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A cost analysis of the use of the rapid, whole-blood, immunochromatographic P.f/P.v assay for the diagnosis of *Plasmodium vivax* malaria in a rural area of Sri Lanka

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Between May 2001 and March 2002, a prospective study was conducted in a malaria-endemic area of Sri Lanka, to determine the cost implications of using the immunochromatographic P.f/P.v test to detect *Plasmodium vivax* infection. All consecutive subjects aged >5 years who presented with a history of fever were recruited. Each was checked for *P. vivax* infection by the standard microscopical examination of bloodsmears and by the immunochromatographic test (ICT). The costs of diagnosis using each method and the sensitivity, specificity and predictive values of the ICT (with bloodmear examination used as the 'gold standard') were estimated, the costs/case detected being simulated for different slide positivity 'rates' and ICT sensitivities. In the detection of *P. vivax*, the ICT had a sensitivity of 70% and a specificity of 99%. The costs of the ICT per subject investigated and per case detected were, respectively, approximately 14 and 20 times more than those of bloodsmear examination. The costs of the ICT per case detected would fall as the sensitivity of the test increased. The ICT gave relatively few false-positive results. The current, relatively high cost of the ICT is the most important barrier to its routine operational use in the diagnosis of malaria. The test is already useful, however, in specific situations.

Despite the problems of drug resistance, malaria — globally the main parasitic disease with high morbidity and mortality — is generally curable if diagnosis is early and treatment prompt. The promotion of prompt and accurate diagnosis, which is the key to effective disease management, is one of the main aims of the Global Malaria Control Strategy (WHO, 2000*a*). A major factor hindering the effective control of malaria is that laboratory diagnosis of the disease is almost always dependent on microscopy; a valuable technique when performed correctly but unreliable and wasteful when poorly executed. Although good microscopical diagnosis may be available at the more central levels of the healthcare system, it is often unreliable or impossible in those remote areas where health-facility coverage is low although the risk of contracting malaria is high (WHO, 2000*b*). The development of rapid diagnostic tests (RDT) for malaria, based on immunochromatographic test (ICT) strips, offers a valid alternative or complement to microscopy (WHO, 1996).

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RDT have mostly been used to detect malarial infection in areas where microscopy is lacking but they have also been found useful in the diagnosis of severe malaria even in areas where microscopy is available (WHO, 2000*b*). If used correctly, any test for malaria with reasonable sensitivity and specificity can contribute to the better and more cost-effective management of the disease, reduce the reservoir of infection in the community (and thereby transmission), and reduce the unnecessary and irrational use of antimalarial drugs (WHO, 2000*c*).

Cost considerations are often perceived as being the most important obstacle to the widespread introduction of RDT. Except when only a few tests need to be performed, the direct costs of any current RDT, per subject tested, are higher than those of conventional microscopy. The costs of organization, supervision, quality control and training of skilled personnel are, however, likely to be lower for RDT than for microscopy (WHO, 2000*b*).

In Sri Lanka, no studies using an RDT for the detection of human infections with *Plasmodium vivax* (which accounts for about 70% of the malarial infections in the country) have been conducted. The main objective of the present study was to determine the cost-implications of using an ICT that can detect *P. vivax* malaria in a moderately endemic area of Sri Lanka.

SUBJECTS AND METHODS

Study Area and Subjects

The blood samples investigated came from the patients aged >5 years who, between May 2001 to March 2002, presented with fever or a recent history of fever in Kataragama (at the Malaria Research Unit of the University of Colombo's Department of Parasitology) or Kurunegala (at the Anti-Malaria Campaign Office) and gave their informed consent. Diagnosis and treatment were provided to all, free of charge. The patients came from the Kataragama and Buttala areas of the Moneragala district or the Kurunegala district of Sri Lanka. Both *P. falciparum* and *P. vivax* are endemic in these areas.

Study Design

Fingerprick samples of blood from each subject were each checked for malarial parasites by two methods: standard microscopy and a commercial ICT — the ICT Malaria P.f/P.v assay (Amrad ICT, Sydney). For the microscopy, Giemsa-stained thick and thin smears were prepared and 100 fields of each thick smear were checked under a light microscope, at $\times 1000$, for the asexual and sexual stages of *Plasmodium*. The thin smears of blood samples found thick-smear-positive were then examined so that the *Plasmodium* species could be identified. All the smears were examined by a trained microscopist in the field and cross-checked by a second microscopist in a laboratory, who was blinded to the field results. (There were no discrepancies between the results of the two microscopists.)

