsticks are based on immunochromatographic assays. They can be divided into two groups according to the type of *Plasmodium falciparum* antigen, histidine-rich protein 2 (HRP2) and Plasmodium glycolytic enzyme; lactate dehydrogenase (pLDH) (Wongsrichanalai, 2001). The first dipstick was developed and field-tested in the early 1990s. Because HRP2 persists after parasite clearance, the presence or absence of pLDH is a more reliable diagnostic target (Wongsrichanalai, 2001).

To supplement, or even replace, microscopy with a dipstick method is a change in the technology of case detection. Therefore, it will affect the cost of malaria control and the economic impact of the disease on the population concerned (Kaewsonthi *et al*, 1996). This change will also lead to significant modifications in the Thai malaria control system, since realizing the benefits of introducting RDT depends upon diagnosis and radical treatment being made available at the primary health care level (Kaewsonthi *et al*, 1996). However, studies investigating this economic impact have been rarely documented. Therefore, an analytical study of the cost-effectiveness of introducing RDTs, as compared with microscopy is needed. This study develops a methodology to analyze the cost-effectiveness of microscopy and RDTs in the diagnosis of malaria in Thailand, from both public and private provider, and patient, perspectives. The methodology utilizers both actual and estimated data. The ultimate objective of this study is to provide information to the policy manager to help make better informed decisions, leading to increased efficiency in providing diagnostic services with better supported arguments for budgets.

## MATERIALS AND METHODS

### Conceptual framework

This study was a randomized blind field trial to assess the cost-effectiveness of three diagnostic models: microscopy, and two on-site RDTs, the DiaMed OptiMAL® and ICT P.f/P.v, used in remote areas without microscopes in the diagnosis of malaria, from both public and private provider, and patient, perspectives. The costs were calculated in terms of Baht spent. Effectiveness was determined independently in terms of the accuracy and true positive value of the test. The results were reported as a cost-effectiveness ratio.

### Study areas and population

The study was conducted between April 2000-March 2001. Two adjacent highly endemic Thailand-Myanmar border provinces, Tak and Kanchanaburi, were randomly selected. They are 426 and 128 km to the west of Bangkok, respectively, and their populations in 2000 were 442,319 and 763,605, respectively (Malaria Division, 2000). They are known to be highly endemic malarious areas with APIs (Annual Parasite Incidences) of 57.19 and 10.08 per 1,000 population, respectively in 2000, (Malaria Division, 2000). The malaria transmission period in both provinces is normally throughout the year, but high transmission periods are around May to September and December to January, of which the latter follows seasonal rains. The people working and living in these areas are therefore at high risk of malaria infection. Many hill tribes reside in the western mountainous border. Agriculture remains the mainstay of the people's livelihood. The average malaria species rates in 2000 were 48.9% *P. falciparum*, 50.48% *P. vivax;* and 49.27% *P. falciparum*, 49.78% *P. vivax* respectively (Malaria Division, 2000). Large numbers of migrant and foreign workers are employees and agricultural workers in these areas. Three widely separate hyperendemic remote subdistricts in each of the two provinces were chosen by stratified random sampling technique. In the very remote areas of these subdistricts, the malaria curative care is mainly provided by village malaria volunteers and mobile malaria clinics. Of the former service, patients have had to wait for the results of their blood films for up to 7 days (data derived from the Subdivision of Epidemiology, Malaria Division, Thailand). Other malaria services, such as the fixed rural malaria clinic, the rural health center or rural hospital, are rarely accessed by these people.

**Study design**

Three diagnostic models: microscopy, on-site ICT Pf/Pv, and on-site DiaMed OptiMAL®, were simultaneously consecutively set up to detect asexual *Plasmodium* parasitemia in the study areas. Microscopy was not conducted as an on-site service like the rest, but it simulated the conventional method, by which the blood films were taken by village health volunteers and then sent for examination at nearby malaria clinics, with the results being sent back within a few days. The study samples were malaria suspect cases who came for malaria service at the study posts. They were selected according to the inclusion criteria, of having fever or having any malaria symptoms, and were randomly blindly allocated to receive service according to any one of the three diagnostic models. Before receiving service, the patients were interviewed about their background history, including name, sex, locality, education, occupation, history of having fever, history of past malaria treatment-seeking, and the their travel cost to receive this service. In addition, all patients attending the service post were questioned to determine external direct and indirect costs.

**Specimen collection and handling**

Blood samples were taken by finger-prick of the study patients. For microscopy, thick and thin blood films were prepared in duplicate by the Village Malaria Volunteer (VMV) at the study site. One thick blood film per patient was sent for examination at a nearby malaria clinic, by the local health official who was responsible for collecting blood from the VMV in that area. For the on-site ICT, blood was collected for the test and duplicate thin and thick blood films were made. For the on-site DiaMed OptiMAL® test, blood samples were collected and thick and thin blood films were also made. The thick and thin blood films for both dipsticks were used as the gold standard method when the dipsticks' accuracy was calculated.

