

## Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials

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### Summary

**OBJECTIVE** To assess the prevalence of counterfeit antimalarial drugs in Southeast (SE) Asia.

**DESIGN** Cross-sectional survey.

**SETTING** Pharmacies and shops selling antimalarial drugs in Myanmar (Burma), Lao PDR, Vietnam, Cambodia and Thailand.

**MAIN OUTCOME MEASURES** Proportion of artemisinin derivatives or mefloquine containing drugs of substandard quality.

**RESULTS** Of the 188 tablet packs purchased which were labelled as 'artesunate' 53% did not contain any artesunate. All counterfeit artesunate tablets were labelled as manufactured by 'Guilin Pharma', and refinements of the fake blisterpacks made them often hard to distinguish from their genuine counterparts. No other artemisinin derivatives were found to be counterfeited. Of the 44 mefloquine samples, 9% contained <10% of the expected amount of active ingredient.

**CONCLUSIONS** An alarmingly high proportion of antimalarial drugs bought in pharmacies and shops in mainland SE Asia are counterfeit, and the problem has increased significantly compared with our previous survey in 1999–2000. This is a serious threat to public health in the region.

**keywords** counterfeit drugs, fake antimalarials, Southeast Asia, malaria

### Introduction

Falciparum malaria is a potentially fatal disease, but a lethal clinical course can be prevented by early diagnosis and treatment with appropriate antimalarial drugs. Early diagnosis and effective treatment is thus a cornerstone of malaria control. In much of the malaria-affected world, the majority of antimalarial drugs are purchased directly by the patient or carer from the private sector (shops, pharmacies, markets, itinerant drug sellers, etc.). In Southeast (SE) Asia, falciparum malaria has become resistant to most of the available antimalarials. The recommended treatment in

most of the region has now changed to combinations containing the highly potent and active artemisinin derivatives combined with a second, slower acting, drug such as mefloquine. Resistance to the artemisinins has not developed yet. An important, but underappreciated, obstacle to malaria control in the region is the widespread dissemination of counterfeit antimalarial drugs, especially of the artemisinins. As fake antimalarials usually contain no active ingredient the unwitting patient is at substantial risk of developing severe malaria and dying. As fake, and thus ineffective drugs, cannot be easily distinguished from the genuine products, this undermines the confidence of the

public and health care workers in the antimalarial. There have been several reports of artemisinin resistance in this region, which were ultimately attributed to fake drugs. In 1999–2000, we conducted a multinational survey to document the prevalence of counterfeit artesunate in SE Asia, which demonstrated that 38% of shop-bought ‘artesunate’ blisterpacks were counterfeit, containing no artesunate (Newton *et al.* 2001). We now report the results of a further larger survey of the quality of artemisinin-containing drugs and mefloquine in mainland SE Asia.

## Methods

### Drug sampling

Between February 2002 and February 2003, samples of antimalarial drugs were purchased from drug sellers, shops and pharmacies in western Thailand, Vietnam, Cambodia, Lao PDR and Myanmar (Burma). The buyers, consisting of expatriate and local health care workers, were asked to purchase artesunate, artemether and mefloquine, wherever they could find it. Buyers were asked to act as ‘normal’ customers. The type of shop or pharmacy where the drug was bought, the stated manufacturer, the source or supplier of the drug, the cost and the buyers’ opinion as to the authenticity of the product were recorded. In addition, one of the authors (PN), who was blinded to the buyers’ opinions, the costs of the products, and all laboratory test reports, classified the artesunate tablets as genuine or fake, based on characteristics of the hologram, blisterpack and packet. These features were highly predictive (100% specificity and sensitivity) in recognizing fake tablets in our previous review 4 years ago (Newton *et al.* 2001).

### Drug testing

Artemisinin derivatives were tested qualitatively for drug content with a simple and reliable dye test, which is based on the reaction between an alkali-decomposition product of artesunate and the diazonium salt ‘Fast Red TR’ (Green *et al.* 2000, 2001). The amount of artesunate or mefloquine present in selected tablets was determined using high-performance liquid chromatography (HPLC) with diode array detection. Levels <0.1 mg/tablet of artesunate were not reliably detectable by the HPLC method.

