Will Visceral Leishmaniasis be eliminated from Nepal? A review of recent (1994-2006) control efforts

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ABSTRACT

The Visceral Leishmaniasis (VL) control program in Nepal launched in 1993 includes provision of free diagnostic test, treatment along with vector control by indoor residual spraying. However, even after 14 years the disease is far from being controlled. Elimination of VL by 2015 has recently been identified as a regional priority with high level of political commitment. We analyzed the VL control effort in Nepal over the period 1994-2006 and tried to formulate recommendations for the VL elimination initiative. To document performance of the VL control program in Nepal we used literature review and a case study. First, we reviewed articles on VL in Nepal published in medical journals through Pubmed, ISI Web of Science, Google scholar and by hand searching. Secondly, the grey literature, mainly the reports on VL drafted by the Ministry of Health was reviewed for the period 1994-2006. Thirdly, a case study is presented to analyze the performance of the VL elimination program in a "pilot district", where the program was launched in 2006. There are only few studies available on VL in Nepal discussing the epidemiology, diagnosis, treatment, vector bionomics, human behavior and prevention. The review of the grey literature from 1994-2006 revealed that the VL incidence rate remained almost constant since 1993 despite the control efforts.

The case study showed that there is a lack of trained human resources, laboratory facilities and treatment guidelines which is hindering the decentralization of the VL elimination program.

Keywords: Kala azar, Nepal, visceral leishmaniasis.

INTRODUCTION

Visceral Leishmaniasis (VL) or Kala azar is caused by *Leishmania donovani* in the Indian subcontinent and East Africa. The disease has a fatal outcome if left untreated and case fatality ranges from 5 to 15% even with treatment.[1] The estimated global annual incidence of VL is 500,000 clinical cases and it accounts for more than 50,000 deaths per year. About 90% of the cases are concentrated in four countries: India, Nepal, Bangladesh and Sudan. We review the situation in Nepal.

VL is said to have occurred in Nepal prior to 1950 but there was no documentary evidence for this. The first documented evidence of VL in Nepal was made only in 1953 by an Indian scientist, NGS Raghavan, who after a survey for vector borne disease in 1949 claimed that VL was endemic in the entire southern lowland called "terai".[2] The first officially recorded case of VL in Nepal was in 1980 from Dhanusha district.[3] VL in Nepal is caused by *Leishmania donovani donovani.* In a study Devkota *et al* were able to isolate the organism in sandflies collected from endemic areas.[4] *Phlebotomus argentipes* is the main vector responsible for VL transmission, which is supported by the fact that the vector was found to be the predominant species in Dhanusha district of eastern Nepal. A study suggested that VL transmission is primarily via *Phlebotomus argentipes* and secondary via *Phlebotomus papatasi.*[5] The Indian sub-continent is the only region in the world from where no reservoir animal host for VL has yet been reported,[6] so only anthroponotic transmission is believed to be prevalent in this area, including Nepal. Although a few leishmanial infections were found in different animal species in India,[7] none were proved to be zoonotic.[8,9] The intense migration between Nepal and India is presumed to facilitate transmission of disease from Bihar state to Nepal.[10] Young adults less than 20 years of age are the most commonly infected group. Twice as many males are affected as females.[5]

VL remains a major public health problem in Nepal. It is endemic in southern parts of 12 districts of Nepal bordering VL endemic districts of India. These districts are Jhapa, Morang, Sunsari, Saptari, Udayapur, Siraha, Dhanusa, Mahottari, Sarlahi, Rautahat, Bara and Parsa. About 5.6 million people residing in these districts are at risk of the disease.[11] The VL control program by the then Ministry of Health (MoH) was established in 1993.

