Cost-effectiveness analysis of artesunate and quinine + tetracycline for the treatment of uncomplicated falciparum malaria in Chanthaburi, Thailand

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A randomized, controlled, malaria-clinic-based field trial was carried out to compare the cost-effectiveness of a 5-day 700-mg oral artesunate and a 7-day quinine + tetracycline regimen for the treatment of uncomplicated falciparum malaria in Thailand. Cost-effectiveness was determined from the providers' perspective and based on curative effectiveness. A total of 137 patients, aged 15–60 years, attending a malaria clinic were followed for 28 days, 60 of them received quinine + tetracycline and 77 received artesunate. Cure rates were assessed on day 5 (artesunate) and day 7 (quinine + tetracycline), using the intention-to-treat approach. Cost-effectiveness and sensitivity analyses were performed by varying the day 5/day 7 curative effectiveness and cost of artesunate. The cure rate with artesunate (100%) was significantly higher than with quinine + tetracycline (77.4%) (relative risk adjusted for sex (aRR) = 1. 32, 95% confidence interval (CI) = 1.12–1.55; referent quinine + tetracycline). Artesunate was more cost-effective than quinine + tetracycline at the following costs: artesunate, ⩽US$ 0.36 per 50-mg tablet; quinine, US$ 0.06 per 300-mg tablet; tetracycline, US$ 0.02 per 250-mg capsule; and services per case found, ⩽US$ 11.49. Because of the higher cure rate and higher cost-effectiveness of the artesunate regimen compared with quinine + tetracycline, we recommend its use for the treatment of uncomplicated falciparum malaria in malaria clinics in Thailand

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Introduction

Malaria is a major health problem in Thailand (*1*), and those who are responsible for its control and for drug policy need to address two important issues when selecting antimalarials for use in the country: the escalating problem of multidrug resistance (*2*) and the scarcity of funds and health personnel (*3*). Ideally, the aim in the choice of a drug regimen for controlling the disease is to maximize the number of malaria cases treated, with the highest degree of cost-effectiveness and without aggravating the existing problem of multidrug resistance.

The need for a cost-effectiveness analysis of the currently used and alternative antimalarials has been recognized by the policy-makers of Thailand's Malaria Control Division. One of the promising alternatives to the standard 7-day quinine + tetracycline regimen in high-resistance areas (*4*) is the 5-day 700-mg oral artesunate regimen, which was shown in a hospital-based study (*5*) to have the same curative efficacy as the former, a more rapid onset of action, and shorter parasite and fever clearance times. Hence, it has the advantage of preventing the development of severe and complicated malaria if used sufficiently early, and a higher potential for reducing mortality than quinine + tetracycline. In addition, by virtue of its milder adverse effects (*5*), shorter course and once-a-day dosing, the probability of noncompliance (with subsequent development of drug pressure from subtherapeutic dosing) and of amplifying multidrug-resistance should be lower. However, oral artesunate costs more and, to date, there is a need to determine its curative effectiveness and investigate whether it is more cost-effective than quinine + tetracycline. The present study was therefore conducted to compare the cost-effectiveness of the two regimens (from the providers' perspective) when they are used in the field (malaria clinic), based on their curative effectiveness.

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Reprint No. **5748**

Materials and methods

Study area

The study was conducted at a malaria clinic in Tabsai Subdistrict, Pong Nam Ron District, Chanthaburi Province, in eastern Thailand from October 1994 to August 1995. The study area lies along the Thai–Cambodian border, a well-known hard core focus for multidrug-resistant falciparum malaria in the country (*2*). Establishment of malaria clinics in these endemic areas, where early diagnosis and treatment are provided free of charge, is one of the major operational strategies adopted for the containment of malaria in Thailand (*3*). These clinics, with no doctors and services provided only by trained paramedics, play an increasingly important role in the control of malaria in the country, and take care of >60% of malaria cases reported by the Antimalaria Programme.

