



Published in final edited form as:

Trop Med Int Health. 2011 September ; 16(9): 1159–1166. doi:10.1111/j.1365-3156.2011.02803.x.

Monitoring drug effectiveness in kala-azar in Bihar, India: cost and feasibility of periodic random surveys versus a health service - based reporting system

Malaviya Paritosh^{1,*}, RP Singh^{1,*}, SP Singh¹, Hasker Epcoc², Ostin Bart², Shankar Ravi¹, Boelaert Marleen², and Sundar Shyam^{1,†}

¹Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

²Epidemiology and Disease Control Unit, Department of Public Health, Institute of Tropical Medicine, Antwerp, Belgium

Abstract

Background and Objective—Visceral leishmaniasis (VL) is a chronic infectious disease that is of major public health importance in the state of Bihar in India. A regional VL Elimination Initiative was launched in 2005 based on the use of the oral drug miltefosine. However, concerns were raised about development of drug resistance. Drug effectiveness cannot be assessed accurately based on the current recording and reporting system of health facilities. In 2009 a random survey was conducted in Muzaffarpur district to document the clinical outcomes of VL patients treated by the public health care system in 2008. We analyze the operational feasibility and cost of such periodic random survey as compared to health facility based routine monitoring.

Methods—A random sample of 150 patients was drawn from registers kept at Primary Health Care centers (PHCs). Patient records were examined and the patients were located at their residence. Both patients and physicians were interviewed with the help of two specifically designed questionnaires by a team of one supervisor, one physician and one field worker. Costs incurred during this survey were properly documented and vehicle log books were maintained for present analysis.

Results—Only 115 (76.7%) of the patients could be located in the first effort and finally 11 patients were not traceable on account of erroneous recording of patients' characteristics and addresses at the CHCs. Per patient follow-up cost was US\$ 15.51 and on average 2.27 patients could be visited per team-day. Human resource involvement constituted 75% of the total cost whereas involvement of physician costs 51% of the total cost.

Interpretation and conclusion—A random survey to document clinical outcomes is costly and labor intensive, but gives probably the most accurate information on drug effectiveness. A health service based retrospective cohort reporting system modeled on the monitoring system developed by tuberculosis programs could be a better alternative. Involvement of community health workers in such monitoring would offer the additional advantage of treatment supervision and support.

[†] Corresponding author, Prof. Dr. Shyam Sundar, Dept. of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. Tel: +91-542-2369632, Fax: +91-542-2367568, drshyamsundar@hotmail.com.

*Both authors contributed equally

Conflict of interest: Authors declare that they have no conflict of interests.

Authors Contribution: PM: Analysis of data and drafting the manuscript, RP: Conducting survey and Data Collection, SP, RS: monitoring the survey, EH, BO, MB: Study design, SS: Principal Investigator All: review the manuscript

Keywords

Visceral Leishmaniasis; Drug monitoring; Drug effectiveness; Public Health System; Recording and reporting; Supervised treatment; patient follow-up; ASHA Network

INTRODUCTION

Visceral leishmaniasis (VL, kala-azar) is a chronic infectious disease, caused by a parasite and transmitted through an arthropod vector. In the Indian subcontinent *L. donovani* is the causative parasite and *P. argentipes*, a phlebotomine sandfly, is the vector. More than 90% of world's VL burden occurs in the Indian subcontinent, Sudan and Brazil. In India, more than 90 percent of the VL cases are reported from a single state, Bihar. A centrally organized and sponsored VL Elimination Initiative has been launched in endemic areas since 2005. The Government of India provides antileishmanial drugs, insecticides and technical support and the state government implements the program through the primary health care system and district hospital in integration with other vector born diseases. Financial assistance is being provided to endemic states since December 2003 to facilitate effective strategy implementation by States under National Vector Born Disease Control Programme (NVBDCP). The goal of the VL Elimination Initiative is to reduce the annual incidence rate of kala-azar and PKDL to less than one per 10,000 population at sub-district level by the end of 2015 (WHO 2005). Several authors have pointed to the need to strengthen the surveillance system in the VL Elimination Initiative (Chappuis et al 2007).

