CHAPTER 2

LITERATURE REVIEW

This chapter will review the literature on (1) treatment seeking pattern of malaria cases; i.e.where the malaria patients go for treatment? what proportion? why? how much do they pay for service? (2) effectiveness of microscopy and dipstick in diagnosis of malaria; i.e.accuracy, sensitivity, specificity, false positive and false negative values of dipstick and microscopy and (3) the costs and cost-effectiveness of malaria surveillance activities.

2.1 Treatment Seeking Pattern of Malaria Cases

Very few studies on treatment seeking pattern of malaria cases have been carried out in Sri Lanka. According to the MOH (1995), 40% of patients use private practitioners for primary medical care. The MOH (1993) states that about 55% of patients use western private medical services and traditional medicine mainly as outpatients whereas there is a high percentage of patients practice self medication. These two papers discuss about the use of public and private health facilities by patients in general, not specifically by the malaria patients. Mills (1995) also has stated that private practitioners are used extensively in Sri Lanka for treatment of malaria despite the free medical care at government health facilities. This paper suggests further studies be carried out to explore the reasons for popularity of private health facilities, since it will be a major policy issue in malaria diagnosis, treatment and financing.

A study on human migration and malaria outbreaks in traditionally non malarious area in Sri Lanka has been carried out from 1989 to 1992 by Kusumawathie (1995). The study shows that 20% of malaria cases among migrants have made their first visit for treatment at a private health facility. The malaria cases may have made more than one visit for treatment per episode per patient. But this paper discusses only the first visit for treatment.

There are many studies carried out in other countries on the treatment seeking behaviour of malaria cases. These studies too show that the malaria patients practice self medication, use private medical services and traditional healers, apart from attending formal health services.

Mills (1993) has studied the treatment seeking pattern of malaria patients in five districts in Nepal. The study shows that 47-63% of the patients had consulted alternative source of treatment before making contact with malaria control agencies. Among the

alternative sources of treatment the most popular treatment sites were private practitioners (22-57%) and drug sellers (23-46%). The faith healers were also popular (23-35%) in two districts. A study carried out in Western Thailand by Hongvivatana and Hoontrakul (1982) has shown that 87% of patients had practiced self medication or used other inappropriate treatment before attending a malaria clinic.

Experience of many countries shows that a considerable proportion of malaria cases practice self medication which is a major problem in malaria control. Foster (1991) states that self medication may account for as much as half of all consumption of drugs specially in rural areas. The following studies also show the magnitude of the problem of self medication by studying the amount of drug consumption through various services and channels.

In Pikine, a suburb of Dakar, Senegal, private traders sell drugs valued at 32 million CFA fances (US$ 125,000) whereas the government provides only 3 million CFA francs worth. The local self-financing schemes provide drugs of 40 million CFA francs worth. Therefore, it is accounted that the private traders sell drugs of some 43% by value (Fassin 1988). In 1983, in Zimbabwe, rural shopkeepers accounted for 43% of the consumption of chloroquine whereas rural health facilities issued about 56% of chloroquine (Raynal 1985). Another study carried out in Suradidi, Kenya, shows that 53% of people in the area bought antimalarials from shops (Mburu and others 1987). In Togo, 83% of children with fever had been treated at home with chloroquine. Two-thirds of the mothers had obtained the drug from private sellers (Deming and others 1989). In Mara, Tanzania, 72% of people got chloroquine from sources other than the official chemoprophylaxis programme. Of them 41% had got chloroquine from unofficial outlets including shops and 10% from the market (MacCormack and Lwihula 1983).

Based on several studies, Foster (1991) estimated the percentage of antimalarials distributed to the consumer through various channels. The results of such estimate are shown in Table 2.1.

There are many reasons for using non formal services by malaria patients. Among those reasons given by people in rural Zimbabwe were: lack of queues, the convenient late hours of the shops, a suspicion of 'free' things, including drugs, their dislike of being asked questions or being physically examined, and the generally more friendly and helpful attitude of the shopkeepers (Raynal 1985). The study carried out in Saradidi, Kenya shows that the reasons for preferring non formal services were that other sources were too far away, the shops were open in emergencies, the hospital or dispensary had no drugs, they had good past experience with the shops, and the shop keeper gave advice, especially on dosage (Mburu and others 1987). Further, Foster (1991) stated that a family makes a decision to self medicate according to the common sense and local belief about disease on what cause of action to be taken. The distance to travel, (Rooth and others 1991; Gilk and others 1989) and the cash required for seeking care too contribute to self medication.