**Malaria diagnostic techniques**

In the microscopic method, thick and thin blood films were made in duplicate and stained with Giemsa. They were then examined by local technicians using the standard documented operating procedures, under 1,000 X power oil-immersion-field. The technician were unaware of the subject's medical status or dipstick test results. The thick blood films were read strictly by 100 microscopic fields, before interpreting the films' results. Parallel with the aforementioned, another thick blood film was independently read by another local technician in the study team. When a malaria parasite was found on the film, parasitemia was counted against 500 white blood cells (WBC), or 5,000 red blood cells (RBC) in the thin blood film if the parasite were more numerous than in the WBC (Wongsrichanalai *et al*, 1999). Thereafter, both thick or thin blood films read by the local technicians were reexamined and parasitemia recounted independently at the Malaria Headquarters laboratory by the third experienced technician, and the blood film results obtained in this step were adopted as the gold standard method. For all cases, parasitemia was enumerated per μl of blood as the average of two slide reading results, based on hematologic estimates of 7,500 WBC/μl and 500,000 RBC/μl of blood.

In the second diagnostic method, the MLO2 ICT™ Malaria Pf/Pv test card (AMRAD-ICT, Sydney, Australia), batch 04130 was used for detecting *P. falciparum* histidine protein 2 (pfHRP2) and malaria pan antigen in the peripheral blood (Garcia *et al*, 1996; Tjitra *et al*, 1999). It is a rapid immunochromatographic assay produced in individual card format, based on a gold-labeled polyclonal antibody and a monoclonal antibody against PfHRP2. To do the test, 10 μl of whole blood were spotted onto a sample pad, then buffer (Reagent A) was dropped onto it, according to the manufacturer's instructions and the test was interpreted 5-10 minutes later. The test result was read by the technician who was blinded to the microscopy result. The test was valid when the control line was visible, and considered positive when the pfHRP2 and/or pan malaria antigen lines were visible. For interpretation, the test was classified as non-*falciparum* malaria (*P. vivax, P. malariae*, and *P. ovale*) if only the pan-malarial antigen line was visible. For *falciparum* malaria, both pan-malaria and pfHRP2 lines, or only the pfHRP2 line, were visible. However, a mixed infection of both *P. falciparum* and *P. vivax* could not be distinguished from infection with *P. falciparum* alone. The line intensity of the test could be graded into four categories: absent (negative), faint (just visible), intermediate, and greater than or equal to that of the control. In addition, the test no longer required a microscope, electricity, or special technical expertise.

The DiaMed OptiMAL® test is an also immunochromatographic test with 10 μl of

fingerprick capillary blood. It was performed by the technician according to the manufacturer's instructions. This test is a dipstick coated with monoclonal antibodies against intracellular glycolytic enzyme, Plasmodium lactate dehydrogenase (pLDH), released from parasite-infected erythrocytes. Differentiation of malaria parasites is based on antigenic differences between the pLDH isoforms. The test can differentiate live from dead *Plasmodium* organisms because pLDH is produced only by live parasites. The DiaMed OptiMAL® test (DiaMed AG, Cressier Sur Morat, Switzerland), batch 710000, was used to detect *P. vivax* and *P. falciparum* malaria in peripheral blood (Palmer *et al*, 1998; Congpuong *et al*, 2001). It is a rapid immunochromatographic assay produced by a test strip, based on a gold-labeled polyclonal antibody and a monoclonal antibody against pLDH. To do the test, 10 µl of whole blood was mixed with the DiaMed OptiMAL® fuffer onto a conjugated well, then an OptiMAL strip was placed in the well and the blood sample was allowed to migrate to the top of the strip. Next, after 10 minutes, the strip was cleared by transfer into a wash well, to which had been dispensed 4 drops of DiaMed buffer. The test result was read by the technician who was blinded to the microscopy result. The test was valid when the first band (control line) was visible and the appearance of the second and third dark bands on the strip indicated malaria-positive. The second and third bands were embedded with monoclonal antibodies produced against the enzyme common to the four target *Plasmodium* species, and the enzyme specific for *P. falciparum* only, respectively. Hence, for *falciparum*-malaria-positive, both second and third bands were visible, whereas only the second appeared for the non-*falciparum*-malaria positive. Mixed infection with both *P. falciparum* and *P. vivax* could hardly be distinguished from infection with *P. falciparum* alone.

