CHAPTER II

LITERATURE REVIEW

This chapter reviews existing literature relevant to early case detection for visceral leishmaniasis. Beginning with the magnitude and burden of the disease, the chapter proceeds towards current practice and its implication on early case detection. An overview of current VL control activities is given in the next section. The chapter also presents a review of past studies on economic evaluation of case detection.

2.1 Magnitude/Burden of Disease

Visceral leishmaniasis (VL) is also known as 'killer disease' in Sudan because of high case fatality rate associated with it. It is estimated that more than 50,000 individuals lost their life in the southern part of Sudan between 1991 and 1993 due to epidemic of VL (TDR, 1998). In the Indian subcontinent alone, the disease has been endemic for many decades. TDR (1998) reports the estimated mortality due to VL in this subcontinent to be 50,000 to 200,000 per year, especially during the epidemics. Nepal, where the current study was based, is a part of this subcontinent and is thus not free from the disease. Nepal's southern part- known as 'Terai' – borders with Bihar state of India, the state that housed 430,000 VL cases over the past 11 years and is again the center of an epidemic VL (Lockwood, 1998). Due to open border with India, population movement between these two areas is inevitable. VL in Nepal is, thus, believed to be an extension from India across the borders of Bihar state through population movement and also believed to have killed thousands in 1960s (Joshi, 1996).

The World Development Report (1993) estimates the burden of leishmaniasis (which also include other types of leishmaniasis in addition to VL) to be substantial in terms of both deaths and disability consequence of the disease. In India, where most of the disease is of VL type, 500,000 DALYs (disability-adjusted life years, a single measure of burden of disease which considers both deaths and disability) in females and 680,000 DALYs were lost in the year 1990. However, the burden mostly comes from deaths, as the disease is fatal if untreated.

2.2 Current practice and its implication on early case detection

A recent study conducted in eastern Terai of Nepal (Koirala, 1998) has revealed several important aspects related to the disease. Basically designed to determine knowledge, attitude and practice about VL of the inhabitants of two villages in that area, the study found that most villagers failed to recognize the common symptoms of VL. These inhabitants were also found to have poor knowledge about transmission of the disease with most villagers perceiving that mosquitoes, instead of sandflies, were responsible for transmission of the infection. Not knowing symptoms of a fatal disease like VL may mean delayed reporting of the case, which often end with the case being dead. The results of this study have been interpreted by the researchers as having an immediate need to impart health education to the villagers about VL through village health workers who are usually trained to detect VL cases in the community. An important consequence of this intervention, if implemented, would be early VL case detection in the communities where the disease is endemic.

MOH (1997) reports that, in their internal assessment, only those cases, who presented themselves to the hospital, health posts and private clinics, were recorded to estimate the magnitude (incidence and prevalence) of the disease. This has an important implication – the underestimation of true number of VL cases which do exist in the communities. Further implication suggests that existing case detection practice, in which patients present themselves to the health centers on their own, is not covering all VL cases, and this observation supports the need to have outreach case detection strategy to control VL in Nepal.

2.2.1 VL control activities in Nepal

At the central level, Epidemiology and Disease Control Division (EDCD) under the Department of health Services, has a Disease Control Section which looks after vector borne disease control – malaria, visceral leishmaniasis and Japanese encephalitis. A training center called Vector Borne Disease Research and Training Center (VBDRTC) acts as a nucleus institution for training the public health personnel and carrying out field operational research on vector borne diseases. This training center works under the close guidance of EDCD (MOH, 1997).

At district level, on the basis of endemicity of vector borne diseases posts of vector control assistants, malaria inspectors, laboratory technicians and laboratory assistants have been sanctioned under malaria/VL programs and laboratory units of public health section. Thus, all control measures are under the EDCD activities and currently cases are detected when they report to the existing health facilities (hospitals and health posts) by themselves (MOH, 1997).

