THE QUALITY OF ANTIMALARIAL MEDICINES IN WESTERN CAMBODIA: A CASE STUDY ALONG THE THAI-CAMBODIAN BORDER

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Abstract. The prevalence, availability, and use of antimalarial medicines (AMLs) were studied in six Cambodian provinces along the Thai-Cambodian border. The study was divided into two parts: the first looked at the quality of AMLs available in Pursat, Pailin, Battambang, Bantey Meanchey, Oddar Meanchey, and Preah Vihear 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®. A subset of samples was sent to quality control laboratories for confirmatory testing. For the second part of the study, face-to-face interviews were conducted using standardized surveys with members of randomly selected households and staff of health facilities in the villages with highest malaria incidence to find out where they acquired their AMLs and which were most frequently used. The results showed an overall failure rate of 12.3% (*n*=46 of 374 total AML samples). The causes of medication sample failure were low active pharmaceutical ingredient (API) content, failed dissolution properties, and unacceptably high levels of impurities. A total of 86.2% of survey respondents (*n*=1,648 of 1,912) reported a member of their household having malaria in the previous year. The most commonly used medicines were paracetamol (67.1% of respondents), Malarine® (A+M co-blistered, 28.6%), artesunate + mefloquine co-blistered (public sector product, 17.3%), quinine (16.7%), and artesunate monotherapy (11.9%). Health staff typically prescribed co-blistered artesunate plus mefloquine in the public sector (67.8%), the artesunate plus mefloquine "social marketing" product from Population Services International (PSI), Malarine® (50.3%) in the private sector, artemether (49.7%), chloroquine (39%) and paracetamol (72.9%) to reduce fever.

Keywords: antimalarial medicine, quality, availability, active pharmaceutical ingredient, western Cambodia

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INTRODUCTION

The border area between Cambodia and Thailand has a history of malaria parasites resistant to a number of therapeutic agents (WHO, 2007). Beginning in the 1960s, malaria in this region first became resistant to chloroquine, followed by sulfadoxine-pyrimethamine (Thimasarn *et al*, 1995; Wongsrichanalai *et al*, 2002). These resistant parasites then spread to the rest of the world, rendering these key chemotherapeutic agents essentially ineffective in treating malaria (Roper *et al*, 2004; WHO, 2010a).

Recently, artemisinin resistant *Plasmodium falciparum* malaria has been documented (WHO, 2005; Denis *et al*, 2006; Vijaykadga *et al*, 2006; Dondorp *et al*, 2009, 2010). As a result, a large-scale containment project was launched and implemented from January 2009 to October 2011, spearheaded by the World Health Organization (WHO) in cooperation with the Cambodian Ministry of Health (MOH), to ensure this deadly form of malaria parasite is contained and eventually eliminated. Funded by the Bill and Melinda Gates Foundation (BMGF), the containment project began following molecular and efficacy studies by a consortium of research institutions working in this border area to characterize the nature and extent of the parasite. This research included the anti-malarial medicines study described in this paper to determine the effects, if any, poor quality anti-malarial medicines in circulation could have on increasing drug pressure and the emergence of drug resistance.

Many resource-limited countries lack robust and effective medicines regulations and medicines regulatory agencies (MRAs). As a result, poor quality, expired, or counterfeit medicines circulate in both public and private markets (Lon *et al*, 2006). Previous investigations in the region have revealed production and circulation of counterfeit anti-malarials, generating concern and spurring targeted research in this area (Newton *et al*, 2008).

This study obtained baseline data on the quality of AMLs circulating in six provinces in western Cambodia along the border with Thailand in areas defined as Zone 1 and Zone 2. This classification is used by the Cambodian National Center for Malariology, Parasitology and Entomology (CNM) to delineate those provinces receiving assistance to contain anti-malarial drug resistant parasites (WHO, 2010 b; WHO, 2011a). Containment Zone 1 includs areas where resistance of *Plasmodium falciparum* to artemisinin had already been documented in Pailin, Battambang, and Pursat Provinces. Containment Zone 2 encompasses a "buffer area" surrounding Containment Zone 1 where resistant parasites are likely to spread but have yet to be detected in the ten provinces along the Cambodian-Thai border.

