TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA IN MYANMAR: A CLINICAL DECISION ANALYSIS

Cho-Min-Naing[1,2] and Allan Saul[1]

[1]Malaria and Arbovirus Unit, Queensland Institute of Medical Research, Brisbane, Qld 4029, Australia;
[2]The National Malaria Control Project, Department of Health, Insein PO, Yangon, Myanmar

Abstract. This study was undertaken to compare cost-effectiveness of three drug regimes for treatment of uncomplicated falciparum malaria in Myanmar. The alternative regimens in this study were chloroquine (CQ), sulphadoxine-pyrimethamine (SP) and mefloquine (MFQ) along with their therapeutic efficacy in Myanmar. The study was performed by modeling a clinical decision tree based on a hypothetical 1,000 adult uncomplicated falciparum malaria cases. Key variables were (i) three drug regimes: CQ, SP and MFQ, (ii) three categories of therapeutic efficacy of each drug: adequate clinical response (ACR), early treatment failure (ETF) and late treatment failure (LTF) according to the 1996 WHO protocol, and (iii) compliance with each drug. In structuring the model, necessary assumptions were made. The cost effectiveness was measured as cost per case cured and cost per case prevented death related to the provided drug, from the provider's perspective. According to the present price and therapeutic efficacy, SP is the most cost effective drug for a case cured in all three categories of efficacy (US$ 0.12 per case cured in ACR, US$ 0.38 per case cured in ETF and US$ 0.54 per case cured in LTF). For a case prevented death, CQ is most cost effective in all three categories (US$ 0.58 per case prevented death in the ACR, US$ 2.14 per case prevented death in the ETF and US$ 2.51 per case prevented death in the LTF). The lowest cost effective regimen is MFQ for both indicators of effectiveness at the present price and therapeutic efficacy. A sensitivity analysis was performed for sensitive values.

INTRODUCTION

Malaria is one of the major public health problems in Myanmar (Myint Lwin *et al*, 1997) and the resistance of *Plasmodium falciparum* to antimalarial drugs is a major contributing factor in the deterioration of malaria control (Ejov *et al*, 1999). It is an important task to update the national antimalarial drug policy, which is crucial for all disease endemic countries. Data on therapeutic efficacy of antimalarial drugs according to the WHO protocol (WHO, 1996) have been reported for urban Dar es Salaam in Tanzania (Premji *et al*, 1999), for Yaounde in Cameroon (Ringwald and Basco, 1999) and for selected areas in Myanmar (Ejov *et al*, 1999). The three levels of therapeutic response, adequate clinical response (ACR), early treatment failure (ETF) and late treatment failure (LTF) were categorised for each drug considered. The criteria designated for these three categories (WHO, 1996) are provided in the appendix.

Where resources are very limited, planners should consider both the efficacy of drugs and their cost when they select medicines to be used in primary health care settings (Sudre *et al*, 1992). A study for current therapeutic efficacy of antimalarials used is desirable for updating of national antimalarial drug policy in Myanmar. We therefore attempted to provide further information required for updating of the national antimalarial drug policy. The regimens considered, chloroquine (CQ), sulphadoxine-pyrimethamine (SP) and mefloquine (MFQ), were based on availability of information on current efficacy in Myanmar. The objective of this study was to use a decision model to compare cost-effectiveness of the three drug regimes for treatment of uncomplicated falciparum malaria, based on their therapeutic efficacy.

Correspondence: Dr Cho-Min-Naing.
E-mail: chominN@qimr.edu.au

METHODS

A decision analysis model focusing on the related sequence of events associated with the process of treatment of malaria by alternative drug regimens was constructed. Decision analysis is the application of explicit, quantitative methods to analyze decisions under conditions of uncertainty (Richardson *et al*, 1995). The major viewpoint adopted in this study was that of the Myanmar national malaria control project (NMCP). The provider's viewpoint was selected because it is the ultimate decision maker in the funding of malaria control programs and is responsible for the organization and administration

of all medical and public health services for malaria in the country (Kamol-Ratanakul *et al*, 1993).