**Measurement of costs for the three diagnostic models**

The costs, classified by activity related to the three diagnostic models, were calculated into a one-month period. The costs were determined by dividing them into internal and external costs. Each cost was consequently classified into direct or indirect costs. The internal costs were those of public or private providers, whereas the external costs were those incurred by the patients. Costs were determined for the fiscal year 2001 and expressed in Thai Baht. The detail of each cost follows:

**Internal direct cost.** Internal direct costs incurred by providers could be classified into the capital and recurrent costs of each activity. The capital costs were the costs of items that could be used for more than one year, including the cost of microscopes, and the assumed costs of the initial training for the blood film takers, microscopists and dipstick testers. These costs were interpreted as annual capital costs (Shepard *et al*, 1998) and then reduced proportionally into one-month costs. The recurrent costs were the costs of items that were used up within one year, including the cost of personnel, supplies, and operational costs. The personnel costs, including salaries and remuneration, could be sub-divided into the costs of blood-slide takers, microscopists, dipstick testers, and supervisors, whereas the supply costs include glass slides, stain, dipsticks, for example, and the operational costs are monitoring and public utilities.

**Internal indirect costs.** The internal indirect costs incurred by the providers, were the costs effected by the missed diagnoses of each diagnostic model, including the costs effected by false-positives and false-negatives. The false-positive costs included forgone treatment costs and malaria service costs, and were estimated for the patients' follow-up. The false-negative costs were estimated as the costs of continued re-service.

**External direct costs.** The external direct costs incurred by the patients were the travel costs incurred to get the service.

**External indirect costs.** The external indirect costs incurred by the patients were classified into two items: the forgone opportunity costs of waiting for treatment and the forgone opportunity costs incurred by the missed diagnosis of each diagnostic model. The former was calculated by multiplying the number of working days lost waiting for the treatment by the national mininum wage for labor in that area. The latter (cost of missed diagnosis) were estimated by using references from the previous study, because this study was not conducted post-service survey. For illustration, the costs incurred by a false-positive result included travel costs, food costs and forgone

opportunity costs of the non-malaria patients and their relatives while receiving follow-up service. These expenditures were estimated by referring to previous studies (Deepor 1993; Tjitra *et al*, 1999), which had shown the unit cost to be 74.89 Baht/case. Likewise, the costs incurred by a false-negative result included travel costs, food costs and the forgone opportunity costs of the malaria patients and their relatives getting re-service. These expenditures were estimated using the same reference (Deepor, 1993), which had shown the unit cost to be 52.77 Baht/case.

The costs were analyzed into two types, aggregate costs and unit costs. The latter were stratified into six levels including unit-cost-per-person-examined, unit-cost-per-all-species-positive-case, unit-cost-per-*falciparum*-case, unit-cost-per-*vivax*-case, unit-cost-per-actual-case and unit-cost-per-non-malaria-case.

**Measurement of cost-effectiveness of the three diagnostic models**

The effectiveness of each model is explained by indicators, *ie* accuracy and true positive rate. The methodology utilizes both actual and estimated data. Light microscopy results were used as the reference standard for analyzing the three diagnostic models. Epi Info version 6.2 (Epi Info, CDC, GA) and Excel 7.0 (Microsoft, CA) were used to calculate test performance and acceptability evaluation indices, including sensitivity, specificity, and positive and negative predictive values, by using the $\lambda^2$ test for trend and correlation analysis.

Cost-effectiveness was determined by comparing the three diagnostic models' total cost, and their effectiveness, by determining the ratios of both aggregate and unit costs from provider and patient perspectives in each diagnostic model with the effectiveness of each model. The results were reported as cost-effectiveness ratio.

**Sensitivity analysis**

As the RDTs' price has been altered, sensitivity analysis should be determined by comparing the unit cost of the actual case performed by various RDT prices and fixed-price microscopy. The purpose of this analysis was to determine the appropriate RDT cost compared with that of microscopy.

**Limitations of this study**

One constraint of this study was that the calculation of the costs could not completely cover all prospective items, such as some capital costs: for example, operation and maintenance of vehicles, buildings, administrative costs. In addition, the forgone opportunity costs incurred by the patient affected by false-positive and false-negative results were estimated by referrence to another study, as we did not conduct any post-service survey.

## RESULTS

**Subject recruitment**

In total, 436 suspected malaria subjects were recruited from October 1 to 31, 2000. One hundred and seventy-seven were from the three study sites in Kanchanaburi and the remainder were from the three study sites in Tak (Fig 1). Most of them were in the age group 1-14 years, and their gender distribution was 55.5% male and 44.5% female. The leading occupations were farmer, agricultural employee, forestry worker and logger. The subjects were randomly separated into three groups: group A was 145 subjects screened by microscopy (responsibility of village malaria volunteers and a not-onsite screening method); group B, 145 subjects screened by on-site Optimal; Group C, 146 subjects screened by on-site ICT.