Study population

Criteria for inclusion in the study were as follows: patients aged 15–60 years attending the Tabsai malaria clinic with uncomplicated falciparum malaria (*6*), which was confirmed by a positive Giemsa-stained peripheral blood film (*7*). Patients with manifestations of severe and complicated malaria, pregnant women, and patients with a history of renal and/or hepatic disease or allergy to artesunate, quinine or tetracycline were excluded. The sample size was calculated with a two-tailed significance level at 5% probability and statistical power of 80%, assuming a 65% cure rate in the quinine + tetracycline group and 95% in the artesunate group. The curative efficacy of these two regimens has been reported in a hospital setting (*5*), but not in the field or clinic. The notoriety of quinine + tetracycline for potential noncompliance when prescribed in the field (*8, 9*) and the claim that noncompliance can lead to treatment failure (*10*) prompted us to use compliance as the surrogate index for cure. Estimates of cure rates were therefore based on compliance. The results of one study showed that the compliance rates with the two regimens in the field were 63–75% for quinine + tetracycline and 78–98% for artesunate (*11*). After consultation with K. Thimasarn (personal communication, 1994) we agreed on a 30% difference in the compliance rate between the two — 65% for quinine + tetracycline and 95% for artesunate. The required sample size for each treatment group was thus calculated to be 41, after allowing for a 20% contingency for losses to follow-up (*11, 12*). The study was approved by the Ethical Review Committee of the Ministry of Public Health of Thailand.

Study design

The study subjects for this randomized, controlled, malaria-clinic-based field trial were allocated (simple randomization) to two treatment groups: group I received artesunate orally for 5 days and group II received quinine + tetracycline for 7 days (control) (*5*). Treatments were written on sealed rolled papers and placed in a container from which each eligible study subject picked one paper. The assignments were unknown to the patients and investigators until the initiation of treatment. Written, free, informed consent was obtained from patients who were eligible for the study. Data on sociodemographic characteristics were obtained through structured questionnaire interviews. Patients in group I were asked to take six 50-mg tablets of artesunate at once (i.e. day 0) while in the clinic and advised to take two tablets (100 mg) as a single dose daily at home after breakfast from day 1 to day 4. Patients in group II were also requested to take the first dose (i.e., two 300-mg quinine tablets and two 250-mg capsules of tetracycline) while in the clinic and advised to take the prescribed subsequent doses (i.e. two tablets of quinine three times a day after meals and two capsules of tetracycline twice a day after meals) at home from day 0 to day 6. The patients were requested to come back for follow-up on day 5 (artesunate group) and day 7 (quinine + tetracycline group) as well as on day 28 for both groups. Analysis and interpretation of curative effectiveness were based on the results of the peripheral blood smear (i.e. either positive or negative for *Plasmodium falciparum)* taken on day 5 (artesunate) and day 7 (quinine + tetracycline). The day 5/day 7 instead of the day 28 cure rate was used as the effectiveness outcome measure since the results of community trials in endemic areas indicate that interpretation of positive results of blood smears obtained on day 28 cannot be used to differentiate between a reinfection and a recrudescence. In addition, the marked attrition of study subjects ($\geqslant$30%) due to losses to follow-up would cast serious doubts on the validity of results on day 28 (*14*).

The estimated cost in the analysis was the financial cost to the Malaria Control Programme (i.e. providers' perspective) (*15*), with costs extracted from both primary and existing secondary data (*16*). In this study, we defined the cost incurred by the provider as the actual cost of delivering service to patients in malaria clinics, which was calculated from the costs of labour and materials and capital costs, using the direct distribution method (*15, 16*). All the above costs, except the cost of antimalarial drugs, were categorized as "routine service cost or overhead cost". The routine service cost (overhead cost) per case of *P. falciparum* malaria found was calculated by dividing the total overhead costs by the total number of *P. falciparum* cases identified in the malaria clinic for the fiscal year 1994. This value was used to determine the cost per case of *P. falciparum* given treatment and, subsequently, the respective total cost of treatment of cases in each regimen. The cost-effectiveness analysis was confined to the level of the malaria sector and focused only on uncomplicated falciparum malaria cases. Costs of hospitalization, complications, and switching to another treatment in case of treatment failure were not considered.

