CHAPTER 1

INTRODUCTION

1.1 Problem Statement and Rationale

Malaria continues to be a major global health problem. The World Health Organization (WHO) estimated that 2,073 million people (over 40% of the world's population), living in more than 100 countries, are exposed to the risk of malaria and that some 270 million of these are infected with malaria parasites. While the number of cases reported to WHO were 5 million annually for the past years, the best estimate is that perhaps 110 million clinical cases occur every year, of which 90 million are in tropical Africa. Global deaths are estimated at approximately 1 million a year (WHO, 1990).

It is the complexity of malaria that has enabled it to resist so successfully the many and varied attempts to eradicate or control it. With this in mind and recognizing that the world wide eradication of malaria disease is not an attainable goal in the foreseeable future. The WHO Expert Committee on malaria in 1985 promoted an epidemiologic approach to the design of control should be determined by the local epidemiologic situation rather than by general control axioms (WHO, 1986).

Most malarious areas now have a complex mixture of both new and persisting epidemiologic problems, and in those areas current malaria control measures often produce only partial and short-lived relief. Continued application of these measure has contributed to the extension and intensification of vector resistance to, or avoidance of, insecticides and of parasite resistance to antimalarial drugs. Plasmodium falciparum (P.falciparum) causes the most serious form of the disease and is common in the tropics. Infection with this parasite can be fatal in the absence of prompt recognition of the disease and its complication and active appropriate patient management. The situation is complicated by the increasing occurrence of P.falciparum parasite that are resistant to chloroquine and other antimalarial drugs.

Over the last decades, reports on chloroquine resistant P.falciparum have accumulated from many parts of the world. The most intense foci are in the Western Pacific region and South East Asian (WHO, 1989). P.falciparum has develop resistance to chloroquine, sulfadoxine - pyrimethamine combination (Fansidar) and to some extent quinine. A high level of resistance to mefloquine (35% - 40%) has been reported from some areas on the Thailand - Cambodian border and Thailand - Myanmar border (Krongthong Thimasan, 1990).

Vietnam is situated in a highly malarial endemic area of the world. The malaria eradication program was started in 1958 in the north

and was extended to the south during the year 1975. In 1991 the malaria eradication programme was converted to malaria control programme because of some technical problems such as malaria parasite was resistant to antimalarial drug, the main malarial vectors avoided or resistant to insecticide, migration of population and lack of fund for malaria eradication programme. In Vietnam, about 35 millions people are exposed to the risk of malaria. Among them, about 15 millions people are living in hyper malaria endemic areas. There were 225,928 people infected with malaria and 2,632 people die due to malaria in 1991.

One of problems in the national malaria control programme is the P.falciparum in high proportion in the country. In 1993 there were 156,069 people infected with malaria and 71.31% of them were falciparum malaria, 27.95% were vivax malaria, 0.74% were mixed, 1,054 people die due to malaria.

Added to high proportion of P.falciparum, there was a high prevalence of resistant strains to antimalarial drugs. The percentage of chloroquine resistant strains was as high as 84.60%. This was followed by Fansidar resistance (75.0%) mainly in the south and some places in the north. The resistance of P.falciparum to chloroquine is also one of main reasons of high mortality rate. Malarial mortality rate in 1992 was 3.80 per 100,000 population and in 1993 was 150 per 100,000 population (Annual report of the Malaria control programme 1992, 1993).

The objectives of national malaria control programme in Vietnam in the present (1991 - 1995) five years planning period are:

1) To reduce mortality due to malaria.
2) To reduce malarial outbreak.
3) To reduce malaria morbidity.
4) To produce artemisinin and artesunate.
5) To extend bed nets treated by permethrine.

The strategy to achieve objective 1 is choosing an effective antimalarial drug regimen to treat resistant falciparum malaria at district hospital. That is the justification for and objective of this study.

1.2 Background of Artemisinin, Quinine and Doxycycline

1.2.1 Artemisinin (Art)

An entirely new group of antimalarial compounds has been studied by Chinese scientists. A plant under the name of qinghaosu (artemisia anua L.) has been used in China for the past 2,000 years. The active compound has now been identified as a sesquiterpene lactone and synthesized under the name of artemisinin. Artemisinin was isolated first in 1972 in China. The derivatives of artemisinin are artesunate and artemether.