In this paper we use the Cambodian definitions of counterfeit and substandard medicines: substandard medicines are those produced by a legitimate manufacturer but do not meet quality specifications set for them; counterfeit medicines are those that are deliberately produced with an incorrect quantity, wrong active ingredients, or are without active ingredients or unregistered products where the amount of active ingredients are deliberately outside the defined pharmacopeial or accepted standard; deliberately or fraudulently mislabeled with respect to identity, source or with fake packaging; or repacked or produced by an unauthorized agent. By definition, there are no quality

guaranties of a counterfeit product.

MATERIALS AND METHODS

This study was divided into two parts: household and health facility surveys at study sites, and sampling and testing of AMLs in the study sites. A randomized sampling method was used for health facility and household surveys and collection of AMLs for quality analysis. The provincial study sites (Fig 1) were selected based on malaria disease burden, evidence of extended parasite clearance times in controlled efficacy studies (indicating the emergence of multi-drug resistance in the *P. falciparum* parasite), the presence of established malaria treatment efficacy study sites, the presence of sentinel sites for medicine quality monitoring.

A Cambodian country study investigation team, hereafter "Study Team", supervised by principal and assistant investigators from the United States Pharmacopeia Drug Quality and Information (USP DQI) program was formed. The DQI 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 representatives from the Cambodian Department of Drugs and Food (DDF)–the national medicines regulatory authority; the National Center for Malariology, Parasitology and Entomology (CNM); and the National Health Products Quality Control Center (NHQC) laboratory. The team consisted of central and provincial investigators; the provincial investigators (provincial drug inspectors) were responsible for carrying out the study in their respective provinces while the central level staff coordinated and monitored study protocol implementation with the provincial investigators.

Household and health facility surveys

The survey design was descriptive and cross-sectional. The study population consisted of interviewees randomly selected from households and health facilities in villages in each province with the highest malaria incidence according to national statistics from the CNM (calculated by Annual Parasite Incidence per one thousand persons per year). Using convenience sampling within each village, heads of households or responsible individuals above the age of 16 were surveyed (total n=1,912 respondents) using a standardized questionnaire. The questionnaire was developed in collaboration with Cambodian Ministry of Health officials, the WHO, and the USP DQI program. These surveys were intended to provide supplementary information specifically 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 malaria situation where the medicine samples were collected.

The health facility survey population (total n=177) consisted of health staff from hospitals, pharmacies, health centers and clinics in both public and private sectors, including licensed and unlicensed facilities, randomly selected according to a standardized protocol.

Sampling and testing of anti-malarial medicines

Methods for AML sample collection and analysis. An adapted Yamane simplified formula (Yamane, 1967) was used to calculate sample size in this study: minimum sample size = $[Z^2 \times (p) \times (1\text{-}p)] / d^2$; where Z = critical value (*eg*, 1.96 at 95% confidence level), p = prevalence (failure

