Middle-East Journal of Scientific Research 17 (9): 1220-1227, 2013
ISSN 1990-9233

DOI: 10.5829/idosi.mejsr.2013.17.09.12277

Kala-Azar Elimination in Bihar: Adoption of Newer Evidence-based Strategies Required for Elimination

[1]Prashant Soni, [2]Ragini Mishra, [3]Ganga Kumar, [4]Prabhat Pandey and [5]Prashant Kumar

[1]District Improvement Coordinator (RMNCH+A), Delhi, USAID ASSIST Project, Delhi, India
[2]State Epidemiologist, State Health Society, Govt. of Bihar, India
[3]MD Bihar State Building Construction Corporation-Cum- Special Secretary, Building Construction Departmen, Govt. of Bihar
[4]State Consultant Social Development, NVBDCP, Govt. of Bihar, India
[5]District Epidemiologist, District Health Society, Patna, Govt. of Bihar, India

Abstract: Kala-azar i.e, Visceral Leishmaniasis (VL) is a menace to Bihar, affecting large number of population. As per WHO, one-third cases of Kala-azar are reported from Bihar itself. Diagnosis and case detection is done by rk39. Miltefosine has been rolled out in 16 highly endemic districts of Bihar; other districts have Amphotericin B and Sodium Stibo-Gluconate as the treatment drugs. Vector Control is solely done by Indoor Residual Spray using DDT. Inspite of so many years of control operations, we have not been able to contain this disease in the State. Of increasing significance is the spreading of Kala-azar foci to newer districts in Bihar which were previously free from the disease. Lack of community participation has been a big lacuna in successful implementation of kala-azar Control Programme. There is an urgent need to revise the strategies used in Kala-azar Control Program with special focus on community participation in targeting areas like case detection, case reporting and referral to appropriate health facilities as well as in Vector control strategies like Indoor Residual Spray.

Key words: Kala-azar · IRS · Sandfly · Kala Azar elimination · Evidence-based strategies

INTRODUCTION

Kala-azar (Visceral Leishmaniasis) is a deadly disease caused by a protozoan parasite *Leishmania donovani* and spread by sandfly (*Phlebotomine argentipes*). The clinical signs and symptoms of Kala Azar include recurrent fever often with double rise, loss of appetite, pallor and weight loss with progressive emaciation, weakness, splenomegaly, hepatomegaly and anemia [1]. It predominantly affects the rural economy characterized by low human development indices and poverty.

Visceral Leishmaniasis has become a priority for the health and economic sectors in terms of annual incidence of the disease; describe the social and economic aspects of the disease; and vector control strategies and effectiveness of different intervention programmes. Kala-azar show epidemic cycles taking place almost regularly every 15-20 years [2]. About 200 million populations are at risk of this disease. Nearly 25,000-40,000 cases and 200-300 deaths are reported every year, but these are possibly gross under estimates and there is a need to determine the true burden of the disease [3]. These official figures are likely to under estimate grossly the real prevalence of this disease [4]. The current status of kala-azar in the State and the number of cases and deaths due to Kala-azar in Bihar district wise from 2006-11 is mentioned in Table 1 and 2 respectively.

The tables (1 and 2) indicates that although in last 3 years (2009, 2010 and 2011) cases have decreased in comparison to 2006, 2007 and 2008 but the remarkable feature of this disease over the years have been their spread to newer foci (districts).Previously the disease was endemic in 31 districts and now in 33 districts. Although case fatality rate has decreased over the years probably due to better case management but it is still substantial.

The increase in number of cases is also supplemented by introduction of several incentives like free diet and loss of wages, shift of large number of patients from

Corresponding Author: Prashant Soni, District Improvement Coordinator (RMNCH+A), Delhi, USAID ASSIST Project, Delhi, India & Ragini Mishra, State Epidemiologist, State Health Society, Bihar, India

Table 1: Current Status of Kala Azar in Bihar at a glance (State VBD data source-data of year 2011 up to Dec 2011)

S.No.	2011	
1	Total Number of Districts endemic	33 out of 38
2	Total Number of PHCs affected	326 out of 470
3	Total Number of Cases	25215
4	Total Number of Deaths	76
5	Total Number of Cases Treated	22930
6	Total Number of Cases under Treatment	1910
7	Total Number of Untreated Cases	195
8	Total Number of Resistant Cases	27
9	Total Number of PKDL Cases	37