The outcome indicator of effectiveness used was the number of expected cases cured on day 5 (artesunate) and day 7 (quinine + tetracycline), obtained by calculating the number of cases cured with the assumption that the number of cases treated in both groups was equal. The average costs per expected number of cases cured were compared between the two treatment regimens. An incremental cost-effectiveness analysis was carried out to provide a more meaningful comparison between the two treatments since it gives the additional cost (to the Malaria Control Programme) associated with the use of artesunate (art) over that of quinine + tetracycline (QT), compared with the additional effectiveness it delivers. Incremental costs were calculated using the formula:

(Expected total cost of treatment (art) — Expected total cost of treatment (QT)) /

(Expected effectiveness (art) — Expected effectiveness (QT))

A sensitivity analysis was performed by varying the cost of artesunate and the number of expected cases cured.

Data analysis

Epi Info version 5.01b (*12*) was used for data entry and analysis. Cure rates were analysed using the intention-to-treat approach, assuming best ("cured") and worst ("not cured") outcomes for those who were lost to follow-up (*14, 17, 18*). Data were compared using either the χ^2 test for two independent proportions or Fisher's exact test whenever appropriate (*19*). Differences in means and medians were tested using Student's *t* test and the Kruskal–Wallis test (*20*). Adjusted relative risks were estimated using the Mantel–Haenzsel test (*21*).

Results

Sociodemographic characteristics of the study population

Of the 137 patients initially recruited, 60 were allocated to the quinine + tetracycline group and 77 to the artesunate group. The study subjects in both groups were comparable in terms of their baseline sociodemographic characteristics ($P > 0.1$ for any variable), except for sex distribution. The proportion of males to females was significantly greater in the quinine + tetracycline group than in the artesunate group ($P = 0.002$). The majority of the study subjects were males, married, and residents of the study area; the mean age was 32 ± 11.5 years for the quinine + tetracycline group and 31 ± 9.4 years for the artesunate group. The predominant occupations of the two study populations were agriculture and logging. Most of the study subjects in both treatment groups had a relatively low income (median monthly income, 4000 *baht*, ca. US$ 160). Close to 90% of the study population were poorly educated, with >75% having completed only primary school.

Only 114 (83.2%) of the subjects originally enrolled in the study (61 from the artesunate group and 53 from the quinine + tetracycline group) came back for follow-up during the first week (i.e. on day 5 or day 7) and only 52 (38%) returned on day 28. The lost-to-follow-up rate for the artesunate group was 20.8% on day 5 and 46.8% on day 28, while that for the quinine + tetracycline group was 11.7% on day 7 and 43.3% on day 28. In terms of their baseline characteristics ($P > 0.3$ for any variable), except for place of residence and occupation ($P < 0.001$), those lost to follow-up were comparable with those who remained in the study. A significantly higher proportion (84%) of patients who remained in the study were indigenous residents of the study area ($P = 0.0004$). The reasons why the non-residents came back for follow-up, apart from being advised to do so in the protocol of the study, were not determined. There was no statistically significant difference between the proportions of the subjects who did not come back for follow-up in both study groups ($P > 0.2$). The majority (52.2%) of those lost to follow-up came from other districts of Chanthaburi or districts outside Chanthaburi. More than two-thirds (74%) of those who were lost were engaged in logging, while only about one-third (32%) of those who completed the follow-up period were in the logging industry ($P = 0.0002$).

Curative effectiveness of the two treatment regimens

The intention-to-treat approach of analysis, assuming best and worst outcomes for those lost to follow-up (*14*), established three categories of cure rates: the rate in those who completed the study; the rate if those lost to follow-up were assumed cured ("best

Table 1: **Comparison of the day-5 cure rate with artesunate (Art) and the day-7 cure rate with quinine + tetracycline (QT) and their respective relative risks among those who stayed in the study, those lost to follow-up but assumed cured ("best" case) and those lost to follow-up but assumed not cured ("worst" case)**

Treatment group	No. cured	No. not cured	aRR[a]	95%CI [a]	*P*-value[b]
Stayed for follow-up					
Art	61 (100) [c]	0 (0)	1.32	1.12–1.55	0.0004
QT	41 (77.4)	12 (22.6)	1.00		
		Crude RR: 1.29			
Lost to follow-up: assumed cured ("best" case)					
Art	77 (100)	0 (0)	1.27	1.10–1.45	0.0002
QT	48 (80)	12 (20)	1.00[d]		
		Crude RR: 1.25			
Lost to follow-up: assumed not cured ("worst" case)					
Art	61 (79.2)	16 (20.8)	1.13	0.89–1.42	0.32
QT	41 (68.3)	19 (31.7)	1.00[d]		
		Crude RR: 1.16			

[a] aRR: relative risk adjusted for sex. 95% CI = 95% confidence interval.