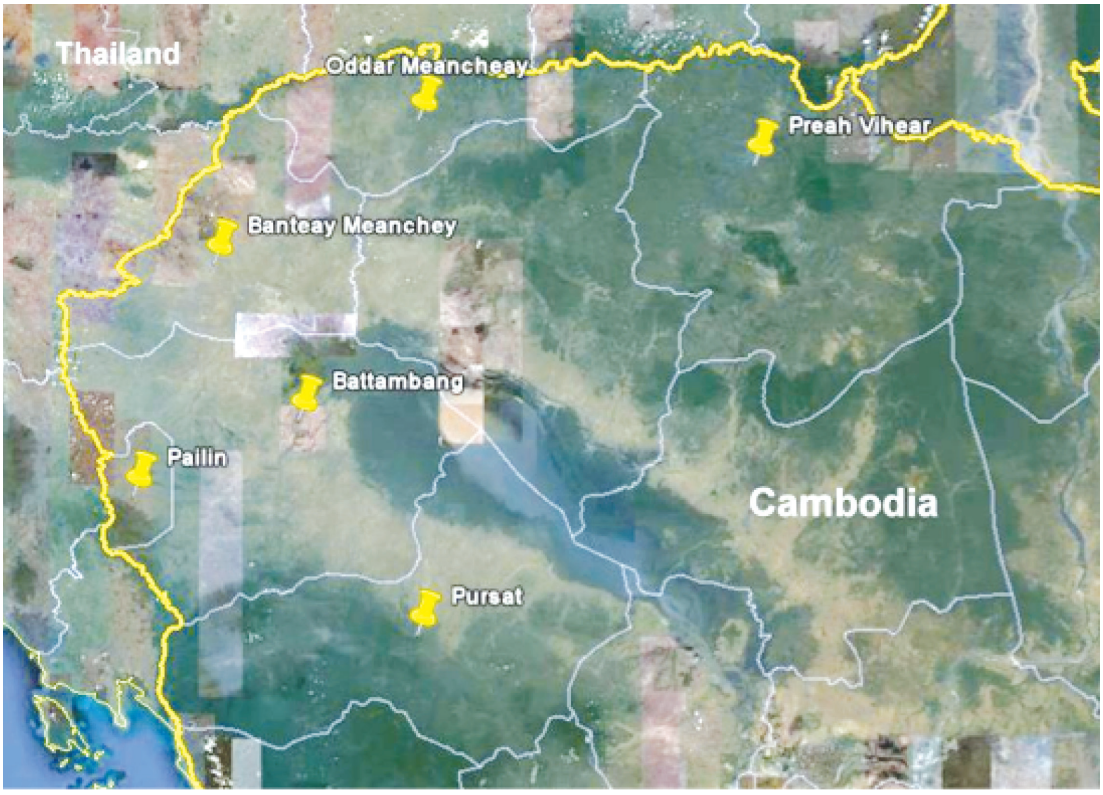

Fig 1–Cambodian provincial study sites. (Map source: Google Earth).

rate), d = confidence interval.

Considering a hypothetical 10% failure rate, based on previous years' data collected during medicine quality monitoring activities in Cambodia, a total of 217 samples were to be collected ($p \approx 10\%$, $n=1.96^2 \times (0.1) \times (1\text{-}0.1) / (0.04)^2 = 217$ samples). The number of units composing a sample was determined by the test methods used, including basic tests (physical/visual inspection, disintegration, and Thin Layer Chromatography (TLC)) and confirmatory testing according to compendial or pharmacopeial specifications. Depending on the product formulations, a predefined number of units per sample were collected as follows: 60 tablets or capsules for single-drug preparations; 80 tablets or capsules for two-product fixed-dose combination (FDC) preparations, and 10 vials for injectable/liquid preparations.

The following AML samples were targeted for collection in this study, depending on availability at sampling locations during the study period: artesunate tablets and injections, artemether injections, artemisinin tablets, dihydroartemisinin (DHA) tablets (including the brand Cotexcine®), amodiaquine tablets, chloroquine phosphate tablets, mefloquine hydrochloride tablets, quinine sulfate tablets and injections, tetracycline hydrochloride tablets, artemether/lumefantrine FDC tablets, artesunate + mefloquine (A+M co-packaged) tablets, artesunate + amodiaquine (co-packaged) tablets, doxycycline tablets or capsules, DHA/piperaquine (PIP), and DHA/piperaquine/trimethoprim.

Fig 2–AML sample collection from a public sector health clinic (Photo credit: Richard Humphries).

Fig 3–AML sample collection at a private sector pharmacy (Photo credit: Richard Humphries).

Fig 4–AML testing with Minilab® methods (Photo credit: Richard Humphries).

Medicine samples were obtained from both public and private sectors according to a protocol translated into the Khmer language to avoid miscommunication and misinterpretation of the study design.

Two techniques were used to acquire medicine samples for testing: "formal" (officially announced) and "mystery shopper" (unannounced) techniques. In public sector outlets, the pharmacist or supervising staff was asked by the investigators for permission to select AML samples from the storage or dispensary area after officially identifying themselves and explaining the purpose of the sampling (Fig 2). In private sector pharmacies or illegal outlets, samples were collected using mystery shoppers acting as patrons or patients (Fig 3); they did not identify themselves as study investigators or ministry officials. This was intended to increase the probability of randomizing samples by reducing bias or intentional actions by the shop owners to purposely exclude certain AMLs.

