

Review Article

A Review on Major Risk Factors and Current Status of Visceral Leishmaniasis in North India

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Abstract: In India, more than 1,00,000 people are affected every year by Visceral Leishmaniasis (VL). VL is a chronic and fatal disease caused by *Leishmania donovani* parasites which are transmitted by infected female sand flies, *Phlebotomus argentipes*. Ninety percent of total cases of the world are reported from India, Bangladesh and Sudan. Several districts of the state Bihar show the occurrence of VL. This is 40-50% of the world cases and 90% of the cases in India. Conversely, information on epidemiology of kala-azar in India remains scanty due to inadequate studies about the various risk factors associated with VL. The present review contributes to the study of the number of cases, deaths, prevalence and incidence caused by VL, spatial distribution, basic epidemiologic features, the vector biology, transmission of the parasite, hosts and most importantly the major risk factors viz. climatic, the physical and biotic factors, the socio-economic conditions, the environmental factors, deforestation due to urbanization, domestic animals and the living standard. For this study we chose five states in India; Bihar, Uttarakhand, Uttar Pradesh, Jharkhand and West Bengal. The study period was from 2010-2017. A decreasing trend was observed in the number of incidences, cases and deaths. But on the contrary, the Post Kala Azar Dermal Leishmaniasis cases (PKDL) showed an increasing trend. The *Gram Pradhans* (Heads of Villages) and the villagers were also questioned regarding the associated risk factors viz. housing conditions- *kaccha* (mud) houses, poverty, use of bed nets, cleanliness, damp floors, cooking fuel, vegetation, the rearing of the domestic animals etc. The study suggests that the control measures have been effective in suppressing/eradicating VL but seeing the PKDL trend it also leaves a suspicion that apart from *P. argentipes* some other flies may also be playing the role as vectors in the transmission of VL. To decrease the transmission of *Leishmania donovani* and to achieve the goal of total eradication of VL from India in near future, a better understanding of the biology underlying transmission and disease with the major risk factors is the pressing need.

Keywords: Control Measures, Endemic, India, Incidence, Leishmaniasis, Phlebotomine, Risk Factors

1. Introduction

Visceral leishmaniasis is a chronic and potentially fatal parasitic disease of the viscera which affects the organs due to the infection by *Leishmania donovani*. The worldwide incidence is estimated to be between 1,46,700 and 2,82,800 cases per year (approx. 0.5 and 2.5 million respectively) [1]. Sixty-six countries in the world have been reported confirmed kala-azar cases [2, 3]. The spatial distribution of leishmaniasis also seems to expand in the Southern parts of Europe [4, 5] and in the Central Europe where the foremost cases of autochthonous origin are recently reported [6].

It is important to note that this disease was not endemic in the past in this region [7, 8, 9]. But it is mainly reported from six countries namely Bangladesh, Brazil, Ethiopia, India, South Sudan and Sudan [10, NVBDCP-website] and 90% of these occur in India, Nepal, Bangladesh and Sudan [3] while it has also been reported that north eastern region of India, southern region of Nepal and eastern and central division of Bangladesh harbor an estimated 67% of the global VL disease burden [NVBDCP-website]. Visceral Leishmaniasis, also known as Kala-Azar (KA) in the Indian subcontinent which is prone to the occurrences of chronic Visceral Leishmaniasis (VL) or Kala-azar and is one of the major causes of morbidity and mortality creating a significant impediment to human

development. Geographical distribution of the disease is endemic in the states of Bihar, West Bengal, Uttar Pradesh, Jharkhand, Delhi, Gujarat, Madhya Pradesh and Kerala in India. 90% of the disease has mainly affected the children below 9-15 years of age and has been causing 50% death incidents annually in India [11]. The reports of Kala-azar cases occurring in Bihar state in India, which is 40% to 50%, of the world cases and is severely affected states and account to 90% of the total recorded cases in India. The disease affects mainly poor and rural communities. Approximately 80% of all cases in the region are reported from the state of Bihar in India [12]. Furthermore, reports of Kala-azar cases occurring in Bihar state in India which is 40%-50% of the world cases accounts to 90% of the total recorded cases in India. At present, it is a severe public health problem in Indian subcontinent, especially in the Bihar state [13]. Visceral leishmaniasis affects the internal organs principally spleen, liver, and bone marrow. It is estimated that more than 90% visceral leishmaniasis infected people are concentrated in lower and middle gangetic plains in India.