Table 2.1 Estimated Percentage of Antimalarial Drugs Distributed by Channel

Sector	Percentage	
Public sector		**40–60**
National Malaria Control Programmes	20–30	
Primary health care and hospital use	20–30	
Private sector		**40–60**
Official ethical pharmacies	20–40	
unofficial outlets and sellers	20–50	
non governmental organizations and clinics	25–40	

Source: Foster (1991).
Note: Private sector totals add to more than 100% since unofficial outlets are often supplied through official pharmacies.

In addition to the patient behaviour, the shortcomings of the supplier also contribute to self medication. Foster (1991) has classified these into three broad categories namely (1) inappropriate policies on malaria treatment, (2) the failure of health services and (3) economic constraints. An example of inappropriate policy is that in the Philippines the policy is to provide malaria treatment on confirmation of malaria by blood slide examination. But it seems that, in some areas, it takes as much as six weeks to get the result of blood slides. In this case, the patient has to wait for six weeks for treatment, but the patient clearly does not wait six weeks and does self medication by purchasing drugs from the shops (Foster 1991). Another example for inappropriate policy on malaria treatment is, in Togo, the National Drug Company sells a minimum of 20 tablets of antimalarials. The price of 20 tablets is not affordable to a large number of patients, therefore they self medicate by buying a few tablets of drugs from the local market (Deming and others 1989). Failure of health services and economic constraints include the poor quality, financial and geographical inaccessibility of health services. The user charges at government facilities reduced utilization of health services and encouraged self medication in Ashanti-Akim district in Ghana (Waddington and others 1989). Over-prescription by health care providers also encourage self medication because the patients can not afford long prescriptions. Instead, they buy few tablets of drugs from private drug sellers (Fassin 1986, quoted in Target 1991).

Ettling and others (1994) have studied household income and household expenditure on the treatment or prevention of malaria in Malawi in 1992. The study found that the most common household expenditure was for malaria drugs although the drugs are available at no cost at government health facilities. Furthermore, the study shows that the households purchase drugs from non health facilities irrespective of the level of household income. For example, among surveyed households, 53% (51% for very low income and 55% for low to high income households) reported having purchased drugs from a non health facility.

It has also been found that people keep stock of drugs at their homes for using when they get malaria in the future. Haak (1988) found in Brazil that many homes had various drugs, some of which had been prescribed by a physician. Tanzanian people too like to keep a reserve of antimalarials for future use (MacCormack and Lwihula 1983).

2.2 Effectiveness of Microscopy and Dipstick

The indicators used to determine the effectiveness of a diagnostic test are the accuracy, sensitivity, specificity, false positive and false negative values of that test. There are many studies that have been carried out to study the above aspects of microscopy and dipstick.

Kodisinghe and others (1995) have carried out a study in Sri Lanka in order to evaluate the effectiveness of dipstick (paraSight-F test) as compared to microscopy. The study shows that the sensitivity of dipstick was 81.9% and specificity was 97.9% when dipstick was compared with microscopy of 100 oil-immersion fields per each blood smear. The authors have re-examined the blood slides which were discrepant between microscopy of 100 oil immersion fields examination and dipstick, by using microscopy of 400 oil-immersion fields. Then the sensitivity and specificity of dipstick were 91.2% and 99.3% respectively. The positive predictive value was 96.9%; negative predictive value was 97.9%.

Dietz and others (1995) had compared the microscopy and quantitative buffy coat analysis (QBC) to the dipstick using malaria cases attending at outpatient clinics in Alta Floresta, Mato Grosso, Brazil in 1993. The study shows that even a highly experienced microscopist can miss mixed infections when he examines the blood smears to provide quick diagnosis (the study used 121 patients; initial thick blood smear (ITS) readings were made to give quick diagnosis. The ITS showed that there were 51 P.falciparum patients out of 121 patients tested. When quantitative thick smear (QTS) readings were made, 5 slides read as P.vivax infections by ITS also showed P.falciparum parasites giving a total of 56 P.falciparum patients). Using QTS as the gold standard, the sensitivities, specificities and predictive values for the dipstick and the quantitative buffy coat (QBC) methods have been calculated. It was found that the dipstick was highly sensitive and specific. The results of that analysis are shown in Table 2.2.