**Screening test results**

In group A, 145 blood samples were collected by the village malaria volunteers at each study site; the blood samples were sent for diagnosis at nearby malaria clinics. The numbers of individuals positive by microscopy for *P. falciparum* with or without *P. vivax*, and *P. vivax* only, were 13 and 5, respectively. Meanwhile, in group B, 145 blood samples were collected by public providers, house visitors, and the numbers of individuals positive by on-site Optimal for *P. falciparum* and *P. vivax* were 20 and 3, respectively. Likewise, in group C, 146 blood samples were collected by the house visitors, and the number of individuals positive by on-site ICT for *P. falciparum* and *P. vivax* were 21 and 5, respectively (Table 1). Prompt diagnosis and prompt treatment were achieved in group B and C, but not in group A. The positive cases found by any of the diagnostic models were treated with anti-malaria drug regimens according to the standard set by the Thai National Drug Policy, 1995. In addition, all blood samples were filmed and sent for confirmation by expert microscopists at the Malaria Headquarters, and their results were used

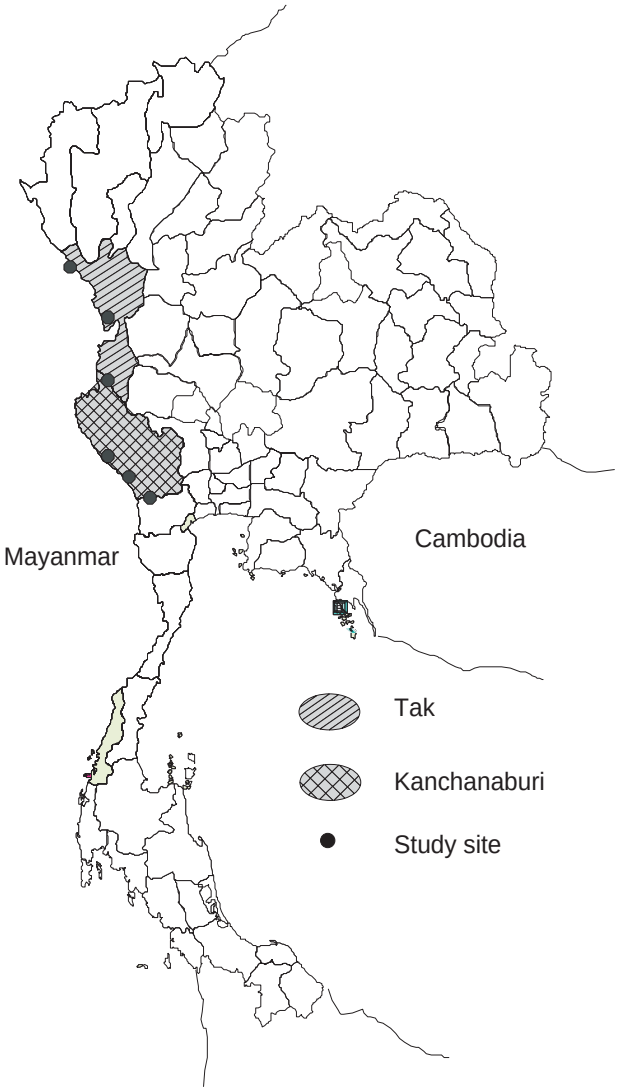


Fig 1–Map showing areas under study in Tak and Kanchanaburi.

as the gold standard. In addition, parasitemia ranged from 80 to 58,240/μl of blood.

**Effectiveness of the three diagnostic models**

The accuracy of each diagnostic model was calculated by comparison with the standard microscopy result. The analysis showed that microscopy and on-site Optimal had almost the same accuracy level (95.17% and 94.48%, respectively) but not the on-site ICT, which showed the lowest accuracy (89.04%) (Table 2). The on-site Optimal showed the highest sensitivity (82.61%) because of its capacity to detect 100% *P. vivax*. The on-site ICT showed the lowest sensitivity, since its capacity to detect *P. vivax* was only 50%.