Artemisinin was also isolated in 1987 in Vietnam from artemisia anua L, a wild shrub species naturally grow in hilly and mountainous areas. It has been used to treat resistant falciparum malaria. As mono-treatment schedule with 10 mg/kg/day for 5 days, the cure rate has been reported to be 85.3% (Nguyen Duy Sy, 1993).

1.2.2 Quinine (Qui)

For more than three centuries, cinchona and its alkaloids, specially quinine, were the only effective drugs available for the relief of malaria. Quinine is also used to treat resistant falciparum malaria for many years. An adult dosage of mono-treatment schedule with 12.5 gm/10 days, the cure rate was 80% (Bui Dai, 1993). Longer treatment schedule is also one of the reasons for its failure, side effect such as visual disturbance, hearing disturbance and cardiovascular effects are also reported.

In Brazil, the cure rate of Quinine in mono-treatment was 77% (Boulos, 1992) and cure rate of quinine for children treatment was 76% (Sabchareon, 1992).

1.2.3 Doxycycline (Dox)

Doxycycline is an antibiotic also used to treat P.falciparum malaria in combination with another antimalarial drugs. A combination regimen of doxycycline with artesunate, the derivative of artemisinin, the cure rate was 80% (Looareesuwan, 1993).

1.2.4 The Combination Treatment Regimens

1) In this study artemisinin was combined with doxycycline (art + dox) to reduce recrudescence rate of falciparum parasite or to increase cure rate of artemisinin in treatment.

Artemisinin (oral): 10 mg/kg/day for 5 days
Doxycycline (oral): 2 mg/kg/day for 5 days

2) Quinine is used with the dose of 30 mg/kg/day in combination with doxycycline (qui + dox) to reduce the day of treatment duration from 10 days to 5 days.

Quinine sulfate (oral): 30 mg/kg/day for 5 days
Doxycycline (oral): 2 mg/kg/day for 5 days

It is necessary to choose the regimen which is more costs-effectiveness to treat uncomplicated falciparum malaria.

1.3. Literature Review

1.3.1 Drug Resistance of P. falciparum

Resistance of P.falciparum to pyrimethamine and biguanide,

proguanil and chloproguanil was recognized as early as 1950 in many areas of the world. The first report on resistance of P.falciparum to 4-amino-quinolines (chloroquine and amodiaquine) was in 1960 - 1961 from Colombia and Brazil. Further reports on drug resistance came from Thailand, Malaysia, Cambodia, Philippines, Indonesia, Vietnam, Burma and other areas of Southeast Asia (Bruce-Chwatt, 1985).

The problem of resistance of P.falciparum strains to 4-amino-quinolines has now been further complicated by the appearance of resistance to combination of sulfadoxine with pyrimethamine (Fansidar). Fansidar was the first line alternative antimalarial drug combination which was introduced in the late 1960s with a satisfactory cure rate of approximately 90%. Currently the cure rate of Fansidar has declined significantly in many part of Southeast Asia. In Thailand, it has decreased from 90% in earlier 1970's to less than 10% in earlier 1980's (Harinasuta,1992). Boulos (1992) combined sulfadoxine and pyrimethamine (Fansidar) to treat falciparum malaria resistant to chloroquine in Brazil showed that the cure rate of this drug was 2.9%.
Reports from Indonesia and from other parts of Indo-China, East Africa on resistance of P.falciparum to Fansidar suggested that this compound was loosing its effectiveness.

Reports on the resistance of P.falciparum to mefloquine also started accumulating from 1984 from different parts of the world such as Thailand and Tanzania (Bruce-Chwatt, 1985).

In Vietnam resistance of P.falciparum to chloroquine was reported in 1969 in the south (Phan,V.T, 1969). The drug resistant P.falciparum increased up to 61.3% in 1973. P.falciparum was not only resistant to chloroquine but also resistant to quinine with the resistant rate being 36.8% (Phan,V.T, 1973).

A report on resistance of P.falciparum to antimalarial drugs found that the resistance of P.falciparum to amodiaquine was 22.55%, to Fansidar was 71.6%, to mefloquine was 1.5% and to quinine was 30.1% (Sy N.D, 1994).

1.3.2 Treatment of Resistant Falciparum Malaria

Many studies on efficacy and effectiveness of artemisinin and its derivatives (artesunate, artemether) have been carried out.

The first clinical studies conducted in China in 1972 showed excellent activity against both falciparum and vivax malaria. Artemisinin was seen to elicit shorter parasite clearance time than chloroquine and more rapid symptomatic response (Li, 1990). It was effective against chloroquine resistant infection and produced rapid recovery in 141 cases of cerebral malaria.

