

1 Review Article

2 **Visceral leishmaniasis (Kala Azar) elimination from Indian sub-continent by 2015?**

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5 **Abstract:**

6 Objective: Review was done to study the achievement of elimination of visceral
7 leishmaniasis (Kala Azar) from Indian sub-continent by 2015.

8 Method: Both electronic and manual databases were searched for studies related to Kala azar.

9 Finding: The burden of Kala azar is grossly underestimated by the health systems in the
10 Indian sub-continent due to over-reliability on passive surveillance. The poly parasitism and
11 co-infections are major emerging problems in world of Kala azar. Resistance had been
12 reported for DDT Indoor residual spraying. There are poor-quality drugs for the treatment
13 and lack of regular supply.

14 Conclusion: Achievement of elimination of Kala azar from Indian sub-continent is still
15 unpredictable. To give pace to the elimination, Kala azar could be addressed as notified
16 disease. There is need to focus on the present strategies and more intensive monitoring is
17 required. Also there is need to assess alternative vector control methods New researches
18 should be explored. Policies to control Kala-azar will have to include many activities that
19 involve public awareness and modifying behaviour. Kala-azar may not affect the national
20 economy or the national GDP, but it devastates the family.

21 **Introduction:**

22 Visceral Leishmaniasis (VL), also known as *Kala azar* or *black fever*, is a vector-borne
23 parasitic disease.¹ *Kala azar* is one of the World's most neglected and poverty-related
24 diseases, affecting the poorest people in developing countries associated with malnutrition,
25 weakness of the immune system, displacement, poor housing, illiteracy, gender
26 discrimination, and lack of resources.² *Kala azar* is spread over large geographical area
27 across the globe with estimated yearly incidence of *Kala azar* is 500,000 cases which lead to
28 loss of nearly 2.4 million disability-adjusted life years (DALYs) each year.³ Since the last
29 century several outbreaks of Kala azar have been affected South East Asia. Various

30 programmes to control the disease have failed despite considerable efforts being done for
31 prevention and control of the disease.⁴

32 This review was done to analyze the bottlenecks in achieving elimination of Kala azar and to
33 identify the additional strategies towards faster achievement of the Goal in South East Asia.
34 Information was collected from various data bases like PubMed, Google Scholar and WHO
35 database using Key words Kala azar, Visceral Leishmaniasis, Neglected tropical diseases,
36 and Black fever. Manual search of literature was done in B.B. Dikshit library and National
37 Medical library, New Delhi. The main focus was kept on community based studies of South
38 East Asia Region. This review generated a number of articles which were further shortlisted.
39 Main finding are being summarized.

40 **Why Visceral Leishmaniasis is a candidate for elimination:**

41 Currently several factors have made a smooth road for achieving the goal of elimination of
42 *Kala azar* from the South East Asia Region.⁵ In SEAR, as the only causative agent is
43 protozoan parasite *Leishmania Donovan*i, only known vector is female Sandfly of genus
44 *Phlebotomus* *Argentipes* and only reservoir is human.^{6,7} Availability of effective and
45 relatively safer drugs like Miltefosine and liposomal Amphotericin for treatment, Indoor
46 residual spray and availability of a rapid diagnostic test (rk39) makes *kala azar* a candidate
47 for elimination.^{8,9} India, Bangladesh and Nepal have demonstrated strong political will and
48 commitment towards elimination of *kala azar* by signing a Memorandum of understanding
49 (MoU) during the World Health Assembly in Geneva in 2005.⁹ The goal of Tripartite MoU
50 was to contribute for improving the health status of vulnerable groups and at-risk population
51 living in *Kala azar* endemic areas of Bangladesh, India and Nepal by the elimination of *Kala*
52 *azar* so that it would no longer be a public health problem.^{3,10}

53 **Epidemiology of Kala Azar:**

54 *Kala azar* is endemic in 88 countries particularly in Africa, Latin America, South and Central
55 Asia, the Mediterranean basin and the Middle East with over 200 million people at risk.^{2,11} In
56 the South East Asian Region *Kala azar* is prevalent in India, Bangladesh and Nepal and with
57 few foci in Bhutan.⁶ It is endemic in 115 districts spread over this four countries namely India
58 (52), Bangladesh (45), Nepal (12) and Bhutan (6).¹¹ In India major tolls of *Kala azar* cases
59 comes from Bihar, Uttar Pradesh, West Bengal and Jharkhand with over 165.4 million people
60 at risk.¹⁰ In India there is resurgence of *Kala azar* in last few year but overall deaths are
61 declining.^{10,11} (Figure 1) Epidemiologically *Kala azar* epidemic cycle takes place almost
62 every 15–20 years.¹² Population at risk is nearly 65 million, 7.5-8 million, and 2.5 lakhs in
63 Bangladesh, Nepal and Bhutan respectively.^{11,13} Regardless of lots of stratagem for

elimination estimated annual incidence of *Kala azar* case is varying from 20 – 25 in India, 5 – 8 in Nepal and 13 –31 in Bangladesh per 10,000 population.⁸