**Cost analysis**

**Internal cost analysis.** The costs were analyzed in terms of aggregate costs for a one-month period detecting 436 suspected malaria subjects diagnosed by the three diagnostic models. The cost analysis for each model is presented in Table 3, and briefly described as follows:

**A. Microscopy:** the total cost was approximately 44,183.22 Baht, which was the sum of the capital costs; 6,464.94 Baht, recurrent costs of 36,001.38, and indirect costs of 1,716.9 Baht. For analysis of this cost, the direct costs (laboratory, treatment, and monitoring) were the sum of the capital costs and recurrent costs; the former were the capital cost of the microscope and the initial training for blood-slide takers [for village malaria volunteers (VMVs)]. The cost of initial training for microscopists was not included in the other two diagnostic models. The costs of taking blood slides, blood slide examination were also not included in the other two diagnostic models. Excluding the indirect costs, microscopy gave 2 false-positive

Table 1
Diagnostic performance of the three diagnostic models.

| Expert microscopist | Group A | Group B | Group C | Total |
|---|---|---|---|---|
| Pf asexual (+/- gametocytes) | 13 | 20 | 21 | 54 |
| Pv asexual (+/- gametocytes) | 5 | 3 | 5 | 13 |
| Negative | 127 | 122 | 120 | 369 |
| Total | 145 | 145 | 146 | 436 |

and 5 false-negative results. Therefore, the cost of missed diagnosis was 1,716.9 Baht.

**B. On-site Optimal, and C. Onsite ICT:** the total cost was approximately 36,173.27 Baht, which was the sum of the capital costs (41.57 Baht), recurrent cost (34,102.02 Baht) and indirect costs (2,029.68 Baht). For analysis of this cost, the direct costs (laboratory, treatment, and monitoring) were the sum of the capital costs and recurrent costs. The former were the capital cost only for the initial training of the RDT testers, whereas the latter was the sum of the costs of RDT test/examination, radical treatment and supervision. Apart from the indirect costs, the on-site Optimal detected more malaria cases than microscopy and gave 4 false-positive and 4 false-negative results. Therefore, the cost of these missed diagnoses was 2,029.68 Baht.

Likewise, the total cost of the on-site ICT was approximately 39,670.61 Baht, including the capital costs (41.57 Baht), the recurrent cost (35,568.72 Baht) and the indirect costs (4,060.32 Baht). Like the on-site Optimal, the on-site ICT detected more malaria cases than microscopy and gave 9 false-positive and 7 false-negative results. Therefore, the cost incurred by missed diagnoses was 4,060.32 Baht.

**External cost analysis.** These costs were mostly travel costs and forgone opportunity costs incurred by patients. The costs were analyzed in terms of aggregate costs for a one-month period using both actual and estimated data. The cost analysis of each model is presented in Table 3 and is briefly described as follows:

**A. Microscopy:** the time costs, due to absence from work from malaria, were likely to be greater for patients in this model, since the time taken to diagnose a case and provide treatment was much longer (approximately 3.9 days). The total cost was approximately 14,317.13 Baht, composed of the sum of the direct external costs (0 Baht) and the indirect external costs (14,317.13 Baht). In the analysis of these costs, there were no direct external costs, as the patients did not have to pay to travel to attend the service. However, they indirectly incurred costs in terms of forgone opportunity costs, composed of their man-days lost waiting for treatment, which was approximately 3.9 days. In addition, they indirectly incurred missed-diagnosis costs from this model, including travel and forgone opportunity costs in getting follow-up service in the case of a false-positive diagnosis and re-service in the case of a false-negative diagnosis. The external indirect cosst were estimated by using references from a previous study, because this study did not conduct any post-service survey.

All suspected malaria cases incurred forgone opportunity costs waiting for treatment, and the aggregate cost amounted to 188,110.89 Baht.

**B. On-site Optimal, and C. Onsite ICT:** their total costs were approximately 510.64 and 1,043 Baht, respectively. The costs occurred were similarto those of microscopy. However, they did not have forgone opportunity costs of waiting for treatment, as they gave prompt diagnosis and

Table 2
Three diagnostic models' test performances for malaria parasites.

| | | Microscopy | On-site Optimal | On-site ICT |
|---|---|---|---|---|
| Sensitivity | All species | 16/21 (76.19%) | 19/23 (82.61%) | 17/24 (70.83%) |
| | Pf | 12/14 (85.71%) | 17/21 (80.95%) | 12/15 (80.00%) |
| | Pv | 4/7 (57.14%) | 2/2 (100%) | 5/10 (50.00%) |
| Accuracy(%) | All species | 95.17 | 94.48 | 89.04 |
| Specificity | | 122/124 (98.39%) | 118/122 (96.72%) | 113/122 (92.62%) |
| Positive predictive value (%) | | 88.89 | 82.61 | 65.39 |
| Negative predictive value (%) | | 96.06 | 96.72 | 94.17 |
| Number of false-positive (case) | | 2 | 4 | 9 |
| Number of false-negative (case) | | 5 | 4 | 7 |

Table 3
Cost identified for the three diagnostic models (Baht) for one month.