1.1. Biology of the Vector

Phlebotomine sand flies are well-known to transmit leishmaniasis, bacteria and viruses which affect humans and animals and have been endemic in India since ancient times [14, 15]. The sandflies carry the parasite from reservoirs to humans. Reservoirs for the parasite are mostly rodents and large domestic and wild mammals. Humans are 'accidental hosts' when they invade the reservoir and vector's ecosystem [16]. They are small bloodsucking insects of which there are about 700 species of six genera of the female *Phlebotomus*, suspected or proven vectors transmitting the parasites from animal-to-animal, animal-to-man and man-to-man' considered to be the disease vectors [2]. The promastigote forms of *Leishmania donovani* parasites enter the human host through the proboscis when the sand fly bites and sucks the blood from an infected person or animal [17]. The parasite survives and multiplies within phago-lysosomes of macrophages as intracellular amastigotes inside the human host (Figure-1).

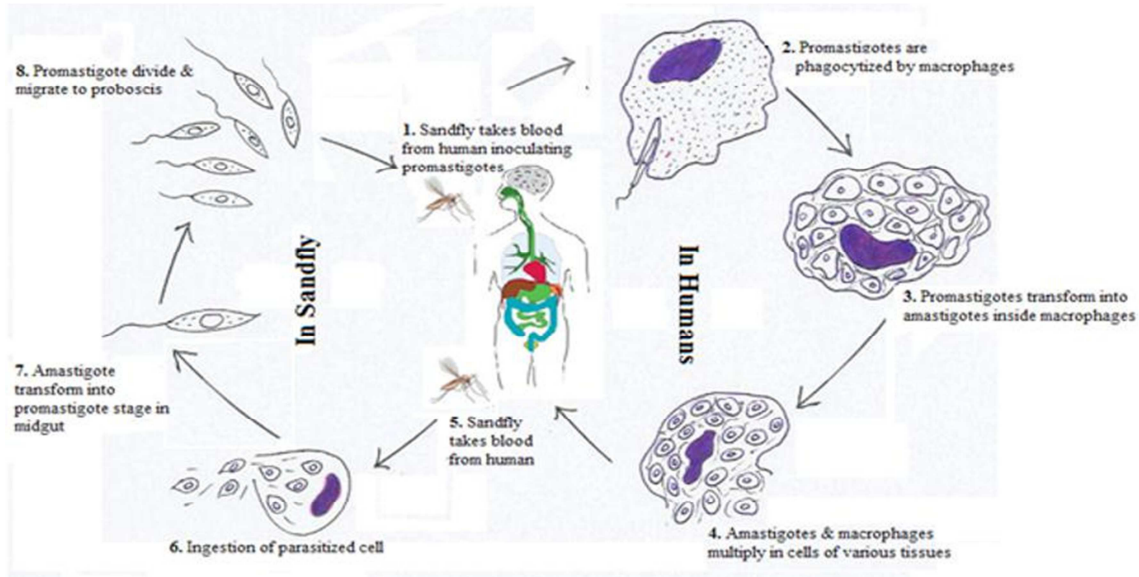


Figure 1. Life cycle of *Leishmania* spp. in *Phlebotomus* spp. & Humans.