VL is mainly confined to the southern plains of eastern and central regions bordering VL endemic districts of Bihar State of India, although a few sporadic cases are occasionally recorded in the western part of the country. Approximately 5.5 million population are estimated to be at risk. A total of 12,558 cases with 336 deaths were reported during 1980-1997 and the case fatality rate varied from 0.23 to 13.36. These VL cases are recorded from the hospital records only. The information on the patients treated elsewhere is not available. Therefore, the existing VL control activities do not have the true estimates of actual VL situation in Nepal. The cases are diagnosed on the basis of disease symptoms and aldehyde tests in the hospitals. Studies on vector of VL have been limited in Nepal. However, in 1992, *Ph. Argentipes* was incriminated as vector of VL in the southern plains of central Nepal (MOH, 1997).

Passive case detection mechanism was initiated for detection of VL cases. Only those cases, who presented themselves to the hospitals, health posts or private clinics, were recorded. This makes it difficult to estimate the actual prevalence of the disease. VL cases are diagnosed and treated in the hospitals by first-line drug sodium antimony gluconate and cases not responding well to the above drug are treated with amphotericin B under medical supervision. The limited surveillance mechanism jeopardizes the management of control operations of VL. However, indoor insecticide spraying was started in for VL control with insecticide Lambda-cyhalothrin. Only those villages were sprayed where VL cases were recorded in previous years. During 1993-95, insecticide spraying was conducted with DDT, Malathion and Lambda-cyhalothrin extending over the VL affected areas covering approximately 1 to 1.4 million population in eight districts of central and eastern regions. In 1997, approximately 1.19 million population in 7 districts were protected by indoor residual spraying. There seems an immediate need of active case detection (MOH, 1997).

The diagnostic procedure is confined to clinical examination of the patients reported to the health facility (hospitals), and if found positive on the examination, a treatment is suggested. The diagnostic test being used is bone marrow aspiration in which an aspirate of bone marrow is made and examined to detect for *L. donovani*, the causative agent for the disease. No rapid test such as k39 dipstick and direct agglutination test (DAT) is used as the routine procedure, except for some research purpose.

2.3 Importance of early case detection

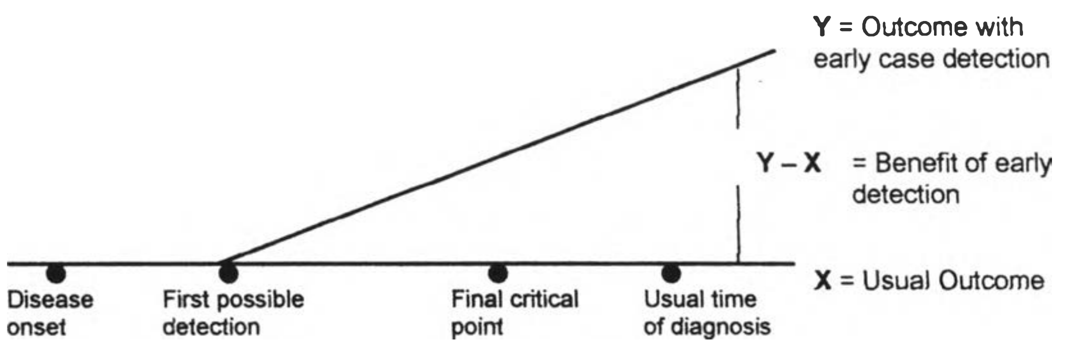
'Early case detection' has drawn a global attention in the past, as it is believed to be producing more benefits than costs as compared with 'passive case detection' in which individuals are allowed to come to health facility to seek health services on their own, in which case patients usually report to the health facility at very late stage of the disease. A WHO (1973) Expert Committee defines early case detection as

> "the detection of disturbances of homeostatic and compensatory mechanism while biochemical, morphological and functional changes are still reversible."