Table 2: District wise cases and deaths due to kala-azar in Bihar, India

		2011		2010		2009		2008		2007		2006	
Sl No	District	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1	Araria	1792	0	2037	0	1575	3	2382	5	3937	6	2587	0
2	Arwal	1	0	2	0	2	0	4	0	7	0	6	0
3	Aurangabad	0	0	0	0	0	0	0	0	0	0	0	0
4	Banka	1	0	0	0	2	0	2	0	0	0	0	0
5	Begusarai	351	2	293	5	272	4	479	12	757	34	874	15
6	Bhagalpur	170	4	105	4	47	2	100	0	101	0	185	4
7	Bhojpur	21	0	15	0	7	0	24	2	31	1	69	5
8	Buxar	14	0	10	0	50	2	10	0	3	0	9	0
9	Darbhanga	1121	0	1019	0	947	1	1497	4	1246	6	728	6
10	E.Champaran	1399	6	1280	14	1365	5	2064	12	3182	19	1614	19
11	Gaya	0	0	0	0	0	0	0	0	0	0	0	0
12	Gopalganj	930	0	877	0	767	0	1136	1	1574	0	1331	1
13	Jamui	0	0	0	0	0	0	0	0	0	0	0	0
14	Jehanabad	20	0	14	0	19	0	11	0	28	0	15	0
15	Kaimur	0	0	0	0	0	0	0	0	0	0	0	0
16	Katihar	963	8	708	8	532	5	744	9	1096	14	895	5
17	Khagaria	349	0	329	0	309	0	588	0	236	0	780	0
18	Kishanganj	222	0	167	0	128	1	214	0	208	0	135	0
19	Lakhisarai	61	0	15	0	5	0	22	0	25	0	24	0
20	Madhepura	1520	4	1721	3	1591	3	1999	2	2692	0	2245	0
21	Madhubani	543	2	630	2	732	2	1013	3	1116	1	1026	3
22	Munger	104	2	60	1	40	1	78	0	23	0	61	0
23	Muzaffarpur	2782	18	2573	22	2329	11	3679	38	4660	36	3966	32
24	Nalanda	18	0	11	0	13	2	42	0	63	0	110	1
25	Nawada	32	0	17	0	61	4	0	0	0	0	1	0
26	Patna	170	3	141	4	133	2	197	5	310	6	499	25
27	Purnea	2232	1	2238	8	2138	1	2016	1	1890	2	1379	2
28	Rohtas	0	0	0	0	0	0	0	0	0	0	0	0
29	Saharsa	2191	4	2230	5	2150	5	2505	7	3826	4	2054	6
30	Samastipur	1233	2	1261	1	1158	3	1922	9	1817	6	1389	6
31	Saran	1733	4	1103	1	1055	2	1596	4	2139	9	1652	2
32	Sheikhpura	59	1	0	0	0	0	0	0	1	0	1	0
33	Sheohar	222	0	95	0	110	0	127	1	208	0	142	0
34	Sitamarhi	1299	12	934	8	726	15	847	24	1168	19	897	10
35	Siwan	786	0	715	1	660	0	754	0	999	0	700	0
36	Supaul	352	0	396	0	386	1	16	4	817	2	622	0
37	Vaishali	2421	3	1989	7	1883	4	2787	3	3275	6	2972	18
38	W.Champaran	103	0	99	1	126	1	239	1	387	1	743	2
TOTAL		25215	76	23084	95	21318	80	29094	147	37822	172	29711	162
	CFR		0.301		0.4115		0.375		0.5053		0.4548		0.5453

Fig. 1: Endemicity of Kala Azar in Bihar: The map shows different colors as per incidence of the disease. Red colored areas are districts with high incidence followed by green, orange and yellow. Blue colored areas are places with lower incidence but are relatively new for the disease spread. Outbreaks have been reported in these new areas which is a matter of concern.

private sector to public sector after introduction of oral drug (miltefosine) and intensive case search programmes. Besides these other factors like complexity of the disease transmission and human factors like poverty, illiteracy and housing pattern also kept contributing to the increase in transmission.

