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Counterfeit and substandard antimalarial drugs in Cambodia

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Summary Counterfeit and substandard antimalarial drugs can cause death and contribute to the growing malaria drug resistance problem, particularly in Southeast Asia. Since 2003 in Cambodia the quality of antimalarial drugs both in the public and private health sector is regularly monitored in sentinel sites. We surveyed 34% of all 498 known facilities and drug outlets in four provinces. We collected 451 drug samples; 79% of these were not registered at the Cambodia Department of Drugs and Food (DDF). Twenty-seven percent of the samples failed the thin layer chromatography and disintegration tests; all of them were unregistered products. Immediate action against counterfeit drugs was taken by the National Malaria Control Program (NMCP) and the DDF. They communicated with the Provincial Health Department about the presence of counterfeit antimalarial drugs through alert letters, a manual, annual malaria conferencing and other training occasions. Television campaigns to alert the population about counterfeit drugs were conducted. Moreover, the NMCP has been promoting the use of good quality antimalarial drugs of a blister co-packaged combination of artesunate and mefloquine in public and private sectors. Appropriate strategies need to be developed and implemented by relevant government agencies and stakeholders to strengthen drug quality assurance and control systems in the country.

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1. Introduction

The problem of counterfeit and substandard drugs is a global concern and contributes to poor treatment outcomes, wastes the already scarce financial resources and may cause drug resistance. It was estimated that the sale and trade of counterfeit drugs accounts for approximately 10% of global pharmaceutical trade, which translates to US$32 billion (IFPMA, 2004; US Food and Drug Administration, 2005). Improper strategies to tackle the problem of counterfeit drugs relative to their large impact on public health have been a key factor (Cockburn et al., 2005). There have been reports of counterfeit and substandard drugs contributing to increased mortality (Jacobson, 2004; Rozendaal, 2001). They are also considered to be one of several factors contributing to the growing resistance to antimalarial drugs, especially in Southeast Asia (Trape et al., 1998). Nowadays, the antimalarial drug resistance situation is serious in Cambodia. Appropriate use of safe, efficacious and good quality antimalarial drugs is the cornerstone of the National Malaria Control Program (NMCP). A drug surveillance network has been established by the NMCP, Ministry of Health, in cooperation with the WHO, the European Commission Malaria Control Project (ECMC), the United States Pharmacopeia Drug Quality and Information Program (USP DQI) and Management Sciences for Health (MSH). The network consists of monitoring antimalarial drug sensitivity, survey of drug use practices and drug product quality. There has been substantial evidence of counterfeit and substandard drugs in Cambodia since 1999 (Rozendaal, 2001). A survey in 1999 by the NMCP and ECMC of drugs marketed in the private sector found that fake artesunate was sold by 71% and fake mefloquine by 60% of 133 drug outlets in eight provinces (Rozendaal, 2001). Another study using a colorimetric field test showed that 25% of artesunate tablets from Phnom Penh and Seam Reap contained no active ingredient (Newton et al., 2001). Despite public warning campaigns in Cambodia (Newton et al., 2002), counterfeit artesunate was still found (38%) in the Lao People's Democratic Republic, Cambodia, Myanmar, Viet Nam and Thailand (Dondorp et al., 2004). This evidence reflected a lack of effective collaboration of strategies and action taken in the region. Efforts have been made by the Ministry of Health to develop pharmaceutical law and regulations, but their enforcement remains weak. Poor regulation and weak law enforcement provide an opportunity for counterfeiters where unscrupulous traders can operate without serious risk of being penalised.

The ongoing study, started in May 2003 in collaboration with the USP DQI and WHO, attempts to obtain evidence-based data from the field on the quality of selected antimalarial drugs. Data have been made available to guide policymakers and drug regulatory authorities in the importance of developing and implementing appropriate strategies and policies to address the drug quality problems in Cambodia.