Medicine samples were collected regardless of the expiry date; however, expired medicines were not tested, rather they were simply documented as being present in circulation. Samples collected were stored in accordance to their storage instructions, with a maximum temperature not exceeding 25°C and kept in a dry environment to prevent any deterioration or contamination.

Analytical testing methods for medication screening. Basic analysis of the AMLs was performed using GPHF Minilab® techniques (GPHF, 2011) (Fig 4). Basic screening tests included physical and visual inspection, simple disintegration, TLC, and data documentation and reporting (Phanouvong *et al*, 2005). 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 in the sample, determine the presence of impurities and quantitatively determine the amount of API in the sample. The results of the testing of the samples were compared with the test results using the reference products. The results were divided into those that passed, failed, and gave equivocal results. All samples that failed or gave equivocal results were sent for verification testing, along with a specified number of samples that passed basic testing. The passed samples selected for confirmatory testing were used for quality assurance to ensure that data generated in the field via screening tests were reliable.

Analytical methods for confirmatory testing. Confirmatory testing using compendial methods was performed at the National Health Products Quality Control Center (NHQC) laboratory, Cambodia; the Bureau of Drugs and Narcotic (BDN) laboratory, Thailand; and the National Institute for Drug Quality Control (NIDQC) laboratory, Vietnam. Each national quality control laboratory used the latest edition of the United States Pharmacopeia (USP) and other internationally-acceptable pharmacopoeias, such as the International Pharmacopoeia, the Pharmacopoeia of the People's Republic of China, or in-house validated analytical methods.

A sample was considered to have "failed" if it did not conform to the recognized standard specifications for identity of API, disintegration, dissolution, and assay for content of API, or any major physical deficiencies such as broken tablets, non-uniformity of color, or improper labeling/packaging. The results from confirmatory testing using compendial methods for each sample were reported using a standardized form provided in the protocol.

The pharmacopeial standards used for verification testing in this study were: the API content acceptance criteria were set in range of 90-110% of the reference standards, disintegration criteria were set to less than 30 minutes for uncoated tables (film-coated or sugar-coated chloroquine and tetracycline not more than 60 minutes), and for the dissolution of at least 60% within 30 minutes (chloroquine at least 75% in 45 minutes, tetracycline at least 80% in 60 minutes).

RESULTS

Data analysis was conducted using SPSS version 15 in consultation with statistical experts from Mahidol University in Bangkok, Thailand. All data are described as numbers or percentages in the tables and figures present in this paper.

Household survey results

Of the 1,912 Cambodians interviewed, 1,648 (86.2%) stated a household member had contracted malaria during the previous year. The top five most-frequently used medicines reported by respondents in this study were paracetamol (67.1%), Malarine® artesunate + mefloquine (A+M) co-blistered, private sector product (28.6%),

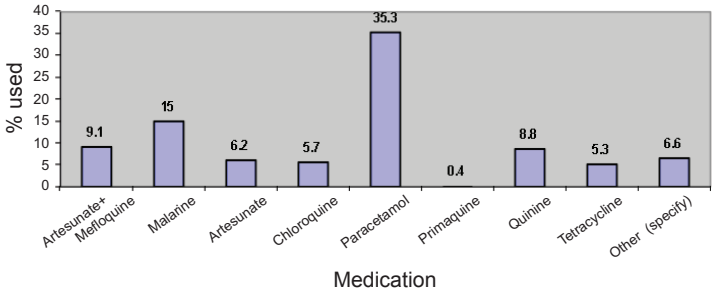

Fig 5–Medications used by respondents to treat malaria.

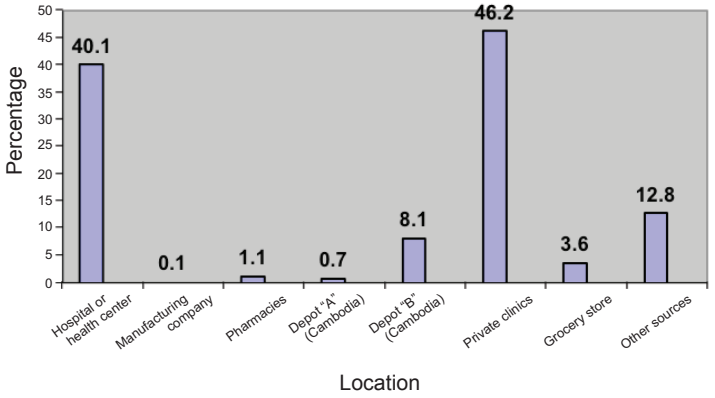

Fig 6–Locations where subjects purchased antimalarial medications.