PKDL Cases: Post-kala-azar dermal leishmaniasis (PKDL) is a late complication of visceral leishmaniasis (VL), which usually appears several months after treatment of a VL episode. PKDL is seen in areas where *L.donovani* is endemic i.e. in India [5]. PKDL is characterized by a spectrum of skin lesions ranging from hypo-pigmented macules, papules to nodules or combinations over the trunk and face that can be easily confused with other skin conditions such as vitiligo or leprosy [6-8] Post kala-azar dermal leishmaniasis (PKDL) accounts for about 5-10% of visceral leishmaniasis in India [9]. Both PKDL and VL are caused by *Leishmania* amastigotes, which are the commonest causative organism for kala-azar in India. PKDL is seen in about 10% of kala-azar patients in our country [10].

Kala Azar Elimination Programme: In 2005, the three countries agreed to initiate a VL elimination programme with high level political commitment and the target of reducing annual VL incidence to 1/10,000 population by 2015 [11,12]. Favouring factors for Kala-azar Elimination are: Human beings as the only reservoir host; *Phlebotomus argentipes* the only vector in the region; VL focalized in 109 districts in three countries; the disease being easy to diagnose even in field settings through recently developed rK39 dipstick test and can be treated completely with effective drugs. The five pillars of the VL elimination strategy identified so far are: (i) providing access to early diagnosis and treatment; (ii) strengthening disease and vector surveillance; (iii) integrated vector management; (iv) social mobilization and networking; and (v) operational research.

Social and Economic Impacts of Kala-azar: VL affects the rural poor, causing significant morbidity and mortality. High cost of diagnosis and treatment causes substantial social and economic hardship for affected families. In endemic areas, increased infection risk is mediated through poor housing conditions and environmental sanitation, lack of personal protection measures and economically driven migration and employment that bring people into contact with infected sandflies. Poverty is associated with poor nutrition and other infectious diseases, which increase the risk that a person (once infected) will progress to the clinically manifested disease. Lack of health care access causes delay in appropriate diagnosis and treatment and eventually increases

leishmaniasis morbidity and mortality. Leishmaniasis diagnosis and treatment are expensive and families must sell assets and take loans to pay for care, leading to further impoverishment and reinforcement of the vicious cycle of disease and poverty [13,14]. Visceral leishmaniasis has a huge social impact due to lost educational potential, reduced economic productivity and stigma. VL results in missed days of work for adults, especially the family breadwinner. Therefore, VL not only occurs in the context of poverty, but through their adverse social impact they may also promote poverty. The stigmatizing nature of VL often causes afflicted individuals to turn away from social contact. The interruption of public health services and forced human migrations has produced resurgences in VL.

Diagnosis: Demonstration of parasites is the most reliable and conventional method for diagnosing VL. The parasite is commonly found in the splenic or bone marrow aspirate and in the buffy coat of peripheral blood (in HIV co-infection). The sensitivity of splenic aspirate smear is more than 95% and is regarded as the gold standard for the diagnosis of Kala-azar. Splenic aspiration carries the risk of severe haemorrhage. The sensitivity of bone marrow smear, the other diagnostic option, is only about 60-85% and the procedure is quite painful. Although several sero diagnostic tests have been developed e.g. ELISA, Indirect fluorescent antibody test; none is in practice because of drawbacks like high cost, need for electricity, complicated technical procedures and unsatisfactory specificity and sensitivity [15]. Direct agglutination test is a cheap, sensitive and specific test and is popular in Africa, but it is associated with drawbacks like batch to batch variation, instability of the antigen, need for incubation and a cumbersome procedure and thus is not popular in India [16]. A rapid immunochromatographic test based on a 39 aminoacid antigen found in the kinesine region of amastigotes of*L chagasi*, has recently been developed and is cheap, easy to use, requires no equipment and has high sensitivity and specificity [17]. However, like other antibody based tests, it remains positive for long periods after cure and cannot be used for predicting cure or in relapses. In several studies from the Indian subcontinent, the strip test was 100% sensitive and 93-98% specific [18,19]. In Bihar, rk39 is the only current method of diagnosing Kala Azar.

Treatment: The treatment options for VL are limited and far from satisfactory. Pentavalent antimonials (sodium stibogluconate; SbV) and Amp B have been the two drugs with proven efficacy for treatment of VL. Both the drugs are given parenteraly and are potentially toxic. Paromomycin, an aminoglycoside antibiotic, is currently undergoing Phase-III clinical trial. Recently, for the first time an oral antileishmanial drug "Miltefosine" has proved effective in treating Indian VL and has been registered for treatment of VL [20,21]. Miltefosine has been rolled out in 16 highly endemic districts of Bihar [22].