To compare dipstick with actual practice in the field, the ITS has been compared with the QTS. Both the dipstick and ITS resulted in five false-negatives while only dipstick gave false-positive readings. In three of the patients with false-negative ITS results, the dipstick result was positive, suggesting that the dipstick may add a degree of sensitivity to actual field practice.

Table 2.2 Accuracy of the PFT and QBC Analysis vs QTS Examination

	PTF vs QTS (121 patients)	QBC vs QTS (121 patients)
True +	50	49
true -	64	64
False +	2	2
False -	5	6
Sensitivity	0.91	0.89
Specificity	0.97	0.97
PPV	0.96	0.96
NPV	0.93	0.92

Source: Dietz and others (1995).

When the dipstick results were compared with the thick blood smear readings obtained by local health care workers, a remarkable difference was seen. The specificity in thick blood smear reading was 84% and the sensitivity was 78% (Dietz and others 1995).

Shiff and others (1993) have studied the performance of dipstick in malaria patients from the Bagamoyo district in coastal Tanzania. The dipstick results were compared with thick blood film examination results. The sensitivity of dipstick was 88.9% and specificity was 87.5%. Positive predictive value of dipstick was 87.7%. The test has given false negative results for the patients with lower levels of parasitaemia indicating that the lower limit of sensitivity of the test was about 40 parasites per microliter of blood.

Peyron and others (1994) have evaluated the accuracy of dipstick for the diagnosis of imported malaria in two french teaching hospitals using 355 travellers referred to the departments for post-travel problems. Every blood sample was tested by the QBC malaria diagnostic test (Becton-Dickinson), by dipstick, and by the thin film method for species identification and quantification. The sensitivity and specificity of paraSight-F test for the detection of P.falciparum were 93% and 99% respectively. The positive predictive value was 91%.

Beadle and others (1994) have evaluated the dipstick antigen-capture assay in three groups of study populations. The first group (adult field study group) consisted of 40 males aged 15-35 years who had volunteered for a malaria immunology study in Saradidi, Kenya. The second group (experimental challenge group) consisted of 20 adult male and female volunteers who participated in a vaccine trial in Baltimore, Maryland. The third group (child field study group) were 173 girls and boys aged 9-14 years who were enrolled in a malaria prophylactic drug study in the same region of Kenya as in the initial adult study.

During the study, blood samples were checked with dipstick and microscopy. The results of adult field study and child field study show that when P.falciparum asexual parasitaemia is greater than 60 parasites per microliter of blood, the dipstick was 96.5- 100%

sensitive. At lower levels of parasitaemia, the sensitivity of dipstick decreases. However, dipstick still detects 70-81% of infections at 11-60 parasites and 11-67% infections at 10 parasite per microliter of blood or less.

Based on the data on sensitivity and specificity of dipstick from studies carried out in several countries, WHO (1995) states that the dipstick is both sensitive and specific. The range of sensitivity in the studies was 84.2% to 93.9%, with two exceptions, i.e. the adult field study in Saradidi, Kenya and the vaccine study in Baltimore, USA. The lower sensitivities in those two studies were apparently related to the presence of parasitaemias lower than 60 parasites/ microliter of blood. In these studies, the specificities varied from 81.1% to 99.5%. The values lower than 90% were observed only in the Kenyan and Tanzanian studies. The WHO (1995) explains this observation as that these two studies had been carried out in holoendemic areas where it is difficult to assess the true specificity, because it is difficult to be certain that an individual with a single negative blood slide is truly parasite free. Positive and negative predictive values of dipstick in all studies ranged from 79.9% to 98.7% and from 72.0% to 100% respectively. Furthermore, these studies also show that the sensitivity of the test decreases with decreasing number of parasites per microlitre of blood. The peak sensitivities of over 96% being observed at parasite levels above 100 parasites /microliter of blood. However, dipstick detects on average of 74.6% of the cases at 10 parasites per microliter or less and 81.3% of cases at parasitaemias of 10-100 parasites /microliter (WHO 1995).

