Evaluation of a simple operational approach for monitoring resistance to antimalarial drugs in Peru

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Summary
Since 1994, the Peruvian Malaria Control Program has used a simplified operational approach for monitoring antimalarial drug efficacy, in which blood smears are taken 7 and 14 days after treatment from all patients diagnosed with malaria at Ministry of Health facilities. The proportion of patients with parasitaemia on one of their return visits provides an indication of the efficacy of the drug being administered. We compared this approach for antimalarial drug resistance monitoring to the more labour-intensive and expensive World Health Organization (WHO) 14-day in vivo efficacy trial at six sites in the Amazon Basin and the north coast of Peru. Although the proportion of treatment failures at 7 and 14 days identified by the operational monitoring system was considerably lower than the results of the WHO in vivo efficacy test, the operational approach did accurately reflect the overall efficacy or lack of efficacy of the drugs being evaluated. Differences in the results of the two methods were greatest in the Peruvian Amazon region, where fully supervised treatment and patient follow-up is very difficult due to the widely dispersed population. While the operational approach cannot be considered an alternative to WHO in vivo testing for evaluating the efficacy of antimalarial drugs or for recommending changes in malaria treatment policy, if treatment is supervised and follow-up blood smears taken as scheduled, this method could serve as a simple, inexpensive and sustainable early warning system for reduced drug efficacy.

Keywords surveillance, antimalarial drug resistance, Peru

Introduction
In vivo drug efficacy testing is generally considered to be the method of choice for obtaining the information required to establish or modify national malaria treatment policies. The approach to in vivo efficacy testing recommended by the WHO (1996) has recently been modified for use in the Americas (PAHO, Pan American Health Organization 1998). According to WHO/PAHO guidelines, patients with uncomplicated Plasmodium falciparum infections confirmed by blood smear are treated under observation with a standard regimen of the drug being studied. Patients are monitored for 30 min to ensure that they do not vomit the drug and are then followed as outpatients with clinical examinations and repeat blood smears 7, 14 and sometimes 21 and 28 days after treatment. The rapidity with which the parasite density falls over the first 3 days and the length of time the patient remains apasasitemic after treatment are used to classify the level of resistance. Although this method was originally intended for monitoring the efficacy of antimalarial drugs against P. falciparum, it has also been used, with slight modifications, to evaluate chloroquine (CQ) resistance in P. vivax (Baird et al. 1997; Fryauff et al. 1998), and standardized guidelines for in vivo drug efficacy testing of P. vivax are currently under development by the WHO.

While the WHO in vivo method is attractive in that it can be carried out in almost all settings and requires no special equipment, it is both labour-intensive and relatively expensive. A team of three to four workers is required for diagnosis, treatment, and patient follow-up, and individual patients must be followed for up to 14 or 28 days. Moreover, in areas where the prevalence of malaria is low, such as the Americas, it may take as long as 3–4 months to enroll a sufficient number of patients to assess the efficacy of a single drug, and the total cost of a trial can approach $10 000 (Ruebush et al. 2003). Consequently, national malaria control programmes may find it impractical to use this method on a routine basis for monitoring antimalarial drug efficacy.
Since 1994, the National Malaria Control Program (NMCP) of Peru has made use of a simplified operational approach for monitoring antimalarial drug efficacy against both *P. falciparum* and *P. vivax* that is integrated into routine health care for febrile patients at Ministry of Health facilities (Programa de Control de la Malaria y Otras Enfermedades Metaéicas 1994). All patients with suspected malaria seen in Ministry of Health outpatient clinics have a thick blood smear for malaria. If malaria parasites are seen, it is NMCP policy that all doses of the treatment be administered under supervision and the patient asked to return for repeat thick blood smears 7 and 14 days later. Patients who are parasitemic on either of these return visits are regarded as treatment failures and are administered alternative therapy. The number of incomplete treatments and the proportion of treatment failures with first- and second-line drug regimens is tabulated by health facility and region to provide insight into the efficacy of those regimens.

