Review Article

Epidemiology of visceral leishmaniasis in India

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ABSTRACT

Kala-azar has re-emerged from near eradication. The annual estimate for the incidence and prevalence of kala-azar cases worldwide is 0.5 million and 2.5 million, respectively. Of these, 90% of the confirmed cases occur in India, Nepal, Bangladesh and Sudan. In India, it is a serious problem in Bihar, West Bengal and eastern Uttar Pradesh where there is under-reporting of kala-azar and post kala-azar dermal leishmaniasis in women and children 0–9 years of age. Untreated cases of kala-azar are associated with up to 90% mortality, which with treatment reduces to 15% and is 3.4% even in specialized hospitals. It is also associated with up to 20% subclinical infection.

Spraying of DDT helped control kala-azar; however, there are reports of the vector *Phlebotomus argentipes* developing resistance. Also lymphadenopathy, a major presenting feature in India raises the possibility of a new vector or a variant of the disease. The widespread co-existence of malaria and kala-azar in Bihar may lead to a difficulty in diagnosis and inappropriate treatment. In addition, reports of the organism developing resistance to sodium antimony gluconate—the main drug for treatment—would make its eradication difficult.

Clinical trials in India have reported encouraging results with amphotericin B (recommended as a third-line drug by the National Malaria Eradication Programme). Phase III Trials with a first-generation vaccine (killed *Leishmania* organism mixed with a low concentration of BCG as an adjuvant) have also yielded promising results. Preliminary studies using autoclaved *Leishmania major* mixed with BCG have been successful in preventing infection with *Leishmania donovani*. Until a safe and effective vaccine is developed, a combination of sandfly control, detection and treatment of patients and prevention of drug resistance is the best approach for controlling kala-azar.

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INTRODUCTION

Leishmaniasis, a complex disease caused by the protozoan *Leishmania*, is spread over large geographical areas around the globe. In India, the disease manifests in two forms: the cutaneous (dry and wet) and the visceral (kala-azar) variety. The disease may be sporadic, endemic or epidemic. About 500 species of six genera of the female *Phlebotomus* are suspected or proven vectors transmitting the parasites from animal-to-animal, animal-to-man and man-to-man.[1] In India, the conditions that favour epidemics of kala-azar are rural areas more than 600 metres 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.[2]

In India, there have been several outbreaks of kala-azar since the last century. Various programmes to control the disease have failed despite considerable work being done on various facets of the disease.[3–8] However, information on the epidemiology of kala-azar in India is scanty. Nonetheless, the available information will be useful to understand the present status of the disease, its prevalence during the last couple of decades and allow the formulation of more effective strategies for its control.

BURDEN OF KALA-AZAR IN INDIA

The incidence of kala-azar in India is among the highest in the world. The global estimate for the incidence and prevalence of kala-azar cases per year is 0.5 million and 2.5 million, respectively.[9] Sixty-six countries have reported confirmed kala-azar cases[1] but 90% of these occur in India, Nepal, Bangladesh and Sudan.[10] In India, the calculated DALYs (disability-adjusted life years) lost due to kala-azar in 1990 were 6.8 million for men and 0.5 million for women. The corresponding global figures are 12 million for men and 8.6 million for women.[11] Following the resurgence of the disease in the 1980s, various reports have stressed the need to control the disease.[12,13]

The treatment of kala-azar is expensive, time-consuming and painful. The cost of a World Health Organization-recommended course of first-line treatment with antimonials is US$ 60–120[14] and the minimum expenditure incurred on the boarding and lodging of two relatives of each patient has been estimated at US$ 92–225.[15] This does not include the cost of nursing care and that of health care delivery. Untreated cases of kala-azar are associated with up to 90% mortality. The mortality with treatment has been reported to be 15% in some parts of the world[16] and 3.4% in specialized hospitals.[17] In India, where a little over 50% of the population has access to health care,[18] the mortality is likely to be much higher. In the pre-DDT era, the Nowgong district of Assam had recorded depopulation due to kala-azar.[19] In Sudan, in a protracted outbreak of kala-azar spanning 10 years, the mortality reached 57%.[20]