Simultaneously with the microscopy, blood samples were tested in the ICT according to the manufacturer's instructions. The ICT Malaria P.f/P.v assay is a rapid, in-vitro, immunodiagnostic test for the detection of circulating *P. falciparum* and *P. vivax* antigens in whole blood. This RDT detects the circulating *P. falciparum*-specific HRP2 (histidine-rich protein 2) antigen and a pan-malarial antigen (possibly aldolase; Moody, 2002). In the assay, a 15-μl sample of whole blood is applied to a sample pad impregnated with colloidal-gold-labelled antibodies directed against the two malarial antigens. In the present study, as generally, the test results were scored positive for *P. falciparum* if the control, HRP2 and panmalarial lines were all visible and positive for *P. vivax* if only the control and panmalarial lines could be seen. (Co-infection with *P. falciparum* and *P. vivax* cannot be distinguished from infection solely with *P. falciparum*.)

The sensitivity, specificity, and positive and negative predictive values of the ICT were calculated, using the results of the microscopy as the 'gold standard'.

Estimating the Costs

All costs were calculated in Sri Lankan rupees (SL Rs), the local currency. At the time of the study, 1000 SL Rs were equivalent to about U.S.$10.40.

BLOOD-SMEAR EXAMINATION

The annual recurrent expenditure of examining bloodsmears was estimated by adding the annual salary of a microscopist to the costs of a year's supply of the necessary supplies (glass slides, blood lancets, Giemsa stain, glassware, cotton wool, alcohol and immersion oil) and those of a year's maintenance of a small laboratory. The prices of the supplies were obtained from the headquarters of the Sri Lankan Anti-Malaria Campaign. The mean annual expenditure needed to support a small laboratory, in terms of electricity, gas and building maintenance, was estimated from the expenses incurred at the field laboratory maintained by the Malaria Research Unit in Kataragama. The total annual costs were then divided by the number of working days in a year (290) and an estimate of the number of smears a microscopist could check adequately in a day (65) to give an estimate of the recurrent costs/smear examined. The capital costs included the replacement value of an Olympus microscope, which was 140,000 SL Rs at the time of the study, annualized over 15 years using a real discount rate of 6%/year. The cost of building space was not included as it will vary from place to place in the country, depending on local land values. The costs of training the necessary personnel were included, discounting the salary of a trainee microscopist during the 15-month training period at 6%/year, and assuming that each microscopist serves a period of 30 years. The other costs of training a microscopist, such as the salaries of the trainers and the reagents used during the training, were not taken into account.

ICT

In estimating the costs of using the ICT, the price of the test strips was simply added to the costs of the equipment used to take the blood samples (i.e. lancets, cotton wool and alcohol swabs). As the blood collection and testing do not require great skill, the personnel costs for the ICT were considered to be limited to those of a technician.

SIMULATION STUDIES

Once the data on costs and the results of the two detection methods became available, the effects on the costs, per case detected, of varying the slide positivity 'rate' (i.e. the percentage of smears with malarial parasites detectable under the microscope) and the sensitivity of the ICT were estimated. In these simulations it was assumed that 1000 blood samples needed to be checked.

Ethical Considerations

Ethical clearance to conduct the study was obtained from the Ethical Review Committee of the University of Colombo's Faculty of Medicine. Prior to the enrollments, verbal informed consent was obtained from the adult subjects and the parents/guardians of the children.

RESULTS

Characteristics of the Subjects

The 328 subjects enrolled, most (64%) of whom were male, were aged 5.2–72.5 years (mean = 28.3 years).

On microscopical examination of their thick and thin bloodsmears, 120 (36.5%) of the subjects were found to have malarial parasites, 99 (82.5%) having *P. vivax*, 21 (17.5%) having *P. falciparum*, and none apparently positive for both species. The 21 subjects who

apparently had pure *P. falciparum* infections by microscopy and the 208 found smear-negative were all considered smear-negative for *P. vivax*.

In Table 1, the results of the microscopy are compared with those of the ICT. Although 99 subjects were considered smear-positive for *P. vivax*, only 72 (including two subjects considered smear-negative) were considered positive for this species in the ICT. Of the seven subjects who were smear-positive only for the gametocytes of *P. vivax*, five were ICT-negative and two ICT-positive for *P. vivax*. For the detection of *P. vivax*, with the microscopy as the 'gold standard', the ICT test had a sensitivity of 70%, a specificity of 99%, a positive predictive value of 97.0%, and a negative predictive value of 88.7%.