2. Materials and methods

2.1. Study sites

The study sites have been designed to overlap geographically with the study sites for monitoring the clinical efficacy of first-line malaria treatment and for community-based antimalarial drug use practice, comprising Pursat, Battambong, Pailin and Preah Vihear provinces bordering Thailand and Laos. These areas have high levels of antimalarial drug resistance and high malaria prevalence (Ministry of Health, 2003). In these four provinces, illegal drug trade practices have been anecdotally observed. (Illegal drug trade refers to practices of production, sale and distribution of drugs without formal authorisation of the Ministry of Health's Drug Regulatory Agency.)

2.2. Drug sampling procedures

A convenient sampling method was used in this project. Before conducting the survey, the national and provincial project teams were trained in the sampling method, good laboratory practices and basic drug testing techniques, including physical and visual inspections, simple disintegration, thin layer chromatography (TLC), data documentation and reporting.

Three rounds were conducted in different areas of the provinces. The first round was conducted in April 2003. The drug outlets in a capital town of each province were selected using a pre-defined sampling protocol (Phanouvong et al., 2004). The second and third rounds covered other drug outlets in the different districts in July and December 2003.

The sampling team, primarily disguised as ordinary customers but at times also dressed up as a formal mission, purchased a sample from each lot of antimalarial drugs available in each outlet, namely: quinine sulfate tablets; chloroquine phosphate tablets; artesunate tablets; mefloquine hydrochloride tablets; tetracycline tablet/capsules; dihydroartemisinin (DHA) tablets; and artemether tablets. When arriving at drug outlets, the team asked to buy whatever antimalarial drugs were available for sale at the store regardless of their price range and lot numbers. During sample collection, all the necessary information about the samples was recorded in a standard report form.

2.3. Laboratory methods

Drug samples collected were analysed at three levels according to established guidelines for sampling of antimalarial drugs (Phanouvong et al., 2004). The first level was basic testing performed at the sentinel sites using adapted testing methods and procedures described in the German Pharma Health Fund Minilab kits (Richard and Andreas, 2002). The tests covered physical/visual inspections, simple disintegration and TLC. The second level involved verification testing conducted by the National Laboratory for Drug Quality Control (NLDQC) in Cambodia using TLC. The third level of testing was confirmation of selected samples at designated reference laboratories, namely: the Bureau of Drug and Narcotics Laboratory in Thailand; the National Institute of Drug Quality Control in Viet Nam; and the United State Pharmacopeia Laboratory in the USA. Testing methods and procedures for confirmatory testing were carried out in accordance with individual pharmacopeial monographs in International Pharmacopoeia Vol. 5, third ed and USP26-NF21. A sample was considered failed if it did not pass any tests, including identity of active pharmaceutical ingredient

Table 1 Drug outlets selling counterfeit drugs

Drug outlets visited for sample collection	Legal outlets (%) ($n = 38$)	Illegal drug outlets (%) ($n = 133$)	Total ($n = 171$)	*P*-value
Counterfeit samples found	22 (57.9)	100 (75.2)	122	0.251[a]
Total sample collection[b]	100	351	451	NA

NA: not applicable.
[a] No statistically significant difference between two types of drug outlets ($P > 0.05$).
[b] One to five samples were collected from each drug outlet.

(API), disintegration, assay for content of API and any major physical deficiencies such as broken tablets, non-uniform colour and improper labelling. A quinine tablet sample was failed because, for example, it contained no API as claimed on the label.

In the field, sample collection, testing, data documentation and reporting were reinforced and supervised by designated staff from the NMCP, NLDQC and Department of Drugs and Food (DDF) to ensure accuracy and consistency.

2.4. Data analysis

Data analysis was done using Epi Info 6 (CDC, Atlanta, GA, USA) and Microsoft Excel 4 for Windows.

The Fisher's exact text was used for comparison of categorical values. Statistical significance was set at $P < 0.05$. All data were described in percentage by tables and description (frequency and proportion).

3. Results

Of 498 listed drug outlets, 391 (78.5%) drug outlets were unlicensed in the four selected provinces based on a list of Pharmacies and Depot of Pharmacies A and B at Phnom Penh and Provinces by the DDF at 31 December 2002. The study teams visited 171 (34.3%) drug outlets to collect samples and a total of 451 drug samples were purchased (Table 1). Of these samples, 351 (77.8%) were from unlicensed drug outlets and 355 (78.7%) were not registered at the DDF. All samples were analysed using the basic testing methods, including visual/physical inspections, TLC and simple disintegration test.