The earliest recorded outbreak of fever which could be ascribed to kala-azar was in 1824–25 in Jessore (presently in Bangladesh). It probably first appeared in Bihar in 1882, and in Assam in 1869 in the Garo Hill district (presently in Mizoram). A large number of cases were also reported from Tamil Nadu. Sporadic cases have been reported from Gujarat, Jammu and Kashmir and Himachal Pradesh. In the pre-DDT era, there have been well-documented epidemics of kala-azar in Assam, West Bengal and Bihar; the last major outbreak was reported around 1944 from Assam.

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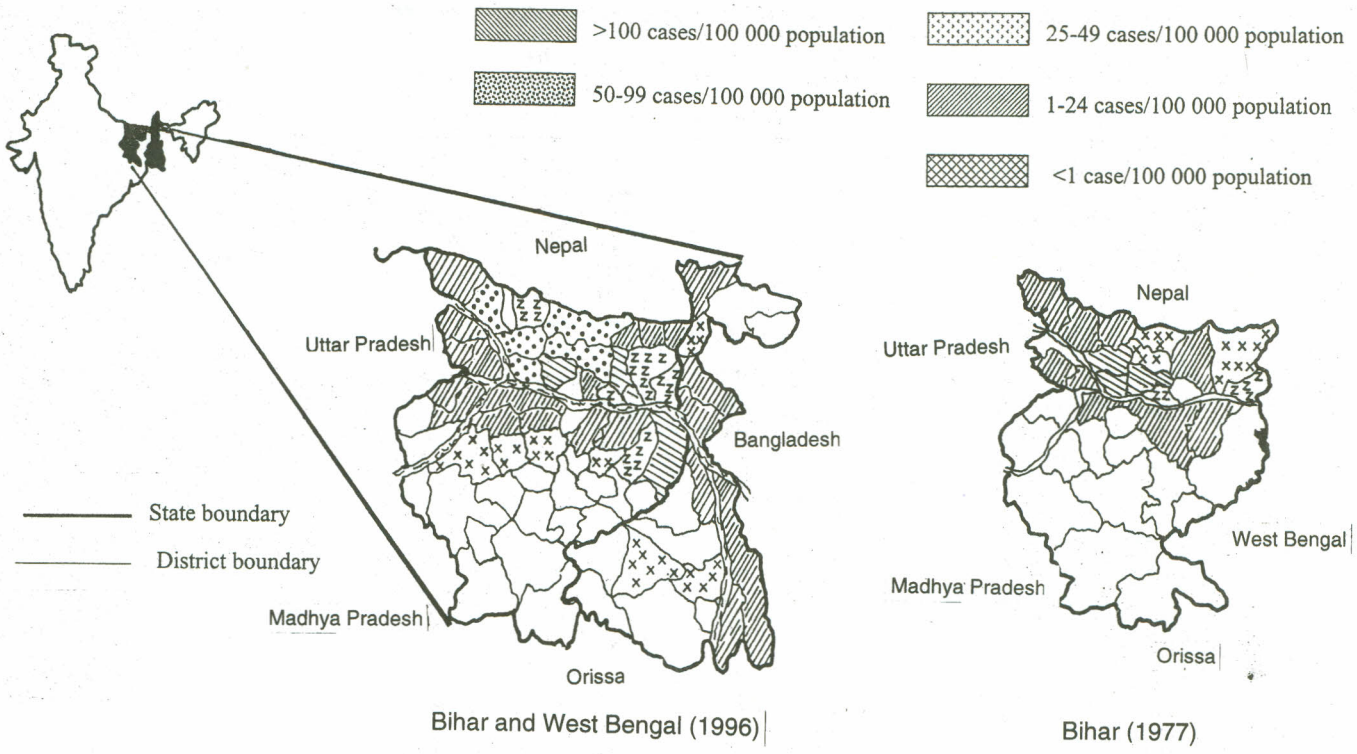