Steps and strategies towards elimination:

In India, first step which decline the incidence of *Kala azar* was residual insecticide spray under National Malaria Control Programme in year 1953 which lead to significant reduction in cases of *Kala azar*.¹⁴ In Bangladesh *Kala azar* virtually disappeared during the ‘Malaria Eradication Programme (1961-1970).¹¹ In India centrally sponsored *Kala azar* Control Programme was launched in endemic areas in year 1990.¹⁵ The program merged with National Rural Health Mission in year 2005 under the name of National Vector Borne Disease Control Programme (NVBDCP).⁷ *Kala azar* is one of the six entities under NVBDCP in India.¹⁰ Government of India in 2002 National Health Policy had set a goal to eliminate *Kala azar* by year 2010, which could not be attained.¹⁶ Presently the Tripartite MoU aims towards reducing the annual incidence of *Kala azar* and post *Kala azar* dermal Leshmaniasis (PKDL) to less than one per 10,000 population at district (or sub-district) level by the end of year 2015. As per current situation uncertainty prevails in achieving this target. *Kala azar* is among the six entities under portfolio of ‘Programme for Research Training in Tropical Diseases’ (TDR) under World Health Organization. Since its foundation in the year 1975, TDR had led five major elimination campaigns for *Kala azar* in South East Asia.

Kala azar elimination is planned in four phases in South East Asia. **Preparatory phase** of two years started in year 2005 followed by **Attack phase** of five years. Year 2012 marks the start of **Consolidation phase** for next three years followed by **Maintenance phase** of at least two to three years.¹¹ Signing of tripartite MoU by three countries commence the beginning of Preparatory phase. Main activities during this phase were pilot total spraying operation, establishment of diagnosis and treatment facilities in endemic countries, monitoring and planning. It is followed by the attack phase. The main activities during this phase included the indoor residual spraying in endemic areas, integrated vector management, early diagnosis and treatment, case detection, and vector surveillance, community mobilization, external country evaluation and building research capacity. Presently the consolidation phase has started for next three years. It is aimed to do active surveillance till no increase in the incidence rate of *Kala azar* occurs at district and sub district levels in endemic countries. Total coverage spraying is modified to limit indoor residual spraying in endemic areas. This will be followed by maintenance phase intending to do surveillance against reintroduction of *Kala azar* until *Kala azar* is no longer a public health problem. This

will be verified by an international review commission followed by certification of the elimination status.^{3, 11}

Major strategies of WHO for elimination of *kala azar* are effective disease surveillance, early diagnosis and treatment, effective vector control, social mobilization of the population at risk, and clinical and operational research.¹¹ India under NVBDCP is sharing these strategies as effective vector control, early diagnosis and treatment, Information education communication and capacity building.¹⁰

Kala azar elimination initiative in India under NVBDCP includes patient coding scheme and monthly *Kala azar* reporting format. The coding would be arranged in the order of Country code, State code, District code, PHC code, Sub-Centre or NGO code and patient code. Patient coding scheme will make possible to track all patients up to the village level. Besides this double counting of *Kala azar* cases will be overcome. The coding scheme is still in preparatory phase.¹⁴

The case definition for suspecting *Kala azar* is history of fever of more than more two weeks not responding to antibiotics and antimalarials.¹¹ The disease usually present along with splenomegaly, anemia and progressive weight loss.¹⁰ This is supplemented by laboratory test mainly direct agglutination, rk39 dipstick and ELISA nevertheless all these tests are IgG based which is relatively long lasting. Confirmatory test is demonstration of parasite in bone marrow, spleen, lymph node aspiration or in culture medium.¹⁰

For almost six decades pentavalent antimonials were used for treatment of *kala azar* till drug resistance emerged in 1970. Newer oral drug that are effective and long lasting are Miltefosine and Amphotericin B.^{17, 18} *Kala azar* have more than 80 percent mortality if not treated.⁴ subsequently early diagnosis and treatment is extremely valuable to reduce case fatality.