Among the collected samples, 197 (43.7%) were labelled as produced in Thailand, 102 (22.6%) in China, 19 (4.2%) in Cambodia, 17 (3.8%) in Switzerland and 48 (10.6%) were claimed to be produced in Germany, India, Australia, France, Viet Nam, Hong Kong, Korea, The Netherlands, England, Belgium, Cyprus or Malaysia. The remaining 68 samples were of unknown origin. The TLC and disintegration test results showed that the average failure rate of quinine was 71.8%, artesunate 19.8% and tetracycline 26.6%, followed by chloroquine 8.5% and mefloquine 7.7% (Table 2). In this study, only 22 samples of DHA and 2 samples of artemether passed the tests. The overall result showed that 122 (27.1%) samples failed TLC and/or disintegration tests. Among failed samples, 22 samples were collected from 17 licensed or legal drug outlets and 100 were from 59 unlicensed or illegal drug outlets. The study showed that counterfeit and substandard antimalarials were available both in licensed and unlicensed drug outlets: 57.9% of 38 licensed and 75.2% of 133 unlicensed drug outlets surveyed sold counterfeit drugs (Table 1). There was no significant difference between licensed and unlicensed drug outlets ($P = 0.251$). Regarding the 61 failed quinine samples, there was no manufacturer's name and address on 13 samples (unknown origins), whilst 47 displayed labels for 'Brainy Pharmaceutical Limited Partnership' (Figure 1), in Thai and English, with no manufacturer's address, and 1 sample had incomplete labelling with no expiry date. Subsequent investigation

Table 2 Testing results of samples by province or city

Name of province or city	No. of sites visited	Quinine		Artesunate		Mefloquine		Chloroquine		Tetracycline	
		N	Failure rate, *N* (%)	*N*	Failure rate, *N* (%)	*N*	Failure rate, *N* (%)	*N*	Failure rate, *N* (%)	*N*	Failure rate, *N* (%)
Battambong	159	19	12 (63.2)	24	6 (25.0)	10	0	25	0	34	9 (26.5)
Preah Vihear	63	18	11 (61.1)	10	3 (30.0)	5	0	18	2 (11.1)	20	7 (35.0)
Pailin (City)	54	22	19 (86.4)	20	3 (15.0)	10	1 (10.0)	25	0	32	9 (28.1)
Pursat	222	26	19 (73.1)	27	4 (14.8)	14	2 (14.3)	26	6 (23.1)	42	9 (21.4)
Total	498	85	61 (71.8)	81	16 (19.8)	39	3 (7.7)	94	8 (8.5)	128	34 (26.6)

Samples were analysed based on actual number of samples collected, not lot or batch-based. Epi Info 6 and Microsoft Excel spreadsheet were used as the method for data analysis.

Figure 1 Label of fake quinine sulfate tablets from Brainy Pharmaceutical.

by the DDF and official confirmation from the Food and Drug Administration (FDA) of Thailand revealed that Brainy Pharmaceutical is not a legitimate manufacturer in Thailand. Among the 47 samples labelled as manufactured by Brainy, 43 samples contained wrong active pharmaceutical ingredients (WAPI) and 4 contained no active pharmaceutical ingredients (NAPI) at all. The other 13 samples from unknown origins contained WAPI and 1 other sample had low API.

All failed artesunates contained NAPI and were labelled as produced by Guillin Pharmaceutical Works in China. It was very difficult to differentiate fake from genuine products by visual inspection. Three mefloquine samples failed the TLC test. Two of the three failed mefloquine samples contained NAPI and another one contained WAPI. They were kept in plastic bottles different from the original containers and without appropriate labelling. Chloroquine samples were stored in the same bottles as mefloquine. Among 94 failed chloroquine samples, 7 samples failed the disintegration test and 1 sample contained NAPI. Of 34 failed tetracycline samples, 25 were labelled as Brainy Pharmaceutical Limited Partnership (Figure 2), the same as the failed quinine samples, whilst 7 samples were of unknown origin. Of the 25 Brainy tetracycline samples, 8 contained NAPI and 17 were substandard containing less than 80% in quantity of API. Among nine samples of unknown origin, two contained NAPI and seven were substandard. The failed drug samples were all unregistered products.