Indoor Residual Spray: Indoor residual spraying is most important intervention in achieving the interruption of transmission of diseases transmitted by Phlebotomine sandlfies. In the 1950s anti malaria spraying under the National Malaria Control Programme (NMCP) and National Malaria Eradication Programme (1958) brought about a virtual cessation of Kala-azar transmission in India. Indoor Residual spraying has virtually eliminated Kala-azar from north-eastern states of Assam, Meghalaya and Tripura and smaller foci in Orissa and Tamil Nadu.

The target of Kala-azar elimination programme was the interruption of Kala-azar transmission by the year 2008. Thus it is imperative that all Kala-azar villages, whether affected now or in the past, are treated with insecticide sprays. The selection of villages for the spray programme is done by the Government as under:

- All villages within a PHC which reported kala-azar cases in the past five years.
- All villages which reported cases during the year of spraying.
- Villages which are free of kala-azar, but on search are found to contain cases conforming to the kala-azar case definition.

The dosage of DDT application is the same as that for anti-malarial spraying, i.e. 1g/m^2 of the wall surface. The inside walls of huts and cattle shed are to be treated with the insecticide. Spraying is to be restricted to the 6 feet of the wall surface. Cattle sheds and kala-azar positive and suspected houses are to be treated on priority.

Spraying is usually started to coincide with the buildup of vector populations and before onset of kala-azar transmission. The transmission season of kala-azar in India is from June to October. The build up in the population of the vector *P. argentipes* starts in March. The effectiveness of DDT deposits lasts for about 10 weeks. Thus, two rounds of spraying to control *P. argentipes* population are undertaken, Ist in February/March and 2nd in June/ July. Two rounds of sprays are given for DDT to provide protection during the entire transmission season [23].

Other Regional Challenges Towards Elimination: There are other regional challenges affecting the programme at the regional level. The regional elimination programme is trying to ensure access to health care and prevention of kala-azar for people at risk with particular attention to the poorest and marginalized groups.

There are 30-100 subclinical infections for every overt case of VL [24]. Malnutrition, immunosuppressive drugs or immuno-compromised state (HIV infection) can convert these subclinical cases into clinical disease [25,26]. HIV-*Leishmania* co-infection is being regarded as an emerging disease, especially in Southern Europe where 25-70% of adults with VL have AIDS as well. VL is now being considered as an important opportunistic infection, among AIDS cases in the Mediterranean basin [27,28,29]. With the spreading global pandemic of HIV infection, the HIV-VL co-infection continues to rise, notably in India and Brazil. In these countries, it threatens to urbanize the VL infection, which is essentially a disease of rural areas. Flood and water-logging in Bihar interferes with IRS operations. Illiteracy and non-cooperation of vulnerable groups is also a regional challenge affecting Kala Azar elimination in Bihar.

DISCUSSION

The current Kala Azar Elimination Programme needs to get strengthened by adopting newer strategies. The evidence-based policy should be designed that motivate to implement and the programmes will be cost-effective. Policies to control VL will have to include many activities that involve public awareness and modifying personal behaviour. The five pillars of VL elimination strategies identified are: early diagnosis and complete treatment; integrated vector management and vector surveillance; effective disease surveillance through passive and active case detection; social mobilization and building partnerships and clinical and operational research which need to be re-enforced to effective implementation [30].

