CHAPTER 2

LITERATURE REVIEW

2.1 Presumptive Treatment and Clinical Criteria for the Diagnosis of Malaria

Olivar and others, (1991) stressed that presumptive treatment during a season with very low transmission of malarial infection may result in a high proportion of mis-diagnoses and resulting mis-treatments. They tried to assess the efficacy of the policy of treating suspected cases of malaria with a course of anti-malarial drugs, without establishing a parasitological diagnosis in Niger. The criteria they used in their study to confirm a diagnosis of malaria attack were (i) parasitaemia greater than 10,000 infected cells/ml, (ii) a positive blood film from patients who had received an effective dose of anti-malarial drug before clinic attendance, and (iii) a positive blood film without any other obvious source of fever from persons who had received insufficient prior anti-malarial therapy. They found that, even in the high period of transmission almost half of the presumptive diagnoses established by clinic personnel were erroneous and this rate was extreme and significantly higher during the period of low transmission. In establishing the criteria to be used they considered prior intake of anti-malarial drugs, intercurrent infections, and parasite density. They stressed the need to review the currently recommended practice of presumptive treatment. They also cited similar findings of Gaye and others (1989).

To identify useful clinical criteria to improve the accuracy of the diagnosis of malaria Genton and others (1994) investigated presumptive malaria cases diagnosed on clinical grounds by the staff of a rural health subcentre in the East Sepik Province of Papua New Guinea. They looked at the effect of various symptoms and signs on the occurrence of a positive blood slide and on *Plasmodium falciparum* densities. They then evaluated the predictive value of each of the clinical criteria

for a positive blood slide and for a *P. falciparum* parasitaemia more than or equal to 10,000 per µl. They used logistic regression for the analysis and identified spleen size, temperature, no cough, no chest indrawing, and normal stools as significant predictors for a positive blood slide in children; no cough and normal stools in adults. Fever, no cough, vomiting, and enlarged spleen were significant predictors for a *P. falciparum* parasitaemia more than or equal 10,000 per µ liter in children; in adults the only predictor was vomiting. They focused their analysis on the assessment of the predictive values as they were interested to improve the diagnosis of individual episodes of malaria. They could not identify a symptom or sign with a good negative predictive value in children because of the low prevalence of negative blood slides in this group although negative predictors would be more helpful than positive predictors in an area where anti-malarial drugs were given to everybody.

Rougemont and others (1991), aware of the need of a rational clinical approach to febrile episodes which can be used in peripheral centers of tropical health care systems and which take into account the usual absence of laboratory facilities in such centers, suggested from their study that simple clinical criteria may be valuable in the selection of febrile patients for anti-malarial treatment. It was said that in the study area, high fever of short duration with no other obvious causes that occurs during the rainy season were found most likely to be malaria. Using a case-control approach based on a conditional logistic model, febrile children were compared with matched controls. The exposure or the independent variable used to explain the febrile episode in the analysis was the presence of one or more parasites in the blood smear. They claimed that under the conditions of their study, a standard smear examination could not show unequivocally whether observed parasitaemia is the cause of the febrile episode and they advocated that the use of a decision making procedure based on simple, well-standardized clinical observations could be more helpful than standard parasite counts in determining the origin of the fever. With the treatment cut-off based on their criteria they claimed that there can be a substantial saving in the cost

of anti-malarial treatment, with a minimum risk of withholding treatment from potentially serious cases.

There are also some studies with results discouraging the use of the clinical criteria. Trape and others (1985) found that clinical criteria were too non-specific to serve as useful diagnostic guides in a semi-immune population exposed to intense and perennial transmission. They stated that the most useful clinical criteria for diagnosing malaria in pre-school children were primarily negative:(i) absence of bronchial or pulmonary rales on auscultation, (ii) absence of tonsillitis and pharyngitis on examination of the throat, (iii) absence of otitis on examination of the ears. But they said these criteria did not rule out the possibility of an association with clinical malaria and were of little use in older children because of the relative rarity of diseases with specific signs.

Delfini (1973) tried to determine the relationship between body temperature and malaria parasitaemia in Western Nigeria. He found that 26.3% of 654 cases who reported for treatment with a temperature 37.0° C., or below harbored malaria parasites; 43.1% of 1,384 persons who reported for a treatment with a temperature above 37.0° C. were positive for malaria parasites on a single microscopic investigation. The differences in both parasite rates and parasite density indices related to body temperature decreased with increase of in age, the minimum values being found in adolescent and adult populations. The clinical manifestations of malaria are dominated by febrile episodes that accompany the destruction of red blood cells during the host cycle of the parasite. If the parasite is *P. falciparum*, fever can be accompanied by pulmonary, cardiovascular, renal, and central nervous system complications, including encephalopathy and death (WHO, 1990).

