Artemisinin based combination therapy for malaria in Viet Nam
Phan, G.T.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 6

Early Diagnosis and Treatment
of uncomplicated malaria in Viet Nam
and patterns of health seeking

Giao T. Phan¹, Peter J. de Vries¹, Binh Q. Tran²,
Nam V. Nguyen³, and Piet A. Kager¹

¹ Division of Infectious Diseases, Tropical Medicine and AIDS, Academic Medical Center,
Amsterdam, the Netherlands
² Tropical Diseases Clinical Research Center, Cho Ray Hospital, Ho Chi Minh City, Viet Nam
³ Binh Thuan Provincial Malaria Station, Phan Thiet, Viet Nam

Submitted for publication
Early diagnosis and treatment of uncomplicated malaria

Abstract

Early diagnosis and treatment of malaria (EDTM) is a key component of malaria control. Success of EDTM depends on health seeking behaviour and the quality of health service. This study assessed self diagnosis and treatment and treatment delay following the introduction of EDTM, based on microscopic diagnosis and treatment with artemisinin derivatives, free of charge, in southern Viet Nam, early 1993. Until 2001, 1698 questionnaires were filled in by patients participating in randomized treatment trials of uncomplicated malaria. The presumptive self diagnosis “malaria” increased from 68% in 1993 to 100% in 2001 and self treatment decreased from 74% to 8% in 2000 and 24% in 2001. The median (maximum) delay between first symptoms and seeking treatment at a public health facility, decreased from 3 (23) to 1.3 (3) days (p< 0.001). This accompanied a significant decline of malaria morbidity and mortality.

In conclusion, by offering an attractive package of EDTM, patients become sensitised to the possibility of malaria and apply less self treatment. EDTM should be provided as soon as possible to all symptomatic patients preferentially aiming at reduction of the long delays while setting an ambitious but realistic maximum. We suggest to set the maximum at two days.
Introduction

Global control of malaria has received a lot of attention lately, not in the least by the World Health Organization’s Roll Back Malaria initiative (RBM). Basic elements of RBM in the fight against malaria are early diagnosis and treatment of malaria (EDTM), preventive measures such as vector control, including insecticide treated bednets (ITNs), early warning and containment of outbreaks, and capacity building related to malaria control. One of the major achievements of RBM is the increased awareness and political interest, required to raise the human and financial resources for such a combined approach \[^{1,2}\]. The basics of RBM were laid at the Ministerial Conference on Malaria in Amsterdam in 1992. Eight years later, African Heads of State, in the Abuja declaration, resolved, amongst others, to strengthen their health care systems so that by 2005 at least 60% of malaria patients will have prompt access to correct, appropriate and affordable treatment within 24 hours of onset of symptoms \[^{3}\]. Such a commitment is urgently needed because malaria is still out of control, particularly in sub-Saharan Africa, where more than one million people die of malaria annually and where 90% of the world’s malaria attributable deaths occur \[^{4}\]. However, the question is if and how the ambitious Abuja targets can be achieved where health care systems are ailing. Providing early, correct, appropriate and affordable treatment within 24 hours after onset of symptoms, requires an improvement of all levels of the health care system of many African nations. This is an enormous task but with great additional benefits to health programmes other than malaria control.

To improve health care systems, a conceptual model is needed. An example is the so called Piot model which describes the use of health services in a quantitative manner by recognising awareness, motivation to seek treatment, the diagnostic process, correct treatment, adherence and treatment efficacy. The Piot model can also be applied to malaria but is does not describe the timeliness of diagnosis and treatment, for malaria, one of the most important determinants of outcome \[^{5}\]. The velocity of arriving at correct and appropriate treatment is usually described in terms of delay, at the patient’s and doctor’s side. Patient delay, the time until presentation to a facility which is equipped to manage malaria, is determined by several socio-cultural factors, generally referred to as knowledge, attitude and practice (KAP) and by physical limitations of distance, transportation etc. Delay by the health provider is part of the responsiveness of the health service, a recently developed concept to measure and compare the quality of health services in different countries \[^{6}\]. In a free market, health seeking
Early diagnosis and treatment of uncomplicated malaria

behaviour and responsiveness are related through the economic principles of demand and supply.

Thus, EDTM in developing countries implies bridging of the social, cultural, economic and physical barriers to bring diagnosis and treatment of malaria as close as possible to the needs of the population at risk. Several strategies can be followed to achieve this either aiming at redirecting health-seeking behaviour, or at improving the responsiveness of health service. Outside Africa, some remarkable successes of providing EDTM were achieved lately, such as in Viet Nam, China, Thailand and Brazil. These examples, each adapted to the local context, provide an opportunity to study and understand the dynamics of EDTM as a health systems intervention.