Table-1: Age and Sex Distribution of VL cases in 2004-2006

Age in years	No. of cases (%)	M:F
<1	3 (0.06)	2:1
1-4	218 (4.75)	1:0.31
5-9	576 (12.57)	1:0.94
10-14	626 (13.67)	1:0.52
≥15	3160 (68.95)	1:0.4
Total	4583 (100)	

There was a revision of the control policy in 1997 and 2002. In 2002 the target was set to reduce VL Incidence Rate (IR)[1] to 1 by the year 2018. Finally, Nepal became signatory with India and Bangladesh in 2005 to regionally eliminate VL by reducing the IR to 10 at district level by 2015. Until recently it has been unclear why in Nepal, despite intensive government efforts through free supply of drugs, indoor residual spraying of insecticides and IEC activities, VL burden remains substantial.[12] The objective of this study was to analyze the VL control effort in Nepal over the period 1994 to 2006 and understand the constraints of the control program.

MATERIALS AND METHODS

We carried out a literature review to retrieve all published articles related to VL control in Nepal. Medline database was searched for articles using key words: "Diagnosis", "Drug Therapy", Prevention and Control" and "Therapy" [in MeSH subheadings] and "Leishmaniasis, Visceral OR Kala azar" [MeSH Major Topic]. About 4560 articles were retrieved. Then with the MeSH Major Topic and MeSH subheadings given above, "Nepal" ["Leishmaniasis, Visceral OR Kala azar"{MeSH Major Topic} with subheadings AND "Nepal"] was combined and re-searched on pubmed, and 48 articles remained. After excluding non-relevant articles and screening manually for the remaining articles, 21 articles were retained for relevance to the subject and used for the literature review. To allow some insight in the reasons for continued transmission, we also reviewed the annual reports and documents produced by the MoH of Nepal on Kala azar from 1994 to 2006. A case study was conducted by a co-author in Saptari district, which was one of the "pilot districts" chosen by the Ministry to implement the Kala azar elimination activities.

RESULTS

LITERATURE REVIEW

The burden of disease in Nepal is difficult to determine, since not all cases are reported to the government health system. Prevalence of infection was found to be 0.6% in Siraha district.[5] The prevalence of disease was between 1.7% and 1.9% in two rural communities (Kasaini and Gidhaniya) of Morang district in eastern Nepal.[13] There are 6 endemic districts in each of eastern and central region out of 5 regions. The IR of VL for the eastern region increased from 4.05 to 38.53 and for the central region it increased from 1.04 to 11.44 from 1985 to 1992. It increased ten times in 7 years period.[4]

A study in 1995 found 8.5% of sero-prevalence in Sarlahi district of eastern Nepal. The ratio of clinical disease to sero-positive was 1:14.2.[5] Another study in two rural communities (Kasaini and Gidhaniya) with high burden of disease, the prevalence of infection by DAT(>1:2000) was between 7.8% and 3.9%.[13] Further, a cross-sectional survey on *Leishmania donovani* infection in 2 clusters of high IRs showed that DAT was positive in 7.5% and Leishmanin Skin Test (LST) was positive in 13.2%, the later one representing past infection.[14] About 5.7% (8 out of 140) of the VL patients were found to be positive for HIV.[15] This study was conducted in 5 endemic districts (Dhanusha,Siraha, Saptari, Jhapa and Morang) which included 39 hospital-based cases, 415 field based cases and 400 HIV- surveillance based cases during June 2003 to May 2004. Serum samples were collected from clinically suspected cases of VL in hospital and field and then tested for VL. In HIV surveillance based study all serum samples positive for HIV were tested. Out of 854 samples tested, 140 were positive for VL.