Structure of the model

A model was constructed incorporating 1,000 hypothetical cases of adult uncomplicated *falciparum* malaria attending a public malaria clinic in Myanmar. These cases were confirmed by microscopy, the conventional diagnostic service.

The decision was modeled by a decision tree, which is illustrated in Fig 1. A clinical decision tree is a schematic display of temporal and logical structure of a clinical situation in which one or more decisions must be made (Weinstein *et al*, 1980).

In this study, the decision node represents the choice among three drug options and has three main branches. The initial decision, represented by the decision node (choice node) at the left of Fig 1 is three drug options for treatment of *P. falciparum* malaria: CQ (upper branch), SP (middle branch), and MFQ (lower branch). The related consequences depend upon the three categories of therapeutic efficacy, ACR, ETF and LTF. The further chance event modeled with probability of good compliance and poor compliance for the drugs provided.

Dynamics of the model

Key variables considered in the model and their estimates were as follows:

1. Three alternative treatment modalities were considered; CQ, SP and MFQ in line with their current efficacy categories in Myanmar.

2. States of therapeutic efficacy of antimalarials in Myanmar categorized as ACR, ETF and LTF were considered for model development. Probabilities of therapeutic efficacy of each drug were extracted from an empirical study in Myanmar (Ejov *et al*, 1999).

3. Since noncompliance is the surrogate index for cure (Honrado *et al*, 1999), estimates of cure are based on compliance with drugs prescribed formally. In the absence of recent country information on this aspect at the time of study, probabilities of compliance for antimalarial drugs provided were drawn from a literature survey of data from countries with situations similar to that in Myanmar.

Table 1 presents the values used in the base case analysis.

Model assumptions

In structuring the model, a number of neces-

Table 1
The selected model variables and values used in the decision model.

Variable	Base case			Range[c]			Source of information (study site)
	CQ	SP	MFQ	CQ	SP	MFQ	
1. Therapeutic efficacy[a]							
ACR[b]	0.666	0.647	0.934	0.5 - 0.75	0.375 - 0.833	0.778 - 1.0	Ejov *et al* (1999)
ETF	0.18	0.206	0.044	0.286 - 0.167	0.375 - 0.111	0.111 - 0	(Myanmar)
LTF	0.154	0.147	0.022	0.214 - 0.083	0.25 - 0.056	0.111 - 0	
2. Compliance	0.8	0.95	0.95	NC	NC	NC	Sudre *et al*, (1992) (African)
3. Drug cost[d] per adult case for each episode	0.075	0.075	1.5	NA	NA	NA	NMCP, 1998 (Myanmar)

[a]Transformed original value of percentage to probability.
[b]ACR stated in this study indicates "Treatment success" in Ejov *et al*, 1999.
[c]Range is rearranged in order to make sum probability of 1.0 for all therapeutic efficacy for each drug.
[d]US$ (value stated as in the project document).
NA denotes "not applicable".
NC denotes "not consider" (explanation is in the text).