Besides reporting incidents, there are some important reasons for monitoring – the treatment compliance and its outcome. The causative parasite, *L. donovani*, has a human reservoir; any patient not fully cured remains infectious to the vector (WHO 1990). Moreover, as Styblo realized when expanding tuberculosis control programs in East Africa in the late 1970s, a disease control program that fails to cure a high enough proportion of patients enrolled may do more harm than good by promoting drug resistance. (Styblo, 1976; Styblo & Bumgarner, 1991) Drug resistance to antimonials is already widespread in the VL endemic region and miltefosine resistance might easily develop if the drug is used on a large scale as monotherapy in an unregulated manner (Sundar et al. 2001; van Griensven et al, 2010).

Failure of VL treatment can present as initial failure or as relapse after treatment is completed, or as post-kala-azar dermal leishmaniasis (PKDL), a dermatological complication of leishmanial infection. These – apart from the clinical problems they pose – increase the reservoir of leishmanial infection and thereby its transmission. (Addy et al, 1992)

The kala-azar elimination initiative has recognized that case detection rates, compliance rates and cure rates are amongst the key indicators to monitor the effectiveness of the initiative undertaken. Nonetheless, the recording and reporting system currently in use lacks adequate provisions for monitoring the VL patients during treatment and their final clinical outcome. Monitoring clinical outcomes is complex in kala-azar, as it conventionally requires an assessment by a clinician 6 months after treatment completion; while the drug treatment itself usually lasts for less than a month.

We conducted a cross-sectional survey of randomly selected 150 kala-azar patients treated during 2008 in all the Community Health Centers of Muzaffarpur district, Bihar State, to document treatment effectiveness (Hasker et al 2010). We noticed that about 40% of patients were still treated with pentavalent antimonials, notwithstanding the program recommendation dated 2005 to use miltefosine as first line treatment. A large proportion of

VL patients in Muzaffarpur in 2008, 28% (95% CI 20–35%), needed retreatment. Especially patients treated with antimonials (Sodium stibogluconate or SSG) had poor treatment outcome with 40% (95% CI 28–52%) requiring a second course of treatment. Among the 40 patients treated on miltefosine, 6 (15%, 95% CI 3–27%) needed a second treatment course. There were some discrepancies between the results obtained through review of the health centre records and those obtained through interviews with patients.

The recording and reporting system currently in use in the health facilities was unable to generate this essential information on treatment outcomes. To better monitor treatment effectiveness, periodic random surveys for all the patients such as the one described here could be an option. While the periodic random survey method is probably more accurate in assessing individual treatment outcomes, it will require a substantial effort from the control program. Another option could be to improve the routine recording and reporting system with involvement of grass root level health workers. Such surveillance method depends on the existing networks of the health system; it might be more appropriate and sustainable in the given context than periodic random surveys. In this study we have analyzed the operational and economical feasibility of a periodic random survey and have documented its strengths and its constraints. We have also identified bottlenecks in the current recording and reporting system at Primary Health Care level. We have made an attempt to suggest an alternate model with the involvement of grass root level functionaries.

METHOD

Description of the study area

Muzaffarpur district in Bihar state is one of the highly endemic districts for kala-azar since 1972. Districts in this state typically have a population of 2–3 million inhabitants, and one district hospital that provides all specialized services. Primary health care in rural areas of India is organized as a 3-tier system. At the top of the pyramid is the *Community Health Centre*, in theory catering for a population of 120,000, which corresponds to the administrative division, called 'Block'. The *Community Health Centre* is staffed with physicians and has a limited number of beds. Each *Community Health Centre* supports four *Primary Health Centres* which is the lowest level of the system at which physicians are available. A PHC in turn should support 6 *Health Sub-centres*, run by auxiliary nurses/ midwives (ANMs). At village level there are volunteer outreach workers known as accredited social health activists (ASHAs). They are supervised by the ANMs and are the link between the community and the health system. The system is well organized with all ASHAs attending meetings at the *Community Health Centre* once every four weeks and ANMs meeting twice a month. (WHO1) Though according to the norms there should be one *Community Health Centre* per 120,000 inhabitants and one *Primary Health Centre* per 30,000, the actual population covered is much higher. The rural areas of Muzaffarpur in which we conducted our research have a population of almost 4 million but altogether there are only 14 *Community Health Centres* and 46 *additional Primary Health Centres*. The establishment of *additional Primary Health Centres* is in progress (See <http://statehealthsocietybihar.org>).