FIG 1. Map showing the kala-azar affected districts of Bihar and West Bengal

At present, kala-azar is a serious problem in Bihar, West Bengal and eastern Uttar Pradesh (Fig. 1). In 1996, Bihar and West Bengal had 33 and 10 affected districts, respectively. Sporadic cases[19–21] as well as outbreaks[22] have also been reported from other endemic and non-endemic areas. Patients from the hills of Uttar Pradesh have been increasingly reporting to Delhi[23–25] and Chandigarh[26] for treatment. However, the disease has remained under control in Assam and Tamil Nadu since the 1950s.

Bihar

Bihar is the worst affected state with exacerbations every 15–20 years since the 1930s (Fig. 2).[27] A similar pattern of cyclical fluctuation was seen in Assam in the pre-DDT era, with outbreaks occurring aproximately every 15 years.[19] Due to the absence of an effective surveillance system in Bihar, only patchy data are available for outbreaks before 1977–78. However, Sanyal *et al.* collected data between 1933–37 and 1956–60 from hospital and dispensary returns (Fig. 2) and found that 16 districts of Bihar had reported kala-azar during 1956–60.[28]

The different control programmes initiated in Bihar included:

1. Opening of kala-azar treatment centres,[28]
2. Mass spraying of DDT under the National Malaria Control Programme (NMCP) and the National Malaria Eradication Programme (NMEP),
3. Kala-azar control programme with UNDP assistance, and
4. A central government-assisted kala-azar control programme in 1991–92.

The three previous control programmes had only a temporary effect on the occurrence of the disease in the state. The kala-azar epidemic in 1974 affected four districts (Vaishali, Muzaffarpur, Samastipur and Sitamarhi) and the north-central and north-eastern districts in 1992. In the inter-epidemic year of 1981, minimum cases were reported due to the initiation of a control programme

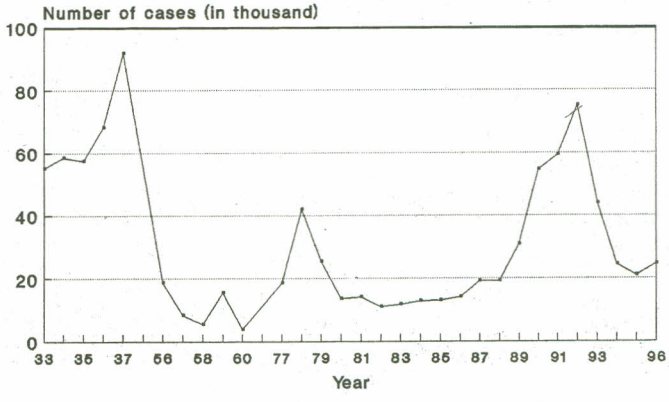

FIG 2. Kala-azar cases in Bihar (data for 1933–37 and 1956–60 from Sanyal *et al.*[28,41] and for 1977–96 from the National Institute of Communicable Diseases and National Malaria Eradication Programme)

in 1977–78 (Table I and Fig. 2). The number of cases reported per 100 000 population was 69 during the 1991–92 epidemic and 36.8 in 1996. A remarkable decline was observed in the Vaishali district. Ten districts of the state (nine to the north and one to the south of the river Ganges) have been reporting more than 75% of the total cases for several years. In 1996, these 10 districts reported 80% of the total cases, with 33 districts accounting for all the cases. Due to administrative and socio-political reasons, several new districts were created in 1996 and this had led to difficulties in analysing the subsequent district-wise data. However, most of these districts are located north of the river Ganges, and a spot map shows an almost similar distribution.