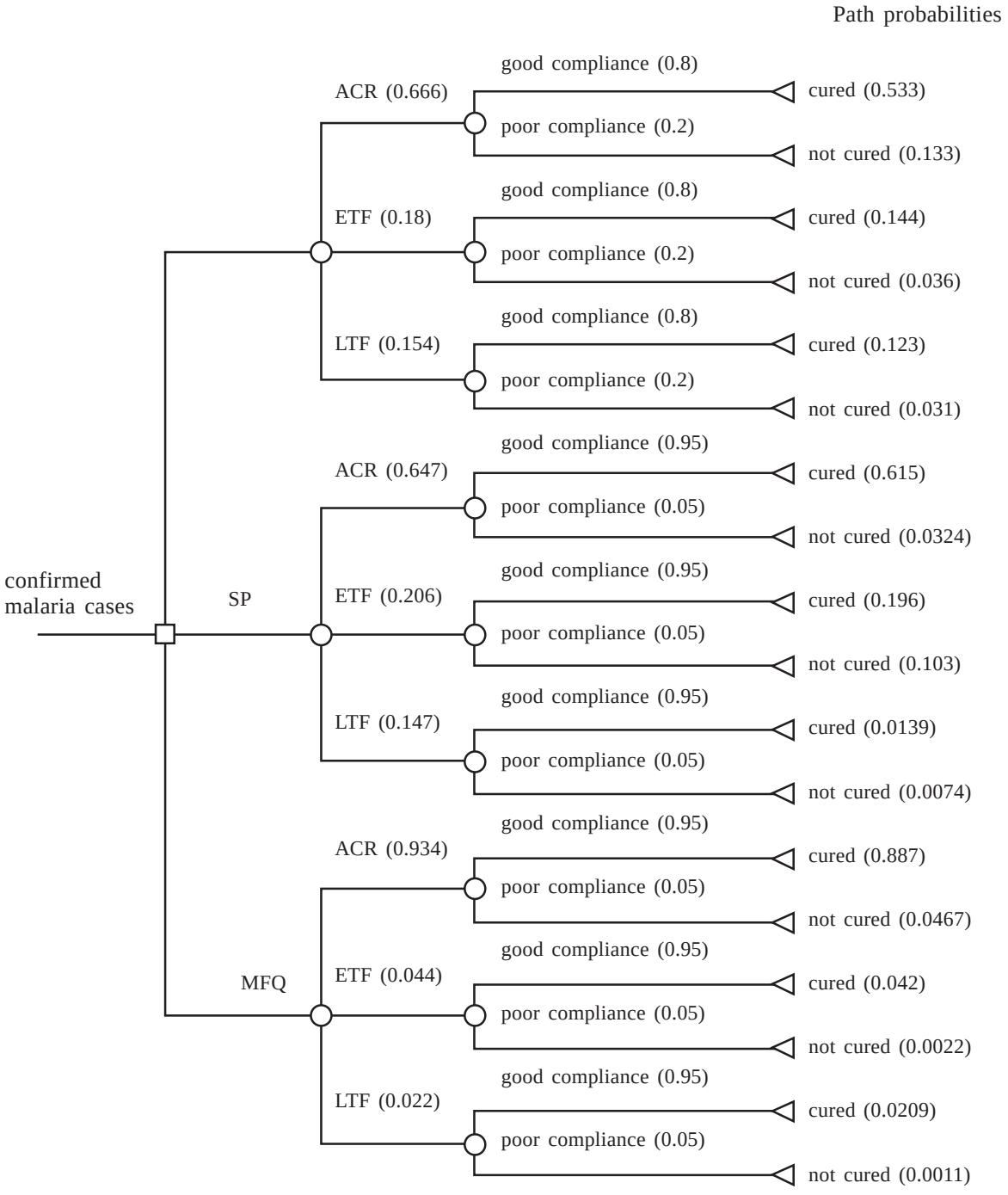

Fig 1- Therapeutic decision tree of three drug regimens for uncomplicated *Plasmodium falciparum* cases using base case probabilities.

NB: CQ denotes chloroquine; SP denotes sulphadoxine-pyrimethamine; MFQ denotes mefloquine
ACR denotes adequate clinical response; ETF denotes early treatment failure; LTF denotes late treatment failure square represents decision node (choice node); circular represents chance node; triangle represents terminal node.

sary assumptions were made:

1. The decision to treat means specific and prompt treatment of malaria according to the standard guidelines of Myanmar NMCP.

2. Three treatment options are mutually exclusive in practiec.

3. There are no serious side-effects due to each drug provided.

4.The probability of death as a function of not-cured is similar in all three regimens.

5. The compliance and effectiveness have a linear relationship. The better the compliance, the greater effectiveness is expected.

6. The variation of compliance rate was assumed depend on the treatment regimen. Equal compliance for single course such as SP and MFQ and the lowest compliance for a three days course of CQ, were proposed. To make the model simple, the range of compliance was omitted.