VL-affected districts were below national average in terms of various socio-economic indicators like literacy rate, per capita income, access to information etc. There was high inequality in household income, cost of treatment, access to education etc.[16] The average annual per capita household income was US$ 82 while the total cost (i.e. direct and indirect) of an episode was US$ 210, which was almost two and half times per episode of an average annual per capita household income. This might have masked the true burden of disease because about 78% of the affected household fell below the absolute poverty line (US$ 78) where financing of the disease related cost had catastrophic consequences.[17]

Table-2: No. of Patients diagnosed in Saptari district

Health Facility	Diagnosis	No. of patients (%)
Zonal Hospital	rK39 or BMA	203(77.48)*
Kanchanpur PHC	rK39	37(14.12)
Kalyanpur PHC	rK39	17(6.48)
Kadarbona PHC	rK39	3(1.14)
Toppa PHC	rK39	2(0.76)
Total		262(100)

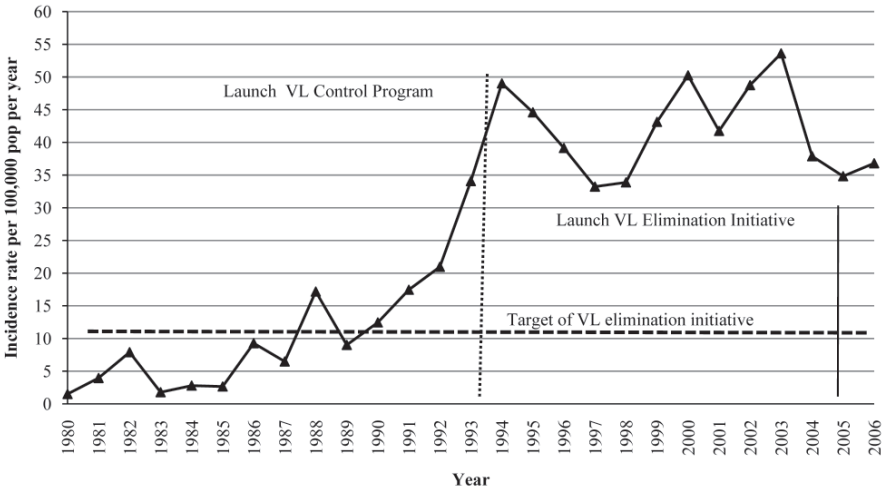


Fig. 1. Reported Incidence rate of VL from 1980-2006 in Nepal (Source: MoH, Nepal)

About 95% of the household had the knowledge of the disease and those were found positive during the follow-up examination. So, having knowledge was not enough to prevent the disease. 64% of the respondents did not know about the risk factors of the disease. 92.6% of them knew about the treatment.[5]

The recommended diagnostic test until 2006 was bone marrow microscopy at district level and rK39 at Health Center level. The VL elimination program recommends the rK39 dipstick since 2005. The DAT or rK39 dipstick test can replace parasitology to treat VL patients at Health Center level in Nepal.[18] Before 2006, the recommended first line treatment was Sodium stibogluconate (SSG) and Amphotericin B as second line treatment. In a randomized open label clinical trial conducted in Eastern Nepal, the VL patients treated with SSG at a dose of 20 mg/kg/day for the period of 30 days showed a cure rate of 93% while another group with equal number of cases treated with the same for shorter duration of 20 days showed a cure rate of 78%.[19] Another prospective study conducted in a tertiary-level hospital located in south-eastern Nepal, in larger group of patients found 90% cure rate. The efficacy of SSG in south eastern Nepal was satisfactory, except for the patients living in Saptari which is closer to the antimony resistant VL endemic areas near India (cure rate 76%). The likely reason for the decreased response to treatment was due to resistant strains of *L. donovani* as demonstrated in India.[20] From 2006, the VL elimination program recommends the use of the oral drug miltefosine.

