

## THE QUALITY OF ANTIMALARIAL MEDICINES IN EASTERN THAILAND: A CASE STUDY ALONG THE THAI-CAMBODIAN BORDER

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**Abstract.** This study examined the prevalence, availability, and use of antimalarial medicines (AMLs) along the Thai-Cambodian border. The study was divided into two parts: the first looked at the quality of AMLs available in six Thai provinces and the second obtained information about the availability and use of AMLs. A randomized sampling methodology was used to select locations and collect samples, which were screened using Global Pharma Health Fund (GPHF) Minilabs<sup>®</sup>. A subset of samples was sent to quality control laboratories for verification testing. For the second part of the study, face-to-face interviews were conducted with members of randomly selected households and the staff of health facilities in villages with the highest malaria incidence to find out where they acquired their AMLs and which were used most frequently. The results of quality testing showed an overall failure rate of 1% (7 of 709 samples) for active pharmaceutical ingredients (API); however, the API failure rate varied from 0.0% to 2.2% by location and the overall failure rates of samples by province varied from 0.0% to 3.4%. A total of 97.9% ( $n=272$ ) of respondents had taken AMLs. The most commonly used medicines were primaquine (30% of respondents), chloroquine (15.8%), artesunate+mefloquine (12%), and quinine (10%). Most respondents (97.9%) had received medications from public hospitals or malaria clinics.

**Keywords:** antimalarial medicine, quality, availability, active pharmaceutical ingredient, Thai-Cambodian border

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### INTRODUCTION

Malaria is a parasitic disease transmitted by various species of the night-biting *Anopheles* mosquitoes, which can transmit different types of malaria parasites. We studied only *Plasmodium falciparum* ma-

laria, a known public health problem and the cause of millions of deaths worldwide, including in Thailand (Tiwari *et al*, 2001; Ghosh *et al*, 2006; Kaur *et al*, 2008). Only good quality, safe and efficacious medicines and other preventive measures can help fight this disease.

Many developing countries have become havens for poor quality, expired, or counterfeit medicines, making it difficult to fight malaria. The term "poor quality" that medicine means fake (a medicine which does not contain active pharmaceutical ingredients (API) or is not what it purports to be), counterfeit (a medicine that is deliberately produced with incorrect or wrong API, mislabeled with respect to its source or identity, made or repacked by unauthorized persons, or contains less than 80% of API), or substandard medications (a genuine medicine which does not meet the quality specifications set for it).

Efforts to dissuade people from selling or using counterfeit or substandard medicines (CSMs) are made in most countries. The sale and use of these medicines is common and is increasingly becoming global concern (Lon *et al*, 2006; European Commission-Taxation and Customs Union, 2007; Newton *et al*, 2008; Bate *et al*, 2009). Countries with stringent medicines regulatory agencies (MRAs) are firmer in enforcing laws than in less developed countries, where laws and regulations are inadequate, ineffective, or out-of-date. If correct measures are in place, poor quality medicines can be detected earlier and more easily. In this study, we examine the CSMs found in selected provinces in Thailand.

In legal terms, a substandard medicine is one that is produced by a legitimate manufacturer which does not meet quality specifications set for it (Kaur *et al*, 2008; Bate *et al*, 2009; WHO, 2012). Counterfeit medicines are those that are deliberately

or fraudulently mislabeled with respect to identity or source (Tiwari *et al*, 2001; Ghosh *et al*, 2006). The testing for counterfeit medicines may have one or more results: wrong API, no API, low or high concentrations of API that do not meet quantity standard limits, or a substitute chemical.

One impact of counterfeit and substandard AMLs is that they contribute to drug resistance, an increasing concern in malaria control efforts. If the drug does not contain an API, then the patient is not being treated. Substandard medication can lead to sub-therapeutic dosing, resulting in suboptimal treatment, prolonged use and drug-resistance. Too high concentrations of API may result in increased or lethal side effects.

To achieve an understanding of the quality of AMLs in eastern border provinces of Thailand, this study was divided into two parts: the first involved randomized sample collecting and testing to check the quality of available AMLs, and the second involved face-to-face interviews with randomly selected household members and health facility staff. These interviews helped researchers understand where people obtained their AMLs, which ones were most frequently used, and whether patients had a knowledge of how to properly store medications to ensure their quality.