Cost identification

In the base case analysis, the costs incurred for three treatment modalities were compared. The costs considered were the financial cost of the drugs for the provider (*ie* the Myanmar NMCP) and these were available from the documents of Myanmar NMCP. The cost of treating one episode of malaria was determined by total drug cost for a full course treatment of malaria incurred by the provider. In Myanmar, antimalarial drugs are provided free of charge to the diagnosed patient in the clinics run by the Myanmar NMCP. The course provided was in accordance with the standard guidelines of the Myanmar NMCP. The price of a 10 tablets (100 mg base tablet) course of CQ (4 tablets on day 0, 2 tablets for day 1 and 2 tablets for day 2) is US$ 0.075, for a three tablets (500 mg sulphadoxine +25 mg pyrimethamine tablet) course of SP (single course on day 0) is US$ 0.075 and for a three tablets (250 mg tablet) course of MFQ (single course on day 0) is US$ 1.50 (National Malaria Control Project, Myanmar 1998).

Routine service costs or overhead costs related to drug provision were excluded, assuming they are the same for each course of drug therapy. So were the capital costs such as building. Costs of switching to another treatment in case of treatment failure were not considered. The costs of treatment of complications due to drugs provided were not included. Thus, total drug costs of treating 1000 adult malaria cases were US$ 75.00 for CQ, US$ 75.00 for SP and US$ 1,500.00 for MFQ.

Outcome measurement

In this study, cured and not-cured cases of malaria with the provided regimen were assessed as immediate outcomes of treatment regimes. The not-cured case may progress to the stage of severe malaria with the related probability of death. A case fatality rate of 3.0% was used for possible death in not-cured cases, though treatment regimen was provided. This value was extracted from the project report (National Malaria Control Project, Myanmar, 1998). The number of cases of prevented death was derived from case fatality rate data for malaria in Myanmar. Cost-effectiveness was therefore measured as (i) cost per case cured, and (ii) cost per case prevented death.

Data analysis

The decision tree illustrated in Fig 1 was constructed and analysed by standard decision techniques using the DATA™ 3.5 for Health Care (TreeAge Software, Inc, Williamstown, MA 01267) computer package. The model included two major immediate outcomes: cured and not-cured with respective regimens.

The path probabilities of outcome for all three treatment options are the product of the probability along the branches leading to that outcome. The values of each variable in the model varied through a range from above to below the base case value to determine if model conclusions were sensitive to parameters. A univariate sensitivity analysis was performed using a range of therapeutic efficacy of antimalarial drugs, which was the most sensitive parameter in this study.

RESULTS

Table 2 indicates the cost effectiveness ratios for three treatment modalities. Among the drugs, SP is the most cost-effective drug for cases cured at current level of efficacy for all three categories and at the present price, while MFQ was the least cost effective drug. Per case prevented death, the most cost effective drug was CQ while MFQ was the least cost effective drug.

A sensitivity analysis for three treatment modalities using the lowest and highest range of therapeutic efficacy is revealed in Table 3. It was noted that SP and CQ are the most cost effective drugs

Table 2
The cost - effectiveness ratios for three modalities of uncomplicated falciparum malaria in Myanmar.

Drug used	Cost[a] per case cured			Cost[a] per case death prevented		
	ACR	ETF	LTF	ACR	ETF	LTF
CQ	0.14	0.52	0.61	0.58	2.15	2.51
SP	0.12	0.38	0.54	2.39	7.5	10.52
MFQ	1.69	35.89	71.77	33.11	702.9	1,405.81

[a]US$

Table 3
Sensitivity analysis for three modalities for treatment of uncomplicated falciparum malaria in Myanmar with range of values.