[b] χ^2 test (Yates' corrected).

[c] Figures in parentheses are percentages.

[d] Referent.

case"); and the rate if those lost to follow-up were assumed not cured ("worst case"). As shown in Table 1, among those who remained in the study all of the subjects receiving artesunate were cured by day 5, while only about three-quarters (77.4%) of the quinine + tetracycline recipients were cleared of the parasites by day 7. The probability of being cured for patients treated with artesunate was 32% higher than for those receiving quinine + tetracycline after adjusting for sex (aRR = 1.32 (95% CI = 1. 12, 1.55), $P = 0.0004$, referent: quinine + tetracycline). Adjustment for sex was carried out to control for confounding since the study subjects differed significantly in this variable.

If the best case outcome were assumed for those lost to follow-up, the cure rate for the quinine + tetracycline group would be significantly lower than that for the artesunate group (80% vs 100% respectively). Those who received artesunate would be approximately 1.3 times more likely to be cured than those treated with quinine + tetracycline after controlling for sex (aRR = 1.27 (95% CI = 1. 10, 1.45), $P = 0.0002$). On the other hand, if the worst outcome were assumed for those lost to follow-up, the cure rate for quinine + tetracycline would be approximately 68%, compared with about 79% for artesunate. The probability of cure (after adjusting for sex) would be 1.13-fold higher (95% CI = 0.89, 1.42) in the artesunate group than the quinine + tetracycline group, although this was no longer statistically significant. However, the point estimate (aRR = 1. 13) did not seem to differ much from those of the two other "scenarios".

The overall results showed that if assumptions on losses to follow-up are taken into account, the cure rate for the artesunate regimen in the malaria clinic ranges from 79.2% to 100%, while that for quinine + tetracycline varies from 68.3 % to 77.4%. The probability of cure will be 13–32% higher for artesunate recipients. The day-28 cure rate for artesunate was 92%, while that for quinine + tetracycline was 81.5% ($P > 0.05$).

Table 2. **Data used for the cost-effectiveness analysis of the two treatment regimens among those who stayed for follow-up**

Variable	Quinine + tetracycline	Artesunate
Effectiveness		
No. of cases treated	53	61
No. of cases cured	41	61
Expected number of cases cured if there were an equal number of cases (i.e. 61) treated in both groups	(61 x 41) ÷ 53 = 47	(61 x 61) ÷ 61= 61
Cost (US$)[a]		
Cost of drug per capsule or tablet		
Quinine	0.06 [b]	0.40
Tetracycline	0. 02 [b]	
Total cost of antimalarial drug per course[c]		
Quinine	2.52	5.60
Tetracycline	0.49	
Cost of services per case found (overhead cost)	11.49[b]	11.49[b]
Cost per case of *P. falciparum* treated (total cost of drug course plus cost of services/case found)	14.50	17.09
Total cost of treatment of cases actually treated	(14.50 x 53) = 768.50	(17.09 x 61) = 1042.49
Expected total cost of treatment, assuming there were 61 cases treated in both groups	(14.50 x 61) = 884.50	(17.09 x 61) = 1042.49
Cost-effectiveness ratio		
Average cost per expected case cured (in US$)	884.50 ÷ 47 = 18.82	1042.49 ÷ 61 = 17.09

[a] Conversion rate: US$ 1 = 25 *baht*.

[b] Secondary data (*15*).

[c] Number of capsules or tablets per course: quinine = 42, tetracycline = 28, artesunate = 14.

Cost-effectiveness analysis

Table 2 shows the data used for the cost-effectiveness analysis of the two treatment regimens for those who completed the study, while Table 3 shows the data for those who were lost to follow-up assuming best/worst outcomes. The results of the sensitivity and incremental cost analyses of the two treatment regimens are summarized in Table 4. Use of the intention-to-treat approach (assuming best/worst outcomes for those lost to follow-up) indicated that the average cost per expected case cured for the artesunate regimen was lower than that for quinine + tetracycline in all three categories only for the following conditions: cost of artesunate is $\leqslant$US$ 0.36 per 50-mg tablet, that of quinine is US$ 0.06 per 300-mg tablet, that of tetracycline is US$ 0.02 per 250-mg capsule, and that of services per case is $\leqslant$US$ 11.49. The average cost per one expected case cured would therefore be US$ 0.20–2.29 lower if artesunate were used instead of quinine + tetracycline. Furthermore, the incremental cost-effectiveness analysis revealed that, compared with quinine + tetracycline, artesunate can result in an extra 815 expected cases cured at an additional cost of US$ 8.85–19.54 per expected case cured.