In 1992, a new Vietnamese National Malaria Control Program (NMCP) was launched. It is often referred to as successful in achieving a significant reduction of malaria morbidity and mortality over the last decade. The NMCP was based on providing EDTM through improvements of the regular health services, on providing insecticide treated bed nets and on health promotion to vulnerable populations (Nguyen Van Nam, unpublished observations). Key was the recognition of EDTM as the only way to prevent complicated disease and mortality in non-immune subjects and that malaria control thus was to be rooted in the regular public health services and that community involvement was essential to achieve maximally responsive primary health care services. Driven by a strong political will, the primary health care service started a process of modernization, even in the most remote regions of the country. The diagnosis of malaria was in most places based on clinical grounds, but some provinces decided to provide microscopic diagnosis at the primary health care level. Antimalarial drug policy, decided at national level, was based on artemisinin as the first line treatment of malaria since 1992, when these were made available by stimulating local production and listing them as subsidized drugs. Artemisinin drugs act rapidly and are well tolerated. They are typically given as three day artemisinins based combination therapy (ACT) but single day regimens or 7 day monotherapy regimens were also applied.

In Binh Thuan province, a mountainous province in the south of Viet Nam, the introduction EDTM was taken up vigorously. A deliberate choice was made to erect health posts in all communes in the malaria endemic areas where microscopic diagnosis treatment of malaria with artemisinin derivatives was offered free of charge. This process started at the end of 1992. To our knowledge this represents the most comprehensive interpretation of EDTM that can be delivered by any health service. We had the opportunity to follow the results of the malaria control program from its early start onwards. The subsequent decline of severe
morbidity, mortality, total incidence and prevalence of malaria in Binh Thuan over the last decade was impressive with no reported malaria attributable mortality at the end of the nineteen nineties (Nguyen Van Nam, unpublished observations). In this study we test the hypothesis that, since the introduction of EDTM in 1992 in Vietnam, patient delay and self-medication decreased and that knowledge and awareness increased. We also studied whether, under these optimal conditions of EDTM, patient delay can be reduced to less than 24 hours, one of the targets in the Abuja declaration.

**Methods**

Starting in January 1993 we performed a series randomised clinical trials studying the efficacy of different drug combinations with artemisinin drugs (ACT) in the treatment of uncomplicated malaria. All studies were carried in Binh Thuan province, except one study, which took place in Provincial Hospital II (1993-1995), Bao Loc in Lam Dong, a mountainous province bordering Binh Thuan; the Binh Thuan study sites were a district hospital (1993-1994) and several primary health care facilities (health posts) (1994-2002). In most study sites the trials represented the first introduction of EDTM and artemisinin drugs, after which EDTM with ACT was provided on a regular basis, free of charge for the most vulnerable population.

Patients with uncomplicated falciparum malaria with a parasite count below 100000/μL (1993 – 1994) or 200000/μL (1995 – 2003) were included [10-12]. There was one study on *P. vivax* infections [11]. As part of the data collection, questionnaires were filled in by all patients with confirmed malaria who were included in the treatment trials. In general, patients who received recent previous treatment with effective antimalarials were not included. However, outside the official health service only chloroquine and sulfadoxine were available and these were exempted from the exclusion rules because of their wide spread resistance and consequent lack of efficacy. Intake of quinine, the other antimalarial agent available outside the official health services, during twelve hours prior to inclusion in a treatment study was also an exclusion criterion. In addition, during the first studies questionnaires were also filled in by patients who presented with fever to the health facility, regardless of whether they had malaria or were included in the treatment studies.

Over the years, the questionnaires did not change. The patients’ perception and practice towards malaria were questioned by asking, among others, about symptoms, when these started, whether the patient thought to have malaria (self-diagnosis), whether drugs had
Early diagnosis and treatment of uncomplicated malaria

already been taken (self-treatment) and how these had been obtained, and whether they slept under a bed net.

The time between the first symptom and presentation to the health facility was an indicator of patient delay. The *P. falciparum* parasite count at presentation (PC0) was available for all patients who were included in the treatment studies. Patients with *P. vivax* infections were not included in the analysis of PC0, only their questionnaires were used.

The data of all available questionnaires were appended in one database and analysed. The hypothesis was tested that, since the introduction of EDTM in 1992, patient delay and self-medication decreased and that knowledge and awareness increased. It was also studied whether, under these optimal conditions of EDTM, patient delay could be reduced to less than 24 hours.