## MATERIALS AND METHODS

A randomized sampling method was used for health facilities, household surveys and collection of AMLs for quality analysis. A country study investigation team, supervised by a principal and an assistant investigator from the United States Pharmacopeia Drug Quality and Information program (DQI) was formed. The DQI



Fig 1—Map of study provinces. (Public domain image credit: US government).

program and its successor, the Promoting the Quality of Medicines (PQM) program, are funded by the United States Agency for International Development (USAID) and implemented by the United States Pharmacopeia (USP). The team consisted of central and provincial investigators; the provincial investigators were responsible for carrying out the study in their respective provinces while the central level coordinated the study and monitored progress.

**Health facility and household surveys**

The study population consisted of interviewees randomly selected from households and health facilities from each village in each province with the highest malaria incidence. The key activities implemented were: 1) survey development; 2) training the study team in how to conduct interviews; 3) gathering necessary information about health facilities and pharmaceuticals, and, 4) mapping sampling locations.

Using a standardized questionnaire, the country study team conducted surveys addressing household and health

facility AML usage. These surveys were intended to provide supplementary information related to the acquisition of AMLs and their use in malaria treatment to help researchers understand possible associations between the prevalence of poor quality AMLs and the presence of malaria where the medicine samples were collected. The number of households randomly sampled per selected village was determined using the Yamane formula (confidence level 95%,  $p=0.5$ , precision  $\pm 5\%$ ). The number of health facilities (hospitals, health centers, and malaria clinics) sampled per province equaled 30% of the total number of facilities in each province (randomly selected). Data analysis of the surveys was performed using SPSS version 15 (SPSS, Chicago, IL).

**Methods for AML sample collection and analysis**

Samples were randomly collected from pharmacies, health facilities and clinics in public and private sectors from six provinces along the Thai-Cambodian border: Buri Ram, Chanthaburi, Sa Kaeo, Si Sa Ket/Ubon Rachathani, Surin and

Trat. The provinces (Fig 1) were chosen based on their malaria burden, AML sensitivity (indicating artemisinin tolerance and resistance) of *P. falciparum*, and the presence of surveillance sites for monitoring malaria treatment efficacy.

The key activities implemented in AML collection and analysis were: developing a study protocol (sampling, testing, data management), training study members, collecting and testing samples, and data analysis.

Four criteria were taken into account to determine the sample size: the level of precision or a sampling error of 4%, the confidence level with an assumption of normal distribution of 95% of the sample values, the degree of variability in the quality of AMLs distributed across the study sites, and the expected prevalence of failed samples (failure rate).

The number of units comprising a sample was determined by the testing method used. These included basic and confirmatory pharmacopeial testing methods. Depending on the product formulation and availability at the sampling location, a predefined number of units per sample were collected. For single-drug preparation dosage forms, 60 tablets or capsules were collected. For preparations of two fixed-dose combinations (FDC), 80 tablets or capsules were collected; and for injectable preparations ten vials were collected. At least 20 units of each sample were obtained if the above criteria could not be met. The samples were collected based on their availability during the study period and at that location. Every attempt was made to obtain all the necessary information about the samples. The data was recorded in a standardized report form.

#### AML sampling techniques

Formal and "mystery shopper" tech-

niques (Sengaloundeth *et al*, 2009) were used to sample medications at public sector institutions (hospitals, health centers and malaria clinics). The study team requested permission to obtain AML samples after identifying themselves and explaining the purpose of the sampling (Fig 2). At private sector facilities, samples were collected by mystery shoppers acting as patrons; they did not identify themselves as investigators. Samples were transported to their testing locations without physical damage, which could affect the examinations.

#### Analytical testing methods for medication screening

Basic analysis of the AMLs was performed using the Global Pharma Health Fund (GPHF) Minilab<sup>®</sup> technique (Fig 3). The evaluation included physical and visual inspection, simple disintegration, and thin layer chromatography (TLC) (Phanouvong *et al*, 2005; Foster and Phanouvong, 2009). A simple disintegration test determined whether uncoated, normal-release, solid-dosage forms of the medication will disintegrate within 30 minutes, providing information about their solubility. TLC was used to identify the presence of API(s) in the sample, determine the presence of impurities and quantitatively determine the amount of active ingredient in the sample. The results of the testing samples were compared with that of the reference products. The results were divided into those that passed, failed, and gave equivocal results. A subset of each group was then sent for verification testing at the Bureau of Drug and Narcotic (BDN) laboratory of the Department of Medical Sciences, Thailand, and the National Institute for Drug Quality Control (NIDQC), Vietnam. The pharmacopeias used were the United States Pharmacopeia (USP 29-NF24), the



Fig 2—Obtaining information regarding the sample on a standardized form. (Photo credit: Christopher Raymond).



Fig 3—Analysis of medicines. (Photo credit: Christopher Raymond).

Table 1  
Samples sent for verification testing.