If the quality of microscopic diagnosis can be assured and health workers and patients comply with the guidelines established by the NMCP, the operational approach to drug efficacy monitoring should provide results very similar to those of a WHO 14-day *in vivo* efficacy trial. However, as the operational approach can be integrated into the routine care of febrile patients, it has the advantage of being much less expensive and potentially more sustainable by ministries of health. To determine how closely the results obtained by these two approaches agree and to identify the role that the operational monitoring approach might play as part of a national antimalarial drug resistance surveillance system, we conducted an evaluation of the operational monitoring approach at six sites in Peru where WHO 14-day *in vivo* drug efficacy tests had been carried out during 1998–99.

**Materials and methods**

In 1998 and 1999, *in vivo* drug efficacy testing using the WHO protocol was conducted at three sites in the Peruvian Amazon region and three sites on the northern Pacific Coast of Peru (G. Stennis, A. Magill, personal communication; Marquño et al. 2000). We compared data from these trials with the results of the operational monitoring system at the same health centres/hospitals and for the same time period during which the *in vivo* efficacy trials were conducted. At each site, all patient treatment registers used in 1998 and 1999 were reviewed for a period of six consecutive months, beginning 3 months before the *in vivo* trials had started. Using the operational definition of a treatment failure (a patient with a positive blood smear on either days 7 or 14 after treatment), the proportion of patients with *P. falciparum* infections who failed treatment was calculated and compared with the proportion of treatment failures in the WHO 14-day *in vivo* efficacy trial at the same site. As many of the patients seen in Ministry of Health facilities had incomplete blood smear data, we only included in the analysis those who had had blood smears taken on both days 7 and 14.

To supplement this information, interviews were conducted with personnel from the same health facilities to document their procedures for patient treatment and follow-up, as well as the definitions they used for classifying *P. falciparum* treatment failures and successes. At the same time, using a standardized checklist for initial and follow-up clinic visits, an investigator recorded information related to blood smear diagnosis, treatment, and the health workers’ recommendations for both initial and return visits of a consecutive series of approximately 50 febrile patients seeking care at each of the six health facilities. As only 2 weeks were spent in each clinic, it was not possible to follow all patients from their initial visit to day 14. Instead, different patients were observed during their initial and follow-up visits and these observations combined to form a complete picture of patient diagnosis, treatment and follow-up. As these interviews and observations were conducted between May and July 2000 (i.e. 1–2 years after the *in vivo* studies had ended), some of the original health centre staff were no longer present.

When the initial WHO *in vivo* trials were conducted in 1998–99, the first-line therapy for uncomplicated *P. falciparum* malaria was CQ on the northern Pacific Coast of Peru and sulphadoxine–pyrimethamine (SP) in the Amazon Basin. A single dose of 0.75 mg/kg of primaquine was added to both regimens as a gametocytocide. At the time the observations on patient diagnosis, treatment and follow-up were made in 2000, malaria treatment policy had changed to SP and primaquine on the north coast and to a 7-day course of quinine, tetracycline and primaquine in the Amazon region.

**Results**

The proportion of CQ and SP treatment failures detected by the operational monitoring approach at 7 and 14 days after treatment was about 35–75% lower than the results of the WHO *in vivo* efficacy trials at five of six sites (Tables 1–3). The only exception was a site in the Amazon Basin where no SP treatment failures were identified by operational monitoring, while the WHO trial demonstrated treatment failures in 32% and 6% of patients at 7 and 14 days. In spite of these differences, the operational monitoring data did, in general, accurately reflect the lack...
of efficacy of SP for the treatment of uncomplicated 
P. falciparum malaria in the Amazon Basin and the high 
efficacy of SP but lack of efficacy of CQ at the three sites on 
the northern Pacific Coast.

Review of patient treatment registers and observation of 
patient treatment and follow-up revealed several possible 
problems with the operational monitoring system and data 
that could explain these differences. These problems 
ocurred more frequently at the three sites in the Amazon 
region than in the three health facilities on the north coast. 