There was limited evidence that bed net provide protection against VL. A case control study showed reduction of risk of infection by 70% when bed nets were used even though they were untreated and had a relatively large mesh size;[21] whereas in another study, bed net did not show any protective effect though it was used by 95.2%.[14]

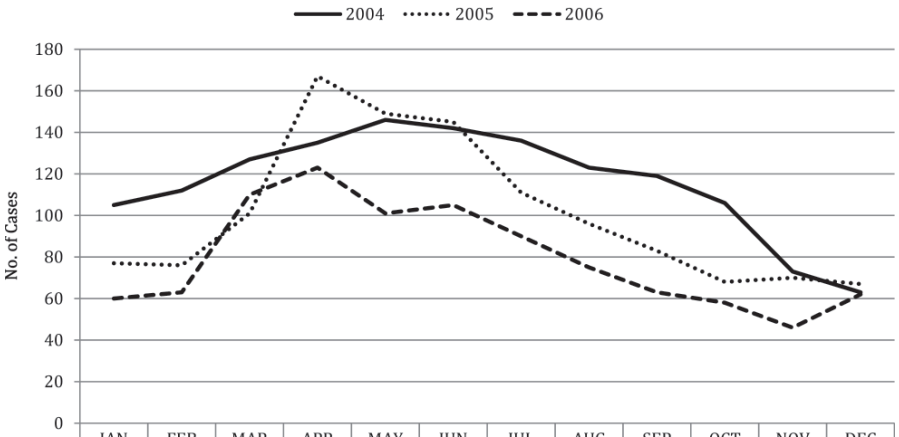
PROGRAM REVIEW

There was no specific department for VL control program. The elimination initiative was supposed to establish a VL elimination unit at Epidemiology and Disease Control Division (EDCD) which was not yet operationalised. At district level, district public health officer is responsible for curative and preventive activities for PHCs, whereas district medical officer is responsible for curative activity only for district hospital. The prevention and curative programs at the district are thus under two separate authorities, and hence coordination between these two authorities is critical for the success of the program. VL in Nepal is mainly confined to the southern plains bordering VL endemic districts of India called the "Terai". However, a few sporadic cases are occasionally recorded from other parts of the country. Approximately 5.6 million people living in the terai were estimated to be at risk of VL. A total of 28,424 cases and 582 deaths had been reported from this disease from 1980-2006 (Fig. 1).

The figures given above do not represent the actual situation because these data reflect only cases reported from the hospitals in the public health sector and patients treated elsewhere (private and traditional healers) are not included. Therefore, VL in Nepal is seriously under reported. Until 2002, the VL cases included in the reporting were diagnosed on the basis of clinical signs and symptoms supported by aldehyde and bone marrow tests in the hospitals. From 2002 onwards many cases were diagnosed with dipstick test.

Table3: Type of drug treatment for VL by health facility in Saptari district

Health Facility	Miltefosine	SAG	Amphotericin B	Total
Zonal Hospital	19	109	75	203
Kanchanpur PHC	0	37	NA	37
Kalyanpur PHC	5	8	NA	13*
Kadarbona PHC	0	3	NA	3
Toppa PHC	0	2	NA	2
Total	24(9%)	159(62%)	75(29%)	258



	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
2004	105	112	127	135	146	142	136	123	119	106	73	63
2005	77	76	101	167	149	145	111	96	83	68	70	67
2006	60	63	110	123	101	105	90	75	63	58	46	62

Fig. 2. Monthly distributions of reported VL cases in East & Central Regions in 2004-2006

Epidemiological Trend before start of VL Control Program

From 1980 to 1989 the IR remained below 10 except in 1988 when the IR was 17.18. The minimum IR was 1.50 in 1980. After 1989 the IR remained quite high and reached up to 20 in 1992 (Fig. 1).

First five year (1994-1999) after the start of VL Control Program

From 1993 onward the IR remained above 33. It was 49.03 in 1994, which was the highest after 1980 and before 2000. This highest IR in 1994 may have contributed to the initiation of VL control program (high case detection rate) in Nepal. It remained below 45 in the remaining years till 1999 (Fig. 1).

Second five year (2000-2005) after the start of Kala azar Control Program

The IR remained in the range of 40 to 50 till 2003. Then it decreased 37.88 in 2004 from 53.61 in 2003 and it further decreased to 34.83 in 2005 (Fig. 1).