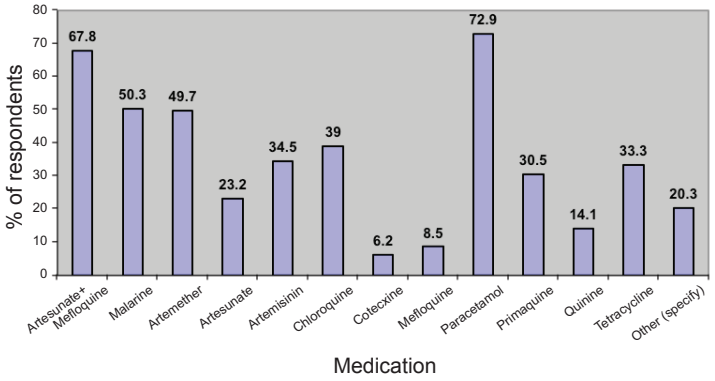

Fig 7–Medicines given by health care providers to treat falciparum malaria.

artesunate + mefloquine co-blistered (public sector product, 17.3%), quinine (16.7%), and artesunate monotherapy (11.9%) (Fig 5). Sources for AMLs were private sector clinics (46.2%) and public health facilities (40.1%) (Fig 6). A total of 98.2% of households reported storing AMLs in areas not designed for medicines storage with no temperature or humidity control.

Health facility survey results

A total of 177 staff from health facilities were interviewed regarding prescribing and dispensing practices for medicines to treat falciparum malaria in the study area. Health staff prescribed the two products on the market containing co-blistered A+M: the public sector A+M co-blistered product (67.8%), and the private sector, A+M social-marketing product Malarine® (50.3%) from PSI (Fig 7). Malarine® was produced for the market to ensure adequate supplies of private sector artemisinin-based combination therapies in circulation in Cambodia. Most health staff (72.9%) reported using the analgesic paracetamol to treat malaria symptoms. Roughly half (49.7%) reported using artemether, and 39% prescribed chloroquine.

Results of AML collection and testing

A total of 377 AML samples were collected (3 products were already expired at the time of collection); 374 were screened using basic tests following the GPHF Minilab® methods of physical and visual inspection, simple disintegration, and TLC. Nineteen (5.1%) failed basic

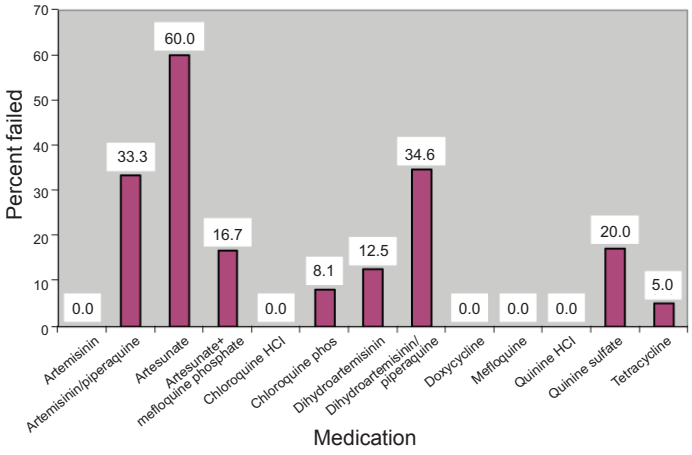

Fig 8–Failed AML samples.

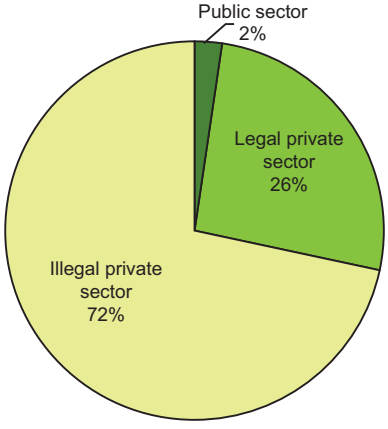

Fig 9–Total percentage of failed samples by sector (*n*=46).