However, if one considers only those individuals who remained with the study (ignoring those lost to follow-up) i.e., explanatory approach (*18*), and the cost of quinine + tetracycline and overhead costs are kept constant, artesunate will still be more cost-effective than quinine + tetracycline at the prevailing price of US$ 0.40 and even up to a ceiling of US$ 0.525 per 50-mg tablet of artesunate. Under these circumstances the incremental costs per additional expected case cured would be in the range US$ 8.85–18.91. If the cost of artesunate is $\geqslant$US$ 0.526 per 50-mg tablet, it becomes less cost-effective than quinine + tetracycline.

Table 3: **Data used for the cost-effectiveness analysis of the two treatment regimens among those who were lost to follow-up, assuming "best" and "worst" outcomes**

Variable	Assuming lost cases were:			
	Cured ("Best" case)		Not cured ("Worst" case)	
	QT[a]	Art[a]	QT[a]	Art[a]
I. Effectiveness				
No. of cases treated	60	77	60	77
No. of cases lost	7	16	7	16
No. of cases cured (observed)	41	61	41	61
No. of cases cured, assuming "best/worst" outcomes for those lost to follow-up	41 +7 = 48	61 + 16 = 77	41	61
Expected number of cases cured if there were an equal number of cases (i.e. 77) treated in both groups assuming "best/worst" outcomes for those lost to follow-up	(48 x 77) ÷ 60 = 62	(77 x 77) ÷ 77 = 77	(41 x 77) ÷ 60 = 53	(61 x 77) ÷ 77 = 61
II. Costs (US$) [b]				
Total cost of treatment of cases actually treated	14.50 x 60 = 870	17.09 x 77 = 1315.93	14.50 x 60 = 870	17.09 x 77 = 1315.93
Expected total cost of treatment if there were 77 cases treated in both groups (assuming "best/worst" outcomes for those lost to follow-up)	14.50 x 77 = 1116.50	7.09 x 77 = 1315.93	14.50 x 77 = 1116.50	17.09 x 77 = 1315.93
III. Cost-effectiveness ratio				
Average cost per expected case cured (US$)[b]	1116.50 ÷ 62 = 18.01	1315.93 ÷ 77 = 17.09	1116.50 ÷ 53 = 27.23	1315 ÷ 61 = 21.57

[a] QT = quinine + tetracycline, Art = artesunate.

[b] Conversion rate: US$ 1 = 25 baht. Other data on costs used in the computation are the same as those shown in Table 2 for those who stayed with the study, namely: 1) cost of drug per capsule or tablet, 2) total cost of antimalarial drug per course, 3) cost of services per case, and 4) cost per case of *Plasmodium falciparum* malaria treated.

Discussion

This is the first study to compare the curative effectiveness and cost-effectiveness of the 5-day 700-mg oral artesunate and the standard 7-day quinine + tetracycline regimens for the treatment of uncomplicated falciparum malaria in the malaria clinic in Pong Nam Ron, Chanthaburi, Thailand. It is also the first study to quantify the relative risks (or more aptly, the probability of being cured) of the two regimens.

The use of the intention-to-treat analysis, assuming best and worst outcomes for those lost to follow-up, was intended to reduce bias due to losses to follow-up (*14,17,18*). It also provided a method for establishing the state-of-the-art range of curative effectiveness of the two regimens when they are used in the field, which to date is not yet the case. These data can be used as the baseline for evaluating the effectiveness of future antimalaria field intervention strategies as well as for carrying out further sensitivity analyses of the cost-effectiveness of the two treatment regimens (e.g. varying the cost of quinine + tetracycline) or other antimalarial regimens (e.g. sequential artesunate + mefloquine).

For ease of interpretation, the index of curative effectiveness used for the cost-effectiveness analysis was expressed as the number of expected cases cured instead of cure rate, since the number of study subjects in the two treatment groups was not equal.