Leishmaniasis is an emerging vector borne disease in India. Knowing the activity of sand flies is important in the influential period of maximum risk of *Leishmania* transmission and for the successful achievement of control programs, *Phlebotomus argentipes* make up a very small proportion of sand flies and ill-considered proactive interference may disturb this balance in favor of this species and other species as potential vectors. The conditions that favor epidemics of kala-azar are rural areas more than 600 meters above sea level, heavy annual rainfall, mean humidity above 70%, a temperature range of 15°C to 38°C with a diurnal variation of more than 7°C, abundant vegetation, subsoil water and alluvial soil. Deforestation, which is a consequence of increasing agriculture, cattle and urbanization, plays an important role in the ecologic niche changes to thousands- of phlebotomine species [18]. Few

information on epidemiology of kala-azar in India and other affected countries, are available due to inadequate studies about the various risk factors associated with this disease [19, 20] and also on the relationship- between anthroponotic transmission and the increasing- cases of VL due to possible urbanization in Uttaranchal. It is important to focus on VL education and policies at an early stage with the aim of encouraging protective measures. Therefore, a review to investigate the presence of *Phlebotomus argentipes* in environments altered by man is a requirement for the better control of VL in endemic areas. Hence, the purpose of this paper is to review the various risk factors including climatic changes (temperature and humidity and speed of the wind), natural calamities, the physical factors (geographical barriers and habitat availability), the biotic factors (distribution and abundance of vertebrate hosts), the socio-economic

conditions (poor nutrition affecting immunity), the environmental factors, the other risk factors including cooking of food on wood fire, rearing of domestic animals, certain vegetation, forests, livelihood and urbanization coupled with deforestation etc. and to discuss their contributions in further understanding of the epidemiology and control of VL in India.

1.2. Rationale and Design of the Study

Globally, the number of vector-borne infections in humans and animals increases rapidly, meanwhile causing almost one third of all cases of emerging infectious diseases [21]. In the Old World, sandfly species of the genus *Phlebotomus* serve as vectors for sandfly borne pathogens such as *Leishmania*, *Bartonella* and several other viruses (for eg. Phlebovirus, Vesiculovirus and Orbivirus) [22]. Sandfly-borne diseases and in particular visceral leishmaniasis are a main public health concern [23] and for its prevention and control, it demands more attention in science and policy [24]. While the spatial distribution of leishmaniasis seems to expand in southern parts of Europe [4, 5] the presence of sandflies as vectors is mainly regulated by the species' climatic requirements on temperature and humidity or soil moisture respectively [25, 26, 27, 28]. Temperature and humidity are the main factors impacting the altitudinal structure of sandfly occurrences [29]. Temperature directly affects insect population dynamics through modification of developmental rates, reproduction and mortality. Weather can also affect insect populations indirectly via alteration of the abundance, distribution and physiology of the host trees. It is known that sandflies react very sensitively to the wind speed and prefer breeding sites sheltered from wind [30, 31, 32, 33]. Few reports from India are available on the role of various ecological parameters like air, temperature, rainfall, wind speed, relative humidity, soil moisture, temperature, pH, and organic carbon [34] are known to influence the ovipositor of gravid female sand flies as well as the survival and development of the larvae [35] Beyond that, high wind speed decreases or even excludes flight activity [30, 31, 32, 33, 34, 35, 36]. For the purpose of inferring geographic distribution for sandflies, the advantages of ecological niche models have been demonstrated on the example of *Lutzomyia* species (*Lutzomyia spp.*) in the New World [37]. For the first time, Peterson & Shaw, (2003) [38] integrated climate change scenarios in order to project future distribution of *Lutzomyia* spp. in Brazil. Recently, range expansions for sandflies of the genus *Lutzomyia* have also been projected for North America in the face of climate change [39]. In addition, no study monitoring the promising urbanization process of *Phlebotomus argentipes* has been performed. Deforestation, which is a consequence of increasing agriculture, cattle and urbanization, plays an important role in the ecologic niche changes to thousands of phlebotomine species [18]. In spite of a lot of efforts done for the eradication of VL in the VL prone areas viz. Bihar or Jharkhand the disease seems not to be under control [40]. Hence it was decided by the authors to study the status of Leishmaniasis in North India to reason out the particular causes as to why full eradication of VL has not yet

reached.

2. Methodology

Keeping in view the above facts it was decided to reason out the discrepancies in the number of incidence /deaths in the five main critical states (Bihar, Jharkhand, West Bengal, Uttar Pradesh and Uttarakhand) known for the occurrence of the VL. To explore the status of Leishmaniasis in India, the following factors have been taken into consideration-

1. Studies on the prevalence and incidence of VL and the effect of climate on Visceral Leishmaniasis transmission and the post Kala Azar Dermal Leishmaniasis (PKDL) cases in North India since 2010- 2017.
2. Studies on the risk and the associated risk factors of visceral leishmaniasis in the study areas.