Although the Peruvian Ministry of Health sets strict 
standards for quality control of microscopic diagnosis of 
malaria, our observations suggested that these procedures 
were not always followed. According to Ministry of Health 
standards, all positive blood smears and 10% of negative 
smears are re-examined by more experienced microscopists 
at a regional laboratory and then the same proportion of 
positive and negative slides, and all slides with discordant 
results, are forwarded to the national reference laborat-
yory for confirmation. Microscopists at peripheral health

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Table 1 Plasmodium falciparum parasitological failures with sulphadoxine–pyrimethamine in WHO/PAHO in vivo efficacy trials and operational monitoring at three sites in the Amazon Basin of Peru 1998–99

<table>
<thead>
<tr>
<th>Site</th>
<th>Year</th>
<th>Patients with P. falciparum infections n (%)</th>
<th>No. with complete day 7/14 data n (%)</th>
<th>Parasitological failures – day 7* WHO/PAHO in vivo test (%)</th>
<th>Operational monitoring n (%)</th>
<th>Parasitological failures – day 14* WHO/PAHO in vivo test (%)</th>
<th>Operational monitoring n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1998</td>
<td>1035 (43)</td>
<td>441 (43)</td>
<td>31 (81)</td>
<td>21 (14)</td>
<td>49 (8)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1999</td>
<td>436 (9)</td>
<td>39 (9)</td>
<td>32 (0)</td>
<td>6 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1999</td>
<td>310 (81)</td>
<td>250 (81)</td>
<td>33 (20)</td>
<td>22 (35)</td>
<td>35 (14)</td>
<td></td>
</tr>
</tbody>
</table>

* Only patients with complete days 7 and 14 data are included.

Table 2 Plasmodium falciparum parasitological failures with chloroquine in WHO/PAHO in vivo efficacy trials and operational monitoring at three sites in northern coastal Peru 1999

<table>
<thead>
<tr>
<th>Site</th>
<th>Year</th>
<th>Patients with P. falciparum infections n (%)</th>
<th>No. with complete day 7/14 data n (%)</th>
<th>Parasitological failures – day 7* WHO/PAHO in vivo test (%)</th>
<th>Operational monitoring n (%)</th>
<th>Parasitological failures – day 14* WHO/PAHO in vivo test (%)</th>
<th>Operational monitoring n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1998</td>
<td>1784 (44)</td>
<td>785 (44)</td>
<td>42 (201)</td>
<td>25 (193)</td>
<td>26 (25)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1999</td>
<td>310 (69)</td>
<td>215 (69)</td>
<td>21 (14)</td>
<td>37 (37)</td>
<td>16 (16)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1999</td>
<td>443 (56)</td>
<td>247 (56)</td>
<td>40 (42)</td>
<td>15 (50)</td>
<td>20 (20)</td>
<td></td>
</tr>
</tbody>
</table>

* Only patients with complete days 7 and 14 data are included.

Table 3 Plasmodium falciparum parasitological failures with sulphadoxine–pyrimethamine in WHO/PAHO in vivo efficacy tests and operational monitoring at three sites in northern coastal Peru 1999

<table>
<thead>
<tr>
<th>Site</th>
<th>Year</th>
<th>Patients with P. falciparum infections n (%)</th>
<th>No. with complete day 7/14 data n (%)</th>
<th>Parasitological failures – day 7* WHO/PAHO in vivo test (%)</th>
<th>Operational monitoring n (%)</th>
<th>Parasitological failures – day 14* WHO/PAHO in vivo test (%)</th>
<th>Operational monitoring n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1998</td>
<td>782 (27)</td>
<td>212 (27)</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1999</td>
<td>414 (97)</td>
<td>403 (97)</td>
<td>10 (4)</td>
<td>3 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1999</td>
<td>450 (81)</td>
<td>363 (81)</td>
<td>3 (6)</td>
<td>3 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

* Only patients with complete days 7 and 14 data are included.
† Based on local policy, blood smears were only taken on day 7 in most cases.
facilities are responsible for selecting the blood smears they forward to the reference laboratory, and at one health centre in the Amazon region, staffed by one experienced and two inexperienced microscopists, only those slides that had been examined by the more experienced microscopist were forwarded for quality control. At another facility in the same region, staff members commented that they believed that microscopists examined follow-up blood smears which were expected to be negative less thoroughly than the blood smears on patients when they first presented with symptoms of malaria.