Following the successful drug treatment, there is a tendency of persistence of antigenaemias slightly longer than parasitaemias which results false positive results by dipstick. For example, in the study carried out by Beadle and others (1994), eight cases out of 91 negatives gave false positive results by dipstick due to persistence of circulating antigen in the blood after treatment.

WHO (1995) states that, according to a study carried out by Singh and others, 110 (97.3%) out of the 113 patients had their parasitaemias cleared by day 2 and all patients were parasitologically negative by day 7. But the antigenaemia persisted in 87 patients (77%) on day 2, in 5 patients (4.4%) on day 7 and in 1 patient (0.9%) on day 28. Similar results were observed in Tanzania where peripheral parasitaemias were undetectable by day 3 whilst antigenaemia was detected on day 5 and 14 in 25% and 3% of patients respectively (Shiff and others 1993). Antigenaemia persisted longer also in patients in the Kenya field studies but was not detectable 6 days after treatment (WHO 1995).

Analysis of all current data indicate that antigenaemia disappeared in 55% of patients on the same day as parasite clearance and 85% of patients were negative by the dipstick assay within one week of this parasite clearance (Dietz and others 1995).

The test does not detect the antigens of P.ovale and P.malariae. Four blood slide positive cases each of P.malariae and P.ovale were

negative in the dipstick assay in Tanzania (Shiff and others 1993) as well as 173 P.vivax and 5 P.malariae blood slides positive cases in Thailand, 115 P.vivax infections in India 3 P.vivax infections in Venezuela (WHO 1995) and 165 P.vivax cases in Sri Lanka (Kodisinghe and others 1995).

There are some studies have been carried out to evaluate the effectiveness of microscopy itself under different locations. For example, Collier and Longmore (1983) have compared the microscopic diagnosis of malaria in field, laboratory and at a hospital in Solomon Islands. The rate of false diagnosis (for thick films) was 3% for the field worker, 9% for the malaria laboratory and 27% for the English hospital. The authors explain that the use of thin blood smear examination at the English hospital resulted high rate of false diagnosis. The reason for the field worker's apparent success is that he is innovated by taking blood films and treating patients, so his work is less tedious, compared to that of a microscopist in the laboratory. This helped him to maintain vigilance and motivation on blood film examination.

The accuracy of the microscopy depends on the experience and the competence of the microscopist and the quality of staining the blood film. Raghvan (1966) has shown another source of influencing the failure to find malaria parasites in a thick film, apart from the shortcoming either to defects in the techniques of preparation of blood film or to the incompetence of the microscopist. This source is called a "chance element".i.e. a proportion of the positive blood films will be missed by chance, no matter how well a film is prepared, and how capable a microscopist may be. This paper deals with the problem of the failure to identify a positive blood sample, owing to limited examination of the blood film.

According to Roghavan (1966), the chance of failing to detect a positive slide depends directly on two factors, namely the volume of blood examined in relation to the total amount on the slide available for examination and the number of parasites present in this total amount. Roghavan (1966) has calculated the probability of declaring a positive slide as negative, when only a sample of microscopic fields is examined. During this calculation, he has assumed that the parasites are randomly distributed in the blood film. According to this calculation, the probability of failing to detect a positive blood film decreases with increasing density of parasites when the number of fields examined remains the same. Again, for a given parasite count, this probability decreases as the number of fields examined increases while the total number of fields available for examination remains the same. The results of such calculations are presented in Table 2.3. Furthermore, the author explains that when a competent microscopist confirms the diagnosis of a negative slide on examining 100 fields, there could be two possible interpretations. (1) that the slide is really negative or (2) that the slide is positive, but with less than 44 parasites in 1000 fields. The second possibility can be excluded if the number of fields examined is increased as shown in Table 2.4.