This suggests that earlier a case is detected and treated, the better it is from the point of view of preventing occurrence of further complications or any long term disability (Park, 1997). As she further argues, "early detection produces greater benefit to those conditions where the time lag between the disease onset and its final critical point is sufficiently long to be suitable for population screening". This 'time lag' period may have several critical points, as shown in Fig. 2, which determine both severity of the disease and the success of any treatment in reversing the disease process. In this simple model, **X** is the outcome of the disease in the usual setting and **Y** is the outcome if the disease were detected at earlier stage. The benefit of any case detection program would, therefore, be **Y-X**. If case detection is done at later stages of the disease condition, benefit of the program goes on decreasing (**Y** moves towards **X**). However, it is of crucial importance to take into account both complexities and costs of any detection programs against the benefits they produce (Fowler and Austoker, 1997; Park, 1997).

Because usual time of diagnosis of VL in Nepal is usually associated with delayed reporting, as suggested by high case fatality rate (MOH, 1997), VL may be considered as a condition to have long 'time lag', as discussed above, in this particular setting. A close look at diagnostic lag period in VL has called for early diagnostic tests elsewhere also (Sunder and Singh, 1991). As such, early case detection of VL should essentially be able to produce higher benefits. At this point, it would be appropriate to review some of the literatures that reported benefits of early case detection.

Fig 2.1 A Model for Early Case Detection



(Adapted from Park, 1997)

2.4 Economic evaluation of case detection: a review of past studies

Early case detection of breast cancer using mammography is perhaps most widely reported economic evaluation in health economics literatures (Erichsen, 1990; Elixhauser, 1991; Skrabanek, 1991; Okubo, 1991; Mushlin and Fintor, 1992; Miller, 1993). Most of these studies have argued in favor of breast cancer screening because the benefits in terms of deaths averted due to breast cancer through early case detection have been found substantial. However, van der Hoek (1997), after studying early diagnosis and treatment of malaria, another vector borne disease condition, through community health volunteers in Sri Lanka, found several difficulties in the intervention in terms of both costs and effectiveness. The study concluded saying that 'a better option for Sri Lanka in short term might be to improve existing general health facilities that are accessible" to the population at large.

There are a very few studies that considered economic evaluation of different alternatives to control or treat visceral leishmaniasis. Thakur (1994) studied the effectiveness of daily versus alternate day regimen of amphotericin B in the treatment of VL and Boelart (1999) looked at cost-effectiveness of competing diagnostic therapeutic strategies. The first study calculated a small component of direct costs and did not relate it to the effectiveness. However, the second study (Boelart, 1999) used decision analysis model for the cost-effectiveness analysis. They found that strategy A (treating all clinical suspects) was the most effective approach in the baseline analysis, averting 0.35 deaths per clinical suspect enrolled or 88 percent of all possible deaths attributable to VL in groups of clinical suspects with probability 0.40 of having the disease. Strategy C (two step testing by means of DAT followed by treatment of patients with high titers as well as those with parasitologically confirmed borderline titer) and strategy D (DAT followed by treatment of positives) each prevented 0.34 deaths per clinical suspects (85%). Parasitological examination (strategy B) prevented 0.21 deaths. The estimated cost-effectiveness ratios of strategies A, B, C and D were USD 1110, 448, 465, 464 per death averted, respectively. On the light of these results, they recommended the use of DAT as the basis of test-treatment strategies for VL in areas where the disease is endemic.