| Types of costs | Microscopy n = 145 | On-site Optimal n = 145 | On-site ICT n = 146 |
|---|---|---|---|
| **Internal** (incurred by providers) | | | |
| **Direct costs** | | | |
| Capital cost | | | |
| A. Microscope | 262.3 | - | - |
| B. Initial training for blood-slide takers | 280.24 | | |
| C. Initial training for microscopists | 5,922.4 | - | - |
| D. Initial training for RDT testers | - | 41.57 | 41.57 |
| Recurrent costs | | | |
| A. Taking blood-slides[a] | 8,740.78 | - | - |
| B. Blood-slide examination[b] | 14,646.2 | - | - |
| C. RDT examination | - | 20,780.22 | 22,011.92 |
| D. Radical drug treatment for positive cases | 1,824.4 | 2,531.8 | 2,766.8 |
| E. Supervision[c] | 10,790 | 10,790 | 10,790 |
| **Indirect cost** (caused by missed diagnosis) | | | |
| Costs for false-positive[d] | 499.00 | 985.24 | 2,417.13 |
| Costs for false-negative[e] | 1,217.9 | 1,044.44 | 1,643.19 |
| **Total internal costs** | 44,183.22 | 36,173.27 | 39,670.61 |
| **External** (incurred by patients) | | | |
| **Direct costs** | | | |
| Travel cost to get service | - | - | - |
| **Indirect costs** | | | |
| Forgone opportunity costs of waiting for treatment | 13,903.5 (100,800.38)[h] | - | - |
| Travel cost caused by false-positive diagnosis[f] | 149.78 | 299.56 | 674.01 |
| Travel cost caused by false-negative diagnosis[g] | 263.85 | 211.08 | 369.39 |
| **Total external costs** | 14,317.13 (101,214.01)[h] | 510.64 | 1,043.4 |
| **Grand total** | 58,780.59 (188,110.89)[h] | 50,154.41 | 55,416.21 |

[a] including personnel costs for taking blood-slides and blood-slide delivery, and materials for taking blood slides; [b]including personnel costs for examining blood-slides or RDT and public utilities; [c]including personnel costs and travel costs; [d]including drug and follow-up costs; [e]including personnel costs for re-taking blood-slides and blood-slide delivery, and materials for re-taking blood-slides; [f]including travel and forgone opportunity costs for getting follow-up services; [g]including travel and forgone opportunity costs for getting re-services; [h]All suspected malaria cases examined by microscopy incurred the foregone opportunity costs of waiting for treatment.

prompt treatment. Therefore, their total external cost was significantly lower than microscopy.

**Unit cost analysis of the three diagnostic models.** The costs were analyzed into unit costs, stratified into six levels, including unit-cost-per-person-examined, unit-cost-per-all-species-positive-case, unit-cost-per-*falciparum*-case, unit-cost-per-*vivax*-case, unit-cost-per-actual-case and unit-cost-per-non-malaria case. On the whole, the unit cost of on-site Optimal was the cheapest, followed by on-site ICT and microscopy, respectively. Using the unit cost per actual case as an indicator for determining the models' effectiveness, the on-site Optimal showed the lowest value (234.39 Baht), whereas microscopy showed the highest

Table 4
Cost analysis of the three diagnostic models.

| Diagnostic model | Cost analysis | Cost (Baht) |
|---|---|---|
| **Microscopy** | Aggregate cost | 58,500.35 (188,110.89)[a] |
| | Unit cost per all-species-positive case | 1,041.82 |
| | Unit cost per *falciparum* case | 1,062.82 |
| | Unit cost per *vivax* case | 994.45 |
| | Unit cost per actual case | 339.53 (944.03)[a] |
| | Unit cost per non-malaria case | 236.27 (931.44)[a] |
| **On-site Optimal** | Aggregate cost | 50,154.41 |
| | Unit cost per person examined | 252.99 |
| | Unit cost per all-species-positive case | 342.29 |
| | Unit cost per *falciparum* case | 347.19 |
| | Unit cost per *vivax* case | 314.10 |
| | Unit cost per actual case | 234.39 |
| | Unit cost per non-malaria case | 218.78 |
| **On-site ICT** | Aggregate cost | 55,416.21 |
| | Unit cost per person examined | 278.86 |
| | Unit cost per *falciparum* case | 369.88 |
| | Unit cost per *vivax* case | 281.65 |
| | Unit cost per actual case | 243.93 |
| | Unit cost per non-malaria case | 224.59 |

[a]All suspected malaria cases examined by microscopy incurred the foregone opportunity costs of waiting for treatment.

(339.53 Baht) (Table 4). However, barring microscopy's all suspected malaria cases incurred the forgone opportunity costs of waiting for treatment, so that the aggregate cost, unit cost per actual case and unit cost per non-malaria case amounted to 188,110.89, 944.03 and 931.44 Baht, respectively.