The effectiveness of control programs for most tropical diseases, particularly malaria, relies on early and frequent treatment to effect disease reservoirs in infected human hosts. (Hongvivatana, 1986).In highly endemic areas, persons with fever should be treated for malaria even when signs of another illnesses causing fever are present (WHO, 1992). The management of malaria without drastically changing the epidemiologic equilibrium requires the establishment of facilities for

diagnosis and treatment as well as health education at the community level that are supported by appropriate referral and epidemiologic information systems, allowing the focal management or prevention of epidemic outbreaks or drug resistance (WHO Expert Committee on Malaria, 1986).

There was no evidence for an association between febrile episode and parasite count during the dry, low transmission season. During the rainy, high transmission season, by contrast, there was a highly significant relation between likelihood of fever and the parasite count (Rougement and others, 1991). The same authors also noted that simple clinical criteria may be valuable in the selection of febrile patients for antimalarial treatment. They also pointed out that rapid spread of chloroquine resistant *P. falciparum* has led to the need for new drugs and treatment schedules, their associated risks are often not compatible with the level of training of front-line prescribers, and their costs are beyond the economic means of the population affected. What is needed is a rational approach to febrile episodes, which can be used in peripheral centers of tropical health care systems which take into account the usual absence of laboratory facilities in such centers. The aim of such an approach would be to limit antimalarial treatment, as far as possible, to true malaria attacks.

Redd and others (1992) found substantial overlap in the clinical definitions and in laboratory findings: 95% of children meeting the WHO clinical definition for pneumonia also satisfied the clinical definition for malaria. Their results contrast with previous findings by Trape and others (1985) and Rougemont and others (1991). Although microscopy may be judged to be prohibitively expensive and not feasible or necessary for management of febrile illnesses in Africa (Rougement, 1991) Red and others stressed that the costs should be compared with those of widespread and unnecessary use of antimalarial drugs. In their study they found that 89% of children had received treatment for malaria, although only 35% had malaria parasitaemia.

In a busy clinic setting treatment of all children with fever for malaria may limit investigation into other causes of

fever and allow other medical disorders to go undiagnosed and untreated.

Kaewsonthi and others (1996), assessing the economic impact of a rapid on-site malaria diagnostic test, pointed out that the majority of cases of malaria worldwide are treated on the basis of clinical diagnosis or self diagnosis, contributing to irrational drug use. They stressed that although microscopy is the time-honored method of laboratory confirmation of malaria including species identification it is not immediately accessible in any endemic nation. Although it is an excellent technology in well trained hands it is available in practice on a more limited scale than is desirable.

Whenever a set of independent variables is to be related to a dependent variable, a multivariable problem will be under consideration. In the analysis of such a problem, some kind of econometric model can be used to deal with the complex interrelationship among many variables. Logistic regression is modeling approach that can be used to describe the relationship of several variables to a dichotomous dependent variable . Other modeling approaches are possible also, but logistic regression is by far the most popular modeling procedure used to analyze epidemiological data when the dependent variable is dichotomous. The logistic function, on which the model is based, provides estimates that must lie in the range between zero and one. An important feature of the logistic model is that it is defined with a follow-up study orientation. That is, as defined, this model describes the probability of developing a disease or the event of interest as a function of independent variables presumed to have been measured at the start of a fixed follow-up period. It can also be applied to study designs other than follow-up. Although logistic modeling is applicable to case-control and cross-sectional studies, there is one limitation in the analysis of such studies. Whereas in follow-up studies a fitted logistic model can be used to predict the risk for an individual with specified independent variables, this model cannot be used to predict individual risk for case-control or cross-sectional studies. Only estimate of odd ratios can be obtained for case-control and cross-sectional studies (Kleinbaun 1994).

2.2 Cost and Consequences

Kaewsonthi and Harding (1984) pointed out that three conditions must be satisfied when cost effectiveness between two processes are to be compared.

They are:

(i) Processes must be real alternative and not complementary.

(ii) Processes must have the same target and achieve the same level of effectiveness.

(iii) Environmental conditions should be similar.