Estimated Costs

As shown in Table 2, the estimated cost of preparing and examining bloodsmears for malarial parasites was 26.86 SL Rs/subject — 25.93 SL Rs (recurrent) plus 0.93 SL Rs (capital). The estimated total cost of performing a single ICT Malaria P.f/P.v test for the diagnosis of malaria was much higher, at 367.26 SL Rs (Table 2).

Simulation Studies

Compared with the costs of bloodsmear examination, the costs of performing the ICT were approximately 14 times greater per subject investigated (367.26 *v.* 26.86 SL Rs) and approximately 20 times greater per *P. vivax* infection detected, when the sensitivity of the test was 70% (Fig.). For both methods of detection, the costs per case detected decrease as the slide positivity 'rate' increases (Table 3) but even at a high slide positivity 'rate' of 50% the ICT would still cost in excess of 1000 SL Rs/case detected (assuming the sensitivity and specificity of the ICT remain at 70% and 99%, respectively).

Assuming the specificity of the ICT remains at 99%, whatever the slide positivity 'rate', improvement in the sensitivity of the ICT would reduce the costs of the test per *P. vivax* case detected (Table 3 and Figure).

DISCUSSION

The development of rapid tests for malaria has revolutionized the diagnosis and treatment of the disease in areas where microscopy is not available. In areas, such as most of South and South–east Asia, where *P. vivax* predominates, diagnostic tests that detect only *P. falciparum* infections may not be a viable alternative to microscopy (Kodisinghe *et al.*, 1997), although they may still be useful in the short-term (Verlé *et al.*, 1996; Bojang, 1999; Coleman *et al.*, 2002; Taylor *et al.*, 2002). The recent development of RDT that allow both *P. falciparum* and *P. vivax* infections to be not only detected but also distinguished has produced more promising tools that could be used on an operational scale by national malaria-control programmes.

The present study was focused on *P. vivax* infections since the incidence of *P. falciparum* infection during the study period was extremely low throughout Sri Lanka. The costs of the microscopical examination of

TABLE 1. *Comparison of* Plasmodium vivax *detection by microscopy (with the examination of 100 thick-smear fields) and immunochromatographic testing (ICT)*

	Results of the microscopy (no. of subjects):		
Results of the ICT	Positive for *P. vivax*	Negative for *P. vivax*	Tested
Positive for *P. vivax*	70	2	72
Negative for *P. vivax*	29	227	256
Tested	99	229	328

TABLE 2. *The estimated costs of examining bloodsmears and performing the ICT Malaria P.f/P.v assay for the detection of* Plasmodium vivax *infections in Sri Lanka*

Category	Cost (Sri Lankan rupees/subject)	
	Microscopy	Assay
RECURRENT COSTS		
Laboratory staff		
Microscopist	6.15	—
Technician	—	3.30
Laboratory orderly	2.96	—
Laboratory labourer	3.18	—
Supplies		
Glass slide	2.90	—
ICT Malaria P.f/P.v kit	—	360.00
Blood lancet	2.00	2.00
Giemsa stain	3.35	—
Glassware, cotton wool and alcohol	3.44	1.96
Immersion oil	0.31	—
Total	12.00	3.96
Maintenance	1.64	—
Total	25.93	367.26
CAPITAL COSTS		
Equipment	0.76	—
Training personnel	0.17	—
Total	0.93	—
Total (recurrent plus capital)	26.86	367.26

TABLE 3. *Simulation of the cost-effectiveness of microscopy and the ICT Malaria P.f/P.v assay for detecting* Plasmodium vivax *infection among 1000 subjects, for different endemicities of* P. vivax *malaria and different sensitivities for the assay (assuming the specificity of the assay remains at 99%)*

Detection method	Sensitivity of assay (%)	Endemicity (% of smears positive)	No. of infections		No. of false-positives	Cost (Sri Lankan rupees/ infection detected)
			Detected	Missed		
Microscopy	—	5	50	0	0	537.20
	—	10	100	0	0	268.60
	—	25	250	0	0	107.44
	—	50	500	0	0	53.72
Assay	70	5	35	15	9	10,493.14
	70	10	70	30	9	5246.57
	70	25	175	75	7	2098.60
	70	50	350	150	5	1049.31
	80	5	40	10	9	9181.50
	80	10	80	20	9	4590.75
	80	25	200	50	7	1836.30
	80	50	400	100	5	918.15
	90	5	45	5	9	8161.33
	90	10	90	10	9	4080.67
	90	25	225	25	7	1632.27
	90	50	450	50	5	816.13
	95	5	48	2	9	7651.25
	95	10	95	5	9	3865.89
	95	25	238	12	7	1543.11
	95	50	475	25	5	773.18