Drug used	Cost[a] per case cured			Cost[a] per case death prevented		
	ACR	ETF	LTF	ACR	ETF	LTF
CQ						
Worst case scenario[b]	0.19	0.33	0.44	0.77	1.35	1.8
Best case scenario[c]	0.13	0.56	1.13	0.52	2.31	4.65
SP						
Worst case scenario[b]	0.21	0.21	0.32	2.39	4.12	6.19
Best case scenario[c]	0.09	0.71	1.41	1.86	13.93	27.61
MFQ						
Worst case scenario[b]	2.03	14.22	14.22	33.11	278.63	278.63
Best case scenario[c]	1.58	Div/0	Div/0	30.93	Div/0	Div/0

[a]US $
[b]Along with the worst efficacy of CQ at the ACR.
[c]Along with the best efficacy of CQ at the ACR.

per case cured and per case prevented death respectively.

Table 4 describes the summary trade-off between the cost effectiveness and therapeutic efficacy. For both scenarios, the worst case and the best case, the results also favored SP as the most cost effective drug per case cured and CQ per case death prevented, while MFQ was the least cost effective for both effectiveness indicators. Put otherwise, results of sensitivity analysis were qualitatively similar to the base case analysis.

Within the drug category, each drug is most cost effective for a case cured in the ACR. The cost effectiveness ratio is higher for their cost per case death prevented than the cost per case cured for all three drugs.

DISCUSSION

As stated by Honrado *et al* (1999), the aim in the choice of a drug regimen for controlling the disease is, ideally, to maximize the number of malaria cases treated, with the highest degree of cost-effectiveness without aggravating the existing problem of multidrug resistance.

Per case cured, SP is superior to CQ, based upon their current efficacy level and price incurred by the Myanmar NMCP. If the compliance of CQ was 20% to 50% (Goodman *et al*, 1999) lower than the 80% in the present study, SP will be more cost effective per case cured. A three days course of CQ has the possibility of lesser compliance than a single course of SP with similar costs of treatment for the

Table 4
A summary of trade-off between therapeutic efficacy and cost effectiveness for three regimens for treatment of uncomplicated falciparum malaria in Myanmar.

Description	CQ	SP	MFQ
1. Efficacy level			
ACR[a]	66.6 (50.0-75.0)	64.7 (37.5-83.3)	93.4 (77.8-90.9)
Failure rate[b]	33.4 (25.0-60.0)	34.6 (16.7-62.5)	6.6 (0.0-22.2)
2. Cost per case cured[c]	US$ 0.14	US$ 0.12	US$ 1.69
3. Cost per case prevented death[c]	US$ 0.58	US$ 2.39	US$ 33.11

[a]ACR stated in this study is identical to "Treatment success" in Ejov *et al*, 1999.
[b]Combination of ETF and LTF.
[c]At the ACR level of efficacy.

two drugs. For a case prevented death, CQ is superior to SP. MFQ, the comparatively least cost effective drug had the highest ACR.

A decision to change first-line (CQ) and perhaps even second line (SP), to MFQ, at least for nonimmune patients (Ejov *et al*, 1999) has not yet been considerable in Myanmar because SP is most cost effective per case cured among three drugs considered. One point that we noted was that the therapeutic efficacy of SP and CQ was obviously on the margin and was statistically not significant (Ejov *et al*, 1999). Ineffective first-line oral treatment causes an increasing proportion of patients to develop severe disease (White, 1996). We support this observation. However, the decision to change the first line drug should be based not only upon the presence of a high level frequency of RIII resistance, but also upon the capabilities of health services to cope with the disease problem (WHO, 1984). The transition from low to high-level resistance is slow for CQ and MFQ, but may be more rapid for SP (White, 1996). We are also aware of the fact that if we replaced SP as a first line drug, there would be trade-off involved in changing the first-line drug (Goodman *et al*, 1999). Trade-offs between the most cost effectiveness and least therapeutic efficacy are true for SP but vise versa for MFQ. Our suggestion is for SP and MFQ to be made available as the second line drug and third line drug respectively at the periphery, or at the first referral level, separately from the decision to replace it as the first line drug for treatment of malaria.