The *Gram Pradhans* (village heads) along with the villagers were contacted and interviewed about the socio-economic conditions, weather, livelihood, poverty, living habits/standards, rearing of the domestic animals and housing conditions. The records of the cases and deaths were also checked [NVBDCP-website]. The primary health centers were also useful in data survey.

3. Results and Discussion

3.1. Prevalence, Incidence and the Effect of Climate on VL Transmission

The report on deaths due to kala azar from 2010-2017 in the five main states of India (almost every year) shows the highest number of incidences in Bihar (23084) and least (0) in Uttarakhand and Uttar Pradesh [13]. Jharkhand is on the second number and West Bengal on the third. We also observe a decline in the number of cases and deaths from 2010 to 2017 in Bihar. More or less the same situation is found in all the five states. If we see the total no. of cases in the North India (in these five states, we observe a decreasing trend in both cases and deaths with a slight discrepancy in the total no. of cases in 2011 (Table-1). Whereas a gradual decrease in the number of cases of kala-azar has been reported from 2010-2017 (Figure-2) suggesting that effective control measures must have been taken to prevent the occurrence of VL.

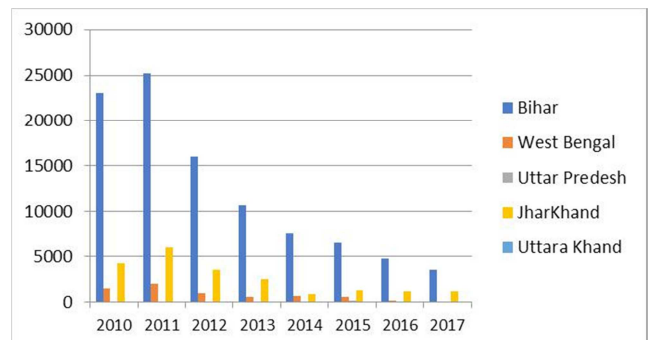


Figure 2. Number of cases of Kala-azar since 2010. Source: <http://nvbdc.gov.in/ka-cd.html>.

Table 1. Kala-Azar Cases and Deaths in India (2010 to 2017). (Data source: NVBDCP, Ministry of Health & Family Welfare, Government of India.).

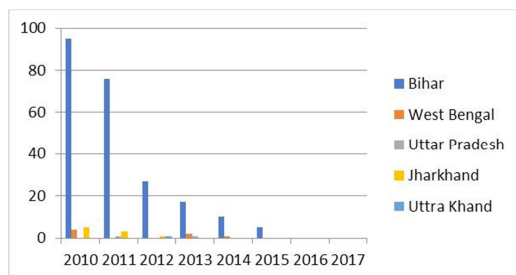
Year	Cases & Deaths	Bihar	West Bengal	Uttar Pradesh	Jharkhand	Uttarakhand	Total
2010	Cases	23084	1482	14	4305	1	28886
	Deaths	95	4	0	5	0	104
2011	Cases	25222	1962	11	5960	0	33155
	Deaths	76	0	1	3	0	80
2012	Cases	16036	995	5	3535	7	20578
	Deaths	27	0	0	1	1	29
2013	Cases	10730	595	11	2515	0	13851
	Deaths	17	2	1	0	0	20
2014	Cases	7615	668	11	937	4	9235
	Deaths	10	1	0	0	0	11
2015	Cases	6517	576	131	1262	3	8489
	Deaths	5	0	0	0	0	5
2016	Cases	4773	179	107	1185	2	6246
	Deaths	0	0	0	0	0	0
2017	Cases	3519	109	92	1184	2	4906
	Deaths	0	0	0	0	-	0

An increasing trend is observed in cases of skin presentation of Kala-azar called 'Post Kala-azar Dermal Leishmaniasis' (PKDL) in the three main states i.e. Jharkhand, Bihar and West Bengal. Uttarakhand and Uttar Pradesh show a promising status of elimination of this disease. PKDL is first