Li (1992) used artermisinin suppository with 386 patients with total dose of 2,800 mg given over three days, a dose of 600 mg at hour 0, 4, on the first day and 400 mg twice daily on the second and the third day. A rapid control of symptoms was observed in 384 cases. The

mean fever clearance time was 14.9 - 38.9 hours. The mean parasite clearance time was 35.2 - 52.8 hours. A 28 days follow up showed the recrudescence rate was 45.8%. Side effects with artemisinin suppository were transient and self-limiting, with 5.9% of tenesmus (21/355), 3.1% abdominal pain (16/355) and 0.8% diarrhea (3/355).

Artesunate tablet was used in a study by Li (1992). There were two groups of patients comprising 50 subjects in each, with a total dose of 280 mg for three days and 440 mg for five days respectively. Given at a dose of 40 mg twice daily with the first dose double, the mean fever clearance time and the mean parasite clearance showed no significant difference between the two groups. The recrudescence rates of inpatients using three days and five days therapy were 51.2% and 4.4% respectively, showing a significant difference.

As many as 23 trials with a total of 1891 patients were carried out in Asian countries to compare the effect of artemisinin with other antimalarial drugs: The mean shortening of fever clearance time was 17% (7.7 hours) compared with intravenous quinine and parasite clearance time (19.8 hours) was 32%. Artesunate appeared to have more rapid action than the other derivatives. No serious toxicity was observed in these trials.

Looareesuwan (1994) reviewed clinical studies on artemisinin derivative in Thailand. Over 1,000 patients had been treated with artesunate or artemether in clinical trials since 1988 which confirmed the earlier Chinese work. Artemisinin derivatives were all well tolerated and had insignificant side effects. Fever clearance time (35.1 $\pm$ 23.4 hours) and parasite clearance time (35.9 $\pm$ 10.1 hours) were shorter than those in patients treated with other antimalarial drugs. However, recrudescence rates were as high as 10% - 100% depending on the dose and duration of treatment.

Artesunate or artemether used alone in a total dose of 600 mg given five days produced cure rates of over 90%. The cure rate depend on the severity of disease even when the same dose and the same duration of treatment were used. Results of clinical trials of artesunate or artemether alone or in combination with other antimalarial drugs in Thailand were summarized in Table 1.1.

Another study with mefloquine - tetracycline and quinine - tetracycline for acute uncomplicated falciparum malaria was caried out on 102 patients in Thailand (Looareesuwan, 1994). Mefloquine was given at a total dose of 1,250 mg (with 750 mg immediately, then 500 mg six hours later) together with tetracycline 250 mg every 8 hours for 7 days. Quinine sulfate 600 mg every 8 hours together with tetracycline was given 94% cured rate. The cure rate of quinine - tetracycline was 98%.

In Vietnam some studies were carried out on the efficacy and effectiveness of artemisinin. Authors also found that the effectiveness of artemisinin used alone or in combination with another antimalarial drug depended on dose and duration used in treatment.

Table 1.1 Results of Some Clinical Trials of Artemisinine Derivatives in Thailand.

Referent & drug	Total dose (mg)	Duration (day)	Number of patient	Cure rate (%)
1. Bunnag and other, 1991.				
* Artesunate (oral)	1200	5	6	100
* Artesunate (oral)	600	5	10	90
* Artesunate (oral)	650	5	21	95
* Artesunate (oral) plus chloroquine 1gm to 5 gm.	200	single dose	5	0
* Artesunate (oral) plus Fansidar (oral) 3 tablets single dose.	200	single dose	5	0
2.Bunnag and other, 1991.				
* Artesunate (oral)	600	5	46	85
* Artesunate (oral)	600	7	43	93
3.Looareesuwan and other, 1992.				
* Artesunate (oral)	600	5	40	88
* Artesunate (oral) followed by mefloquine 25 mg/kg divided into 2 doses	600	5	39	100
4.Looareesuwan and other, 1993.				
* Artesunate (oral)	300	2.5	50	90
* Artesunate (oral) plus doxycycline 200 mg/day for 7 day.	300	2.5	55	81
* Artemether (oral)	750	7	58	9
5.Karbwang and other, 1992.				
* Artemether (oral)	700	5	34	97
* Artemether (oral)	500	5	40	74
6.Bunnag and other, 1992.				
* Artemether (i.m) for uncomplicated malaria	480	5	33	84
	600	5	28	92
* Artemether (i.m) for severe malaria.	480	5	53	65
	600	5	53	76
7.Looareesuwan and other (in press).				
* Artemether (oral)	750	7	58	98
* Artemether (oral) followed by mefloquine 25 mg/kg divided into two doses	600	7	53	98