We recognize that a high proportion of ETF to the first-line antimalarial drug is itself a strong indicator of the need to change the first line treatment (WHO, 1996). But a level at which the proportion of treatment failures considered is acceptable, and a level of treatment failures which is unacceptable should be clearly defined for Myanmar. In general, CQ, the existing first line drug for treatment of malaria has a comparatively higher proportion of ETF in Myanmar (Ejov *et al*, 1999) than it has in urban Dar es Salaam, Tanzania (Premji *et al*, 1999).

MFQ, which is least cost effective per case cured and for per case prevented death despite having the highest value of ACR among three regimens, should be reserved as an emergency drug. At the present price, MFQ is the least cost effective option among three treatment regimens. If there is an expected downgrading level of efficacy from ACR to ETF, MFQ would be 20 times more expensive than the ACR level. For CQ and SP, 2.7 and 2.1 times more expensive, respectively. If the downgrading is expected from ACR to LTF, MFQ would be 41 times more expensive, while CQ and SP would be 3.3 and 3.5 times more expensive respectively. This fact is not without implications for clinical economics. If it were possible for the price of MFQ to be reduced to the level of SP or CQ, what would happen is an interesting and crucial issue. Put otherwise, at what price level shall MFQ be made available to preserve its current efficacy level in Myanmar? The simple answer is to keep the controlled price, which should be above the equilibrium price. This suggestion does not mean encouraging profit maximization monopolistic drug manufacture. It does mean preventing expected negative externalities due to indiscriminate use of MFQ. Our assumption is that the utilization of MFQ is price sensitive, *ceteris paribus*. Since the objective of the

study is not to set up the price, what should be the controlled price of MFQ is beyond our present scope.

For a national policy for the use of antimalarial drugs, the current situation regarding drug availability, regimens in use, quantity of drugs required, sources of drugs, availability and cost of drugs at each step in the drug delivery system (WHO, 1984) are determinants to be considered. Keeping these facts in mind, our recommendation is (i) to make availability of SP at the periphery level, (ii) to keep MFQ as a drug of emergency use and make availability at the peripheral level with strict utilization policy, (iii) a continuous monitoring of drug efficacy level in Myanmar, and (iv) to consider the selection of drug based on the area specific therapeutic efficacy of antimalarial drugs.

We observed two caveats of this work. The available drug efficacy level is only for selected areas in Myanmar (Ejov *et al*, 1999), and thus our results cannot represent the whole country. Since malaria is not equally distributed throughout Myanmar, geographic variations of drug efficacy level are expected. An area- specific drug efficacy level is therefore valuable especially for the high risk areas before a national drug policy is drawn up. In addition, other regimens such as quinine and tetracycline, artesunate, and artesunate + mefloquine combined must also be considered for comparison, if their therapeutic efficacy is categorised as ACR, ETF and LTF. Since to date there is no available information on therapeutic efficacy as ACR, LTF and ETF for other antimalarial drugs in Myanmar, we recommend a future study to do so.

Decision analytic structuring has many advantages over an intuitive approach to clinical decision making. The ability to focus on one aspect of the decision problem at a time without losing sight of the whole, which compels the decision maker to consider the relation between the information acquired and subsequent decisions that might be affected (Weistein *et al*, 1980) is an advantage of our study.

In conclusion, this study has attempted to provide information to those who will use our finding to answer the question of which of the three drug regimens is more cost effective for the treatment of uncomplicated *falciparum* malaria (Honrado *et al*, 1999) in Myanmar from the provider's perspective. Of course, accuracy of diagnostic techniques was a determinant for the changes in therapeutic efficacy of antimalarial used in the long-term. Therefore, a decision model incorporating the accuracy of various diagnostic services available in Myanmar is our concern, and it is presently underway.

ACKNOWLEDGEMENTS

This study was completed while Cho-Min-Naing was in receipt of a training fellowship from UNDP/ World Bank/WHO Research and Training in Tropical diseases (ID 980849). The views expressed are those of the authors, not of the Myanmar National Malaria Control Project.