### Statistics

Descriptive statistics were performed using SPSS 11.0 statistical package (SPSS Inc., Chicago, MI, USA). Comparisons of the proportions of counterfeit drugs between

the current and previous survey were made by chi-square testing with continuity correction. Differences between countries in normally distributed variables were assessed by Student’s *t*-test.

## Results

A total of 303 samples were obtained from the five countries (Table 1). In Thailand, uncomplicated malaria is treated through the Ministry of Public Health Malaria Centres. Antimalarials are available in the private sector, but artemisinin derivatives and mefloquine are effectively restricted to the public sector. Thus, obtaining these drugs from pharmacies or shops is difficult, which explains the smaller sample size in this country. None of the drugs bought was beyond the expiry date written on the package.

### Artesunate

Of the 188 ‘artesunate’ blisterpacks collected 99 (53%) were counterfeit, containing trace or no artesunate. Compared with the survey on counterfeit artesunate tablets we conducted between August 1999 and August 2000, there was an overall 15% increase in the proportion of fake tablets (95% CI: 3–27,  $P = 0.02$ ). Of the surveyed countries, only Myanmar had a significant decrease (18%; 95% CI: 1–36) in the prevalence of counterfeit artesunate tablets. In Vietnam, artesunate was searched for around both Ho Chi Minh City and Hanoi, but the availability of genuine artesunate in the private sector appeared to be very restricted in Hanoi and the two samples purchased were genuine. In contrast, counterfeit artesunate was widely available in Ho Chi Minh City.

There was 100% agreement between a negative ‘Fast red’ dye test result and a negative result on HPLC analysis. As confirmation of the ‘Fast red’ dye test, result the artesunate content was quantified in a random subset of 56 tablets from different manufacturers with a positive ‘Fast red’ dye test, labelled as containing 50 mg artesunate. Mean (SD) artesunate content was 45.6 (2.5) mg. All fake artesunate tablets, containing no or only artesunate, were labelled as produced by Guilin Pharma, Guanxi, China. The proportion of Guilin Pharma artesunate tablets (both genuine and counterfeited) compared with the total number of artesunate tablet samples was 55% in Thailand, 67% in Lao PDR, 94% in Cambodia and 46% in Myanmar. There was a tendency for the fake artesunate to be cheaper, with an average (SD) price of a fake tablet of 0.11 (0.08) US\$ *vs.* its genuine counterpart of 0.15 (0.05) US\$, but this difference was not statistically significant. Counterfeit drugs were as often bought in local pharmacies

**Table 1** Number of counterfeit drugs per country obtained between February 2002 and February 2003

Drug	Country (%)					Total (%)
	Thailand	Lao PDR	Cambodia	Myanmar	Vietnam	
Artesunate tablet	3/11 (27)	25/46 (54)	5/22 (23)	10/48 (21)	56/61 (92)	99/188 (53)
Mefloquine tablet	0/2 (0)	0/2 (0)	1/10 (10)	3/30 (10)	NA	4/44 (9)

Number of fake samples are given out of the total of samples tested.

as in other types of local shops. Information on the drug supplier to the shop was only rarely provided to the buyer.

The local buyers predicted counterfeit samples with a sensitivity of 50% and a specificity of 95%. The positive predictive value in detecting a counterfeit drug based on this subjective judgement was 24%, and the negative predictive value, to identify genuine drugs, was 63%. Based on packaging characteristics, as described above, a judgement on authenticity was also given by one of the authors (PN) on 155 samples with intact blisterpacks. This predicted that the tablet was 'fake' with a specificity of 94%, a sensitivity of 93%, a positive predictive value of

94% and a negative predictive value of 92%. Compared with our last survey, where all counterfeit tablets could be identified by the same observer, his ability to detect counterfeit drugs had deteriorated. This was caused by the emergence of two new generations of counterfeit Guilin Pharma artesunate tablets which were collected in southern Lao PDR and northeast Cambodia. Fake samples obtained in Myanmar, Vietnam and Thailand could all be identified by the slightly different hologram sticker, but 80% of the fake samples from Cambodia and 44% of the fake samples from Lao PDR had a hologram on the blisterpack that was almost indistinguishable from the real product (Figure 1).