Table 2.3 Probability (%) of Missing a Positive Slide When Only a Sample of Microscopic Fields out of 1000 is Examined

Number of parasites in 1000 fields	Number of fields examined						
	100	150	200	300	400	500	600
1	90.0	85.0	80.0	70.0	60.0	50.0	40.4
2	81.0	72.2	64.0	49.0	36.0	25.0	16.0
3	72.9	61.4	51.2	34.3	21.6	12.5	6.4
4	65.6	52.2	41.0	24.0	13.0	6.2	2.6
5	59.0	44.4	32.8	16.8	7.8	3.1	1.0
6	53.1	37.7	26.2	11.8	4.7	1.6	0.4
7	47.8	32.0	21.0	8.2	2.8	0.8	0.2
8	43.0	27.2	16.8	5.8	1.7	0.4	*
9	38.7	23.1	13.4	4.0	1.0	0.2	*
10	34.8	19.7	10.7	2.8	0.6	0.1	*
11	31.3	16.7	8.6	2.0	0.4	*	*
12	28.2	14.2	6.9	1.4	0.2	*	*
13	25.4	12.1	5.5	1.0	0.1	*	*
14	22.9	10.3	4.4	0.7	*	*	*
15	20.6	8.7	3.5	0.5	*	*	*
16	18.5	7.4	2.8	0.3	*	*	*
17	16.7	6.3	2.3	0.2	*	*	*
18	15.0	5.4	1.8	0.2	*	*	*
19	13.5	4.6	1.4	0.1	*	*	*
20	12.1	3.9	1.2	*	*	*	*
21	10.9	3.3	0.9	*	*	*	*
22	9.8	2.8	0.7	*	*	*	*
23	8.8	2.4	0.6	*	*	*	*
24	7.9	2.0	0.5	*	*	*	*
25	7.2	1.7	0.4	*	*	*	*
26	6.4	1.5	0.3	*	*	*	*
27	5.8	1.2	0.2	*	*	*	*
28	5.2	1.1	0.2	*	*	*	*
29	4.7	0.9	0.2	*	*	*	*
30	4.2	0.8	0.1	*	*	*	*
35	2.5	0.7	0.1	*	*	*	*
40	1.5	0.6	*	*	*	*	*
44	1.0	0.5	*	*	*	*	*
45	0.9	0.4	*	*	*	*	*

Source: Raghvan (1966).
Note: The asterisk (*) indicates a probability of less than 0.1%

Table 2.4 Number of Microscopic Fields to be Examined to Ensure 99% Probability of Detection of Blood Films with Malaria Parasites.

No.of parasites in 1000 fields	No.of fields to be examined	No.of parasites in 1000 fields	No.of fields to be examined
1	990	23	181
2	900	24	175
3	785	25	168
4	684	26	162
5	602	27	157
6	536	28	152
7	482	29	147
8	438	30	142
9	400	31	138
10	369	32	134
11	342	33	130
12	319	34	127
13	298	35	123
14	280	36	120
15	264	37	117
16	250	38	114
17	237	39	111
18	226	40	109
19	215	41	106
20	206	42	104
21	197	43	102
22	189	44	99

Source: Ragvan (1966).

2.3 Costs and cost effectiveness of malaria surveillance activities.

Kaewsonthi and Harding (1984) explain how to determine costs and performance of malaria surveillance and monitoring process in Thailand. During this study, all methods of malaria surveillance have been studied. These methods are malaria clinics (MC), malaria village volunteer(MVV), village health center (VHC), hospitals (H), mobile clinics (MC) and ACD. During this study the total cost of surveillance has been determined. The costs are classified as internal, external and direct and indirect costs by activity. The costs of operational services are determined by using apportionment and measured criteria.

The authors explained that in the system developed for apportionment of costs, a range of criteria can be applied at each stage of apportionment e.g. personnel based, salary based, responsibility based, functional based, time based, index based and direct. Since it is difficult to decide which are the most appropriate criteria to use for apportionment at each stage a system has been developed to allow study of the effects on using any combination of

criteria. The system provides direct costs of operational units at division, region and zone levels under the budget headings of the malaria control programme in Thailand. Costs derived from divisional, regional and zone budgets are subdivided into direct and indirect costs. Divisional, regional and zone expenditure is kept separate to identify the component costs at each stage.

The cost-effectiveness of surveillance methods mentioned above has not been studied by the authors because these surveillance methods have different targets, different level of effectiveness and the processes are not real alternatives. Therefore, the authors have evaluated the performance of surveillance activities and operational services instead of cost-effectiveness, by using the following criteria. (1)effectiveness of each process, i.e. the extent of targets achieved; (2) time (days), i.e. time taken for completing an activity; (3) performance (%), i.e. the degree to which a task is successfully completed, (4) relative contribution (%), i.e. the extent to which each surveillance method contribute to total surveillance; and efficiency, i.e. cost per blood slide examined and/or positive blood slide examination.