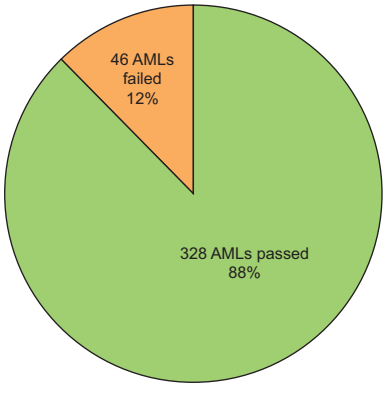

Fig 10–Total number of passed and failed AML samples (*n*=373).

screening testing in the field. One hundred sixty-nine samples (100% of the failed and equivocal samples, and a selection of "passed" samples) were sent to national quality control laboratories for confirmatory testing using compendial methods; 46 AML samples failed confirmatory testing (Tables 1 and 2). The overall sample failure rate was 12.3%.

Medications with the highest failure rates were artesunate (monotherapy) at 60% (15 of 25 samples), dihydroartemisinin/piperaquine at 34.6% (9 of 26 samples), artemisinin/piperaquine with 33.3% (2 of 6 samples), quinine sulfate at 20% (5 of 25 samples), artesunate + mefloquine phosphate at 16.7% (2 of 12 samples), and dihydroartemisinin at 12.5% (1 of 8 samples) (Fig 8).

A total of 26.1% of samples either failed API content acceptance criteria or did not contain any API at all, including five quinine sulfate samples. Medications that failed assays for content tests were artesunate, ranging from 0% - 88.3%, artesunate + mefloquine co-packaged formulations with 77.7% artesunate content; artemisinin/piperaquine, ranging from 4.8% (artemisinin)/50.7% (piperaquine) to 48.6% (artemisinin)/50.4% (piperaquine), and dihydroartemisinin with 87% API content. Low API content products result in sub-therapeutic dosing, which can lead to treatment failure. Sub-therapeutic dosing can exert

Table 1
Reasons for sample failure.

Medication	Reason for failure	No. of samples
Artesunate	API comprises 86.96%.	1
	API comprises 88.3% and related substances more than 2%.	1
	API comprises 0% and disintegration in more than 60 minutes.	3
	Dissolution in less than 60% and related substances comprising more than 2%.	1
	Related substances comprising greater than 2%.	9
Artesunate + Mefloquine	Impurities in artesunate greater than 2%.	1
	Artesunate comprises 77.7% and related substances comprising more than 2%.	1
Artemisinin + Piperaquine	Artemisinin comprises 48.6% and piperaquine comprising 50.4%.	1
	Artemisinin comprises 4.8% and piperaquine comprises 50.7%.	1
Dihydroartemisinin	API comprises 87.0%.	1
Dihydroartemisinin + Piperaquine	Dissolution of DHA of 4.7% to 79.2% and PIP of 0.8-96.5%.	1
	Dissolution of DHA and PIP of 0% in 45 minutes.	5
	Dissolution of DHA 0-82.5% and PIP 0-119.4% in 45 minutes.	2
	Dissolution of DHA of 2-73.2% and PIP of 0.5-99.1% in 45 minutes.	1
Chloroquine	Dissolution of <75% in 45 minutes.	1
	Disintegration in >60 minutes.	6
Tetracycline	Dissolution of 1.04%-13.8% in 60 minutes.	3
	Dissolution of 25.3% -35.2% in 60 minutes.	1
	Disintegration in >60 minutes.	1
Quinine	No API	5
	Total	46

API, active pharmaceutical ingredient; DHA, dihydroartemisinin; PIP, piperaquine

selection pressure on the malaria parasite which can quicken the emergence of drug resistance (WHO, 2010b).

Twenty-one samples failed dissolution and/or disintegration tests. Products failing dissolution testing are considered to be of poor quality, resulting from either substandard manufacture of a legitimate product or deliberate counterfeiting. These products will be poorly absorbed into the bloodstream, thereby reducing bioavailability of the therapeutic molecule. Many samples tested contained a higher level of impurities and/or other related compounds than are accepted according to monograph criteria, which could be toxic and/or lead to treatment failure; although related compounds may possess some therapeutic value, it is unknown if they are equivalent to the primary API.