Active pharmaceutical ingredient	Number of samples
Artesunate	6
Chloroquine phosphate	37
Mefloquine hydrochloride	3
Primaquine phosphate	9
Quinine dihydrochloride	2
Quinine sulphate	8
Sulfadoxine/Pyrimethamine	1
Tetracycline hydrochloride	30
Total	96

International Pharmacopoeia, the Pharmacopoeia of the People’s Republic of China, and/or in-house validated analytical methods.

Samples were first tested for appearance and identity of the API; if the sample failed this test, no further tests were conducted. If the identity test was correct, then an assay for content test was performed. If the drug sample failed the assay for content test, no further testing was conducted. If the sample passed the identity and assay for content tests, dissolution testing was conducted. Dissolution is regarded as an important technique in both product development and quality control for solid dosage forms (Liddell *et al*, 2007). Dissolution problems suggest absorption and permeability are affected, leading to poor bio-availability of the medicine (Egan and Lauri, 2002; Kale *et al*, 2007; Franco *et al*, 2008).

This process continued until all pharmacopoeial tests were conducted. With artesunate samples, related substances or impurity tests were also performed.

A sample failed if it did not conform to the standard specifications for identity of API, disintegration, or dissolution. It also would be considered failed if there were any other major physical deficiencies, such as broken tablets, non-uniform color or improper labeling.

Of the 709 samples, 96 (13.5%) were selected (Table 1), based on established criteria, for verification at two national quality control laboratories (BDN/Thailand and NIDQC/Vietnam). Samples that failed Minilab<sup>®</sup> testing were re-evaluated through verification testing to determine the reason for failure (Table 5). The same number of samples that passed the Minilab<sup>®</sup> testing and failed Minilab<sup>®</sup> testing

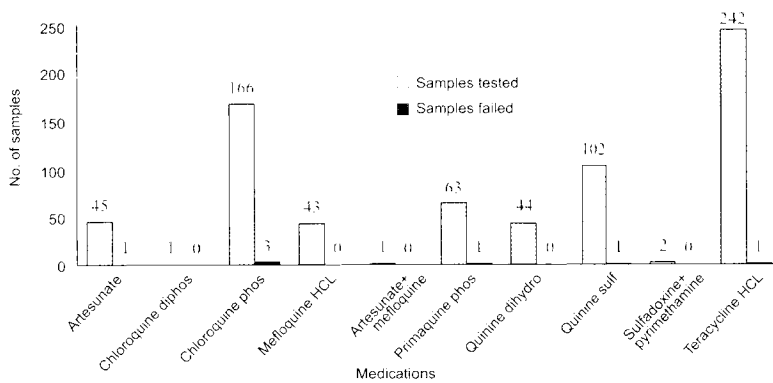


Fig 4—Failure of samples by medication type.

were submitted for verification testing. The AMLS for which the greatest number of samples were sent for verification testing were tetracycline HCl and chloroquine phosphate, followed by primaquine phosphate, quinine phosphate and artesunate (Table 1).

## RESULTS

A total of 709 AML samples (Table 2) were collected from six study sites in Thailand – 53% from the public sector and 47% from the private sector (Table 3). The study protocol was translated into the Thai language to avoid miscommunication and misinterpretation.

The failed samples (Fig 4) were collected from private retail pharmacies in Trat ( $n=1$ ), Surin ( $n=3$ ), Ubon Rachathani ( $n=1$ ), and Sakaeo ( $n=2$ ) Provinces (Table 4). Artesunate had the greatest percentage of failures at 2.2% (1 of 45 samples) followed by chloroquine phosphate at 1.8% (3 of 166 samples). Other AMLs that failed quality testing were primaquine phosphate, tetracycline HCl, and quinine sulphate (Table 5). One sample each of tetracycline HCl and chloroquine phosphate did not meet dissolution criteria. The

artesunate sample passed the assay but failed the requirement for related substances. One sample each of primaquine phosphate, chloroquine phosphate and quinine sulphate did not contain any of the API listed on its label. These are considered counterfeit medicines. Chloroquine diphosphate and sulfadoxine/pyrimethamine were the least collected

samples, indicating these medicines are not as easily available in the market due to loss of efficacy in treating malaria.

Chloroquine phosphate, mefloquine hydrochloride, tetracycline hydrochloride and primaquine phosphate were being circulated as single-dose tablets; doxycycline was rarely found in the market. Sulfadoxine/pyrimethamine and artemether/lumefantrine tablets were among the fixed-dose combinations available, while artesunate/amodiaquine were available as co-packaged tablets in Thailand. There were few other AMLs available in the market.