REFERENCES

Ejov MN, Tun T, Aung S, Sein K. Response of *falciparum* malaria to different antimalarials in Myanmar. *Bull WHO* 1999; 77: 244-9.

Goodman CA, Coleman PG, Mills A. Cost-effectiveness of malaria control in sub-Saharan Africa. *Lancet* 1999; 354: 378-85.

Honrado ER, Fungkdda W, Kamolratnakul P *et al*. Cost-effectiveness analysis of artesunate and quinine + tetracycline for the treatment of uncomplicated *falciparum* malaria in Chanthaburi, Thailand. *Bull WHO* 1999; 77: 235-43.

Kamolratanakul P, Chunhaswasdikul B, Jittinandana A. Cost-Effectiveness analysis of three short course anti-tuberculosis programmes compared with a standard regimen in Thailand. *J Clin Epidemiol*. 1993; 46: 631-6.

Myint Lwin, Htein Lin, Nay Linn *et al*. The use of personal protective measures in control of malaria in a defined community. *Southeast Asian J Trop Med Public Health* 1997; 28: 254-8.

National Malaria Control Project, Myanmar. *1996, Annual Report*. Yangon. 1999.

National Malaria Control Project, Myanmar. *Project Document* (Unpublished). Yangon. 1998.

Premji Z, Makwaya C, Minjas JN. Current clinical efficacy of chloroquine for the treatment of *plasmodium falciparum* infections in urban Dar es Salaam, United Republic of Tanzania. *Bull WHO* 1999: 77: 740-4.

Richardson WS, Detsky AS. For the evidence-based medicine working group. User's guides to the medical literature VII. How to use a clinical decision analysis. Are the results of the study valid? *JAMA* 1995; 273: 1290-5.

Ringwald P, Basco LK. Comparison of *in vivo* and in vitro tests of resistance in patients treated with chloroquine in Yaounde, Cameroon. *Bull WHO* 1999; 77: 34-43.

Sudre P, Breman JG, McFarland D, Koplan JP. Treatment of chloroquine-resistant malaria in African children: A cost-effectiveness Analysis. *Int J Epidemio*l 1992; 21: 146-54.

Weinstein MC, Fineberg HV, Frazier AS, Neuhauser D, Neutra RR, McNeil BJ. *Clinical Decision Analysis*. Philadelphia: WB Saunders, 1980: 33-4.

White NJ. The treatment of malaria. *N Engl J Med*. 1996; 335: 800-6.

WHO Scientific group. Advances in malaria therapy. Geneva. *WHO Tech Rep Ser* 1984: 711.

WHO. Assessment of Therapeutic Efficacy of Antimalarial Drugs for Uncomplicated Falciparum Malaria in Areas with Intense Transmission. Division of Control of Tropical Diseases, Geneva and Division of Integrated Prevention and Control, Regional Office for Africa, Brazzaville. WHO/MAL/96.1077. 1996; 12-4.

Appendix

Overall classification of therapeutic response (WHO, 1996).

1. Early treatment failure (ETF)
   - Development of danger signs or severe malaria on Day 1, Day 2 or Day 3, in the presence of parasitaemia;
   - Axillary temperature ≥ 37.5ºC on Day 2 with parasitaemia > of Day 0 count;
   - Axillary temperature ≥ 37.5ºC on Day 3 in the presence of parasitaemia;
   - Parasitemia on Day 3 ≥ 25% of count on Day 0.

2. Late treatment failure (LTF)
   - Development of danger signs or severe malaria in the presence of parasitemia on any day from Day 4 to Day 14, without previously meeting any of the criteria of ETF;
   - Axillary temperature ≥ 37.5ºC in the presence of parasitemia on any day from Day 4 to Day 14, without previously meeting any of the criteria of ETF.

3. Adequate clinical response (ACR)
   - Absence of parasitemia on Day 14 irrespective of axillary temperature, without previously meeting any of the criteria of ETF;
   - Axillary temperature ≥ 37.5ºC irrespective of the presence of parasitemia, without previously meeting any of the criteria of ETF.