However, most studies carried out on VL have been found to concentrate only on the effectiveness of diagnostic test for case detection at health facilities and did not consider costs side. In a prospective study (Jha, 1996), which recruited 80 potential cases of VL in India has demonstrated the effectiveness of direct agglutination test (DAT) as 100 per cent sensitive and specific in detection of VL in Indian setting. The study, however, did not look at the costs side. A number of similar studies have been reported (Oskam, 1999; Agarwal and Jain, 1996; el-Masum, 1995; Sinha and Sehgal, 1995), which have established both efficacy and effectiveness of DAT as screening test for VL. DAT has been found to be 100 percent sensitive and 99.2 per cent specific in Nepalese setting, too (Joshi and Singhasiraanom, 1998). Likewise, Pal (1991) emphasize the use of DAT as suitable diagnostic test to detect VL under rural conditions of India for its good efficacy, simplicity in use and less costs involved, although they did not look at costs of the tests explicitly. This observation is similar to conclusions made by earlier studies carried out in Sudan (Abdel-Hameed and Harith, 1987) and in Kenya (Harith, 1987). Another serological test known as k39 dipstick has newly been introduced as a rapid and non-invasive method of diagnosing VL. It is an immunochromatographic strip testing of blood from a finger prick for leishmanial (k39) antibody, which has been shown to be an accurate and rapid diagnostic method in India and is being tested elsewhere (Murray, 2000). A study carried out in India by Sundar (1998) to assess the diagnostic usefulness of this test found that it was 100 percent sensitive and 98 per cent specific in detecting the VL cases. The study also concluded that the test was well suited for use in field conditions. However, the online literature search during the preparation of this proposal was unable to find studies that have evaluated both costs and consequences of early case detection of VL using standard economic evaluation framework.

All the above mentioned studies have well established the efficacy and effectiveness of serological tests like DAT to detect VL at the earlier stage. However, as Drummond (1997) argues, "few of us would be prepared to pay a specific price for a package whose contents are unknown, and conversely, few of us would accept a package, even if its contents were known and desired, until we know the specific price being asked". The implication, therefore, is that in either situation a decision will only be made when a linkage of costs and consequences is considered. Moreover, in health sector where market is often not readily available, decision to determine an efficient allocation of limited resources should be taken examining both costs and consequences of competing alternatives (Folland, 1997). Thus, although effectiveness of diagnostic tests has well been established as discussed in above paragraphs, the magnitude of costs associated with this effectiveness still remains to be studied.

2.5 Measure of Effectiveness in Reported Studies

One of the primary objective of economic evaluation is to relate the costs of any program to its consequences. Consequences or outcomes of any program can follow a spectrum, giving different outcomes at different levels. It is, therefore, the analyst's judgement to decide what outcome is the most relevant in order to answer the primary research question. While CBA uses the monetary value of the consequences as its outcome, CUA uses something like Quality Adjusted Life Years (QALYs) gained. On the other hand, CEA usually looks at the intermediate outcomes, such as number of cases detected in a screening program, and calls the outcome or consequences as the program's "effectiveness" (Drummond, 1997).

The reported studies on CEA provide a number of effectiveness measures used. The selection of the measure of effectiveness was guided by either the nature of the programs under evaluation or the objectives of the evaluation. As Drummond (1997) argues, as long as there is one unambiguous objective of intervention(s), as in the case of two therapies, cost per year of life gained could be good measure of effectiveness. Screening programs may be compared in terms of costs per case found. Importantly, when the effectiveness of any health intervention program is already established, choice of effectiveness measure usually takes final outcome, such as life years gained. Intermediate output such as cases detected may also be taken but care must be taken to establish a link between them and a final output. The underlying implication is that there should be the investigator's effort or explanation to show that the intermediate outputs themselves have some value. The following table gives an idea about measures of effectiveness chosen in past studies carried out to evaluate different programs with same objectives.