### Data analysis and results of household and health facility medicines survey

A total of 1,243 households and 32 health facilities were visited where interviews were conducted (Fig 5). Among those households, 33.5% reported a member having malaria during the previous year. Nearly 98% of respondents obtained their AMLs from public sector hospitals, health centers and malaria clinics (Fig 6). Most households (71.3%) had no appropriate storage locations for their medicines and kept them on open shelves, exposed to both heat and humidity.

Table 2  
Sample results.

Active pharmaceutical ingredients	Number of samples tested	Sample that failed		Sample that passed	
		Number	Percent	Number	Percent
Artesunate	45	1	2.2	44	97.8
Chloroquine diphosphate	1	0	0.0	1	100
Chloroquine phosphate	166	3	1.8	163	98.2
Mefloquine hydrochloride	43	0	0.0	43	100
Mefloquine + Artesunate	1	0	0.0	1	100
Primaquine phosphate	63	1	1.6	62	98.4
Quinine dihydrochloride	44	0	0.0	44	100
Quinine sulphate	102	1	1.0	101	99.0
Sulfadoxine/Pyrimethamine	2	0	0.0	2	100
Tetracycline hydrochloride	242	1	0.4	241	99.6
Total	709	7	1.0	702	99.0



Fig 5—A study investigator conducting household interviews at a village in Sakaeo Province, Thailand. (Photo credit: Sanya Sook-Kam).

Table 3  
Sample sources.

Facility	Number of samples
Public sector	
Hospital	254
Malaria clinic	124
Private sector	
Retail drug outlets	18
Clinic	6
Street vendors	1
Pharmacy	305
Other	1
Total	709

The most commonly used AML among subjects was primaquine (30.2%), followed by chloroquine (15.8%) (Fig 7). This is in agreement with the health facility survey where health care providers stated they most frequently gave their patients primaquine (87.5%) or chloroquine (84.4%) (Fig 8). Since one counterfeit sample each of chloroquine and primaquine

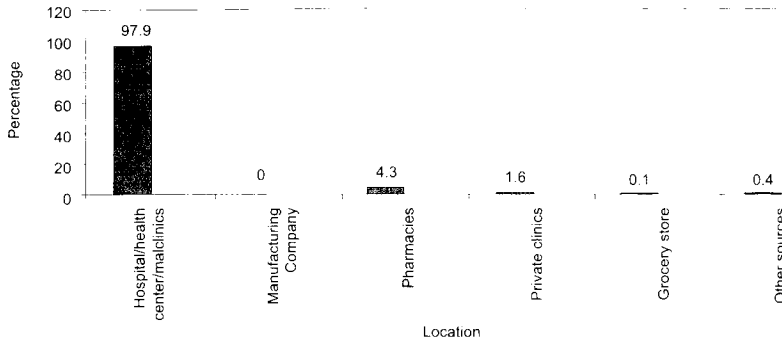


Fig 6—Locations where subjects purchased antimalarial medication.

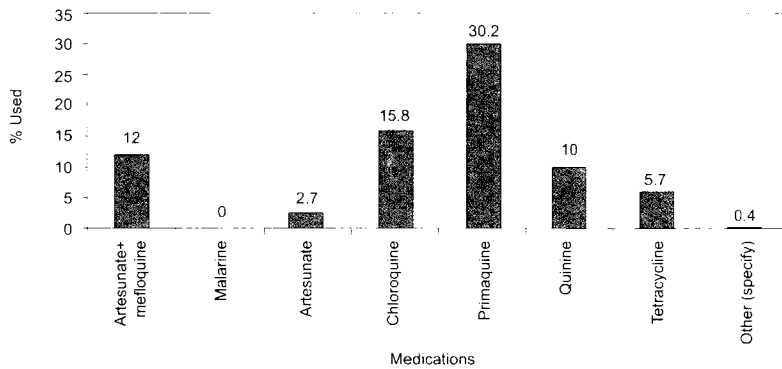


Fig 7—Medicines used by respondents to treat malaria.

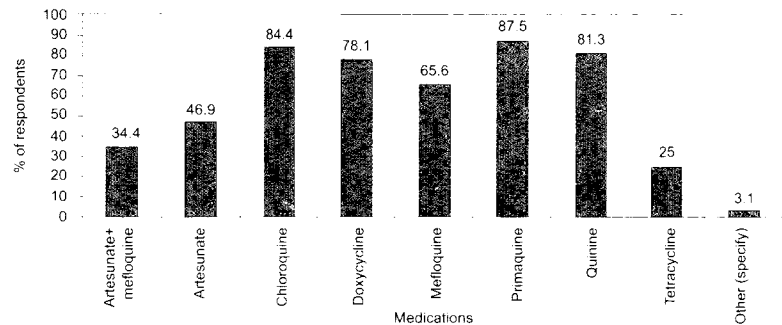


Fig 8—Medicines given by health care providers to treat falciparum malaria.

private clinics and retail pharmacies to treat malaria were primaquine, chloroquine, quinine and doxycycline (Fig 8).