They also described the performance criteria in their study. Efficiency is described as a measure of the relationship between the outcome from a process and the input. It may be expressed as a percentage efficiency (where inputs and outcomes are in the same unit); as cost-benefit (where the benefits or outcomes are expressed in money terms and related to input costs); and as input/output ratios (where units are disparate). The benefits, that can be expected when using the clinical criteria in diagnosing malaria instead of fever as a sole criterion before giving the presumptive treatment, are the costs saved from the avoidance of unnecessary treatment, and benefit/cost analysis can be undertaken.

Barlow and others (1986) stated that the allocation of resources in the public health sector can be improved if cost effectiveness ratio and benefit cost ratio are estimated for proposed projects. A cost effectiveness ratio measures the cost of achieving a unit increase (decrease) of a variable whose augmentation (diminution) is a social objective. A benefit cost ratio compares project costs with a monetary estimate of project benefits. It can be regarded as a special case of cost effective analysis, in which the measure of effectiveness is the augmentation of monetary magnitude such as national income. In the health area several different measures of project effectiveness have been used; the most common are variants of the following concepts:

(i) the number of persons protected
(ii) reduction in the number of cases of a specific disease (''case-years prevented'')
(iii) number of deaths averted (''lives saved'')
(iv) increase in the number of healthy years of life.

Reviewing studies on benefit cost ratio of malaria control, the authors noted that the main types of economic benefit identified were additions to output made possible by increase in the quantity and quality of labor. The authors added that labor quantity was augmented by reduction in the mortality and absenteeism, labor quality or working efficiency was improved by reduction in debility. Other benefits sometimes quantified include reduction in treatment costs, and gains from the migration of labor into previously malarial zones, ''the new lands effect''. Some benefit/cost ratios were found to be highly favorable while others were not. The variability of these estimates were attributed to widely varying assumptions about the marginal product of labor and about the effects of disease control on rates of mortality, absenteeism, and debility. Some studies had broad definition of economic benefits others a narrow one. The benefit cost studies of malaria control obtained their estimates of economic effects by making numerous medical and other assumptions often based on little or no evidence, in the context of an economic simulation model, either explicit or implicit.

The authors continued that there was also the strong possibility, in view of the powerful demographic effects of malaria control, that the output increase will be accompanied by a population increase, and that an economic crisis will be produced. A program that can be shown to generate a large increase in income can at the same time eventually lower per capita income, because it produces an increase in population that is proportionately larger than increase in income. This means that the justification for malaria control is more likely to be found in its health effects than in its effects on per capita income. As there is reduction in the number of a specific disease with increasing activity of the control program, cost effectiveness ratio measured in terms of costs per case prevented can increase. In these cases when these effectiveness measures are applied in cost effectiveness analysis it becomes

questionable whether the disease should be completely eradicated or whether it is economically justifiable to control the endemicity to a certain level, since the cost per case or per death prevented will be higher when the morbidity and mortality rates are lower (Pornchaiwiseskul, 1993).

To estimate a health program's costs, classification of the components is necessary. A good classification depends on the needs of the particular situation or problem, but the following requisites need to be applied:

(i) It must be relevant to the particular situation;
(ii) The classes or categories must not overlap;
(iii) The classes chosen must cover all possibilities.

The widely applicable and useful classification is by inputs. It groups inputs into categories whose components have similar characteristics. If used properly this type of classification has many merits including:

(a) Involvement of a manageable number of categories which are general enough that they can be applied to any health program;

(b) Distinguishing two important categories of resources that are used in the course of a year and are usually purchased regularly and those that last longer than one year;

(c) Focusing attention on the operating costs of investments in vehicles, equipment, and buildings by making these distinct categories.

There are some secondary classifications in addition to the one just mentioned because resources have other characteristics that are important. The first of these involves the kind of activity or function for which the resources are used. They include: training, supervision, management, monitoring and evaluation and logistic or transport. Costs can also be classified by level, by source and by currency. It is important to avoid mixing the features of resources in the same list because there is the possibility of either double counting or totally missing that input (Creese and Parker, 1994).

There are two general approaches to collecting and using cost data in the health sector (Mills and Gilson, 1988). They are the direct accounting approach and the statistical approach. The first approach focuses on the costs directly associated with a particular activity. Identification and measurement of the costs incurred in providing a particular intervention or in treating a particular patient are required. As it is not always easy to identify the resources used in many activities it often proves difficult in practice. Activity costing and disease costing are typical examples of the direct accounting approach. It is usually the basis for calculating costs in economic evaluations. The other approach focuses on the costs associated with types of activity or types of patients instead of on those associated with individual activities or individual patients. It addresses the issues of why costs differ, and by how much.