The failed AML samples were collected from both public and private sector facilities (Table 2 and Fig 9). One of 23 AML samples (4.3%) from public sector facilities failed confirmatory testing; 45 of 146 samples (30.8%) from private sector facilities failed confirmatory testing. Seventy-two percent of the failed private sector AMLs were from illegally-operating retailers (Fig 9). Sample failure rates by sector should not be confused with overall

Table 2
Reason for failure of AMLs and sampling location.

Medication	Sample collection location	Reason for failure
Legal public sector outlet		
1. Quinine	Health Center storeroom in Pailin	Wrong active pharmaceutical ingredient.
Legal private sector facilities		
2. Artemisinin + Piperaquine	Pharmacy in Pursat	Assay content for both components.
3. Artesunate	Pharmacy in Pursat	Assay content and disintegration.
4. Artesunate	Pharmacy in Pursat	Assay content and disintegration.
5. Chloroquine	Depot pharmacy in Pursat	Disintegration.
6. Dihydroartemisinin + Piperaquine	Depot pharmacy in Pursat	Dissolution and assay content for both components.
7. Dihydroartemisinin + Piperaquine	Pharmacy in Pursat	Dissolution and assay content for both components.
8. Chloroquine phosphate	Pharmacy Depot B in Oddar Meanchey	Disintegration.
9. Tetracycline	Consultation room cabinet in Oddar Meanchey	Disintegration.
10. Artesunate	Depot pharmacy in Preah Vihear	Assay content and dissolution.
11. Quinine	Depot pharmacy in Preah Vihear	Assay content and disintegration.
12. Quinine	Depot pharmacy in Preah Vihear	Assay content and disintegration.
13. Quinine	Depot pharmacy in Preah Vihear	Assay content and disintegration.
Illegal private sector drug outlets		
14. Artesunate	Drug outlet in Battambang	Impurities.
15. Artesunate	Drug outlet in Battambang	Impurities, dissolution.
16. Artesunate + Mefloquine	Drug outlet in Battambang	Impurities, dissolution.
17. Artesunate + Mefloquine	Drug outlet in Battambang	Impurities, dissolution.
18. Dihydroartemisinin + Piperaquine	Drug outlet in Battambang	Dissolution for both components.
19. Tetracycline	Drug outlet in Battambang	Dissolution.
20. Artemisinin + Piperaquine	Drug outlet in Pursat	Assay content for both components.
21. Chloroquine	Drug store in Pursat	Disintegration.
22. Chloroquine	Drug store in Pursat	Disintegration.
23. Dihydroartemisinin	Drug outlet in Pursat	Assay content.
24. Dihydroartemisinin + Piperaquine	Drug outlet in Pursat	Dissolution and assay content for both components.
25. Dihydroartemisinin + Piperaquine	Drug outlet in Pursat	Dissolution and assay content for both components.
26. Dihydroartemisinin + Piperaquine	Drug outlet in Pursat	Dissolution and assay content for both components.

Table 2 (Continued).

Medication	Sample collection location	Reason for failure
27. Dihydroartemisinin + Piperaquine	Drug outlet in Pursat	Dissolution and assay content for both components.
28. Dihydroartemisinin + Piperaquine	Drug outlet in Pursat	Dissolution and assay content for both components.
29. Dihydroartemisinin + Piperaquine	Drug outlet in Pursat	Dissolution and assay content for both components.
30. Artesunate	Drug outlet in Pailin	Assay content.
31. Artesunate	Drug outlet in Pailin	Related substances.
32. Artesunate	Drug outlet in Pailin	Related substances.
33. Artesunate	Drug outlet in Pailin	Related substances.
34. Artesunate	Drug outlet in Pailin	Assay content and related substances.
35. Artesunate	Drug outlet in Pailin	Related substances.
36. Chloroquine	Drug outlet in Pailin	Disintegration.
37. Chloroquine	Drug outlet in Pailin	Disintegration.
38. Chloroquine	Drug outlet in Pailin	Dissolution.
39. Quinine	Drug outlet in Pailin	Wrong active pharmaceutical ingredient.
40. Tetracycline	Drug outlet in Pailin	Dissolution.
41. Tetracycline	Drug outlet in Pailin	Dissolution.
42. Artesunate	Drug outlet in Bantey Meanchey	Impurity.
43. Artesunate	Drug outlet in Bantey Meanchey	Impurity and dissolution.
44. Artesunate	Drug outlet in Bantey Meanchey	Impurity.
45. Tetracycline	Drug outlet in Bantey Meanchey	Dissolution.
46. Artesunate	Drug outlet in Preah Vihear	Assay content and disintegration.