Strategies for Surveillance: Government agencies in India collect data via passive case detection (Desjeux, 1999) which grossly underestimates the number of cases. Most cases are diagnosed but not reported by private medical practitioners. Private Doctors are not required to report cases to the state health system. The social and cultural stigma linked to VL and high prevalence among the poor results in a large percentage of individuals failing to seek treatment at public health facilities (Ranjan *et al*., 2005). Hence, it is not possible to obtain directly reliable estimates of VL incidence using the surveillance system in place. Under-reporting is one of the main constraints towards the elimination [31]. ASHAs, being the interface between community and health staff, should be utilized and motivated towards active case detection. There should be orientations of ASHAs before each IRS possibly in the months of January and April since these months correspond to those when IRS operations preparation begins. The subsequent months (February and May) should be utilized to inform community regarding the sprays and their co-operation needs to be sought. This will improve both the active and passive surveillance. In addition, Active Case Detection should be done at least two times in a year in the months of June and October (at the start and end of the Kala Azar Transmission period) like done in pulse polio rounds. Current incentive for ASHAs (Rs 50 per case for case detection and Rs 150 for treatment completion) for Kala-azar should be raised in order to motivate them for active case detection. In Bihar, active case detection is occurring in the camp mode replacing Kala-azar fortnight, once a month targeting four villages [32]. However, this should be done on a wide scale like in polio rounds. IEC/BCC strategies should be employed on a large scale to aggressively search for suspected cases as well as before the IRS. The State has rolled out a National Programme i.e., Integrated Disease Surveillance Project to capture morbidity data on 22 infectious diseases including Kala-azar as state specific disease. Under this programme, reporting from private sectors is also encouraged, but their link with this programme has some constraints like lack of motivation of private sector to provide information to government system, lack of sufficient man power in the absence of which assignment of task to a specific person that can bring report from private facilities or practioners becomes difficult. This is further afflicted with lack of incentives provided to them with respect of distance they have to cover between private facility and the place where they are supposed to report. Mobility support is also one of the challenges for the Health workers which need proper attention.

Entomological surveillance in the State has been weak. The State has initiated a study on monthly vector density to generate Early Warning Signals of impending outbreaks. Study on insecticide susceptibility status of Vectors on a regular basis is not being actively pursued. State has hired Vector Borne Consultants in endemic districts who can do this surveillance on regular basis. Data sharing between various Research Institutions in the State and State Programme Officer needs to be strengthened. Involvement of Academic institutions can also provide valuable support to the programme.

Strategies for Community Participation in Kala Azar Elimination: Since community plays a pivot role towards success of any health Programme, community should be motivated towards increasing passive surveillance and support in the Indoor Residual Spray. Efforts should be made to include one of the members from the targeted village, to be included in Indoor Residual Sprays for Quality improvement of spray. Spray monitoring should be done by the community.

Strategies for Treatment: Mitefosine should be rolled out in all the districts and since clinical half life of miltefosine is long (170 hours) and there is a possibility of resistance to the same [33], DOTS guidelines should be prepared and introduced. DOTS providers should be identified and additional incentives should be provided to them for DOTS. A referral system should be established for Kala-azar patients. Patients should be given some incentives for travel to PHC or referral to higher centers for better treatment.

Strategies for PKDL and HIV/TB co-infection with Kala-azar Cases: Active Surveillance with special efforts to find PKDL cases should be intensified. There should be establishment of a Regional Health Center equipped to deal with PKDL, HIV and TB co-infected and for other unresponsive cases. A specialist should be made available to treat all such cases. Special incentives should be provided to PKDL cases treated completely. There should be the provision for skin biopsy at the district hospitals in all the districts of Bihar.

Strategies for Nutrition: Rapidly developing anemia [34] is one of the symptoms in Kala azar and since this develops rapidly and accounts for malnutrition, treatment of anemia should be included along with medications. A special diet with good nutritious value and fortified with iron should be developed and provided to Kala-azar patients.

Strategies of Vector Control: In addition to chemical control using IRS, vector control should be supplemented by other hygiene measures. LLINs are effective against sandfly. Houses with cracks and crevices should be filled with mud or lime before the spray. Cowdung [35,36], being one of the important sources of sandfly breeding, be managed in different ways. Before the night, cowdung should be collected and dried on the roof or some place more than 6 feet high. One of the remarkable traditions in Bihar is sleeping in the cattle-shed in order to prevent stealing of cattle and this can be a site of sandfly bite. There should be a recommendation of developing a (Machan) wooden block which should be installed at a height of 6 feet for sleeping and mandate of using Long Lasting Insecticide Nests (LLINs) for any person sleeping in cattle-shed. Some studies show resistance of sand flies to DDT in some areas of Bihar. There should be continuous operational research to find out resistance to DDT in areas with high prevalence and provision of using alternate insecticides.

Strategies of Clinical and Operational Research: There should be consistent clinical and operational research towards finding out compliance to the drugs and implementation of different strategies and their effects. Entomological studies should be regularly carried out finding out newer advances for sandfly control.