**Figure 1** Evolution of counterfeited holograms on blisterpacks containing fake artesunate tablets. Top left, the genuine hologram. Top right, the first fake 'hologram', found after 1998, which lacked the three-dimensional appearance of a real hologram. Bottom left, the fake hologram, which started to appear in 2002–03 in Lao PDR and Cambodia, featuring a well-crafted hologram, but with a slightly different outline of the depicted mountains. Bottom right, the latest detected counterfeited hologram, almost indistinguishable from the genuine counterpart, but lacking the company name (only visible under magnification, arrow in top left picture).



Because of the urgency to communicate this finding, the features of the packaging have been published before this survey was completed (Newton *et al.* 2003). In summary, the second generation fake hologram is, unlike the first generation fake grey sticker (Newton *et al.* 2001, 2003), a true hologram. However, the mountain silhouette is different, the colour blue of the writing is slightly different, and the legend 'Guilin Pharma' written at the bottom of the image is missing. The legend can just be seen with the naked eye, but can only be read with a magnifying glass. On all four samples collected the printing (of code '00902', manufacture date '09/00' and expiry date '09/03') is less clear than the printing on the genuine blisterpack. The third generation fake hologram from southern Lao PDR is indistinguishable from the genuine hologram apart from the absence of the legend 'Guilin Pharma'. The blisterpack printing is clear and both samples collected have the code 010901 with manufacture and expiry dates of 09/01 and 09/04, respectively.

#### Other artemisinin derivatives

Besides artesunate tablets, a smaller number of other artemisinin compounds and formulations was collected: artesunate for injection (11 samples), artemether tablets (22 samples), artemether for injection (30 samples), artesunate/mefloquine pre-packed fixed combination (Malarine<sup>TM</sup>) (five samples), dihydroartemisinin tablets (four samples) and 'Cotecxin<sup>TM</sup>' (dihydroartemisinin). None of these proved to be counterfeit.

#### Mefloquine

Mefloquine samples were obtained in Thailand, Lao PDR, Cambodia and Myanmar. Of the 44 samples, four (9%) were substandard, containing instead of the labelled 250 mg, a mean (SD) amount of 18.1 (3.3) mg. In contrast with the counterfeit artesunate tablets, these tablets did contain some active drug. All counterfeit tablets were labelled as made by Mepha Ltd, Aesch-Basel, Switzerland. The tablets were obtained as separate tablets from wholesale pots containing 100 tablets, with no individual packaging. The visual characteristics of the fake tablets were undistinguishable from the genuine product.

#### Discussion

An alarmingly high proportion of antimalarial drugs bought in pharmacies and shops in mainland SE Asia continue to be fakes, and despite recent publicity the problem appears to have increased compared with our previous survey in 1999–2000. Although the method of

purchasing the drugs in both surveys was identical and carried out by the same consortium of investigators, the change in prevalence of fake drugs should be interpreted with some caution, since small differences in the way the drugs were obtained cannot be ruled out. Artesunate tablets labelled as 'Guilin Pharma' have been severely targeted by counterfeiters. The decrease in counterfeit artesunate in Myanmar can be explained by the under representation of 'Guilin Pharma' artesunate tablets in the sample. There have been recent reports of fake artemether injection, a key drug in the treatment of severe malaria, in Myanmar (The New Light of Myanmar 2001), but we did not find fake artemether or artesunate injection in this survey.