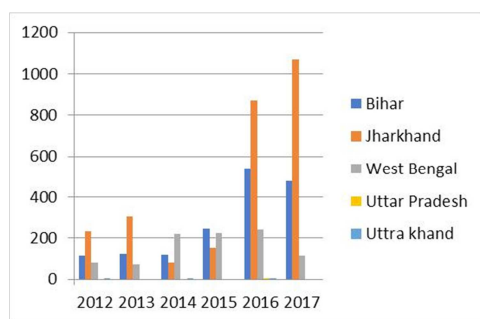
characterized by discoloration of the skin and later distinct, clear and evident manifests as lesions. These lesions are reservoirs for the parasite. A person with lesions can therefore become infectious if bitten by a sand fly, leaving a source of infection within the community (Table 2).

Table 2. Post-Kala-azar Dermal Leishmaniasis (PKDL) situation in India since 2012 (As per the reports received from states up to October 2017).

S. No.	States Affected	Number of Cases					
		2012	2013	2014	2015	2016	2017
1.	Bihar	113	122	119	247	542	477
2.	Jharkhand	234	304	81	153	873	1069
3.	West Bengal	82	73	221	225	240	115
4.	Uttar Pradesh	0	0	0	0	2	0
5.	Uttarakhand	1	0	1	0	1	0
Total		430	499	422	655	1658	1661



a.



b.

Figure 3 a. Number of Deaths due to Kala-azar since 2010. Source: <http://nvbdc.gov.in/ka-cd.html>. b. Post-Kala-azar Dermal Leishmaniasis (PKDL) situation in India since 2012. Source: <http://nvbdc.gov.in/ka-cd.html>.

On the other hand, Data from Jharkhand, Bihar, West Bengal, Uttar Pradesh and Uttarakhand shows that the number of deaths due to kala-azar since 2010 is decreasing gradually which was very high in 2010 due to several geo-climatic factors (Figure 3a).

But the number of PKDL cases (Figure 3b) suggests that efforts are been done by the WHO and other agencies like NVBDCP, Ministry of Health and Family Welfare, Government of India to eliminate VL to much extent and a vision is clearly seen about the total eradication of kala-azar in the coming few years [40]. But the rise in PKDL cases also indicates that the infection may be circulating within the affected communities and also may be due to relapses of VL/PKDL and therefore better surveillance system, effective and accessible treatment and reporting system is the urgent need.

Leishmaniasis is also climate-sensitive and affects its epidemiology in several ways viz., changes in temperature, rainfall and humidity can have strong effects on vectors and reservoir hosts by altering their distribution and influencing their survival and population sizes. Small fluctuations in temperature can have a profound effect on the developmental cycle of *Leishmania* promastigote in sandflies, allowing transmission of the parasite in areas not previously endemic for the disease. The Visceral Leishmaniasis vector (sand fly)

abundance has been found in the months between June and September with *P. argentipes* most active abundance while the temperature range was between 27.5°C and 31°C [41]. The impact of temperature on sand fly populations is rapid and the distribution, vegetation condition and synoptic temperature to an overall accuracy. The northeastern regions of India, southern region of Nepal and eastern and central divisions of Bangladesh in South-East Asia are prone to endemic regions of VL transmission. Climate change and extreme weather events affect plants and animals and the direct impact of anthropogenic climate change has been documented on every continent, in every ocean, and in most major taxonomic groups [42].

The VL status in North India after this review confirms that longevity and survival of vector populations of Kala-azar is significantly determined by the geographically controlled factors viz. the climate (temperature, relative humidity and rainfall), soil types and soil moisture [43]. These have been progressively affecting the vegetation growth and density, and then the conditions on the surrounding environment. Introduction of new technique- Geographical Information Systems (GIS) and remote sensing is a strong step in stratifying a region into different areas of transmission risk thereby providing a guideline to mapping the areas under the risk of visceral leishmaniasis transmission in India [44]. The distribution of phlebotomine sandflies varies highly within its range, depending on local environmental factors, such as precipitation and temperature, physical factors, such as geographical barriers, habitat availability and biotic factors such as the distribution and abundance of vertebrate hosts [45]. Natural calamities drought, famine and flood can lead to massive displacement and migration of people to areas with transmission of *Leishmania*, and poor nutrition could compromise their immunity [46]. The clinical manifestations are dependent both on the infecting species of *Leishmania* and the immune response of the host. In the last two decades VL has been recognized as an opportunistic disease in the immune-compromised, particularly in patients infested with human immunodeficiency virus (HIV) [47].

