Correspondence

Monitoring Antimalarial Drug Efficacy

Str—We welcome the article by May-xay et al. [1] on monitoring chloroquine and sulfadoxine-pyrimethamine therapy efficacy in the Lao People’s Democratic Republic, and their compilation of all available data in the country. On the basis of the high failure rate of the first-line and second-line antimalarial drug therapies, they recommend a change to the national drug policy.

However, a study of this quality demonstrates most clearly the necessity—and advantages—of adherence to a standard protocol for the sake of comparison of data and clarity of results. We would like to point out some statements regarding the protocol for monitoring the efficacy of antimalarial drugs that could be misleading to the readers familiar with the earlier versions of the World Health Organization (WHO) protocols. The first standardized WHO in vivo malaria test was developed in 1967. In 1996, the recommendation for application of this test in areas of high malaria transmission was modified to include only symptomatic children in a therapeutic efficacy test. Also in 1996, a second protocol was developed specifically for areas of low-to-moderate transmission. Both protocols were subsequently discussed and updated during an informal consultation in Geneva in 2001 [2] and are now available as a single document [3].

It is true that the shorter 14-day length of follow-up underestimates the overall treatment failure rate. But according to the WHO protocol, 14-day follow-up is recommended only in areas of intense malaria transmission and not in areas of low-to-moderate transmission, such as the Lao People’s Democratic Republic, where 28 days of follow-up is recommended. Moreover, programs that are able to maintain study quality during a longer period of assessment and have access to molecular techniques are encouraged to do so. On the basis of accumulated experience and the time it takes to completely clear a drug from the body (6 times the elimination half-life), follow-up for longer than 14 days is appropriate for therapy with amodiaquine, chloroquine, and sulfadoxine-pyrimethamine (28 days); for artesether-lumefantrine therapy (42 days); and for mefloquine therapy (63 days). It is not clear why the failures of single-drug therapy (accounting for 4% of the total number of treatment failures) observed between days 28 and 42 of follow-up suggest that “P. falciparum resistance to chloroquine and sulfadoxine-pyrimethamine is serious [1, p. 1027],” but it is obvious that the longer follow-up in this study was not cost-effective. Longer follow-up increases the number of patients lost to follow-up and the chance of reinfection (which should lead to the exclusion of the patient from the study, because of the administration of rescue treatment) and requires additional human and financial resources.

The WHO protocol [3] also recommends that, in all areas, regardless of the intensity of malaria transmission, the evaluation of antimalarial treatment efficacy should emphasize enrollment of children aged <5 years with clinically apparent malaria. The rationale is that, even in populations with little acquired immunity (as occurs in areas of low or highly seasonal malaria transmission), younger children often have a less favorable therapeutic response to antimalarial drugs than do older children and adults. In areas of low malaria transmission, exclusive enrollment of children aged <5 years is likely to pose logistic difficulties, thus patients of all ages can be enrolled. But in the present study, exclusion of children aged <5 years possibly underestimates the true treatment-failure rate.

In clinical trials with supervised treatment, the term “drug resistance” is often used somewhat loosely. According to the standardized definition of resistance [4], neither the 1973 protocol nor the 2001 protocol is able to determine true resistance. Although most of the treatment failures are due to drug resistance, some treatment failures may be due to incomplete absorption or rapid clearance of the drug.

On the basis of previous studies, including this one, it is redundant to classify treatment response with both the previous RI-II-III resistance classification system and the new ACPR-ETF-LTF (“adequate clinical and parasitological response, early treatment failure, late treatment failure”) classification system, since results are most often similar. The new classification is more appropriate for symptomatic patients and includes not only clinical criteria (as mentioned in the table) but also parasitological criteria. Moreover, the 1973 protocol has been distorted and adapted many times, and at least 5 different definitions of RI-II-III can be found in the literature, rendering data incomparable between the studies. As resistance to various antimalarial drugs continues to spread throughout regions in which malaria is endemic, the establishment of national and interregional networks for monitoring antimalarial drug efficacy becomes essential. Using a standardized protocol is essential for comparison.

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References


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Reply

Sir—We thank Dr. Ringwald for his comments [1] on our article describing a clinical trial of treatment of uncomplicated Plasmodium falciparum in Laos [2]. We agree with the necessity and advantages of adhering to standard protocols but believe that, until such protocols are applied universally, additional information should be provided to allow comparison with previous research performed using different protocols. Because both classifications are used in Laos, we presented the data using both classification schemes (see figure 1 in Mayxay et al. [2]). In addition, as described elsewhere [3], the 2 classification schemes may not give equivalent results and interpretations.

As stated in Patients and Methods, our study was conducted in 2001, before publication of the 2 documents mentioned by Dr. Ringwald on the assessment of antimalarial drug efficacy in low-transmission areas [4, 5]. We used the original 1973 protocol definitions [6], as stated in our article, and detailed the definitions for both the RI-II-III resistance classification system and the new ACR-ETF-LTF (“adequate clinical response, early treatment failure, late treatment failure”) classification system [2, p. 1023] to ensure that there would be no confusion and that the results of our study could be compared with previous clinical reports.

With no previous clinical trial evidence from Laos assessing the extent of antimalarial drug resistance, we conducted patient follow-up for 42 days, because we were uncertain whether 28 days would be of sufficient duration to detect treatment failures resulting from relatively low levels of drug resistance. Anecdotal reports claimed that both drugs were still effective in Laos. We believe that the longer follow-up in this study was prudent and cost-effective. There were no patients lost to follow-up, and there were no reinfections after 28 days. We estimate that abbreviating follow-up to 28 days would have led to a 17% reduction in the total study budget, excluding capital expenditure. However, if we had conducted a 28-day study and found few treatment failures, we would have remained uncertain as to how many low-grade treatment failures were occurring after 28 days. It was important to assess this in detail, at a time when decision-makers in Laos were debating the changing of antimalarial treatment policy, because we knew that the evidence from these studies would be very important in determining treatment choices.

The finding that all but 1 case of RI resistance occurred before day 28 of follow-up strongly suggests that resistance to chloroquine and sulfadoxine-pyrimethamine (SP) in Laos is a serious problem. As resistance in a parasite population worsens, the time to recrudescence shortens [3].

Although it was not logistically possible in our study, we agree that children aged <5 years should be enrolled, and that not including such patients will underestimate the true treatment failure rate. In more recent clinical trials, we have included children >1 year of age. We also agree that incomplete absorption or rapid clearance of the antimalarial drug could lead to recrudescence infections [3], but we did not have the facilities to gather the necessary plasma drug concentration measurements. In general, both chloroquine and SP are well absorbed. In a study designed to test whether treatment with an antimalarial drug is effective, the key evidence required by policymakers is the true treatment failure rate after drug ingestion (assuming that the drug is of adequate potency), irrespective of whether the failure is caused by pharmacokinetic or pharmacodynamic factors.

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