sample failures for which the failure rates are calculated using the total number of samples (n=374) tested/screened as the denominator (Fig 10).

Samples of first- and second-line AML products that failed quality analysis were mostly collected from legal, private sector Pharmacy Depot A and B sites (Pharmacy Depot A sites are staffed by a pharmacy assistant and Depot B sites are staffed by a registered nurse or midwife). Failed samples were also collected from legal, private sector "consultation rooms," private pharmacies (staffed by a certified pharmacist), and illegal drug retailers or unregistered grocery stores.

DISCUSSION

During the study period, the first-line treatment regimen for *P. falciparum* infection recommended by the national malaria program was artesunate plus mefloquine, available in co-blistered formulations in public (A+M generic) and private

(Malarine® from PSI) sectors. During the implementation of the malaria containment project, DHA+PIP and Malarone® were used in specific, containment-related activities (such as focused screening and treatment). For first-line treatment failure, quinine plus tetracycline was recommended. Chloroquine was the treatment of choice for *P. vivax* and *P. malariae* infections. Co-infections were treated with A+M and for severe or complicated cases, intramuscular artemether plus mefloquine tablets were given.

In September 2008, the Cambodian MOH banned the production, importation, sale and registration of artemisinin monotherapies in the public and private sectors. However, the subsequent roll-out of the national ban was not immediate in its application, illustrated by the availability of artesunate monotherapy and dihydroartemisinin monotherapy found at private sector outlets in this study. An official declaration by the MOH was made on March 23, 2009 to increase the reach of this ban.

After completion of this study, the malaria containment project along the Thai-Cambodian border scaled up efforts to investigate private sector providers to remove banned products and develop a public-private mix strategy to ensure that suspected malaria cases are referred directly to public sector health facilities (PATH, 2011). At the time of this manuscript's submission, DHA/PIP was the drug of choice in Containment Zone 1, although national treatment guidelines are currently being updated to expand the use of DHA/PIP throughout Cambodia. The implementation of the Affordable Medicines Facility-malaria (AMFm), funded by The Global Fund to Fight AIDS, Tuberculosis and Malaria, will subsidize DHA/PIP procurement (manufactured by Sigma Tau), provided it is listed by the WHO Prequalification Program as quality-assured (WHO, 2010b).

The Department of Drugs and Food of the Cambodian Ministry of Health successfully implemented a strategy to close down many illegally-operating drug outlets in the country (USP, 2010b). The DDF reported there were 1,545 legal pharmacies and drug shops in Cambodia, and only 10 illegal drug outlets were still in operation. This illustrates a positive trend in political will to increase oversight and regulation of pharmacies and drug outlets. The majority of counterfeit and substandard medicines come from private sector sources, usually operating without a license. Closure of these outlets will reduce the number of illegally-sold products circulating in the future.

The Cambodian DDF should continually follow up with manufacturers, distributors, health centers, and pharmacies to include post-marketing surveillance of products and compliance with Good Manufacturing, Good Distribution, and Good Dispensing Practices standards. Changes in Cambodian national treatment guidelines for malaria to reduce the availability of antimalarials in the private sector, combined with ongoing surveillance and enforcement, will be important components in malaria treatment over the next few years. Cambodia also needs to develop a functioning pharmacovigilance center, particularly to report adverse drug events and other issues associated with widespread use of newer malaria medications.

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. Inconsistency in availability of various medicines from province to province could have altered overall results, especially since the study area covers Zones 1 and 2 along the border, where efforts to contain drug resistant malaria have altered the availability of some medicines in those zones compared to the rest of the country. The sample sizes from public and private sectors were not equal; a skewing of data may have resulted in underreporting of poor quality medicines circulating in the public sector.

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