3.2. The Associated Risk Factors

Socio-economic conditions in North-India, such as poor housing and domestic sanitary conditions (such as a lack of waste management or presence of open sewerage) may increase sandfly breeding and resting sites, as well as their access to humans. Sandflies are attracted to crowded housing as these provide a good source of blood-meals. Another group of factors are related to housing conditions. Studies have shown that when walls, roofs, and floors are not made of durable materials, cracks can be formed becoming a shelter or a gateway for vectors into the households [48], while in endemic sites thatched, mud plastered roof tops of households with crack and crevices on it as well as on walls may serve as effective day-resting habitats for these nocturnal feeder species, mainly tiled, dry, non-porous roof tops without any cracks/ crevices in endemic foci cannot be a resting habitat for the adult population. Again, loose, wet solid with rich organic

debris, on house floors in endemic sites not only serve as a very good resting habitat/food source for thriving and probation of immature stages of vector sandfly but also act as resting habitat of newly emerged adult population. Damp floors or dampness in the home is another risk factor [49]. The use of bed nets was found to be protective in some studies hence decrease the incidence of VL [49, 50, 51]. Lack of cleanliness because of illiteracy is also a cause for sand fly propagation and the parasite transmission. In a study highest numbers of the VL cases were found living in the house which were huts (36%) and kachha (mud) houses (30%) and 65% of VL cases having less than 40,000 incomes per year [52]. Thus, poverty could be the major determinant for the transmission of visceral leishmaniasis in the Jharkhand and Bihar. The occurrence of granaries inside the houses was found to be extensively associated with visceral leishmaniasis because they are usually kept inside the houses. Perhaps, better housing and improved living conditions in diseased areas of Jharkhand, Bihar and West Bengal could decrease the transmission of the disease by eliminating conditions suitable for the breeding of sand flies inside the houses. VL was reported curable in highly endemic village of West Bengal only by improving the housing conditions. High rates of infection indicated that transmission persisted in this community. Factors associated with infection included residing in homes with mud walls [53, 53, 54], dampness in homes, proximity to bodies of water, livestock ownership, sleeping dressed or under a bed net, or in a cot were associated with a lower risk. Poor housing conditions were associated with a higher risk, while personal protection measures against vectors were effective [49]. Studies investigating risk factors for visceral leishmaniasis (VL) on the Indian Subcontinent have shown contradictory results related to the role of domestic animals. In some studies, having animals in or around the house was a risk factor, in others it was protective [53]. Due to rearing of animals the dampness of the floor increases which is significantly associated with altered risk of VL [50]. Sleeping near the domestic animals and improper drainage system was significantly associated with visceral leishmaniasis. But [55] confirms that keeping animals inside the house is not a risk factor for VL in Bihar, India rather improving housing conditions and personal protection efforts for the poor has the potential to reduce VL incidence. On social grounds, human behavior, such as sleeping outside or on the ground may increase the risk for leishmaniasis. Starvation due to diets lacking protein-energy, iron, vitamin A and zinc increase the risk that an infection will progress to kala-azar [56]. In Bihar, low casts (Musahars) due to poverty are unable to take the treatment [57].