In India mainstay of vector control is through indoor residual spraying (IRS) of DDT up to six feet height from the ground being biannually.³ Indoor Residual spraying has nearly eliminated *Kala azar* from north-eastern states of Assam, Meghalaya and Tripura.¹⁹ IRS is conducted in all villages which reported *Kala azar* cases in the past five years or during the year of spraying and in villages which are free of *Kala azar*, but are on search for cases of *Kala azar*.¹⁹ In Bangladesh and Nepal DDT is not recommended as under National policy. Another available option is use of Pyrethroid. IRS must be carried out within a radius of one kilometre of water bodies harboring the vector.¹¹ In addition to *Kala azar* medicines and insecticides, cash assistance is also being provided to endemic states since December 2003 to facilitate effective strategy implementation.¹⁰

For success of elimination, social mobilization is vital. It is required for the success of early diagnosis and treatment, for promoting treatment seeking, supporting indoor residual spraying and reducing human vector contact. The NVBDCP is exercising information education and communication system for effective behavioural change communication. More clinical research is required to develop new drugs and diagnostics.

Challenges in elimination:

The key indicators of *Kala azar* elimination are case detection rate, treatment completion rate, coverage rate for vector control and social mobilization.²⁰

The burden of *Kala azar* is grossly underestimated by the health systems in the Indian sub-continent due to over-reliability on passive surveillance.^{21,22} Though *Kala azar* patients ultimately report to health centers and hospitals, diagnosis is often missed in the early stages of infection and delayed due to lack of diagnostic facilities at peripheral levels of health system with a consequent delay in treatment and sustaining the human reservoir.⁷ Many *Kala azar* cases go undiagnosed in a web of unqualified medical practitioners which further adds to considerable delay in diagnosis and treatment.²³ Patients who are going to private sector for treatment usually stops in between due to cost leading to prolong transmission.¹⁸ Strategy is to improve reporting by strengthening diagnosis and treatment besides involving the private sector.

To give pace to the elimination, *Kala azar* could be addressed as notified disease.²⁴ There is wide gap in training and support of staff with technical and management expertise. As prevention and control activities for *Kala azar* are increasing in India there is need to strengthen health system.¹¹

The poly parasitism and co-infections are major emerging problems in world of *Kala azar*. In recent years the threat of HIV and *Kala azar* co-infection is amplifying. To date, co-infection with leishmaniasis and HIV has reached 35 countries. The risk of developing *Kala azar* in endemic areas is about 100 to 1000 times higher in individuals infected with HIV. HIV infection also impairs treatment response and increases the likelihood of recurrence.²⁵ If HIV epidemic spreads to the general population where kala azar is endemic, it may have disastrous consequences.¹¹

Resistance had been reported for DDT Indoor residual spraying and use of insecticide treated nets are inconclusive so there is need to assess alternative vector control methods. Governmental indoor residual spraying was not in operation in Bangladesh till year 2010 and sub optimum in India and Nepal in attack phase.²⁶ A research strategy is required to develop

new methods for vector control considering air and water pollution, deforestation, habitat fragmentation, ecological disruption and changing agricultural practices which all have an impact on the incidence, prevalence and spread of infectious diseases.²⁴

Post Kala Azar Dermal Leshmaniasis (PKDL) patients have probably epidemiological importance in *Kala azar* transmission as the lesions can harbour a large amount of Leishmania parasites, and as such could constitute a reservoir in the community capable of triggering a new epidemic.¹⁷ As PKDL causes little or no clinical discomfort, and PKDL treatment with intramuscular SSG injections is long (3–4 months), painful and cumbersome, few patients seek treatment.

A generic Miltefosine pharmaceutical product emerged in Bangladesh for the treatment of visceral leishmaniasis and use in the national elimination programme. Poor-quality drugs for the treatment of this fatal neglected tropical disease are not only life-threatening but also have a devastating impact on public health and elimination programme targeting this disease.²⁷ *Kala azar* patients belong to the poorest quintile of the population, which make them highly dependent for drug provision by National elimination programme. These extremely vulnerable patients deserve to be protected by national or regional drug regulators who should take responsibility by implementing the necessary precautions to prevent poor-quality drugs.²⁷ Shortage and supply delays of *Kala azar* drugs, unavailability of diagnostics at the health center level often contributes to the community's poor public perception of the public health systems and as consequent low community participation in *Kala azar* control program activities.^{8,28} Production of medicines for neglected tropical diseases ought to become attractive to manufacturers of generic drugs.²⁴