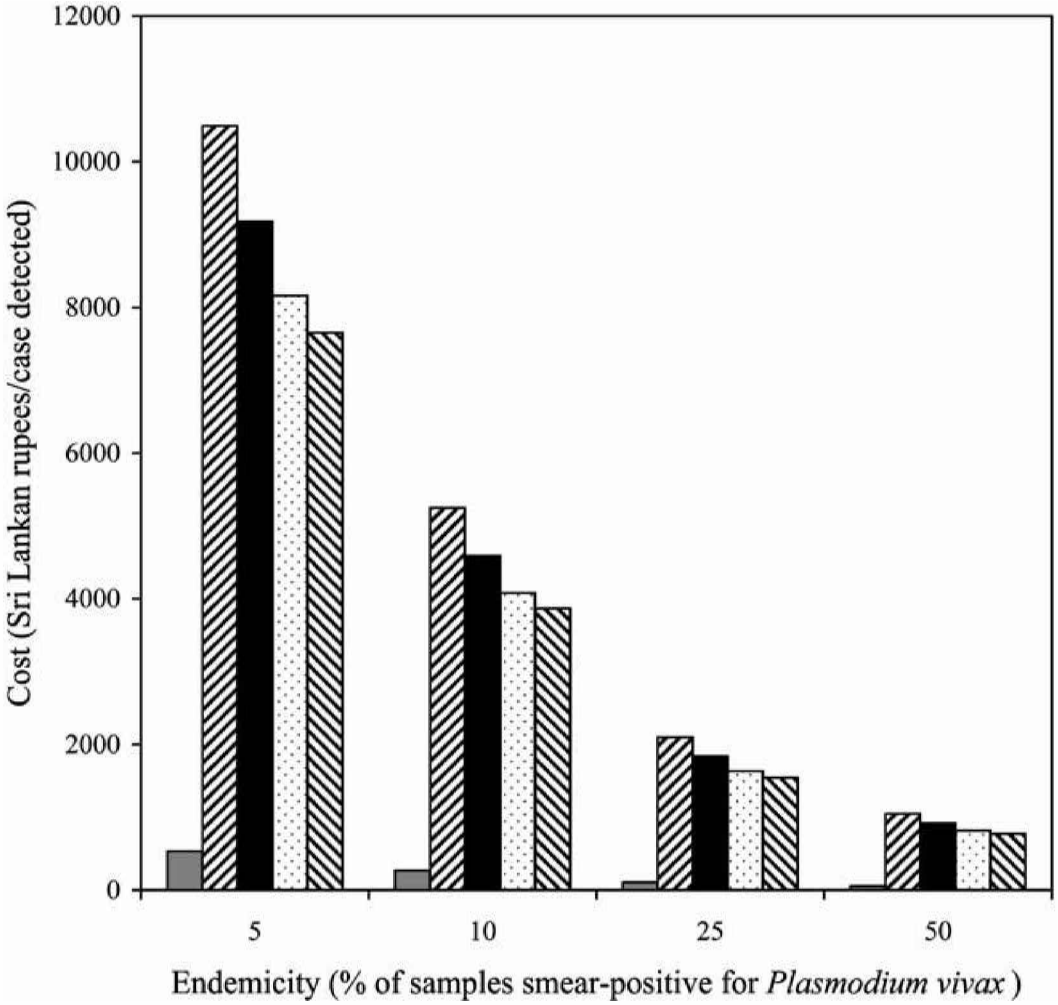

FIG. The estimated costs of microscopy (▒) and the ICT Malaria P.f/P.v assay, in the detection of *Plasmodium vivax* infection. The results for the assay are shown for different endemicities of *P. vivax* malaria and with the sensitivity of the assay set at 70% (▨), 80% (■), 90% (▩) and 95% (▧), assuming the specificity of the assay remains at 99%.

bloodsmears and those of the ICT were compared assuming that, as now, only microscopists attached to the national malaria-control programme in Sri Lanka performed the microscopy. Such microscopists, who have been specially trained to check smears for malarial parasites, are required to examine a maximum of 65 slides/working day. During the main transmission season, most microscopists examine 65 slides/day, as bloodsmears are then produced from every fever case. At other times of the year, when there is much less transmission, it is unlikely that a microscopist would examine 65 slides a day and the cost of detecting a case by microscopy would therefore then be higher than estimated here. In the present study, the cost of the training necessary to perform the ICT, which is a very simple assay, was considered negligible.