VL diagnosis and treatment are currently available only at *Community Health Centres*. VL diagnosis in these centers is based on presenting signs and symptoms, and the results of an rK39 rapid immunochromatographic test. If required, e.g. in case of presumed recurrence, parasitological examination is performed at higher health facilities like district hospital or medical college. Monotherapy with 28 days of oral miltefosine is the recommended first-line regimen in the elimination initiative. Six months after treatment completion, patients are invited for a follow-up visit to determine final treatment outcome. If the patient has

completed treatment and is in good clinical condition at the end of the follow-up period, he is considered cured.

Patients and Data Collection

The lists of all VL cases, treated in 2008, were collected from all the 14 *Community Health Centers (CHC)* totaling 1879 cases. A random sample of 150 cases was selected as described elsewhere (10). The sample size required to estimate a proportion of 10% (expected proportion of patients not completing treatment/ follow-up) with a precision of $\pm 5\%$ and α -error of 0.05 and a power of 90% is 138, 12 patients were added taking into account the possibility of patients not being available or not agreeing to participate. Locations of the patients are shown in Figure 1, and were representative of all patients in the district. We checked the records of the patients kept at their respective CHC and noted the information related to their date of reporting, date of diagnosis and initiation of treatment, type of drug given and final outcome of the treatment. Two interview questionnaires were used; one to interview the physicians in the CHCs and a second for patients. We prepared a visit plan to minimize the travel costs and time. We allowed a maximum of three visits to locate and interview a patient; if contact was not possible within those 3 visits, the patient was considered as untraceable. For locating patients, help from health workers like ASHA, ANMs, and local community leaders were sought. In case of a minor, patient's guardian was interviewed. If a patient was not available for interview or had died, adult family members or nearest relatives were interviewed. The flow chart of the entire procedure for interviewing patients is given in figure 2. Medical records of patients were verified by the physician to confirm the diagnosis. The research team comprised of an experienced physician and a well trained field worker with sociology background. The research team used its own vehicle for transportation. On an average, the team worked for 8 hours per day including transportation and refreshment time in between.

Cost Estimation

For calculation purposes we recorded the time necessary in 'Team-days' and maintained a vehicle log book, account book and other financial documents as well. We calculated various costs and total distance travelled from Kala-azar Medical Research Centre (KAMRC) in Muzaffarpur city, the nodal centre for operating the study. Calculation of time (team-days) and costs of transportation for obtaining information from CHCs and patients were done separately. In our calculation, we did not include the costs of investments and amortization, in particular the costs of a car and GPS devices for recording the Lat/Long points of the patients' homes.

Ethical Aspects

Ethical clearance was obtained from the Ethical committee of Banaras Hindu University in Varanasi, India, as well as from the ethics committee of the University of Antwerp, Belgium. Any person identified with (suspected) VL in the process of the study, whether due to treatment failure/relapse or a first episode, was eligible for free diagnosis and treatment at the Kala-azar Medical Research Centre (KAMRC).

RESULTS

Out of 150 randomly selected patients, households of only 139 could be located and out of those 139, one patient had died. We could locate 115 cases on the first visit, 24 cases required a second visit. Eleven patients could not be traced even after three attempts, and were considered as 'untraceable'. Out of 115 cases that could be located in the first visit, we could interview only 101 cases on the same day; 14 cases required a second visit to be interviewed. The remaining 24 cases that were located in the second visit could all be

interviewed during that same visit (Table 1). After each unsuccessful attempt to locate a patient, before making a next attempt we explored the reasons in consultation with ANMs and ASHAs. The most common reasons were (i) improper registration of name and incomplete addresses of the patients recorded in the CHC register; (ii) a false identification given by patients as they might be originating from a CHC area other than the one they sought treatment in; (iii) the patient was a visiting relative of a household in the CHC area and returned to his/her original permanent residence; or (iv) patient originated from the same CHC area but migrated elsewhere.