Hien,T.T (1992) used four comparative studies involving 240 acute falciparum malaria patients treated with different regimens of oral artemisinin. Four other studies had been carried out with a suppository form of artemisinin involving 105 uncomplicated and complicated falciparum malaria patients. All regimens were effective and safe with parasite clearance time ranging from 25.8 to 41.8 hours. These studies confirmed the high recrudescence rate previously described with less than five days treatment, although a single dose of 500 mg was enough to clear the parasite within 24 hours.

Four comparatives studies on artesunate were also carried, two oral and two parenteral (i.m and i.v) with 109 patients. The results show that artesunate may be the more effective of the artemisinin drug. The mean parasite clearance time ranged between 16-28 hours and even a single oral dose of 100-200 mg resulted in a rapid clearance of parasite within 28 days.

In another study (Dai,B. 1992) on the effectiveness of artemisinin used alone with adult dose of 1 gm/day for 3 days (total dose of 3 gm/3 days) the cure rate was 89% compared with 85.3% of quinine sulfate with the total dose of 12.5 gm/5 days.

According to Sy (1993), with an artemisinin dose of 10 mg/kg/day for five days with 102 falciparum malaria patients, the average parasite clearance time was 1.5 ± 0.65 days and average fever clearance time was 1.8 ± 0.56 days. The recrudescence was 14.7%. In another study on effectiveness of artemisinin with 10 mg/kg for three days, the cure rate was 91.4%.

A treatment regimen of quinine sulfate 30 mg/kg for seven days with 67 falciparum malaria patients showed the cure rate 87.1% compared with 94.45% of quinine sulfate dose of 30 mg/kg for seven days in combination with tetracycline 20 mg/kg for seven days (Sy, 1993).

1.3.3 Costs in Malaria Control Programme

Some economic analyses of internal costs and external costs were conducted in Thailand (Kaewsonthi, 1989). When clinical cost were assigned to positive cases seeking treatment at the clinics, costs per positive case were 343 Baht to 556 Baht between different zones. Average costs incurred by positive case were 534 Baht (from 519.9 to 564.8 Baht). Average direct costs incurred by positive case were 400.6 to 458.2 Baht and average indirect costs were 106.8 to 119.3 Baht in different zones.

No cost analysis has been made of artemisinin treatment, and therefore no literature exists on the subject matter. The implication of this is that a study such as this present one is needed to fill this gap.

1.4 Research Questions

1.4.1 Primary Research Question

What is the effectiveness of Art + Dox and Qui + Dox regimen in the treatment of falciparum malaria?

1.4.2 Secondary Research Questions

(1) What is provider costs and costs incurred by patient through treatment by each regimen?

(2) Which of the two treatments, Art + Dox or Qui + Dox is the more cost-effective?

1.5 Research Objective

1.5.1 General Objective

To analyze costs and effectiveness of Art + Dox in comparison with Qui + Dox drug regimens to identify the more cost-effective drug regimen to treat falciparum malaria at district hospitals in Vietnam.

1.5.2 Specific Objectives

(1) To identify, measure and value the provider costs and costs incurred by patient of two treatment regimens.

(2) To identify and measure the effectiveness of two the treatment regimens.

(3) To provide method of analysis as a basic to select the more cost-effective treatment regimen.

1.6 Scope of Study

The study of efficacy of two regimens Art + Dox and Qui + Dox was performed in a district hospital in the south of Vietnam over one year from Apr, 1994. The district has a high percentage of P.falciparum with a parasite proportion and drug resistance of P.falciparum as high as 60% to 80% nerspectiveiy.

Falciparum malarial inpatients remained in the district hospital for 28 days to measure the effectiveness of regimens; economic data were not measured to analyse cost-effective of drud regimens. Therefore the study was extended to identify and measure the cost data for cost-effectiveness analysis of these treatment regimens. Costs incurred by provider and costs incurred by patient coming and staying in hospital for treatment are included. Costs incurred by patient before they come to hospital is not included since it may be assum that

the costs are the same for both groups.

The outcome from the study is to select the more cost-effective regimen for falciparum malaria treatment at district hospital level.