**Determining the cost-effectiveness ratios of the three diagnostic models.** Using the unit cost for the actual case compared with the accuracy and true positive rate as the indicator of effectiveness, the cost-effectiveness ratios are shown in Table 5. The on-site Optimal test showed the lowest cost-effectiveness ratio, both for all malaria species and for each malaria species, followed by on-site ICT and microscopy, respectively.

**Sensitivity analysis.** Sensitivity analysis compared the unit cost for an actual case, by various RDT prices and fixed price microscopy, as presented in Fig 2. The purpose of this analysis was to determine the appropriate RDT price compromising with that of microscopy. It was shown that, to equal the unit cost per actual case of both microscopy and RDT, it could be increased by up to 200 Baht per test.

## DISCUSSION

The occurrence of malaria epidemics in remote areas, the development of drug resistance, and the resultant morbidity time of patients can be further reduced by providing early diagnosis and prompt treatment to malaria patients. Microscopy cannot provide a satisfactory level of on-site malaria diagnosis. A diagnostic method that can improve early on-site diagnosis is preferred for malaria control in Thailand. RDTs may improve on-site diagnosis, because the test is simple, less time-consuming, requires no electricity or sophisticated equipment, or well-trained manpower. However, in considering implementing RDTs in Thailand, there is a need to analyze their cost-effectiveness compared with microscopy. Therefore, this study has developed a methodology to analyze the cost-effectiveness of the three diagnostic models, including microscopy, on-site Op-

Table 5
Comparison of cost-effectiveness of three diagnostic models.

| Categories | Cost-effectiveness ratio | | |
|---|---|---|---|
| | Microscopy | On-site Optimal | On-site ICT |
| All malaria species[a] | 357.4(339.53:0.95)<br>993.72(944.03:0.95)[d] | 246.73(234.39:0.95) | 274.10(243.93:0.89) |
| All malaria species[b] | 446.75(339.53:0.76) | 282.40(234.39:0.83) | 343.56(243.93:0.71) |
| *P. falciparum*[c] | 394.80(339.53:0.85) | 289.37(234.39:0.81) | 304.91(243.93:0.80) |
| *P. vivax*[c] | 595.67(339.53:0.57) | 234.39(234.39:1.00) | 487.86(243.93:0.50) |

[a]Using accuracy rate as effectiveness.
[b]Using true-positive rate for all malaria species as effectiveness.
[c]Using true-positive rate to *P. falciparum* or *P. vivax* as effectiveness.
[d]All malaria suspected cases examined by microscopy incurred the foregone opportunity costs of waiting for treatment.

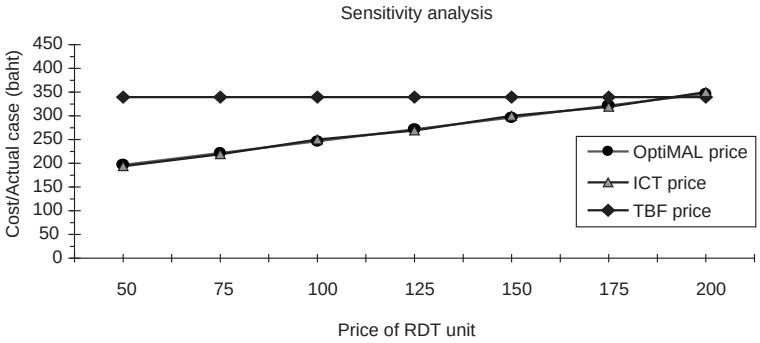


Fig 2–Sensitivity analysis of unit cost per actual case and different unit-priced RDTs.

timal, and on-site ICT, from public and private provider, and patient perspectives, using both actual and estimated data. In addition, research was required, to investigate alternatives and design how data might best be gathered and costs determined.

The effectiveness of microscopy and the two on-site RDTs were evaluated by indicators, *ie* accuracy and true positive rates. Analysis of the data showed that microscopy and the on-site Optimal test had about the same effectiveness and better than the on-site ICT (Table 2). The on-site Optimal test showed the highest sensitivity, because of its capacity to detect 100% *P. vivax*, followed by microscopy and on-site ICT. However, the sensitivity of microscopy was unsatisfactory (76.19%) even if the microscopists in the field were well-experienced, and the equipment and staining procedures were of good quality. However, in field situations it is very difficult to expect 99% accuracy with microscopy, because of the non-availability of competent microscopists, especially in peripheral areas.