West Bengal

Pre-partition Bengal experienced several major outbreaks of kala-

TABLE I. District-wise distribution of reported kala-azar cases from Bihar in 1981, 1991 and 1996

District	1981			1991			1996		
	n	(%)	Frequency per 100 000	*n*	(%)	Frequency per 100 000	*n*	(%)	Frequency per 100 000
Samastipur	1124	(7.9)	53	6932	(11.6)	255	4124	(16.7)	132
Muzaffarpur	1126	(7.9)	48	8323	(14)	282	2667	(10.8)	79.8
Darbhanga	224	(1.6)	11	4277	(7.2)	170	2581	(10.5)	90.9
East Champaran	829	(5.9)	34	2018	(3.4)	66	2128	(8.6)	61.7
Madhubani	616	(4.3)	26	3593	(6)	127	1903	(7.7)	60.4
Vaishali	716	(5.1)	43	9658	(16.2)	451	1674	(6.9)	67.6
Saharsa	760	(5.4)	26	2752	(4.6)	246	1569	(6.4)	123
Madhepura	–		–	1268	(2.1)	108	1201	(4.9)	91.5
Sahebganj	–		–	2411	(4)	327	853	(3.5)	105
Sitamarhi	195	(1.4)	10	2477	(4.2)	159	824	(3.3)	47.1
Begusarai	312	(2.2)	21	2435	(4.1)	134	434	(1.8)	21.2
Purnea	5621	(39.7)	156	1331	(2.2)	71	534	(2.2)	25.3
Bhagalpur	324	(2.3)	12	1785	(3)	93	135	(0.5)	6.3
Saran	216	(1.5)	10	2105	(3.5)	82	692	(2.8)	24.0
Siwan	108	(0.8)	6	1216	(2)	47	202	(0.8)	8.4
Khagaria	83	(0.6)	–	1308	(2.2)	132	514	(2.1)	45.3
Katihar	973	(6.9)	68	950	(1.6)	52	644	(2.6)	30.8
Godda	–		–	1742	(2.9)	202	327	(1.3)	34.3
Patna	191	(1.3)	6	1296	(2.2)	36	164	(0.7)	4.1
Gopalganj	247	(1.7)	18	756	(1.3)	44	318	(1.3)	16.5
Munger	575	(4.1)	17	483	(0.8)	51	35	(0.1)	3.4
Bhojpur	–		–	69	(0.1)	4	54	(0.2)	2.7
West Champaran	–		–	89	(0.1)	4	640	(2.6)	24.2
Nalanda	1		0.06	206	(0.3)	10	52	(0.2)	2.3
Jahanabad	–		–	35	(0.06)	3	16	(0.06)	1.2
Nawada	–		–	35	(0.06)	3	1		0.1
Gaya	4		0.13	14	(0.02)	0.5	3		0.1
Aurangabad	–		–	13	(0.02)	0.8	9		0.1
Suppaul	–		–				194	(0.8)	12.9
Kishanganj	–		–	–		–	211	(0.9)	19.2
Ararea	–		–	–		–	274	(1.1)	14.9
Banka	–		–	–		–	7		0.5
Buxar	–		–	–		–	72	(0.3)	6
Dumka	–		–	8	(0.01)	0.5	–		–
Ranchi	–		–	3		0.1	–		–
Rohtas	–		–	26	(0.04)	1	–		–
Giridih	2		0.12	–		–	–		–
Dhanbad	1		0.05	–		–	–		–
Total	14 165		20	59 614		69	24 665		36.8

Figures within parentheses indicate percentage of yearly cases

azar (1824–25, 1832–33, 1857 and 1943–46). The present resurgence started after 1980. Table II shows the reported kala-azar cases during the last 10 years. The epidemic attained a peak during 1987 with 4447 reported cases, most of which were from the districts of Malda followed by West Dinajpur (combined north and south). The minimum cases since the last outbreak (1986–87) were reported in 1994. During the present resurgence, Darjeeling district reported 26 kala-azar cases for the first time in 1990, which increased to 142 by 1995. The higher stretches of Darjeeling district are environmentally unfavourable for the transmission of kala-azar.[2]