A time based analysis of nominal data was done with logistic regression, using S-plus 2000 (release 2, Mathsoft Inc., MA, USA). The time course of data with a non-Normal distribution such as the patient delay and initial parasite count was visualized using the LMS method (LMS pro, Institute of Child Health, Cole & Green).

A possible difference between the selection of patients at the Provincial Hospital and the district and community health facilities was taken into consideration during analysis. The district health center attracted malaria patients from the neighboring population and was thus grouped with the commune health facilities.

**Results**

Questionnaires of 1698 patients were available, including 474 from Bao Loc Provincial hospital, 578 from Duc Linh District hospital, and 646 from Binh Thuan community health posts. Of these, 643 febrile patients suspected of malaria were examined for malaria during 1993 and 1994, but not included in the treatment studies, mainly because of non-consent. Recent intake of antimalarial drugs, verbally confirmed, was not a common reason for non-enrollment. During the first two months of the study in Bao Loc, presence of antimalarial drugs in the urine was assessed by ELISA. Chloroquine, quinine, mefloquine and sulfadoxine/pyrimethamine were detected in 56%, 72 %, 2% and 54% respectively There was no difference in these percentages between those included in the studies and those not included. This implies that the included patients represent the general population of febrile patients seeking help at a health facility.

There was no difference of the mean [95% CI] patient delay between the patients presenting at the provincial hospital (3.0 [2.8-3.3] days) and patients at the other health
facilities (3.0 [2.7-3.3] days) (p = 0.4). There were no significant differences between patients who were included in the treatment trials and those who were not with respect to the self diagnosis “malaria” (72% and 67% respectively p = 0.06), self treatment (73% and 75% respectively, p = 0.3), use of bed nets (97% and 99% respectively, p = 0.05) and mean [95% CI] patient delay (3.3 [3.1-3.6] and 3.1 [3.0-3.3] respectively, p = 0.1). Therefore, all questionnaires of patients included and not included in the treatment trials of all health facilities were taken together for analysis of the changes of knowledge, attitude and practice over time.

The geometric mean [95% CI] PC0 among patients in the Bao Loc Provincial Hospital was 18244 / μl [15978-20830], significantly higher than in the other health facilities: 14482 / μl [12470-16819] (p = 0.01).

The trends of self-diagnosis and self-treatment, fitted with binary regression, are shown in Figure 1. Correct self diagnosis increased significantly by year (RR 2.72 [2.721-2.722], p < 0.001) from 68% in 1993 to 100% from 2000 onwards. Self-treatment decreased from 73% in 1993 to less than 9% in 2000 and 24% in 2001 (RR [95% CI] 2.72 [2.71-2.72], p< 0.001). Those with the correct self-diagnosis “malaria” were less inclined to self-treatment than those who did not, but in both instances self-treatment decreased over time (RR [95% CI] 1.35 [1.25-1.49] p < 0.001).

![Figure 1. Self diagnosis and self treatment in malaria patients, after the introduction of an early diagnosis and treatment policy at primary health care level in 1993.](image)

The proportion of malaria patients already suspecting malaria as their diagnosis and the proportion of patients taking drugs before seeking help at a public healthcare facility broken down by self diagnosis “malaria” Mean estimates (continuous lines) and 95% CL (broken lines) were predicted by binary regression.
Early diagnosis and treatment of uncomplicated malaria

Patient delay also declined over the years with a significant negative correlation between inclusion date and patient delay (Pearson’s R = -0.184, p < 0.001). Figure 2 shows the median and 2.5 and 97.5 centiles of the patient delay, generated with the LMS method. Most of the improvement was achieved by reduction of the extreme long delays, with a maximum delay in 1993 of 23 days to 3 days in 2001, but also the median delay decreased from 3 days in 1993 to 1.3 days in 2001. This however, implies that more than half of the subjects did not arrive at the health facility within 24 hours after onset of symptoms.

Figure 2. Delay in seeking help by malaria patients after the introduction of an early diagnosis and treatment policy at primary health care level in 1993.
Delay in days is given for every individual malaria patient. The median (continuous line) and 2.5 and 97.5 centiles (broken lines) were estimated with the LMS method.
The parasitaemia at presentation did not change over time, but this is probably an artifact because in 1995 the upper threshold of the initial parasitaemia in the treatment studies was raised from 100,000/µl to 200,000/µl.

**Discussion**

These results show that the knowledge of Vietnamese malaria patients about the cause of their ailment improved over the last decade. They also changed towards preferentially seeking help for what they thought was malaria, at the public facilities for primary health care instead of relying on self-medication.