While it is NMCP policy that all antimalarial treatments be administered under supervision, it is much more difficult to comply with this standard in the Amazon region, where the population is so widely dispersed and many patients live far from a health facility. Initial treatment doses were frequently not taken in the presence of the health worker and many patients were told to return every 2–3 days and were given sufficient medicine to take at home. In such cases, treatments were generally recorded in patient treatment registers as complete, although the health worker had no way of being sure. At one health centre in the Amazon region where student nurses were allowed to handle treatments without adequate supervision, administration of incorrect drugs (i.e. quinine for a case of \textit{P. vivax} malaria) or dosages was occasionally observed. Instructions on how to take the medications were generally verbal, rather than written, and it was not clear that patients fully understood the treatment regimens, particularly in the case of the complicated 7-day regimen of quinine (three times a day), tetracycline (twice a day), and primaquine (once daily). Moreover, tablets of quinine, tetracycline and primaquine, and different days’ dosages were mixed together in the same packet. On the north coast, in contrast, treatment doses were routinely supervised at two of the sites, except on Sundays and holidays, when the health facility was closed and patients were given medications to take at home. At the third site, treatment doses were not always supervised. No errors in drug administration were observed on the north coast.

The proportion of patients who had follow-up blood smears taken on both days 7 and 14 was low in both regions (Tables 1–3). However, the variability from one site to the next was greater in the Amazon Basin, where the proportion of patients with both follow-up blood smears ranged from 81% at a health centre which draws essentially all its patients from a single village to just 9% at an isolated health facility near the border with Brazil and Colombia. At two of the sites on the northern Pacific Coast, both follow-up blood smears were taken in only about 50% of patients; at the third site a decision had been made by the local health department to only take follow-up blood smears on day 7 after SP treatment. Although follow-up blood smears were routinely recorded as having been taken on days 7 and 14 after treatment was initiated, patients often did not return on time and blood smears were taken several days earlier or later in both regions.

Finally, problems were noted in the way Ministry of Health staff interpreted and reported the results of the resistance monitoring data. Some health workers were unclear about the definitions of treatment success and failure, and even within the same health facility, the quality of record keeping varied with changes in health staff. At some sites, patients who had returned for only one of their two follow-up blood smears were reported as a successful treatment if that blood smear was negative. At one health centre in the Amazon region, workers interpreted the results of the follow-up blood smears in such a way that the frequency of treatment failures was under-reported. Table 4 shows the results of follow-up blood smears on five patients with \textit{P. falciparum} malaria treated with SP. Although all of these patients appeared to have been infected with resistant strains, health workers continued taking blood smears until they became negative and then

Table 4 Blood smear results on five patients with uncomplicated \textit{Plasmodium falciparum} infection treated with sulphadoxine–pyrimethamine, Amazon Basin, Peru, January–February 1999

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 14/15</th>
<th>Day 20/21</th>
<th>Day 28/29</th>
<th>Day 31</th>
<th>Day 36</th>
<th>Recorded result of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+F*</td>
<td>Neg</td>
<td>Neg</td>
<td>+F</td>
<td>Neg</td>
<td>Not done</td>
<td>Neg</td>
<td>Sensitive</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Neg</td>
<td>Neg</td>
<td>++F</td>
<td>Neg</td>
<td>Neg</td>
<td></td>
<td></td>
<td>Sensitive</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>F gam.†</td>
<td>Neg</td>
<td>+F</td>
<td>Neg</td>
<td>+F</td>
<td>Neg</td>
<td></td>
<td>Sensitive</td>
</tr>
<tr>
<td>4</td>
<td>+F</td>
<td>Not done</td>
<td>Not done</td>
<td>Neg</td>
<td>+F</td>
<td>F gam.</td>
<td>Neg</td>
<td>Sensitive</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>+F</td>
<td>Not done</td>
<td>F gam.</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td>Sensitive</td>
<td></td>
</tr>
</tbody>
</table>