A previous study (*5*), which compared the two treatment regimens showed that in the hospital setting (where compliance was complete) there was no significant difference in their curative efficacy. However, the results of the present field study show that the curative effectiveness of the artesunate regimen was significantly higher than that of quinine + tetracycline in the malaria clinic setting. Nevertheless, it should be borne in mind that the possibility of zero additional benefit for artesunate cannot be

Table 4: **Sensitivity analysis of the average cost per expected case cured and their respective incremental costs, varying the cost of artesunate and the number of expected cases cured among those who stayed for follow-up and those lost to follow-up (assuming "best" and "worst" outcomes)**

Cost of artesunate and treatment regimen[a]	Cost per case treated (US$)[b]	Expected effectiveness (number of expected cases cured)	Expected total cost of treatment (US$)[b]	Average cost per expected case cured (US$)[b]	Incremental cost per additional expected case (US$) [b]
US$ 0.36 per 50-mg tablet					
Stayed for follow-up					
QT	14.50	47	884.50	18.82	
Art	16.53	61	1 008.33	16.53	8.85
If lost ones were cured ("best" case)					
QT	14.50	62	1 116.50	18.01	
Art	16.53	77	1 272.81	16.53	10.42
If lost ones were not cured ("worst" case)					
QT	14.50	53	1 116.50	21.07	
Art	16.53	61	1 272.81	20.86	19.54
US$ 0.40 per 50-mg tablet [c]					
Stayed for follow-up					
QT	14.50	47	884.50	18.82	
Art	17.09	61	1 042.49	17.09	11.29
If lost ones were cured ("best" case)					
QT	14.50	62	1 116.50	18.01	
Art	17.09	77	1 315.93	17.09	13.30
If lost ones were not cured ("worst" case)					
QT	14.50	53	1 116.50	21.07	
Art	17.09	61	1 315.93	21.57	24.93
US$ 0.44 per 50-mg tablet [c]					
Stayed for follow-up					
QT	14.50	47	884.50	18.82	
Art	17.65	61	1 076.65	17.65	13.73
If lost ones were cured ("best" case)					
QT	14.50	62	1 116.50	18.01	
Art	17.65	77	1 359.05	17.09	16.17
If lost ones were not cured ("worst" case)					
QT	14.50	53	1 116.50	21.07	
Art	17.65	61	1 159.50	22.28	30.32

[a] QT = quinine + tetracycline, Art = artesunate.

[b] Conversion rate: US$ 1 = 25 *baht.*

[c] The prevailing cost of artesunate.

ruled out because, although the balance of evidence suggests an incremental benefit in favour of artesunate, the statistically insignificant difference in the curative effectiveness observed in the worst case scenario indicates that there may be no difference between the two regimens. Although the point estimates in the three scenarios seem to be similar, a larger study (with reasonable power) should be carried out to verify this.

The results also revealed that, among those who remained in the trial, the cure rate for quinine + tetracycline on day 7 in the field was lower than the day-7 cure rate previously reported in a hospital-based study (77.4% vs. 100%, respectively) (*5*). In contrast, the cure rates for artesunate on day 5 were the same (i.e. 100%) for both this malaria-clinic-based field study and the hospital-based study (*5*). This difference might be attributable, for example, to the lower compliance with quinine + tetracycline when used for home treatment or other factors; this also needs further investigation.

The results of the cost-effectiveness and sensitivity analyses of the two regimens provide explicit evidence to show the various "cut-off points" at which the use of artesunate becomes more cost-effective or less cost-effective than standard quinine + tetracycline. The results of the incremental cost-effectiveness analysis assume a significance of economic importance for drug policy decision-making at the national level. If the Malaria Control Programme were to switch to the artesunate regimen used here, an extra 8304–14 536 falciparum malaria cases could be cured (compared with the quinine + tetracycline combination) at an additional cost of

US$ 128 562–162 260. This supplementary cost is equivalent to 0.56–0.71% of the total budget of the Malaria Control Programme; this was calculated using the data shown in Table 4, where the cost of artesunate = US$ 0.36 per tablet, the expected effectiveness of quinine + tetracycline = 77.05–86.89% and that of artesunate = 100%, and the incremental cost for every additional expected case cured was in the range of US$ 8.85–19.54. These costs should be compared with the total budget for the Malaria Control Programme in 1994 (US$ 22 948 644) and the number of falciparum malaria cases treated (63 336) in that year (Malaria Control Division, Ministry of Health of Thailand, 1995).