Manpower required and estimation of cost

To collect the patients' information from all the 14 CHCs, the team had to spend 10 team-days; an average of 0.7 team-days per CHC and had to travel a total of 700 kilometers. To follow up 150 patients it took a total of 210 visits in 66 team-days with an average of 3.18 visits per team-day. The 'effective coverage' of patients, (meaning a patient could be located and interviewed or finally could not be located), was 2.27 patients per team-day. The average distance travelled for effective coverage per patient was 35.2 kilometers (Table 2). The total cost incurred for obtaining information from all 14 CHCs was US\$ 275.05 (Table 3A). Per patient average follow up cost was US\$ 15.51 with a total of US\$ 2328.09 (Table 2 and Table 3B). Thirty-five patients could not be located during the first visit, which resulted in additional costs and human resources requirements. Being able to locate all patients upon the first visit would have led to a 25% reduction in human resources requirement and would have reduced the total costs from US\$ 2,603.05 to US\$ 1,932.55.

Costs on human resources made up a major portion of the total costs at each stage of the study. It constituted 70% and 75% respectively for collecting information from 14 CHCs and for follow-up of patients (Table 3A and 3B).

DISCUSSION

We studied the cost and feasibility of a periodic random survey to establish final treatment outcomes of a sample of 150 kala-azar patients treated in 2008 in the Muzaffarpur district by CHCs. We were able to interview 139 out of 150 patients sampled and established the final treatment outcomes at the cost of approximately 2,600 US Dollar, including 10, 66, and 76 working days of a physician, a social scientist and a driver respectively. To our surprise none of the 139 patients were followed up at six months at CHCs. Patient's characteristics (name, age, sex, and head of households) and addresses recorded at CHC facilities were often incomplete and at times erroneous, and failures of majority of the patients to report at six months were the major bottlenecks, identified in the study. Lack of motivation and training of health care workers are major handicaps in incomplete capture of the data.

A sensitivity analysis showed that the cost could have been reduced by 35% and human resources requirements by 25% if proper addresses would have been available. Involving a medical doctor in patient interviews constituted 51% of the total cost incurred. This cost could have been reduced by replacing medical doctors by paramedical workers, who in turn could refer the suspected drug failure/relapse to CHC. However, the advantages and disadvantages of such a strategy need to be worked out. If applied to the entire endemic region on a regular basis, the affected population size will decrease gradually so will be the cost of such a monitoring system. Even then it is a very costly and labor intensive approach. If such random surveys are adopted as a national strategy for monitoring treatment effectiveness, they would need to be carried out at periodic intervals, quarterly or at least bi-annually.

Yet data on treatment effectiveness are essential elements in monitoring the effectiveness of a disease control program. Several alternative approaches are possible, such as the establishment of sentinel sites or a more global monitoring system such as the system used by tuberculosis control programs. In the tuberculosis control program recording and reporting system requires treating physicians to report on a quarterly basis not only the numbers of patients treated but also, with a delay of 12–15 months, the final treatment outcome for each of these patients (WHO 2009). The similar approach could be adopted in VL for knowing final outcomes of all the VL patients on a quarterly basis with a delay of 6–9 months.

An option that should be further explored in obtaining the final treatment outcome is to involve the available network of village health workers. In Indian context ASHAs, under National Rural Health Mission (NRHM), could be considered for this. They are available in each and every village and have regular meetings at the CHCs with doctors. ASHAs could also be considered for supervised treatment with miltefosine, similar to DOTs strategy in tuberculosis control program. Therefore, they may be used both for compliance during the treatment and for reporting final treatment outcome after six months post treatment. Use of mobile phones could be a cost effective way of reporting. Nowadays mobile phones are present everywhere in India; from another study conducted by us in the same district we know that even among the poor rural population 35% of households own at least one mobile phone (unpublished data). Besides, patients, health care workers at CHCs and ASHAs should be motivated with training as well as performance based incentives for six months follow up or in-between, if there are any signs and symptoms of relapse. This model is depicted in figure 3.