Extrapolation of health service data to the general population may include potential bias. For example, if chloroquine is the only drug available at the free market and when there is much chloroquine resistance, then the population of people seeking help at health facilities will be enriched with failures of chloroquine treatment with a history of self treatment and long patient delay. The introduction of artemisinins on the free drug market, would lead to less treatment failures, since there is no resistance known against artemisinin drugs. This would translate into less self medication and patient delay. Although we did not perform systematic market surveys on malaria drugs, our general impression is that in the endemic areas in which our studies took place, the prescription of artemisinin drugs was restricted to the public health posts, not in the least due to the local government’s policy to discourage and even prohibit private clinics to be involved in malaria treatment with artemisinin drugs, to subsidize diagnosis and treatment free of charge at the public health posts and to increase awareness and knowledge by health promotion campaigns. This all contributed to keeping the bias small and the observed changes are therefore most likely true changes in behaviour induced by the attractiveness of the EDTM package at the primary health care level and the health promotion campaigns.

What are the ingredients of a palatable EDTM package? In principle, a malaria patient consults a health provider for an expert diagnosis and treatment. The quality of the malaria diagnosis at a primary health care post depends on the skills of the attending health care worker (HCW) and the availability of laboratory confirmation. A microscope is often not available in endemic areas and, consequently, malaria is usually diagnosed on clinical grounds, which it is not very accurate. Microscopic diagnosis and restricting treatment to confirmed malaria patients can be cost-effective but this has not been confirmed yet. In contrast, a too rigid decision tree which requires microscopic confirmation before any
Early diagnosis and treatment of uncomplicated malaria

treatment can be given for malaria could promote self treatment and therefore a HCW should have some freedom to diagnose and treat “clinical malaria”[17].

Rapidly effective medication may be considered an essential component of the health service response. Lack of antimalarial drugs or use of ineffective drugs, especially in areas with multi-drug resistant *Plasmodium falciparum*, causes delay in cure, severe disease or death and will encourage subjects to seek other means of treatment. Compliance with medication is also a determinant of treatment effectiveness. Poor compliance may cause delay of cure. In the case of artemisinin drugs, untimely discontinuation of the treatment course reduces the eradication time, leading to recrudescence [10]. Patients frequently have difficulties to comply with long course regimens, particularly after defervescence, and the remaining medication is often reserved for future episodes of fever in the household [18]. Short courses of ACT should circumvent this problem [19,20].

Soon after their introduction in Binh Thuan, the ACT regimens became appreciated by the population for their rapid effects and good tolerability and also because the previously available agents were renowned for their poor efficacy (S/P and chloroquine) or poor tolerability (quinine).

Accompanied by the reorganization of the Vietnamese public health service, the EDTM package thus became more attractive, at least in Binh Thuan. The provider came closer to the patients with more primary health care posts and more community health care staff. To date, expert microscopic diagnosis of malaria is available at all times of the day and effective drugs are available, free of charge, in sufficient quantities. Health promotion programmes and other primary health care programmes were launched simultaneously and community participation is organised through village health co-workers. These disseminate knowledge, monitor the use of bed nets and attend to febrile subjects who are unable to go to a health facility [9]. This explains the reduction of self-treatment and the increase of the proportion of subjects seeking primary care for malaria at a public health post in the first instance.

This also decreased the patient delay by almost two days, similar to what was observed in Sri Lanka after establishing a village treatment center [21]. This is a significant reduction, considering that children may die after less than three days of untreated symptomatic malaria [21,22]. The reduction of delay was not supported by a reduction of the initial parasite count. Parasite density is probably not a good indicator of the progress of the disease because it may be influenced by several other factors such as a varying degree of immunity and an exponential increase of the parasite density over time, which is not linearly correlated with the evolution of symptomatic disease. Moreover, the criteria for inclusion of patients into the
treatments studies, the main source of the questionnaires, limited the upper level of the parasite count, thereby obscuring the trends at higher values. In addition, as mentioned previously, in 1995 the upper threshold of the initial parasitaemia in the treatment studies was raised from 100,000/μl to 200,000/μl.

The reduced patient delay probably resulted in diagnosis and treatment of malaria at an earlier stage of disease. During the same period, severe morbidity and mortality in Binh Thuan decreased to very low levels, an effect of arresting progress of disease at an early stage. (Nguyen Van Nam, unpublished observations) The decline of total incidence, an effect of prevention by insecticide treated bed nets, was much slower.