Kala-azar may not affect the national economy or the national GDP, but it devastates the family. This is because the poorest of the poor who are maximally affected by the disease sink deeper into poverty following an attack of *Kala-azar*. The strategy for elimination of *Kala azar* should focus intersectoral coordination aimed at improving the socio-economic status of the poorest of the poor in the community. *Kala azar* leads to a loss of about four lakhs DALYs every year in Nepal amounting to a loss of approximately US\$ 140 million annually.²⁹ The evidence-based policy needs to be developed to make Programme more cost-effective.¹³ Elimination of *Kala azar* in member countries of the WHO South-East Asia Region is relevant for achieving the Millennium Development Goals (MDGs) by alleviating poverty.¹¹

Policies to control *Kala-azar* will have to include many activities that involve public awareness and modifying behaviour. Planning of prevention and control measures for *Kala*

azar should take into account the possible effects of migrants and moving population. The allocated budget per person per year for risk population by national programme for Bangladesh, India and Nepal as estimated are around 0.2, 0.4 and 0.3 US\$ for Bangladesh, India and Nepal respectively.¹³ Support from International agencies and Nongovernmental organization need to be achieved to overcome the economic constraints.

Future course towards elimination:

To combat the problem of treatment failure in kala azar and to reduce length of therapy, combination of at least two effective anti leishmanial agents is a need to be assessed.¹⁷ Regular availability of drugs around the year, good quality drugs, less waiting time at clinics, easily approachable, doctors with good communication skills and flexible clinic hours may ensure greater compliance. Reporting of cases of PKDL should be an integral part of the surveillance and monitoring system. Early identification can be improved by counseling *Kala azar* patients on the risks and the signs of PKDL during their treatment.

Environmental management for vector control (EVM) and integrated vector management (IVM) should be emphasized more. Role of newer methods like long-lasting insecticide-treated net and plastering household walls need to be explored for effective vector management. Community cooperation is to be gained for indoor residual spraying.

Need for Vaccine:

Vaccine against leishmaniasis for general human use is still under trials. Presence of an effective vaccine is one of the pillars for achieving elimination. Major factor of which vaccine is not being in use is the lack of a conceived market for human leishmaniasis vaccines. More over leishmaniasis is a regional problem and not global one.³⁰

Endemic country of SEAR needs to concentrate on more of research work for intensive active case detection to estimate the correct burden of disease. This could be house to house search also known as blanket screening, index case approach by snowballing, camped base approach or incentive based approach.

Nearly 50% of the problem of kala-azar is in the districts located on the international borders. The porous international border between India and Nepal accentuate the problem through uninhibited population movement and migration. Regular exchange of information at the local level, institutional networking for capacity development and use of similar protocols for diagnosis and treatment and synchronization of prevention efforts can contribute significantly to the elimination efforts. Improved quantitative information systems need to be made so that information about the epidemiology, transmission and burden of Kala azar and PKDL is accurately assessed. Effective behaviour change communication is needed to sensitize the

people. Electronic media will prove to be a powerful tool for this. Public private partnership and involvement of NGOs needs to be strengthened. Political commitment and development of accountability is urging of the time. Though three endemic countries have three more years to achieve the set targets but it is still far off the expectation.

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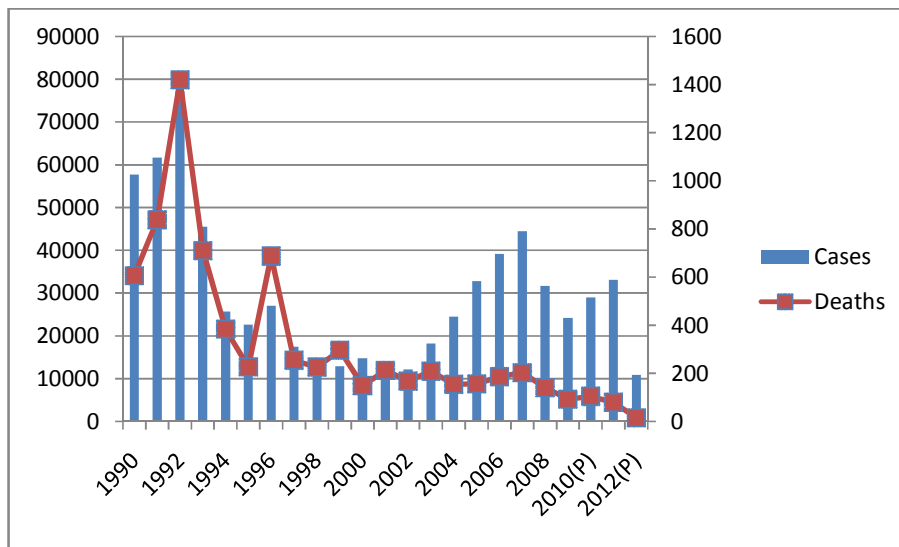


Figure1: Showing the trend of cases and death due to Kala azar in India