West Bengal had two foci of kala-azar in the current outbreak.[29] It seems that the infection was apparently introduced during 1980 to the northern districts of Malda, Murshidabad and the southern district of 24 Parganas (North) from adjoining areas of Bihar and Bangladesh, respectively. The movement of the disease in the state could be traced from 24 Parganas (North) to adjoining Nadia, Hooghly and 24 Parganas (South) districts by 1986 and to Burdwan by 1987. From Malda, it moved northward to West Dinajpur by 1984 and to Darjeeling by 1990. The southwest districts of West Bengal reported very few cases. From the neighbouring southeast districts of Bihar also only occasional cases were reported. The maximum number of cases were reported from West Dinajpur district during 1984 and from Malda and Murshidabad districts during 1987. This was followed by a sharp decline. However, the number of cases from 24 Parganas (north and south) showed little variation.

CLINICAL ASPECTS

The usual clinical features of kala-azar include general malaise, high fever, loss of weight, hepatosplenomegaly, anaemia, dark skin and extreme emaciation. However, extreme emaciation and pot belly are infrequently seen at present, as more and more cases report early for treatment. Hati *et al.*[30,31] reported an uncommon presentation of lymphadenopathy in the outbreak from Malda district of West Bengal. Sometimes, this may be the only clinical

TABLE II. Reported Kala-azar cases in West Bengal (1987–96)

District	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
Malda	2013	1294	1290	1024	526	300	267	84	73	149
West Dinajpur	1341	573	1078	654	322	362*	–	–	–	–
W. Dinajpur (N)							121	18	11	1
W. Dinajpur (S)							130	138	101	450
Murshidabad	860	816	669	760	745	465	397	426	578	716
24 Parganas (N)	51	35	296	371	244	269	256	250	452	420
24 Parganas (S)	103	179	130	112	64	78	73	133	136	110
Darjeeling	–	–	–	26	81	81	45	86	142	72
Nadia	16	7	63	30	29	12	3	5	15	64
Hooghly	15	18	6	32	2	6	2	7	4	2
Burdwan	48	146	61	28	17	1	4	2	0	3
Total	4447	3068	3593	3037	2030	1574	1298	1149	1512	1987

* This district was bifurcated into two in 1993

TABLE III. Age and sex distribution of kala-azar cases in different time periods

State	Year	Percentage distribution of cases in different age groups			M:F ratio	Source of data
		0–9	10–19	≥20		
West Bengal[38]	1925	21.1	43	35.9	3.2:1	Hospital
West Bengal[39]	1931	39.5	34.9	25.6	3.2:1	Survey
West Bengal[30,31]	1989–91	53.5	33.5	13	1.2:1	Outbreak
Bihar[40]	1928	37.8	32.9	29.3	2.8:1	Hospital
Bihar[41]	1979	29.3	27.4	42.7	1.7:1	Survey
Bihar[42]	1984	14	33	53	5.5:1	Hospital
West Bengal[43]	1995	17.5	31.3	51.3	na	Hospital
Bihar[33]	1989	37.9	26.9	35.2	1.8:1	Survey

na not available

TABLE IV. Age and sex distribution of patients with post kala-azar dermal leishmaniasis

Year	Percentage of cases in different age groups				M:F
	0–9	10–19	20–29	≥30	
1927[32]	7.7	35.9	30.8	25.7	3:1
1989[33]	44.9	22.4	26.5	6.1	1.4:1
1990[34]	11.0	45.0	23.0	21.0	
1970–89[44]	16.2	32.8	27.4	23.6	1.3:1

manifestation.[1] The clinical features of post kala-azar dermal leishmaniasis (PKDL) have remained almost the same over the years.[32,33] The lesions are seen on the face, trunk, genitalia (scrotum, penile shaft), extremities, tongue, palms and soles in decreasing order of frequency[34,35] and rarely on the areolae[36] and in the larynx.[37]