DISCUSSION

The overall sample failure rate in the participating sites was 1.0% (Table 4). The low failure rate for antimalarials collected from the selected sites is an indication that the quality of AMLs was good.

Mefloquine + artesunate co-blistered combination preparations are not popular in Thailand because of side effects caused by mefloquine leading to adherence issues, inappropriate use, and inaccurate dosing, which may cause treatment failure (Marsh, 1998; Kouyate *et al*, 2007; Wongsrichanalai and Meshnick, 2008). Since the 1960s, sulfadoxine/pyrimethamine combination has proven ineffective to treat malaria in Thailand (Wongsrichanalai and Meshnick, 2008),

were found, this is cause for concern. The vast majority of patients obtained their medicines from legal retail outlets or the public sector (Fig 6); these counterfeit medicines were obtained at legal outlets.

The medications usually given by Thai healthcare providers at public health facilities (hospitals and malaria clinics),

which may explain why it is not as popular as other AMLs found in the survey sites.

Some AMLs that The Thai FDA and National Medicine Control Policy have prohibited to be sold in the private sector were found circulating in the market during this study, such as artesunate and



Table 4  
Sample failures by province.

Province	No. of samples	No. failed	% failed
Buri Ram	80	0	0.0
Chanthaburi	199	0	0.0
Sakaeo	142	2	1.4
Si Sa Ket/Ubon Rachathani	63	1	1.6
Surin	87	3	3.4
Trat	138	1	0.7
Total	709	7	1.0

Table 5  
Reasons for sample failure.

Active pharmaceutical ingredients	Reasons for failure	No. of samples
Primaquine phosphate	Identification test result: no active ingredient	1
Tetracycline hydrochloride	Dissolution test result: 0% - 0.8% for tetracycline hydrochloride	1
Chloroquine phosphate	Dissolution test result: 35.0%-39.8% for chloroquine phosphate	1
	Identification test: no chloroquine, but contained quinine sulphate	1
Artesunate	Related substances: above reference limit	1
Quinine sulphate	Identification test: no quinine, but contained chloroquine	1
	Total	7

mefloquine. AMLs are not allowed to be sold as monotherapy but were found during the survey and were available without a prescription. The third-most-used AML among patients after primaquine and chloroquine was artesunate monotherapy. Patients and private sector vendors must be made aware that artesunate should not be taken alone; artemisinin-based monotherapy is associated with the development of drug resistance resulting from increased single-drug pressure on the parasite (Dondorp *et al*, 2010).

Household and health center surveys carried out in tandem with AML sample

collection revealed the antimalarial preparations commonly used by the local populations and included products that did not comply with quality standards. The presence of counterfeit primaquine in the private sector in Surin Province, together with other failed products in this study, attest to the need for adequate and extensive quality control and assurance systems for antimalarial medicines in this area.

National regulatory authorities need to communicate with manufacturers, distributors, health centers and pharmacies to include post-marketing surveillance

of product quality. This could include in-depth reporting and oversight of manufacturing, importation, and distribution of antimalarials, especially along border zones. Strict controls must be enforced. Medicines must be traced from manufacturer or importer, through the distribution chain, and ultimately to the outlet where the patient receives the medicine.

The Thai-Cambodian border presents a unique set of challenges for monitoring and ensuring the quality of antimalarial medicines circulating in the market. This is the first study of this type undertaken here. The researchers hope follow-up studies will further complement the data generated. This study demonstrated the presence of failed anti-malarial samples from all six study sites. The primary reasons discovered for product failure included the absence of API, an incorrect API and failure of the product to pass dissolution testing.

The Thai Ministry of Public Health and provincial regulatory authorities should be lauded for their efforts to strengthen current quality assurance strategies by developing on-going and reliable AML sampling and testing in both the public and private sectors. Ninety-nine percent of AML samples in this study passed analysis. AML quality must continue to have a high priority among policymakers in Thailand and in the Greater Mekong Sub-region in order to stave off the looming threat of drug resistance and its concomitant economic and public health fallout.

Although every effort was made by investigators to reduce sampling and testing error, the study had some limitations, including the fact that the provincial study teams may not have strictly observed the sampling protocol or performed field

laboratory tests at the same level of expertise. This could have resulted in some bias in the results and data interpretation.

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