In 2004, 2005 and 2006 altogether 1588, 1463 and 1531 cases of VL respectively were recorded in the Annual Report from 12 VL endemic districts. One case was recorded from Okhaldhunga (hilly region) and 2 cases from Makwanpur (hilly region) district in 2005 which also shows sporadic nature of the disease.

Age group-wise distribution of 4583 VL cases during 2004-2006 showed around 70% of affected were in the productive age group(e"15 years) and most of them were male (Table-1). The reason may be the behaviour of sleeping outdoors and not covering parts of the body mostly due to hot temperature. The age and sex distribution were almost similar in all years.

The reporting of VL cases showed the peak in April and May in all years (Fig. 2). The knowledge of seasonality is important for conducting indoor residual spraying activities.

Indoor residual insecticide spraying (IRS) was started in 1992 for Kala-azar control. As per the policy, the spraying is done with synthetic pyrethroids[2] and two times a year in priority-selected affected areas. IRS is carried out only in those villages where VL cases were recorded in previous years or in an outbreak situation.

CASE STUDY

The main thrust of elimination program was to initially implement the diagnosis (rK39 dipstick) and treatment (Oral drug Miltefosine) at the PHC level and zonal hospital. Saptari district was selected as a pilot district to test, refine and evaluate the appropriateness of all procedures for the implementation of VL elimination program. The health facilities visited and observed for this case study area were: Sagarmatha Zonal Hospital; Kanchanpur PHC; Kalyanpur PHC; Kadarbona PHC; and Toppa PHC.

Around 77 percent of the VL cases were diagnosed using rK39 at zonal hospital, among which 37 times the diagnosis were performed by parasitology. Bone Marrow Aspiration test for LD bodies was only available at or above district level health center. Kanchanpur and Kalyanpur PHC had 14 and 6% of all the patient diagnosed respectively. Very few numbers of patients were diagnosed in Kadarbona and Toppa PHC, which may be due to shortage of supply or stock out of diagnostics or drugs at those PHCs. During the observation, it was found that rK39 dipstick was not available round the year in PHCs and zonal hospital. The reason for non-availability of diagnostic test was that it was stocked out for the period of 3-4 months in the store of District Public Health Office (DPHO) and even in the central store of EDCD, Kathmandu (Table-2).

Out of 262 patients, 258 received treatment at different health centers and all of them completed the treatment. Only four patients were referred elsewhere and did not have any record on the status of the patients. Even after the implementation of elimination program to provide miltefosine, 62% of the patients were treated with conventional SSG, whereas only 9 percent of the patients

were treated with new drug miltefosine. Even the zonal hospital had treated only about 15 percent of the patients (19 Miltefosine+109 Sodium Antimony Gluconate=128) with miltefosine. On the other hand Kalyanpur PHC had treated 62 percent (5 out of 8) patients with Miltefosine and they were using the drug even in the absence of guidelines and protocols from MoH. Miltefosine was given in only one PHC out of four in the district. Among the 75 patients treated with second line drug for VL (Amphotericin B), only 37 had undergone parasitological detection of LD bodies. Treatment with Amphotericin B in rest of the 38 patients might have been started on clinical basis (Table-3).

We tried to find out why patients were treated with SAG more than Miltefosine at all level of the health facilities in Saptari district. Firstly, the guidelines developed for the elimination program by the MoH to implement the diagnosis and treatment at district level was not available in the health centers. Second, the base line laboratory investigation (serum urea, creatinine, and transaminase) required to be performed before the start of Miltefosine and during the follow-up were not available at the PHC level. But the zonal hospital, which has a good laboratory facility, also treated only 15 percent of the patient with Miltefosine. Third, the auxiliary health workers at PHCs were not familiar with Miltefosine because they were not trained to diagnose and treat VL. Even at the level of zonal hospital, many physicians preferred to prescribe SAG instead of Miltefosine because they were used to the conventional treatment and some physicians were not familiar with the new treatment strategy.