* \textit{Plasmodium falciparum} parasite densities are given in semi-quantitative terms, as used by the Peruvian National Malaria Control Program, where the number of pluses (from + to ++++) is an indication of parasite density.
† F gam. = \textit{P. falciparum} gametocytes only.
reported the infections as sensitive to SP. Finally, errors were noted in tabulating data at the local level and the figures reported to regional health offices did not always agree with patient registers.

Discussion

*In vivo* testing is generally considered the method of choice for assessing the efficacy of antimalarial drugs against *Plasmodium* spp., because it most closely parallels the response of individual patients to those drugs. WHO guidelines for such trials are increasingly being used by investigators and public health workers to assess drug efficacy and have proven extremely useful in obtaining the information necessary to develop or modify national malaria treatment policies (Barat et al. 1998; East Africa Network for Monitoring Antimalarial Treatment 2001). A major drawback of WHO 14- or 28-day *in vivo* efficacy tests is that they are labour-intensive and relatively expensive, making them somewhat impractical for routine surveillance of drug efficacy by malaria control programmes, particularly in areas with low to moderate malaria transmission. In Peru, for example, the duration of enrollment in a series of *in vivo* efficacy trials conducted between 1998 and 2001 ranged from 8 to 13 weeks and the cost was nearly $10 000 per trial (Ruebush et al. 2003).

Our evaluation of the operational monitoring system of the Peruvian NMCP showed that it has the potential of serving as a simple and inexpensive means of antimalarial drug resistance surveillance. The results of the operational monitoring approach accurately reflected the lack of SP efficacy for *P. falciparum* malaria in the Amazon Basin of Peru and the efficacy of SP and lack of efficacy of CQ on the country’s northern Pacific Coast. On the north coast, it was even able to detect the very low proportion of SP treatment failures identified by the WHO 14-day *in vivo* test. In spite of this, the operational monitoring approach, as currently implemented in Peru, is not without problems in that the proportion of treatment failures was considerably lower than that seen in the WHO *in vivo* efficacy trials. Moreover, at one of the three sites in the Amazon region, the operational monitoring approach failed to detect quite high levels of SP resistance.

For an operational approach to antimalarial drug efficacy monitoring to provide information similar enough to that of the WHO *in vivo* efficacy test to be of use to a malaria control programme, several requirements must be met. First, all patients must have a microscopic diagnosis of malaria and the quality of that diagnosis must be ensured. Secondly, all doses of the antimalarial drug must be administered under supervision of a health worker. Thirdly, follow-up on scheduled days will need to be ensured, and if patients do not return on their own, health workers will need to trace them to their homes. Finally, the data collected at the peripheral health facilities must be accurately recorded using standardized definitions of treatment success and failure, and then tabulated and transmitted to the central level for analysis and interpretation.

Overall, the accuracy of blood smear diagnosis in Peru appears to be quite high. Of slides forwarded during 1999 from health centres and hospitals to the regional reference laboratory, 99.1% were reported to be in agreement with their original diagnosis, and 99.4% of those diagnoses were later confirmed by the national malaria reference centre at the Instituto Nacional de Salud. Since follow-up blood smears are not analysed separately, it was not possible to verify the report from one health centre that follow-up blood smears were being examined with less care than the initial blood smears on febrile patients. In a small survey conducted at four health facilities in the city of Iquitos and surrounding rural areas during 2000, we were able to confirm the generally high accuracy of blood smear diagnosis in the Amazon Basin. All thick blood smears taken from febrile patients over a 2-week period at each health centre were saved and re-examined by two expert microscopists. The final diagnosis of the two expert microscopists agreed in 93.6–100% of cases with the results of the health facilities’ microscopists (unpublished data).