Strategies for Environmental Modifications: Since Kala azar affects the poorest segments of the society; there should be the provision of proper housing in highly-endemic Kala-azar prone areas. Govt. of India has taken initiatives in the form of construction of Pucca houses to Mushahar community and Rs 12.03 crores have already been released under Indira Vikas Yojana to the state of Bihar [37-40].

Strategies for Inter and Intra-Sectoral Convergence: A Kala-azar Task Force should be made functional. The members of this Task Force should include members from both Health and Non Health sectors. This would help in sensitizing the community from all spheres regarding kala-azar prevention, treatment and elimination.

ACKNOWLEDGEMENT

The Authors are thankful to Mr Sanjay Kumar, Secretary Health-cum-Executive Director, State Health Society, Bihar for his unending support to improve the situation of diseases prevalent in the State. Thanks are also due to State Kala-azar Department and Integrated Disease Surveillance Project (IDSP), Bihar staffs for providing valuable data included in the report.

REFERENCES

1. www.nvbdcp.org-signs and symptoms of Kala Azar.
2. Alvar, J., S. Yactayo and C. Bern, 2006. Leishmaniasis and poverty. Trends Parasitol., 22(12): 552-7.
3. Desjeux, P., 1992. Human leishmaniases, epidemiology and public health aspects. World Health Stat Q, 45(2-3): 267-75.

4. Bern, C. and R. Chowdhury, 2006. The epidemiology of visceral leishmaniasis in Bangladesh: prospects for improved control. Indian J. Med Res., 123: 275-88.
5. Zijlstra, E.E., A.M. Musa, E.A.G.E.L. Khalil, I.M. Hassan and A.M. El-Hassan, 2003. Post-kala-azar dermal leishmaniasis. Lancet Infectious Diseases., 3: 87-97.
6. Zijlstra, E.E., A.M. Musa, E.L. Khalil, I.M. EI-Hassan and A.M. El-Hassan, 2003. Post-kala-azar dermal leishmaniasis. Lancet Infectious Diseases, 3: 87-97.
7. Ramesh, V. and A. Mukherjee, 1995. Post-kala-azar dermal leishmaniasis. Int. J. Dermatol., 34: 85-91.
8. Zijltra, E.E., A.M. EL-Hassan and A. Ismael, 1995. Endemic Kala-azar in eastern Sudan: Post-kala-azar dermal leishmaniasis. Am. J. Trop Med Hyg., 52: 299-305.
9. Zijistra, E.E., A.M. Musa, E.A. Khalil, I.M. el-Hassan and A.M. el-Hassan, 2003. Postkala-azar dermal leishmaniasis.Lancet Infect Dis., 3: 87-98.
10. Parija, S.C., 1996. Text Book of Medical Parasitology. 1st ed. Chennai, India: All India Publishers and Distributors, pp: 83.
11. Regional strategic framework for elimination of VL from SEA Region, 2005-2015. New Delhi: WHO SEARO. SEA-VBC-85., Rev., 1: 22.
12. Communicable diseases: kala-azar status in SEA region 2005. (online). Available at URL http://www.searo.who.int/en/Section10/Section2163.htm.).
13. Alvar, J., S. Yactayo and C. Bern, 2006. Leishmaniasis and poverty. Trends Parasitol., 22(12): 552-7.
14. Desjeux, P., 1996. Leishmaniasis: public health aspects and control. Clin Dermatol., 14: 417-23.
15. Sundar, S. and M. Rai, 2002. Laboratory Diagnosis of Visceral Leishmaniasis. Clin Diag Lab Immunol., 9: 951-8.
16. Sundar, S. and M. Rai, 2002. Laboratory Diagnosis of Visceral Leishmaniasis. Clin Diag Lab Immunol., 9: 951-8.
17. Sundar, S., S.G. Reed, V.P. Singh and P.C.K. Kumar, 1998. Murrary. Rapid accurate field diagnosis of visceral leishmaniasis. Lancet, 351: 563-5.
18. Sundar, S., S.G. Reed, V.P. Singh, P.C.K. Kumar and H.W. Murrary, 1998. Rapid accurate field diagnosis of visceral leishmaniasis., Lancet, 351: 563-5.
19. Bern, C., S.N. Jha, A.B. Joshi, G.D. Thakur and M.B. Bista, 2000. Use of the recombinant k39 dipstick test and the direct agglutination test in a setting endemic for visceral leishmaniasis in Nepal. Am. J. Trop Med. Hyg., 63: 153-7.
20. Sundar, S., F. Rosenkaimer, M.K. Makharia, A.K. Goyal, A.K. Mandal, A. Voss, *et al.,* 1998. Trial of oral miltefosine for visceral leishmaniasis. Lancet, 352: 1821-3.
21. Jha, T.K., S. Sundar, C.P. Thakur, P. Bachmann, J. Karbwang, C. Fischer, *et al.*, 1999. Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis. N Engl J. Med., 341: 1795-800.
22. State Kala Azar data.
23. Kala-azar/Guidelines for Vector Control in KA Elimination available at URL http://nvbdcp.gov.in/iec.html.
24. Ho, M., T.K. Siongok, W.H. Lyerly and D.H. Smith, 1982. Prevalence and disease spectrum in a new focus of visceral leishmaniasis in Kenya. Trans R Soc Trop Med Hyg., 76: 741-6.
25. Cerf, B.J., T.C. Jones, R. Badaro, D. Sampaio, R. Teixeira and W.D. Johnson, Jr., 1987. Malnutrition as a risk factor for severe visceral leishmaniasis. J. Infect Dis., 156: 1030-3.
26. Alvar, J., C. Canavate, B. Gutierrez-Solar, M. Jimenez, F. Laguna, R. Lopez-Velez, *et al.*, 1997. Leishmania and human immunodeficiency virus coinfection: the first 10 years. Clin Microbiol Rev., 10: 298-319.
27. Alvar, J., C. Canavate, B. Gutierrez-Solar, M. Jimenez, F. Laguna, R. Lopez-Velez, *et al.*, 1997. Leishmania and human immunodeficiency virus coinfection: the first 10 years. Clin Microbiol Rev., 10: 298-319.
28. Desjeux, P., 1999. Global control and Leishmania HIV co-infection. Clin Dermatol., 17: 317-25.
29. Desjeux, P., 2001. The increase in risk factors for leishmaniasis worldwide. Trans R Soc Trop Med Hyg, 95: 239-43.
30. Govt of india, 2006. Annual Report 2005-06, Ministry of Health and Family Welfare, New Delhi.
31. Mubayi, A., C. Castillo-Chavez, G. Chowell, C. Kribs-Zaleta, N.A. Siddiqui, N. Kumar and P. Das, 2010. Transmission dynamics and underreporting of Kala-azar in the Indian state of Bihar. J. Theor Biol., 262: 177-185.
32. state PIP., 2011-12 Bihar, pp: 340.
33. Shyam Sundar[1] and Piero L Olliaro., 2,3, Miltefosine in the treatment of leishmaniasis: Clinical evidence for informed clinical risk management.
34. www.nvbdcp.org-Kala Azar signs and symptoms.