3.1. Study limitations

The authors accept that this study has methodological limitations specifically with regard to sampling and data analysis. The study was not necessarily representative and one should not generalise for the whole country. However, it provides useful information regarding the problems of counterfeit and substandard antimalarials in the four provinces participating in the study.

4. Discussion

A very high proportion of antimalarial drugs collected during the survey were found to be counterfeit and substandard. The failure rates of quinine and artesunate were very alarming and worrying. All failed artesunate tablets were labelled as produced by Guillin Pharmaceutical Works with a hologram similar to the genuine one. Artesunate tablets were the most frequently received as the first-line malaria treatment of choice. Twenty-eight percent of 1187 clients interviewed received artesunate according to a report of Drug Use Practice Survey in 2002 (NMCP, unpublished report). Quinine samples had the highest failure rate (71.8%). Most failed samples were labelled as manufactured by Brainy Pharmaceutical Limited Partnership. Quinine was found to be the second most popular antimalarial drug after artesunate. In the same survey areas, more than 70% of quinine samples

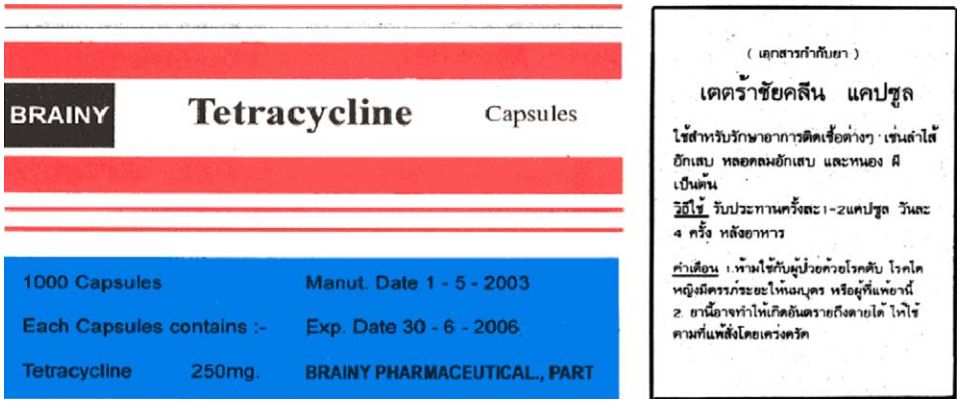

Figure 2 Label of fake tetracycline tablets from Brainy Pharmaceutical.

were found containing NAPI or WAPI. The chance of receiving counterfeit quinine could be incredibly high, maybe higher than 71%, for those who sought treatment in the private sector. Tetracycline was the second largest sample that failed the tests. Tetracycline was also commonly used as an antibiotic to treat other infectious diseases. The study also found 3 (out of 39) samples of mefloquine that contained NAPI and WAPI despite the launch of two campaigns against counterfeit mefloquine tablets in 1999 and 2000. However, the study team observed that mefloquine was found least during sample collection. The failure of chloroquine in the disintegration test is a concern since chloroquine is recommended for *Plasmodium vivax* in the national treatment guidelines. Chloroquine is also widely used in private markets.

Some failed products collected carried no information about their manufacturer, including those claimed to be imported. Tetracycline capsule samples, for example, carried 'Brainy Pharmaceutical Limited Partnership', but there was no address on the label, printed in Thai and English. This company was confirmed as not being registered at the FDA of Thailand. Some products that failed quality testing were sold without names in plastic bags or bottles and it was impossible to identify their sources.