When deciding to involve ASHAs, it is necessary to consider her additional work load. With an annual incidence of VL of below 2.2/1000 (Mondal et. Al. 2009), the amount of extra work involved will probably be fairly limited though. A system based on the suggested formats is currently being piloted in three sentinel CHCs in Muzaffarpur, Bihar in the framework of the Kaladrug-R research project. (Kaladrug 2010)

Limitations

Our assessment was limited to the public sector; many patients are treated in the private sector and were therefore not included in this study. Though, with increasing diagnostic and treatment facilities for VL management and provision for cash incentives at CHCs, more patients are being drawn to the public sector. However, even if the public sector does not treat all patients, it still needs to account for final treatment results of those it did treat.

CONCLUSION

The recording and reporting system on clinical outcomes of VL at CHCs and district level needs to be improved and must be a routine practice in disease control programs. Conducting periodical surveys is an approach that provides reliable results but is very costly and labor intensive. There is an urgent need to identify and assess alternative approaches. The proposed approach to comprehensively assess the final outcome needs to be evaluated for operational feasibility and cost-effectiveness.

Acknowledgments

This work was supported by NIAID, NIH TMRC Grant No. 1P50AI074321.

REFERENCES

- Addy M, Nandy A. Ten years of kala-azar in west Bengal, Part I. Did post-kala-azar dermal leishmaniasis initiate the outbreak in 24-Parganas? *Bull World Health Organ.* 1992; 70(3):341–346. [PubMed: 1638662]
- Chappuis F, Sundar S, Hailu A, Ghalib H, Rijal S, Peeling RW, Alvar J, Boelaert M. Visceral leishmaniasis: what are the needs for diagnosis, treatment and control? *Nat Rev Microbiol.* 2007 Nov; 5(11):873–882. [PubMed: 17938629]
- Mondal, Dinesh; Singh, Shri Prakash; Kumar, Narendra; Joshi, Anand; Sundar, Shyam; Das, Pradeep; Siddhivinayak, Hirve; Kroeger, Axel; Boelaert, Marleen. Visceral Leishmaniasis Elimination Programme in India, Bangladesh, and Nepal: Reshaping the Case Finding/Case Management Strategy. *PLoS Negl Trop Dis.* 2009 January.3(1):e355. [PubMed: 19159009]
- Hasker E, Singh SP, Malaviya P, Singh RP, Shankar R, Boelaert M, Sundar S. Management of visceral leishmaniasis in rural primary health care services in Bihar, India. *VL Supplement, TMIH.*
- Kaladrug, R. homepage on the internet. 2010. LeishRisk; 2010. Available from: <http://www.leishrisk.net/leishrisk/Default.aspx?Menu=MenuMain&MIID=35&WPID=41&L=E>.
- National Vector Borne Disease Control Program (NVBDCP). Available from: <http://nvbdcp.gov.in/kala-new.html>
- Styblo K, Bumgarner R. Tuberculosis can be controlled with existing technologies: evidence. *Tubercu* *Surveill Res Unit Progress Report.* 1991; 2:60–72.
- Styblo K. Surveillance of tuberculosis. *Int J Epidemiol.* 1976; 5(1):63–68. [PubMed: 1262116]
- Sundar S, Pai K, Kumar R, et al. Resistance to treatment in Kala-azar: speciation of isolates from northeast India. *Am J Trop Med Hyg.* 2001; 65(3):193–196. [PubMed: 11561703]
- van Griensven J, Balasegaram M, Meheus F, et al. Combination therapy for visceral leishmaniasis. *Lancet Infect Dis.* 2010; 10(3):184–194. [PubMed: 20185097]
- Veen J, Raviglione M, Rieder HL, Migliori GB, Graf P, Grzemska M, Zalesky M. Standardized tuberculosis treatment outcome monitoring in Europe. *Eur Respir J.* 1998; 12:505–510. [PubMed: 9727811]
- World Health Organization. Country office for India: primary healthcare resources in India. [accessed March 2010]. Available from: http://www.whoindia.org/LinkFiles/Health_Systems_Development_Primary_Health_Care_Primary_health_care_resources_.pdf
- World Health Organization. Control of the leishmaniases. Report of a WHO Expert Committee. *World Health Organ Tech.Rep.Ser.* 1990; 793:1–158. [PubMed: 2124015]
- World Health Organization. Regional office for South-East Asia (2005). Regional Strategic Framework for Elimination of Kala-azar from the South-East Asia Region (2005–2015). [accessed March 2010]. Available from: http://www.searo.who.int/LinkFiles/Kala_azar_VBC-85_Rev_1.pdf
- World Health Organization. Treatment of tuberculosis: guidelines for national programmes. WHO/HTM/TB/2009.420. Geneva, Switzerland: WHO; 2009.