Under field conditions, compared with the results of the routine microscopy (in which

100 microscopical fields of every Giemsa-stained thick smear were checked), the ICT was 99% specific but only 70% sensitive. Storage and use of the ICT dipsticks at room temperature may have reduced their sensitivity (room temperatures often exceeded 30°C), although this practice is recommended by the manufacturer and there is seldom any alternative in primary-healthcare institutions in areas where malaria is endemic. Relatively low sensitivities against *P. vivax* have been seen, however, in other studies in which the ICT Malaria P.f/P.v assay has been evaluated. Singh *et al.* (2000), for example, reported a sensitivity of 72% and a specificity of 99%. Tjitra *et al.* (1999) considered the sensitivity (75% overall) and positive predictive value (50%) they recorded for the ICT to be inadequate for *P. vivax*; only 29% of the light parasitaemias (<500 parasites/μl) found by microscopy gave a positive result in the ICT. Coleman *et al.* (2002) also thought that the ICT Malaria P.f/P.v assay was not sufficiently sensitive in the detection of *P. vivax* infections.

In terms of the cost/subject investigated, the ICT was 14 times more expensive than the routine microscopy, even when any training costs for use of the ICT were ignored. The microscopy would become slightly more expensive per subject if the microscopists checked fewer than 65 thick smears/day but would remain far cheaper than the ICT. Schapira (1989) reported that the cost to the Mozambique government of the diagnosis of malaria is much lower with the diagnosis based on microscopy (only about U.S.$0.0053/subject tested, assuming that there are 6000 subjects/year and that a microscopist remains in service for >30 years) than if ICT were used. The ICT dipsticks would have some advantages, however, such as ease of use, fixed unit costs (irrespective of the number of tests/year) and no requirement for a microscope. Palmer *et al.* (1999) gave the general costs of malaria diagnosis by microscopy and rapid diagnostic tests to be U.S.$0.12–0.40 and about U.S.$1.00/subject tested, respectively, although costs as low as U.S.$0.60 have been achieved for ICT that only detect *P. falciparum*

The high cost of the ICT Malaria P.f/P.v assay will be an enormous obstacle to the assay's wide-spread use in many developing countries. The health systems responsible for most malaria-endemic regions have to grapple with many other major public-health problems, often on a very limited budget. Although technological improvement will no doubt lead to rapid tests that have better sensitivities and are therefore more cost-effective in operational use, it seems likely that such tests will remain far more expensive than microscopy. Though the facilities for microscopy may be lacking in some areas, it will be more advantageous, in the long-term, to develop these facilities rather than to rely solely on the use of RDT (which may not be sustainable). There may still be a place for the use of RDT in the short-term, however, until microscopy facilities are developed.

The low sensitivity of the currently available ICT has implications for the burden of malaria and its transmission in a given area. When a diagnostic test is available, it is unlikely that antimalarial drugs will be given unless a positive result is obtained. If, in the present study area, all malaria diagnosis was based on the ICT Malaria P.f/P.v assay, 30% of the *P. vivax* infections would be left untreated, at least at the first consultation, and this would result in considerable, preventable morbidity. In Sri Lanka, most cases (>80%) of *P. vivax* malaria have gametocytes in their peripheral blood when they seek treatment (Fernando and Wickremasinghe, 2002) and such cases, if undetected and untreated, will remain as potential reservoirs of infection, perhaps for long periods. Even though the cost per case detected by the ICT is significantly greater than the cost of microscopy, the actual difference in the costs will be many-fold greater if the number of cases prevented is also considered. If routine microscopy were to be replaced with ICT Malaria P.f/P.v, the inability of the ICT to detect 30% of the

P. vivax infections detectable by microscopy would markedly increase the social burden posed by *P. vivax* malaria.

The high specificity of the test ensures that the number of false-positives with the ICT is small. If the ICT were in operational use there would therefore be very little undue drug pressure and very little wastage of antimalarial drugs.

The present results indicate that the usefulness of the ICT Malaria P.f/P.v assay is limited to specific situations: short-term use in areas where microscopy is not yet available and emergency clinical management. Although the latter is generally associated with *P. falciparum* infections, in the present study it was impossible to evaluate adequately the ICT in the detection of such infections because too few *P. falciparum* infections were observed. The relatively high cost of the RDT currently available appears to be the most important factor limiting their operational use, especially in areas where *P. vivax* predominates and transmission is not intense. In the present study, however, only the costs to the providers were considered. The true, societal cost-effectiveness of ICT Malaria P.f/P.v assay may be much higher than the cost-effectiveness estimated here; this is an area for further research.

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