Whether or not this additional cost is worth paying for can be assessed not only in terms of the difference in curative effectiveness we have demonstrated in this study, but also in terms of the following: the higher potential of artesunate for lower mortality from severe and complicated malaria (because of its rapid action (*5*)); and the lower propensity of artesunate for producing drug pressure (from subtherapeutic doses and multidrug resistance, because of the higher probability of compliance due to fewer adverse reactions and simplicity of the regimen (*5*)).

The answer to the question, "Which of the two drug regimens is more cost-effective for the treatment of uncomplicated falciparum malaria in the malaria clinics in Thailand from the providers' perspectives?" must be left to the discretion of those who will use these data. However, since the chances are high that a considerable proportion of the patients who come for treatment to the malaria clinic will be lost to follow-up because they belong to migrant populations, particularly in the border areas (*21*), the use of the results of the intention-to-treat approach, assuming best and worst outcomes for those lost to follow-up, would be more appropriate than the explanatory approach and is the one we recommend.

One limitation to the cost-effectiveness analysis in this study is the exclusion of costs from the patients' perspective as well as those of hospitalization, treatment of complications, and further treatment of those who were not cured in the quinine + tetracycline group (both from the providers' and patients' perspectives). Inclusion of these in the analysis is expected to make the difference in cost-effectiveness even more marked, with artesunate being more cost-effective, and would most likely corroborate the analysis. This is because of the lower probability, with artesunate, of developing malaria complications and of the need for hospitalization due to its faster parasite clearance time (*5*). Failure to include these aspects in the analysis deprives us of a more composite assessment of the cost-effectiveness of the two regimens, which will inevitably leave some gaps in the evaluation of the usefulness of the study to policy-makers. Nevertheless, since to date there is no other available information on this issue, the results obtained here can still provide some baseline data, albeit incomplete, which can be used as a guideline for formulating drug policies to control malaria in Thailand.

In conclusion, the higher curative effectiveness and higher cost-effectiveness of the artesunate regimen suggested by the balance of evidence demonstrated in this study serve as the basis for recommending that it replace standard quinine + tetracycline for the treatment of uncomplicated falciparum malaria in Thailand, especially in areas of high drug resistance. This recommendation is strengthened if these findings are assessed in the light of artesunate's more rapid onset of action, which could result in reduced mortality, better compliance with lower drug pressure, and a lower propensity to add to multidrug resistance. A larger, block randomized study, which includes costs of hospitalization or treatment of complications and recrudescence (both from the providers' and patients' perspectives) as well as a sensitivity analysis using various costs for quinine + tetracycline, needs to be carried out. The results of such a study should not only rule out the possibility of a zero additional effect for artesunate, but also provide a more comprehensive cost-effectiveness analysis of the two regimens. ■

Acknowledgements

This investigation received financial support from project ID 931128, which was funded by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, and from Amador R. Honrado, Jr and family. We gratefully acknowledge the assistance and cooperation of the malaria staff and study subjects in the Tabsai malaria clinic, Pong Nam Ron District, Chanthaburi, Thailand.

Résumé

Analyse coût-efficacité appliquée au traitement du paludisme à falciparum non compliqué par l'artésunate et par l'association quinine/tétracycline à Chanthaburi (Thaïlande)

Les données relatives au rapport coût-efficacité des antipaludéens actuels ou de leurs substituts apportent une aide précieuse à la décision en matière de politique pharmaceutique. La présente étude répond à la demande d'information exprimée par les responsables de la Division de lutte contre le paludisme.