In contrast to costs there are many different terms to describe the product of an activity or program. They are consequences, outcomes, outputs, benefits, results, impacts or effects. These terms are similar, but should not all be used interchangeably. A major distinction in economic language is between *benefits* and *effectiveness* or *effects*. Strictly speaking, benefits refers to only those outcomes that are measured in terms of money, while effectiveness or effects are terms used for outcomes that are not expressed in financial terms, such as the numbers of lives saved by a health intervention (Creese and Parker, 1994)

The relevant costs and benefits to consider are not those of the whole activity, but only those relating to the potential expansion (or contraction) in service. Strictly speaking the margin refers to the cost or benefit of producing one more unit of output. However, in general usage it is taken to refer to the additional costs and benefits from a given change in service delivery (Drummond, 1993).

According to Mills and Gilson (1988), all economic evaluation methods involve three basic steps:

(i) identification of costs and consequences
(ii) measurement of costs and consequences
(iii) valuation of costs or costs and consequences.

Table 2.1: Types of Costs and Consequences Relevant to the Economic Evaluation of Health Care Projects/Programs

Costs

1. Organization and operating costs within the health care sector (e.g. Health care professionals' time, supplies, equipment, power and capital costs) → Direct Costs

2. Cost borne by patients and their families:
   out of pocket expenses
   Patient and family inputs into treatment
   time lost from work → Indirect Costs
   Psychological costs

3. Costs borne externally to the health care sector, patients and their families

Consequences

1. Changes in physical, social or emotional functioning (*effects*)

2. Changes in resources use (*benefits*)
   for organizing and operating services within health care sector:
   - for the original condition → Direct benefits
   - for unrelated conditions → Direct benefits

   relating to activities of patients and their families:
   - savings in expenditure or leisure time → Direct benefits
   - savings in lost work time → Indirect benefits

3. Changes in the quality of life of patients and their families: (*utility*)

Source: MF Drummond and GL Stoddart, (1985). "Principles of Economic Evaluation of Health Programs", World Health Statistics Quarterly. 38(4): p 360.

They also stressed that all economic evaluation should consider adjusting costs and consequences for differential timing, and should incorporate incremental and a sensitivity analysis.

Table 2.1 shows the types of costs and consequences relevant to economic evaluation in the health sector. Although it may be impossible to measure and value all these items it is important that they are, at least, identified in order to clarify any possible analytical bias in favor of and the most easily measurable items.

The differences between the consequences identified in the Table help to distinguish the differences between cost effectiveness analysis, focusing on effects, cost benefits analysis, focusing on benefits, and cost utility analysis, focusing on utility.

The measurement of costs and consequences in developing countries is difficult because of lack of routine statistical data. Data on expenditure may be out of date and is unlikely to be fully accurate even when it is available. As there is lack of routine epidemiological data and the weakness of epidemiological evidence linking health care inputs health status outcomes it is even more difficult to measure consequences in terms of health status effects.

In valuation costs there are instances where there is no monetary price or where this price does not accurately reflect the value of alternative productive use of resources (the economic price). The prices may also not reflect the social costs of activities (the social price). The techniques of shadow pricing comes into play in order to value costs appropriately. Valuing the consequences of health projects/programs is even more complex than valuing costs.

Although it is less problematic in benefit/cost analysis to choose an appropriate unit of effect compared to cost effectiveness analysis, it still is not free of problems. Valuing a diverse range of consequences that includes changes in

health status, savings in public and private expenditure on treatment, and economic returns from the exploitation of natural resources (especially land) permitted by programs such as malaria control are some of the problems among which valuation of health status improvements in monetary terms is the greatest. Two main approaches are generally suggested: The human capital approach and the willingness to pay approach (Mills and Gilson, 1988).

Costs and consequences often occur at different times and health projects/programs may also differ with respect to the point at which consequences occur. Unlike curative programs preventive programs may have a delayed impact. Allowance for these differences can be made through the technique of discounting assuming people prefer benefits which occur sooner rather than later.

Whatever technique of economic evaluation is used it is important to undertake an incremental analysis. It is essential that the additional costs be evaluated separately from the total and average costs of the existing programs. Given the range of assumptions inherent in most economic evaluation it is essential to test the sensitivity of the study results to changes in these assumptions. Sensitivity analysis also allows clarification of the level of detail required in a study. Some studies may generate fairly reliable results using rough data; others may require more accurate estimation of the variables.