35. Sharma, N.L., V.K. Mahajan, N. Ranjan, A.K. Negi, K. Inder and S. Mehta, 2009. The sand flies of the Sutlej river valley, Himachal Pradesh (India): some possible vectors of the parasite causing human coetaneous and visceral leishmaniases in this endemic focus. J. Vector Borne Dis., 46: 136-40.
36. Singh, R., S. All and V.K. Saxena, 2008. Breeding ecology of visceral leishmaniasis vector sandfly in Bihar state of India., Acta Tropica., 107(2): 117-20. doi: 10.1016/j.actatropica.2008.04.025).
37. mohfw.nic.in/NRHM/Presentations/NVBDCP.pps.
38. Abou-Deif, M.H., M.A. Rashed, M.A.A. Sallam, E.A.H. Mostafa and W.A. Ramadan, 2013. Characterization of Twenty Wheat Varieties by ISSR Markers, Middle-East Journal of Scientific Research, 15(2): 168-175.
39. Kabiru Jinjiri Ringim, 2013. Understanding of Account Holder in Conventional Bank Toward Islamic Banking Products, Middle-East Journal of Scientific Research, 15(2): 176-183.
40. Muhammad Azam, Sallahuddin Hassan and Khairuzzaman, 2013. Corruption, Workers Remittances, Fdi and Economic Growth in Five South and South East Asian Countries: A Panel Data Approach Middle-East Journal of Scientific Research, 15(2): 184-190.