The analysis of the costs of microscopy and the dipsticks were calculated using actual and estimated data, which had been proportioned into a one-month period. Microscopy showed the highest total internal cost ($p < 0.05$) because the cost of microscopy is composed of three capital costs, the microscope, the initial training for blood-slide taker and the initial training for the microscopist. On the other hand, the other two models are made up of only one capital cost, the initial training for RDT testers, which was one hundred times cheaper than the initial training required for the other two models. Disregarding the recurrent costs, the first model (microscopy) had more elements in running the test, beginning from taking blood slides to supervision. In general, the costs involved in blood-slides and blood-slide examinations included the salaries of the technicians (but not the VMV), laboratory supplies and materials, laboratory remuneration, and public utilities for laboratory work. However, the second and third (RDT) models did not have the

cost of making blood-slides but the costs of the RDTs per test were quite expensive supplemented by the personnel costs for giving service. In addition, the cost of radical drug treatment and supervision normally occurred with all models.

Estimation was made to measure the internal indirect costs caused by missed diagnoses in both false-positive and false-negative cases. These costs were quite straightforward depending on the test. Application of the on-site ICT should be cautiously considered, as high numbers of missed diagnoses occurred implicating the investment. Comparison of the two on-site RDTs, showed the on-site Optimal to be preferable.

Setting aside the external costs incurred by the patients, and assuming the travel cost was zero for all diagnostic models, patients paid the least when attending the on-site Optimal (approximately 510.64 Baht) because they did not have the foregone opportunity costs of waiting for treatment, as they did with microscopy. In general, the on-site ICT should show more or less the same external costs as the on-site Optimal, but the high missed-diagnosis rate implicated on increased total cost. The total external costs of microscopy were very expensive, compared with the other two models, since there was neither prompt diagnosis or prompt treatment, and the patient paid a foregone opportunity cost of waiting for treatment. Moreover, if all suspected malaria cases incurred foregone opportunity costs of waiting for treatment, the aggregate cost, unit-cost-per-actual case and unit-cost-per-non-malaria case increased more than 200%. While these external costs were very rough estimates, it was clear that the external costs were a major part of the total cost/case (see Tables 3 and 4), and the comparison of costs among the models within the one-month period and among the three models was, therefore, difficult.

The unit costs for the three models were averaged from various perspectives. However, the unit cost of the on-site Optimal test appeared most likely to be the lowest, whereas microscopy was the most expensive. Moreover, the unit-cost-per-actual-case of the the on-site Optimal was cheaper than the on-site ICT, although they were not significantly different ($p > 0.05$). Both were significantly cheaper than microscopy ($p < 0.05$) (Table 4). In other words, it seemed that the average unit cost of RDTs, even if continually changing (but not microscopy), could be as high as 200 Baht per test, and reach about the same cost as microscopy (Fig 2), even thought there were many factors affecting the costs of the RDTs.

By way of overview, the on-site Optimal proved the most cos-effective, compared with the other two models ($p < 0.05$) (Table 5) in all aspects, both for all malaria species and for each malaria species, except for the cost-effectiveness ratio between the on-site Optimal and the on-site ICT in detecting *falciparum* malaria, which was not significantly different. This finding could be explained by the observation that their sensitivity in detecting *P. falciparum* was about the same, but not for *P. vivax.* In other words, the cost-effectiveness of microscopy might be very much lower if all suspected malaria cases incurred the foregone opportunity costs of waiting for treatment.

Finally early diagnosis and prompt treatment services in remote areas not having a microscope can be improved using on-site RDTs. Optimal was the most cost-effective, whereas microscopy was less cost-effective, especially when the cost-effectiveness of microscopy and the dipstick from the patient perspective was considered, where the dipstick was always cost-effective. Even though the on-site Optimal was cost-effective for some conditions, as mentioned previously, its cost-effectiveness will depend on its shelf-life, which is one year from the date of production. If a large stock of dipstick were to expire each year, the cost-effectiveness of the dipstick would fall further. Again, the dipstick must be imported; the cost of importation has to be considered in making a decision for implementing the dipstick in Thailand. In addition, though most of the private sector may not be able to afford the dipstick at that price, the provision of the dipstick at a subsidized price would be helpful for involving the private sector in the early diagnosis and prompt treatment of malaria. It is also worthwhile to provide RDTs at the point-of-service, by considering their cost-effectiveness in different situations, rather than sending blood-slides for diagnosis at nearby malaria clinics, which serves little purpose in the early diagnosis and appropriate treatment of malaria.

## ACKNOWLEDGEMENTS

This project was supported by the Malaria Division, Thailand, DiaMed SEA, Thailand and Becton and Dickinson, Thailand. Dr Kaemthong Indaratna, Center for Health Economics, Faculty

of Economics, Chulalongkorn University, Thailand, Dr Krongthong Thimasarn, the former Malaria Division Director, Thailand as well as the staff of Malaria Division, Office of Vector Borne Disease Control Number 1 Phra Puthabat and Number 5 Nonthaburi, are thanked. We gratefully acknowledge the important revisions suggested by an anonymous reviewer.

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