At two of the three health centres on the northern Pacific Coast, nearly all doses of antimalarial treatments were supervised. In contrast, in the three health facilities in the Amazon region, even the initial dose was often not supervised and it is highly likely that at least some patients did not complete their treatments. In such cases, the operational monitoring data would more accurately reflect drug effectiveness than efficacy. As treatment regimens become more and more complex, as in the case of the 7-day course of quinine, tetracycline and primaquine for *P. falciparum* infections used in large parts of the Peruvian Amazon region since 2000, the number of supervised treatments would be expected to fall, and even greater differences might be seen between the proportions of treatment failures detected by the operational monitoring approach and the WHO *in vivo* test.

Follow-up blood smears were taken on both days 7 and 14 from fewer than 50% of patients in both regions, and at one centre in an isolated area of the Amazon Basin, only 9% of the patients had both smears taken. If a disproportionate number of patients who failed to respond to treatment missed their follow-up visits, this could explain the lower proportion of treatment failures detected by the operational monitoring system. In addition, blood smears were frequently taken several days before or after the
patients’ scheduled days 7 and 14 visits, making it difficult to know how to interpret those data.

Although our sample of health facilities was small, we observed considerable variation in the recording and interpretation of the operational monitoring data. Health workers did not always use the same definitions of treatment success and failure and at one health centre in the Amazon region, patients with positive blood smears on days 7 or 14 were followed until their blood smears became negative and were then reported as treatment successes. In addition, errors were made in tabulating data at the local level and the figures reported to regional health offices did not always agree with the patient registers.

One way to improve the quality of the operational monitoring data would be to limit data collection to selected sentinel sites, so that greater emphasis could be placed on training and supervising health workers and ensuring directly observed therapy and adequate follow-up at those sites. As antimalarial drug resistance patterns tend to be fairly uniform within contiguous geographical areas with a similar epidemiology of malaria, there is really no reason to conduct surveillance in all Ministry of Health facilities. Instead, once a malaria treatment policy has been changed, information from a smaller number of geographically representative health centres and/or hospitals in each region would almost certainly be sufficient for routine monitoring.

One potential weakness of the health worker interviews and observations of patient–health worker interactions should be noted. As our observations were made 1–2 years after the WHO in vivo tests had been carried out in the same health facilities, several of the staff members had changed and this may well have affected the quality of patient care and the procedures used for diagnosis, treatment and follow-up. To avoid some of the problems we observed when less experienced health workers took over, it will be critical that all workers responsible for the operational monitoring of antimalarial drug resistance be well versed in the recommended procedures for patient treatment and follow-up, as well as data recording and interpretation.

While the operational approach used by the Peruvian NMCP for antimalarial drug resistance monitoring cannot be considered an alternative to standardized WHO in vivo efficacy trials as it would be difficult to ensure correct microscopic diagnosis and fully supervised treatment and follow-up of all patients, we do believe that it can serve as a useful adjunct to those trials. In fact, the operational monitoring system, as used in Peru, would appear to be quite robust, as it accurately reflected the overall efficacy or lack of efficacy of both CQ and SP in two different regions of the country, in spite of the problems we identified. It also has the potential for providing data on a much larger number of patients than an in vivo efficacy trial, which usually has an enrollment of 50 to 60 subjects, and of being able to monitor drug efficacy levels throughout the year. It could even be used in areas where it might not be feasible to carry out an in vivo trial because of the low incidence of malaria or the elevated cost of conducting a trial in a relatively inaccessible area. With modifications to improve some of the treatment, follow-up, and data interpretation and reporting deficiencies we identified, the operational monitoring approach could serve as a simple, inexpensive and sustainable method for routine surveillance of antimalarial drug efficacy by NMCPs, once baseline data on drug efficacy is available. If an apparent change in drug efficacy were detected using this approach, a WHO in vivo drug efficacy trial could be conducted to verify the results and provide the necessary information for recommending a change in malaria treatment policy.

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