A report on the distribution of licensed and unlicensed drug outlets has raised the issue of weak law enforcement regarding pharmaceuticals (Department of Drugs and Food, 2001). A list of drug outlets indicated that 78.5% of 498 drug outlets were unlicensed in the four provinces. In Pailin, a new city established in 1996, all drug outlets were operated without license. In the three other provinces, almost all unlicensed drug outlets were found in remote areas far from regular access of provincial authorities. The study team observed that drugs were being sold in general market places such as booths, grocery shops and general stores with inadequate storing conditions. Vendors sold drugs repacked in plastic bags without appropriate labelling, which might have caused product mismatching and endangered health. (Plastic bags contained four to seven kinds of drugs mixed together, including an antipyretic, a vitamin, chlorpheniramine, an antimalarial drug and an antibiotic; for example, a plastic bag may contain a paracetamol tablet, a vitamin C tablet, an aspirin tablet, a tetracycline capsule and an artesunate tablet.) Most plastic bags were not sealed or were loose and drugs were exposed to moisture, humidity and heat. In addition, there was no name or address of the manufacturer on these plastic bags. A report of Drug Use Practice Survey in 2002 suggested that these drugs in plastic bags contained WAPI, NAPI or were substandard (NMCP, unpublished report). Additionally, most people with fever usually sought help from the private service for a couple of days and discontinued treatment when they felt a bit better, and this could result in late recrudescence (Nosten et al., 1994).

In the surveyed provinces, people used the private sector (82%) rather than seeking help from the public sector. The real risk for people living in remote areas was high access to poor quality drugs, including antimalarials, because they were less informed about the problems of counterfeit and substandard medicines and were more likely to buy cheaper drugs from small drug outlets in their villages (NMCP, unpublished report).

In the same survey areas, treatment failures from the first-line regimen of a combination of artesunate and mefloquine kept increasing according to the results of Anti-malarial Drug Sensibility Monitoring of the NMCP in 2002 (Ministry of Health, 2004). Poor quality antimalarial drugs might be one factor contributing to the increase in resistant strains, as well as inappropriate drug use practice (NMCP, unpublished report; Rozendaal, 2001).

Based on the evidence regarding counterfeit and substandard antimalarial drugs from the present study, immediate administrative actions against counterfeit drugs were taken by the NMCP and DDF, Ministry of Health of Cambodia. They issued ministerial circulars to Provincial Health Departments about the problem and announced warnings through annual malaria conferences and training occasions. In addition, television spot announcements were broadcast and posters were used to warn the public of the presence, sale and distribution of counterfeit drugs. A few months after these activities, 'Brainy' quinine and tetracycline quickly disappeared from the private market, probably because the label was easy enough to recognise. It is still of concern that sellers of both quinine and tetracycline may remove these drugs from the original containers and keep them in simple unlabelled plastic bottles to sell as unlabelled tablets.

In Cambodia, institutional incapability owing to the lack of financial resources and qualified personnel makes regulation and law enforcement extremely difficult, a situation further weakened by poor economic conditions and the lack of public awareness of drug quality issues. The NMCP is promoting the use of good quality artemisinin-based combination therapy (ACT), including artesunate and mefloquine (called A + M) for use in the public sector, and the same drug (named as Malarine®) for use in the private sector. The NMCP is introducing awareness-raising activities about the use of recommended drugs through community health education, posters, radio and television spots, and mobile video shows. Importantly, the strategy is targeted to people living in remote areas at high risk.

5. Conclusion

The evidence has shown that counterfeit and substandard antimalarials have been an increasing and serious concern in Cambodia. It will be an avoidable public health tragedy if a lack of political will on the part of key stakeholders, especially the government and medicine traders, as well as necessary action allow these fake drugs to undermine the hope that ACT offers for malaria control in this country and the region. The problem will also result in the emergence and spread of resistance to the artemisinin derivative drugs, which are considered the most efficacious antimalarial agent to date. A collaborative effort is urgently needed to combat counterfeit and substandard antimalarials in order to control malaria and save more lives from this deadly disease.

Conflicts of interest statement

The authors have no conflicts of interest concerning the work reported in this paper.

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