Table 2.1 Examples of effectiveness measures used in cost-effectiveness analysis

Study reference	Clinical field	Effectiveness measure
Logan et al. (1981)	Treatment of hypertension	MmHg blood pressure reduction
Schulmar et al. (1990)	Treatment of hypercholesterolaemia	% serum cholesterol reduction
Hull et al. (1981)	Diagnosis of deep vein thrombosis	Cases of DVT detected
Schulpher and Buxton (1993)	Asthma	Episode-free days
Mark et al. (1995)	Thrombolysis	Years of life gained

(Source: Drummond (1997))

Cuckle (1995) used “affected pregnancy detected” as the measure of effectiveness while comparing different antenatal screening programs for cystic fibrosis. Another study (Lidbrink, 1996), which examined a slightly different aspect of breast cancer screening (that is, implications of false positive results of mammography) defined its main outcome measure as “extra examination and investigations required and the costs of these procedures”. Honrado (1990), while studying different drug regimen for malaria treatment in Thailand, have used a number of effectiveness measures in one study. Starting from ‘cases treated”, they moved on to “cases cured”. Since there were not an equal number of cases treated in two groups, they calculated an “expected number of cases cured if there were an equal number of cases treated in both groups” and considered it as their final effectiveness measure.

Some studies have also defined measures of effectiveness by using simple formula. In their study of three short course anti-tuberculosis treatment programs compared with a standard regimen in Thailand, Kamolratanakul (1993) defined effectiveness as whether an anti-tuberculosis regimen does work. They expressed this “effectiveness” as [(Number of patients admitted *minus* Number of patients dropped out *minus* Sputum non-conversion rate *minus* sputum relapse) *divided* by number of patients admitted]. Later they compared each regimen in terms of cost per effectiveness as defined above.

A recent study (Boelaert, 1999) has used decision tree approach to evaluate four different diagnostic-therapeutic strategies for visceral leishmaniasis. They defined four possible outcomes as follows.

1. **VL treated**: a true case of visceral leishmaniasis is correctly diagnosed and treated accordingly. (Case of true positive)
2. **Erroneously treated**: a person without visceral leishmaniasis is incorrectly diagnosed and wrongly receives treatment for the disease. (Case of false positive)
3. **VL untreated**: a true case of visceral leishmaniasis is missed by the test and consequently is not appropriately treated. (Case of false negative)
4. **Correctly ruled out**: an individual without visceral leishmaniasis in whom the disease is correctly ruled out and who does not receive specific treatment for the disease. (Case of true negative)

Although these outcomes were the terminal of the branches of the decision tree used in the analysis, they may well be considered as effectiveness measure in conventional CEA, depending on how better the diagnostic test performs in terms of its sensitivity and specificity.

2.6 Other approaches in defining effectiveness

However, some economic evaluation literatures (Murray and Lopez, 1996; Drummond, 1997) mention that all above approaches to define effectiveness measure have been criticized by some as saying that these measures only look at one side of the coin, that is, the quantity of life, not the quality of life. They argue that any health intervention program is not capable of producing healthy years of life immediately after one undergoes the intervention. There might be a possibility that the patients may live with disability due to the underlying disease, which deteriorates their quality of life. A new approach called "Quality-adjusted life years (QALYs)" was developed, in which it was attempted to consider both quantity of life a health intervention saves and the quality of the lives thus saved. Most studies use this approach, as it has gained lots of popularity in the past, although critics of QALYs blame it for being a subjective measure. Very recently, the concept of disability adjusted life years or DALYs has hit the health economics arena (Murray and Lopez, 1996). As it is argued, DALY is a single measure of health effects that captures the impact of both premature deaths and disability. However, there are a number of assumptions underlying this single measure. DALYs has weighted different age groups as having different value in the society and also incorporated discounting the future benefits. Some blame DALY life as having problems with ethics following these assumptions (Arnesen and Nord, 1999).

Some methods developed to value the health effects of intervention programs in monetary terms have led some researchers to consider CBA framework to evaluate different programs. Benefits of screening, for example, may consist of three components. 1) the improvement in treatment quality resulting from early detection 2) the value of reassurance for negative test results, and 3) the external benefit for earlier detection has in limiting the spread of disease. The first component of benefit may further have future medical costs averted, greater productivity and other subjective benefits. There are some methods for valuation of these benefits such as human capital approach or willingness-to-pay approach, but are facing criticism over the past (Folland, 1997).