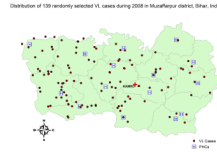


Figure 1.



Figure 2.
Flow chart showing the follow up procedure of Kala-azar patients at their homes



Figure 3. Model showing supervised treatment with miltefosine, recording/reporting and referral system involving ASHA as gross root workers

Table 1

CHC wise detail of total registered VL cases, no. randomly selected and no. of visits required for effective Follow-up of 150 patients.

CHC Name	Area (Sq Km)	Total Population (Dec. 2008)	Total VL Cases in 2008	Number randomly Selected	No. of Visits required for effective follow-up			Unsuccessful after three attempts
					One	Two	Three	
Aurai	219	277600	42	2	0	2		
Bochahan	221	220139	163	11	7	3	1	
Giaghat	233	242624	97	8	5	3		
Kanti	311	403030	143	22	16	5	1	
Katra	193	228312	42	3	3			
Kurhami	301	411197	115	14	11	2	1	
Minapur	250	309405	91	5	5			
Motipur	333	364909	190	19	12	5	2	
Muraul	180	216999	8	1	1			
Musahari	170	298592	90	4	2	2		
Paroo	347	326924	420	28	20	4	4	
Sahebganj	212	218573	203	11	7	4		
Sakara	205	288582	65	6	4		2	
Saraiya	273	297029	167	16	8	8		
Total	3448	4103915	1836	150	101	38	11	

Table 2

Effort and cost for collecting information from CHC and patients.

Efforts and Cost of information from 14 CHCs		Efforts and cost of information from 150 patients	
Total no of team-days required	10	Total team-days required	66
Total no. of CHC visits required	14	Total no. of patient visits (attempts) required	210
Average team days required per CHC	0.7	Average visit paid for 'effective coverage' of one case	1.4
Average no. of CHC covered per team- day	1.4	Average no. of patient visits per team day	3.2
Total distance travelled	700 Km	Total distance travelled	5280 Km
Average distance travelled per CHC	50 Km	Average distance for effective coverage of a case	35.2
Total Cost	US \$275.05	Total cost	US \$2328.09
Average cost per CHC	US \$19.65	Average cost per patient	US \$15.52

Table 3(A)

Break-up cost for collecting information from CHCs

Heads	Sub-heads	Amount (US\$/Team-Day)	Team-Days Consumed	Total Amount (US\$)	
Human Resource	Supervisor	10.83	10 Team-days		
	Field Worker	5.76			
	Driver	2.88			
	Sub-Total	19.47		194.70	
Transportation	Fuel/Lubricant	5.31			53.10
	Maintenance				12.63
Snacks		0.65			6.50
Stationary/Printing					6.50
Communication				1.62	
			Grand Total	275.05	

Table 3(B)

Break-up cost for collecting information from Patients

Heads	Sub-heads	Amount (US\$./Team-Day)	Team-Days Consumed	Total Amount (US\$)	
Human Resource	Physician	18.04	66 Team-days		
	Field Worker	5.76			
	Driver	2.88			
	Sub-Total	26.68		1760.88	
Transportation	Fuel/Lubricant	6.06			399.96
	Maintenance				95.67
Snacks		0.65			42.88
Stationary/Printing					21.66
Communication				7.04	
			Grand Total	2328.09	