Age

In India, children in the age group 5–9 years were most affected[1] and the male–female ratio was 2:1. Table III shows the age and sex distribution of patients with kala-azar in West Bengal and Bihar.[30,31,33,38–43] All age groups were affected. However, among hospitalized patients, [30,40,42,43] 14%–37.8% were in the 0–9 years age group. In contrast, during epidemics,[30,31] 53.5% of the patients belonged to this age group, while in population surveys,[33,39,41] 29.3%–39.5% of cases were in the 0–9 years age group. There was a male preponderance in both hospital-based and population surveys. However, this was much higher (5.5:1) in hospitalized patients.[42] Up to 7% of treated and cured kala-azar cases developed PKDL.[33,39,41] In some cases, PKDL developed without the patient suffering from clinical kala-azar.[32] Table IV shows the age and sex distribution of PKDL cases from Bihar and West Bengal. A community survey[33] for PKDL showed a very high percentage in the 0–9 years age-group in contrast to other hospital-based studies.[32,34,44] Thus, it is possible that most of the kala-azar and PKDL cases in this age group and among women remain unreported in the community.

The intrinsic incubation period of kala-azar varies from 10 days to 9 months[45] and may extend up to 10 years.[46] The issue remains as confusing as ever with various workers reporting different incubation periods (4–6 months to one year,[39] 40 hours to 9 months,[42] and 10 days to over one year[1]).

Household infection

A number of infected persons remain asymptomatic or have subclinical disease.[1] Clustering of cases has also been documented. A recent study[47] showed 31.3% of households with more than one case. Of the 122 blood samples cultured from healthy subjects, 11 were positive for promastigotes of *L. donovani.*[48] In another study, 17.5% of healthy household members were leishmanin test-positive[48] indicating a high level of subclinical infection in the community. At the same time, between 0% and 50% of healthy people develop PKDL.[32,33,44] These lesions remain potential sources of infection in the non-epidemic years.

Seasonal distribution

Kala-azar cases have occurred throughout the year, but more so between April and August. Figure 3 shows the seasonal distribution of reported kala-azar cases during 1978, 1986, 1993–94 and 1995–96. A large proportion of cases were reported in the winter months during epidemics (1978, 1993–94) in contrast to the non-epidemic years (1986, 1995–96). Napier[38] had also reported a similar pattern of a higher number of cases between May and October.

CONTROL EFFORTS

Efforts at controlling kala-azar in India have been largely influ-

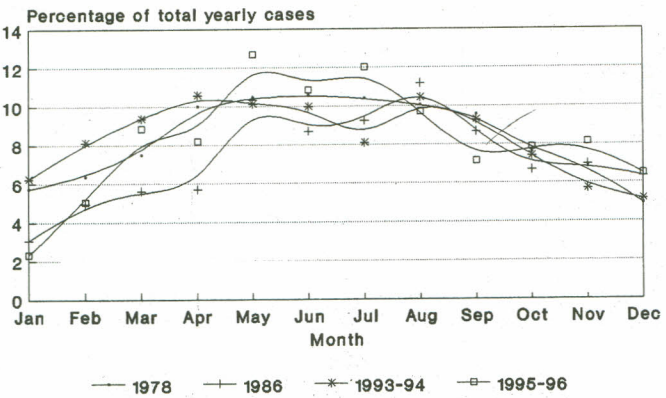

FIG 3. Distribution of kala-azar cases in Bihar in different months of the year (data for 1978 is from Sanyal *et al.* and for the rest of the years from the National Institute of Communicable Diseases and National Malaria Eradication Programme)

enced by the malaria control programme, except in the states of Bihar and West Bengal. After the success in kala-azar control through mass spraying of DDT in the 1950s, there has been no resurgence of the disease in several erstwhile endemic states including Assam. Thus, kala-azar control programmes are centred mainly around control activities in the states of Bihar and West Bengal.