The quality of the packaging of the fake 'Guilin Pharma' artesunate tablets has become much more sophisticated, to such an extent that they have become almost indistinguishable from the genuine product. The efforts of the manufacturer to produce a hologram to prevent counterfeiting have been brutally counteracted. However, it is even more difficult to identify fake drugs, such as the mefloquine discovered in this survey, if tablets are not packaged individually. The clues available in the fake packaging are not available.

It is possible that the substandard mefloquine could have been the genuine product adversely affected by poor storage condition, but as the potency was only 7% of the genuine product, it is more likely that they were deliberately counterfeited. As the substandard mefloquine tablets did contain a small quantity of the active compound (insufficient for cure), parasites will be exposed to sub-therapeutic concentrations of the drug if these tablets are used to treat patients. This will facilitate the multiplication of parasites with intrinsic resistance to the drug and contribute to the spread of drug resistance (White 1999).

Despite the appearance of well-crafted new 'generations' of fake drugs, information and education explaining the distinguishing features of counterfeit drugs could help to reduce the probability of purchasing fakes, provided this information is updated regularly. One experienced observer was able to identify most of the counterfeit artesunate, and was much better at identifying fakes than the less informed buyers who contributed to the study. In Cambodia, a poster and TV campaign informing the general public on counterfeit artesunate has apparently driven the trade in counterfeit artesunate in Cambodia further underground and may have reduced the problem (Rozendaal 2000), although in the present survey fake artesunate was still a significant health hazard representing 23% of the artesunate tablets purchased. It is even more important to keep health care workers and pharmacies or other drug outlets informed with actual details on

appearance and prevalence of counterfeited drugs. A periodic brochure provided by the health authorities containing this information should be recommended, as is published by the Nigerian National Agency for Food and Drug Administration and Control. Health care workers should be aware that cases of treatment failure might be caused by administration of fake drugs.

Besides anticounterfeiting packaging techniques introduced by the manufacturer, such as holograms, and the provision of information by the health authorities, simple and inexpensive methods to identify fake drugs are useful. Several international NGOs working in SE Asia use the colorimetric assay to test their purchases of artemisinin drugs. The German Pharma Health Fund has developed the 'Minilab' for analysing the authenticity of a wide range of essential drugs. Simple methods to evaluate other antimalarial drugs are currently being evaluated. Regular screening of antimalarial drugs from the wholesalers, in pharmacies, and in other drug-outlets should be a routine task of the health authorities to prevent severe malaria and death because of fake drugs.

A key to reducing the prevalence of fake drugs is the provision of a secure supply of quality-assured antimalarials via strictly regulated production, import and distribution of genuine antimalarials by government or other organizations. In Thailand, most malaria is treated in government-organized malaria centres, which are supplied with quality-controlled drugs. In Cambodia, quality-controlled artesunate and mefloquine are blisterpacked together under the name of 'Malarine' and distributed to the private sector. We have not detected counterfeited tablets in these packages.

The production and distribution of counterfeit antimalarial drugs is criminal. It should be regarded as attempted murder, since malaria is a deadly disease if not treated properly. Law enforcement with active prosecution of manufacturers and distributors of counterfeit drugs should therefore have priority. However, recent publicity in different media, including earlier reports on the scale of the problem in the medical literature (Newton *et al.* 2001, 2002; Rozendaal 2000), and the subject remains low on the political agenda. Encouragingly, the World Health Organization has recently begun a project to combat counterfeit drugs in the Greater Mekong Subregion (Frankish 2003). Counterfeit drugs are not only a problem in SE Asia, with rampant drug counterfeiting in countries such as Nigeria and India and reports from North America and Europe (Anonymous 2003a,b). With artesunate now sold over the counter in West Africa, there is a great risk of the dissemination of counterfeit artesunate in Africa. Fake

drugs are also not only a recent problem. As early as 1913, Dr Carl L. Alsberg, chief of the Bureau of Chemistry in the Department of Agriculture at Washington, USA said 'Fake drugs do incalculable harm to the misguided sick, who grasp the false hope they hold on to' (Anonymous 1913). Health and law enforcement authorities have an important responsibility here and much more vigorous action is required.

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