The basic laboratory test, serum urea, creatinine, serum bilirubin and pregnancy test, required to start the treatment with miltefosine were not available in any of the PHCs. We observed that there was irregular supply of chemicals and reagents for laboratory activities even for other tests like hemoglobin, total count and differential count, urine routine examination, ESR etc and shortage was there for a long period of time. It was also found that there was a lack of instruments required for daily laboratory activities. Only the zonal hospital was equipped with these tests along with parasitology facility to conduct bone marrow aspiration test. Lack of guidelines, training of health workers, delays in production of IEC materials and lack of strong monitoring and feedback system were significant factors hindering decentralization and hence the VL elimination program.

DISCUSSION

In Nepal, the number of VL cases increased significantly from 1993 to 2000 and remained more or less constant thereafter. It is clear that the transmission of the infection is not controlled despite ongoing control program for more than 10 years through free supply of drugs, indoor residual spraying and IEC activities. The elimination initiative was started in 2005 in collaboration with two neighboring countries and WHO to reduce the IR to 10 by 2015. This target seems quite ambitious. It started without adequate funding, training of human resources, adequate drugs and diagnostics, and guidelines for treatment and diagnosis. In the affected areas the PHCs are ill-equipped, skilled personnel are not available and laboratory diagnosis is not feasible which may limit the target of elimination program.[22]

Case management

Passive case detection is one of the strategies of the control program. Even with the available diagnostic facility all cases reaching to the public health system are not diagnosed due to the lack of either human resources or laboratory facility. Our case study also showed that there is lack of human resources and laboratory facility in PHCs. Complete and adequate surveillance data for VL in the subcontinent has been lacking mainly due to underreporting and under-diagnosis. Desjeux found a 1:5 ratio of declared to undeclared VL cases in community surveys in India,[23] whereas Singh *et al* found the ratio of 1:8.[24] The current free provision of VL drug in Nepal may promote the adequate use of drug and relieve economic burden on patients to prematurely interrupt the treatment but does not solve the constraints of transport and cost of hospitalization. The majority of the VL patients admitted to the hospital receive only few days of SSG until clinical improvement and their treatment is completed as outpatient in peripheral health facilities. Though patients with PKDL have been recognized as an important reservoir for VL, it remains neglected part of the control program. PKDL is a well-recognized entity in Nepal[25] but there is no provision for the diagnosis or treatment within the control program.

Management and coordination

All the curative and preventive activities of the elimination program are supervised by DPHO at district level, whereas the same activities at district hospital or zonal hospital are supervised directly by the regional health directorate. So, there is a lack of coordination between the district or zonal hospital and DPHO which may hinder the implementation of elimination program. The pilot district was selected where there is zonal hospital, which is well equipped with human resources and laboratory facilities. It will be difficult to reproduce the elimination program in the rest of the endemic districts where there is district hospital which lacks adequate laboratory facilities and has only two medical officers.

Logistic supply and management

The lack of regular supply of drugs and diagnostics has been a major obstacle for access to drugs and diagnostics within the region. In Bangladesh, SSG shortages both in the government supply system and in the private sector were common during the last few years.[26] The VL control program in Nepal is a priority – 1 category program of the MoH, and they have been able to supply VL drugs regularly to the endemic districts. But it has not been effective yet in making them available at primary health centers. Similarly, the government has not been able to regularly supply the diagnostic test kits even at the district level.

Surveillance system

There are very few studies conducted to understand the situation of the VL in Nepal. The only means of surveillance is the record of the reported cases in the form of Annual Report. Although the number of reported cases is reasonably well known, there are doubtless numerous unreported cases, whose number can only be estimated. Recent studies in India have estimated that only some 25% of cases enter the government medical system, so are reported in the official statistics.[27] Many other visit traditional healers and private physicians and some other die at home for lack of funds to obtain treatment.[28] There is also problem of over-reporting when patients visit more than one reporting center.

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