Around 1937, 20 kala-azar treatment centres were opened in Bihar[28] resulting in a considerable reduction of cases. Mass spraying of DDT undertaken by the NMCP and NMEP coupled with effective treatment through kala-azar clinics resulted in a virtual eradication of the disease in the 1960s. Subsequently, when the NMEP entered the maintenance phase in 1961, DDT spraying was withdrawn. This probably allowed the disease to resurge resulting in a severe epidemic in 1974. A reduction in the morbidity and mortality due to the disease was recorded following the kala-azar control programme initiated by the National Institute of Communicable Diseases (NICD) with UNDP assistance in four epidemic districts in 1977. Though this programme was withdrawn in 1979, the decline in mortality and morbidity continued till 1981–82. Until 1989–90, kala-azar control activities were undertaken by the state governments. During 1990–91, a central government-sponsored kala-azar control scheme was initiated for the endemic states of Bihar and West Bengal.

Spraying of DDT has been the cornerstone of kala-azar control since the 1950s. Two rounds (February–March, May–June for Bihar and May–July, August–October for West Bengal) of DDT spraying were recommended.[49] In Assam, two rounds of DDT spraying over nine months (April–December) had yielded good results. It has been shown[50] that *Phlebotomus argentipes*, the vector of Indian kala-azar, reappears in 9 months after a one-time DDT spray of 1 g/m^2. Thus, the long gap between the 2 rounds of insecticide spraying in Bihar and West Bengal might have allowed the vector to rebuild its numbers. If the insecticide spray strategy as applied in Assam had been adopted for Bihar during 1991, it is possible that kala-azar would have ceased to be a public health problem in 1994.[51] Other workers have suggested surveillance of *Phlebotomus argentipes* density as a better option.[47] Localized intensive spraying around dwellings of known kala-azar cases taking the village as a unit, with early case detection and proper treatment could also be effective in controlling the disease. Prioritization of areas for control activities based on the endemicity level, distribution of PKDL cases, distribution and density of vector species, identification of the population at risk and high-risk groups should be used to identify areas for insecticide spraying. An extensive insecticide spray operation is neither cost-effective nor necessary.[47] An ecological management study in which plastering the walls and floor up to one foot from the angles on both sides has shown good results in reducing the indoor density of sandflies.[52]

The World Health Organization as well as the kala-azar control programme managers in India are increasingly trying to involve the community in kala-azar control efforts by decentralizing the planning process.[53] Such an effort proved useful in the Vaishali district of Bihar. Thakur *et al.* were successful in controlling kala-azar in a remote tribal area with the help of a non-governmental organization.[54]

After a detailed kala-azar survey[28] conducted by NMEP/NICD in 1977–78, only a handful of epidemiological studies were undertaken.[42,47,48,55] These studies[42,55] revealed that despite the government's initiative, more than half the cases of kala-azar attended private clinics for treatment and under-reporting had decreased from 5 times[28] to 2–2.5 times.[55]

DISCUSSION

Kala-azar has re-emerged from near eradication in the past. In the pre-DDT era, outbreaks of kala-azar had been occurring at almost regular intervals in Bihar and Assam.[19] A similar cyclical pattern was also reported from Brazil.[56] The repeated resurgence (Fig. 2) of the disease in Bihar is a commentary on the inefficacy of the control programmes that have been implemented to date. Fortunately, in India, the proven vector *Phlebotomus argentipes* is so far susceptible to DDT, though there are some reports of its developing resistance to the insecticide.[57] Sodium antimony gluconate (SAG), the main drug used for treatment, is still efficacious. However, a report from Kenya suggests that the organism might be developing resistance to this drug.[58]

In Bihar, there has been a considerable decline in the morbidity and mortality from kala-azar since the last outbreak in 1991–92. Since 1992, the kala-azar morbidity has declined by 67.3%. Yet 24 665 cases were reported during 1996; 1.74 times more than the number in 1981 (Table I and Fig. 2). The corresponding decline in mortality was 72.9%.[21] However, the total number of cases and deaths have increased 2–5 times.[14,55] Two foci of kala-azar were introduced in West Bengal almost simultaneously.[29] In one area, the number of cases has declined considerably compared to the other area where it is still on the increase. Whether this is due to a failure of control measures or due to some other factor needs to be ascertained.