Some studies have also found that using wood as a cooking fuel was a risk factor arguing that it would increase exposure when it is used in open environments [48]. Other studies have however identified this as protective arguing that probably the smoke drives away the vectors [58]. Environmental factors also affect the occurrence of visceral leishmaniasis. The presence of vegetation plays a significant association with VL in univariate analysis. Presence of banana trees around the house was

extensively associated with visceral leishmaniasis [59]. The village areas of Jharkhand and Bihar are usually surrounded by the high density of vegetation such as banana trees, seasonal crops, bamboo trees and herbs. Hence, they are more prone to dermal/cutaneous leishmaniasis. Bamboo trees (*Bambusa ruginosa*) in the pre-domestic areas are most significant factors, because these trees provide shade and consequently engineer dark and humid weather condition in the neighborhood areas of the house locations, and also creating suitable quiescent sites for Visceral Leishmaniasis vector population. The large amount of VL vector profusion is occurring in the months of July to September, and hence, it is suitable season for development of VL vectors as during these months starts the rainy season and the plants, such as *Amaranthus spinose* (*Amaranthaceae*), *Musa sapientum*, and *Croton sparciflorous* grow well and become very rich sources of breeding habitats and thus, it attracts *P. argentipes* [54, 60, 61].

Crop vegetation types have also been correlated with Kala-azar transmission in India. During summers (March-June) and rainy season (July- October) there is increasing trend of irrigation as well as water areas, with edible shrubs and plants, alluvial soil types, dark colored alkaline in nature (pH 7.2-8.5), calcareous with chief inorganic constituents of silicon, iron and aluminum. This type of soil enhances its capability of retaining water as well as successful growth and abundance of edible shrubs, plants or agricultural crops. Public health measures such as case detection and treatment, the control of sand flies, the conjunction elimination of infected stray dogs and health education can be effective in controlling the disease [62]. These results will be useful for further improvement in the VL control programs for intervention strategies in respect of various socio-economic and the environmental factors that affect the occurrence of visceral leishmaniasis. Intensive and constant monitoring of sandflies on the edge of the forest and in intermediate areas is recommended to detect local patterns and periods of higher vector abundance which will allow for better preventive anti-vector intervention [63]. Using the results of this investigation, health workers in such areas may be better able to control and prevent leishmaniasis.

Epidemics of both cutaneous and visceral leishmaniasis are often associated with migration and the movement of non-immune people into areas with existing transmission cycles. Occupational exposure as well as widespread deforestation remains important factors. The incidence of leishmaniasis can be affected by changes in urbanization and the human incursion into forested areas. One frequent factor is the human settlements close to a primary forest. When the ecological environments are disturbed, humans are more likely to be exposed to reservoirs and vectors increasing the risk for Acute Cutaneous Leishmaniasis (ACL) [64]. A deeper understanding of both sand fly and host biology and behavior is therefore essential to ensuring effectiveness of vector interventions and avoiding unintended counterproductive (hindrance) consequences etc. at an early age at the domestic or sylvatic areas with the aim of encouraging the use of protective measures that reduce vector exposure [65]. Efforts

have been constantly made for the elimination of Kala-azar from the Indian Sub-continent; but the goal has not been yet achieved [67].

4. Conclusion

A person with PKDL lesions can be a source of infection and should be treated likewise. Good nutrition can eliminate the transmission of VL to much extent as a host with poor immunity is often overpowered by the parasites of the disease. VL status in North India confirms that longevity and survival of vector populations of Kala-azar is significantly determined by the major risk factors, such as geographically controlled factors- the climate, environmental conditions such as vegetation, temperature, humidity, rain, wind speed, natural calamities, socio-economic conditions, poverty, livelihood and deforestation (due to urbanization). Some of the important associated risk factors need to be taken care of such as poor sewerage, crowded housing, non-use of bed-nets, lack of cleanliness due to illiteracy, presence of granaries inside the houses, sleeping near domestic animals, improper drainage system, human behavior, vegetation around the house, crop and soil type (water retentive), stray dogs (reservoirs of the parasite) in the locality and human settlements close to the forests all are the cause of sand fly propagation and the parasite transmission in Bihar, Jharkhand and West Bengal. The study further suggests that effective control measures have been taken in North India and elimination of kala-azar can be achieved in near future if we take in account the various risk factors mentioned above into consideration with the elimination programs with renewed vigor, effective drugs, diagnostics, better insecticides, modern surveillance techniques, absence of animal reservoir in the Indian subcontinent, services of health workers, awareness programs, education and prevention policies and strict supervision and support from the Government agencies.

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