Dans cet essai de terrain randomisé et contrôlé qui s'est déroulé en milieu médicalisé, on a comparé le rapport coût-efficacité d'une dose de 700 mg d'artésunate administré *per os* pendant 5 jours à un traitement de 7 jours par une association quinine/tétracycline pour le traitement d'un paludisme à falciparum non compliqué

(du point de vue du soignant), le critère retenu étant l'efficacité curative. Sur les 137 patients âgés de 15 à 60 ans qui fréquentaient un centre antipaludique de Chanthaburi, 60 ont reçu l'association quinine/ tétracycline et 77 l'artésunate. Les malades ont été suivis pendant 28 jours et les taux de guérison évalués le cinquième jour (groupe sous artésunate) et le septième jour (groupe sous quinine/tétracycline. Le coût a été déterminé du point de vue du dispensateur de soins et les données correspondantes obtenues à partir d'informations primaires et secondaires. Les analyses portant sur le rapport coût-efficacité et sur la sensibilité ont été effectuées dans les conditions suivantes : variabilité du coût du médicament et de l'efficacité thérapeutique; approche basée sur l'intention de traiter; scénario le plus mauvais ou le meilleur pour les malades ayant échappé au suivi.

Le taux de guérison a été meilleur avec l'artésunate (100%) qu'avec l'association quinine/ tétracycline (77,4%) risque relatif ajusté sur le sexe (aRR) = 1,32; intervalle de confiance à 95% = 1,12-1,55; référence : quinine/tétracycline. L'analyse coût-efficacité a révélé que l'artésunate était plus rentable que l'association quinine /tétracycline lorsqu'on se basait sur les coûts suivants : artésunate : ⩽US$0,36 par comprimé de 50 mg; quinine : US $0,06 par comprimé de 300 mg; tétracycline : US $0,02 par gélule dosée à 250 mg; coût des services : US $11,49 par cas.

Comme le traitement par l'artésunate est plus rentable et permet un taux de guérison plus élevé que le traitement par l'association quinine/tétracycline, nous recommandons que les dispensaires antipaludiques de Thaïlande l'adoptent pour la prise en charge du paludisme à falciparum sans complications.

Resumen

Análisis de la relación costo-eficacia del artesunato y la combinación quinina más tetraciclina para el tratamiento del paludismo falciparum sin complicaciones en Chanthaburi (Tailandia)

Los datos sobre la relación costo-eficacia de los medicamentos antipalúdicos actualmente disponibles y de los alternativos son importantes a la hora de adoptar decisiones en materia de política farmacéutica. El presente estudio constituye una respuesta a la necesidad de información sobre este asunto expresada por las instancias normativas de la División de Lucha contra el Paludismo de Tailandia.

En un dispensario antipalúdico se hizo un ensayo aleatorizado controlado para comparar la relación costo-eficacia (desde la perspectiva de los dispensadores) de un tratamiento de cinco días con artesunato por vía oral (700 mg) y otro de siete días con la combinación de quinina más tetraciclina para el paludismo falciparum sin complicaciones, sobre la base de la eficacia curativa. De 137 pacientes que acudían al dispensario antipalúdico de Chanthaburi (de edades comprendidas entre los 15 y los 60 años), 60 recibieron quinina más tetraciclina y 77 artesunato. El seguimiento de los pacientes duró 28 días y las tasas de curación se evaluaron los días quinto (grupo de artesunato) y séptimo (grupo de quinina más tetraciclina). El costo se consideró desde la perspectiva de los dispensadores, y los datos sobre los costos se derivaron de los datos primarios y de los secundarios disponibles. Los análisis de costo-eficacia y sensibilidad se hicieron variando el costo del medicamento y la eficacia curativa, para lo cual se utilizó el análisis por intención de tratar, aplicando resultados positivos (curación) y negativos (no curación) en los casos de pérdida de seguimiento.

La tasa de curación con artesunato (100%) fue mayor que la obtenida con quinina más tetraciclina (77,4%) (riesgo relativo ajustado en función del sexo (aRR) = 1,32; IC 95% = 1,12-1,55; referencia: quinina más tetraciclina). El análisis de la relación costo-eficacia reveló que el artesunato era más rentable que la quinina más tetraciclina, como se indica a continuación: artesunato, ⩽US$ 0,36 por comprimido de 50 mg; quinina, US$ 0,06 por comprimido de 300 mg; tetraciclina, US$ 0,02 por cápsula de 250 mg; y US$ 11,49 de los servicios por caso.

Debido a la tasa más alta de curación y a la mayor rentabilidad del tratamiento con artesunato, en comparación con la quinina más tetraciclina, se recomienda su uso para el tratamiento del paludismo falciparum sin complicaciones en los dispensarios antipalúdicos de Tailandia.

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