A sizeable proportion of kala-azar cases in women and children in the 0–9 years age group are not reported (Table III). This is also true for PKDL (Table IV), as these lesions cause no perceptible problem. In an endemic situation, persons in the younger age groups are more affected. Sub-clinical infection in kala-azar is up to 20%.[48] People who are now 30 years or older were likely to have remained uninfected in childhood and adolescence, as kala-azar was on the decline during the 1960s. This makes them susceptible even at a much later age. This might be the reason for a larger number of cases in the older age groups in the present outbreaks in Bihar and West Bengal.[43]

The under-reporting of cases among women and young children may be due to various prevailing socio-cultural and economic reasons among the people of these areas, which make them reluctant to bring women and children to hospital. Similar obser-

vations have been reported from Colombia and Costa Rica.[16] Thus, a kala-azar and PKDL survey should be undertaken to determine the extent of the current problem. The importance of detecting and treating patients with PKDL for effective control of kala-azar has been emphasized.[43]

Lymphadenopathy is a common presenting feature of kala-azar in the Mediterranean region,[27] where the vector/agent differs from the one in India.[1] About 5% of kala-azar patients in Iran develop lymphadenopathy and, recently, *Leishmania tropica* has been isolated from lymph nodes during an outbreak.[59] The reports of lymphadenopathy as a major presenting feature in India raise the possibility of a new vector or a variant of the disease. This urgently needs to be investigated. In areas where malaria and kala-azar are endemic, co-existent malaria and kala-azar may lead to difficulties in diagnosis and appropriate treatment. Nandy *et al.* indicated widespread co-existence of malaria and kala-azar in Bihar.[60] In the absence of good laboratory support, physicians resort to therapeutic trials in all suspected cases. This might lead to non-responsiveness and the development of resistance to conventional drugs.

Once the disease occurs in a patient and is treated, it confers lifelong immunity.[1] However, recently there have been two reports to the contrary from India.[61,62] Several investigators have reported visceralization of *Leishmania tropica*.[63–65] This organism is mainly zoonotic and has been isolated from a newborn puppy.[66]

It has long been accepted that man is the only reservoir of kala-azar in India. However, there is always a chance of *Leishmania* adopting some other animal reservoir.[57] No study has attempted to look for such an animal reservoir. The increasing non-responsiveness of kala-azar in India to SAG could also be due to the presence of *Leishmania tropica.* This is a matter of grave concern for public health administrators in India, especially in the states of Bihar and West Bengal. It has been presumed that only *Leishmania donovani* causes kala-azar in India, which means that the Indian population is highly susceptible to infection by *Leishmania tropica.* This, coupled with unresponsiveness to the first-line drug could easily lead to a major disaster.

Present research scenario

Most of the current research is being directed towards the development of newer and more effective drugs against kala-azar. These include amphotericin B,[67–70] gold salt,[71] co-trimoxazole with antitubercular drugs,[72] verapamil,[73] paramomycine,[74] and gamma-interferon.[75]

Clinical trials in India have reported encouraging results with amphotericin B and it has now been recommended by NMEP as a third-line drug.[21] A number of plant extracts have been tried against leishmaniasis with some success in the laboratory[76,77] but are of little use clinically.

The complexity and variety of epidemiological settings for foci of leishmaniasis makes it difficult to develop universally adaptable control measures, except for a vaccine.[16,78,79] Phase III trials with a first-generation vaccine (killed *Leishmania* organism mixed with a low concentration of BCG as an adjuvant) produced encouraging results.[16] A non-human primate model has been developed to evaluate various vaccines/drugs for leishmaniasis caused by *Leishmania donovani*.[80] Preliminary studies using autoclaved *Leishmania major* (ALM) mixed with BCG have been successful in preventing infection with *Leishmania donovani.*[16]

However, until a safe and effective vaccine is developed, a combination of sandfly control, detection and treatment of patients, and prevention of drug resistance is the best approach for the control of this disease.[47,51,81]

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