Two important questions remain. Is the 24 h criterion in the Abuja declaration also a clinical requirement, and can this criterion be fulfilled for half of the population.

Looking at malaria from a clinical perspective, the most striking feature is its very rapid progression to severe disease. It is somewhat surprising that in all the definitions of severe malaria and guidelines for treatment, delay is not included. This is probably explained by the difficulties of assessing the duration of symptoms in holoendemic areas. However, it was shown in Vietnamese patients with complicated malaria that the reported duration of symptoms was 4.2 (95% CI: 3.9-4.5) days [23]. Others found minimally two or three days of delay in fatal cases of malaria [24,25]. From all studies it is clear that complications and fatality rates increase with longer delay.

In a review of treatment seeking studies, McCombie showed that delay in seeking treatment for malaria of at least 3 days is common, due to cost of medicine, travel and work but also to difficulties in accessing the official health sector [26]. Our study demonstrates that mainly the very long intervals of delay decline when an attractive package of EDTM is offered. This is probably the mechanism by which severe morbidity and mortality were reduced in Binh Thuan. At the same time, this was achieved while the median delay was still 1.3 days in 2002. This offers a background for the Abuja targets and questions whether the 24 hours criterion is realistic. Which nations in sub-Saharan Africa will be able to copy this best example from Viet Nam, which took ten years, in less then half the time? Moreover, it also shows that setting targets for half of the population is not rational when the problems are caused by the extreme long delays. It is probably more appropriate to set a maximum time span between first symptoms and receiving adequate and effective treatment as a target. Although there are no strict definitions we tentatively state, in view of the Vietnamese experience and also based on our general clinical impression, that two days is the maximum tolerable delay for symptomatic malaria.
Early diagnosis and treatment of uncomplicated malaria

The Vietnamese NMCP made a deliberate choice to provide EDTM through the public health care system and not to promote self-treatment, simultaneously realising that a responsive (primary) health care sector is the precondition for a restrictive drug policy. However, in the absence of professional health care, self-treatment may be life saving and indeed is the dominant mode of treating malaria worldwide [26-31]. The obvious disadvantage is the risk of injudicious drug use, leading to reduced efficacy or increased toxicity and selection of resistant parasites [26,31]. Nonetheless, several approaches to improve self treatment have been studied, such as providing pre-packed antimalarial drugs to households, mother groups or teachers combined with training, or by training shop keepers [32-35]. A crucial question is if ACT regimens are robust enough to be used by non-professionals who are not equipped to handle the aspects of efficacy, tolerance, resistance, interactions with other drugs such as anti-retroviral agents, and parasite recurrence and to monitor treatment response.

Cost is the biggest obstacle for malaria control and thus also for EDTM. An African household spends approximately 2-25$ on treatment for malaria monthly, sometimes adding up to 5-13% of the total household expenditure [4]. Where people are poor, the health service is usually also poor and both frustrate the balance between health needs and responsiveness of the health service. This entanglement can only be solved by financial and political support and economic improvements. In Viet Nam, struck by poverty after several wars, the malaria situation deteriorated during the 1980s and peaked in 1991 with a recorded incidence of 1.09 million, 4646 deaths and 144 outbreaks [7,36]. The new malaria control strategy of 1992 started simultaneously with structural reforms of the public health care system, redirecting resources to peripheral and poor regions [37]. This decentralisation was not in all aspects successful, and often increased inequity, self treatment and higher costs [38]. However, the malaria control program stood out with great political and financial support and morbidity and mortality of malaria declined dramatically in the following ten years (Nguyen Van Nam, unpublished observations) [7,39]. Although it is difficult to prove that these interventions were the only cause of the success, this experience unambiguously demonstrates that a malaria control programmes can be implemented if there is strong government commitment, community involvement and adequate investments [40].

In conclusion, the Vietnamese malaria control program showed that it is feasible to improve the people’s knowledge on malaria and reduce self-treatment and patient delay, by investing in a strong primary health care system, based on community involvement, and ensuring access to early diagnosis of malaria and treatment with artemisinin based drug
combinations for all vulnerable populations. This probably contributed to the reduction of malaria morbidity and mortality in Viet Nam over the last decade. Early diagnosis and treatment should be provided as soon as possible to all, and health intervention packages should preferentially target the reduction of extreme long patient’s and doctor’s delay and set a realistic maximum to this delay.

On clinical grounds we suggest a maximum of two days for all patients, which is an ambitious target, even for Viet Nam.

References

Early diagnosis and treatment of uncomplicated malaria


Early diagnosis and treatment of uncomplicated malaria