Ettling and others (1991) have compared the costs of three types of malaria clinics that use microscopy in Maesot District in Thailand in 1985 and 1986. The three clinics were large central clinic in Maesot town, a peripheral clinic in a subdistrict town and a periodic clinic at village level. The institutional, community and social costs have been determined during this study.

The institutional costs considered in this analysis were the financial costs to the antimalaria programme in Thailand. These costs included manpower, rent, public services, transportation, and supplies such as glass slides and stains. Manpower costs of both clinic staff and supervisors were determined by using zone accounts, and allocating to the clinics on the basis of activity log-books kept by clinic staff during the study period. The clinics have examined the blood slides collected from other service points, apart from its own blood slides. Therefore, the cost of slide collected and examined of the clinic itself has been determined by considering the relative time required to assess positive and negative blood slides.

Rent and public services costs were determined from zone accounts and allocated proportionately in the same way as manpower costs. Transportation for the day to day operations and supervision of the clinics was provided by motorcycle. Vehicle fuel and maintenance costs were estimated at a daily rate and allocated to clinic operations from log-books kept by all zone field staff, depending on the number of days of use of vehicle by mobile clinic and supervisor. The daily operational costs included the amortized 1985 local purchase price of a motorcycle, assuming a 5 year life and a discount rate of 8% per annum. Costs of supplies were calculated from headquarters and zone records by multiplying the cost per smear by the number of attendees at each clinic.

The costs to patients and family included direct expenditure on the treatment of the illness prior to arrival at the malaria clinic and on the round-trip transport to the clinic for both patient and accompanying family members. Treatment costs included expenditure on drugs, consultations, and traditional therapies made by the patient or family at either private or government facilities before attending a malaria clinic. Indirect costs included earnings lost by patients and/or relatives who cared for them during the period of illness, as well as those lost by patients and family while travelling to and attending the clinic.

Community costs were determined from interviews of a random sample. The average costs for a positive case and for a negative case were calculated and applied to its patient population. Lost earnings were valued at 25 baht per day, based on the annual household income in the study area applied to 365 days for two adults per household. Days on which adult patients reported that they were ill and could not work were valued at the full 25 baht; lost earnings on days on which patients reported fever and/or headache, but not a total inability to work, were valued at 6.25 baht. Time lost by children was valued using the same rate as for adults, assuming that at least one adult relative had to tend a sick child and thereby forfeit their regular income or production.

Costs of episodes of illness for non-attendees at malaria clinics were estimated from bimonthly census surveys. The patients who reported a malaria-like illness in the preceding two months were interviewed employing a method similar to that used to interview clinic patients.

The greatest number of patients at the lowest average institutional costs per smear and per positive case diagnosed (US$ 0.82) were seen at the large central clinic. The peripheral clinic in Popphra, a subdistrict town, had moderate institutional costs per smear and per positive case (US$ 1.58). The periodic mobile clinic had low average institutional cost per smear, but the highest cost per positive case (US$ 3.53). Community costs (those paid by patients and their families) were lowest in the periodic clinic.

Kaewsonthi and others (1996) have developed a computer software programme containing three mathematical models to determine and to compare the cost and outcome of microscopy and dipstick. These models can be used to assess the total and average costs, the aggregate and average aggregate costs to the supplier and to the consumer for microscopy and dipstick. The model 1 compares two services, i.e. service without microscopy (i=1) and service with microscopy (i=2) at the point of service. Model 2 compares dipstick at service i=1 with the microscopy at service i=2. The model 3 compares dipstick at service i=1 and i=2. These models are applicable to calculate the cost of microscopy and dipstick in any country. Therefore, the author use this programme to calculate the cost and outcome of microscopy and dipstick in the proposed study.

Unfortunately the author did not find any study carried out on economic analysis of dipstick.

By studying data and methods used by the research mentioned earlier in order to determine the effectiveness and cost of microscopy and dipstick, the present study develops a methodology to analyse the cost-effectiveness of microscopy and dipstick in Sri Lanka. The concepts and the methodology are presented in Chapter 3.