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Visceral Leishmaniasis (*Kala Azar*) Elimination from Indian Sub-continent by 2015

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AG and SSM conducted the review. Author MN helped draft the article. Author CL was involved in review of the highlighting the shortcomings in the article and in editing. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Objective: To review the progress towards the goal of elimination of visceral leishmaniasis (*Kala azar*) from the Indian sub-continent by 2015.

Method: Both electronic and print databases were searched for studies related to *Kala azar*.

Finding: The burden of *Kala azar* is grossly underestimated by the health systems in the Indian sub-continent due to over-reliance on passive surveillance. Poly-parasitism and co-infections are the major emerging problems in the world of *Kala azar*. Resistance has been reported for DDT indoor residual spraying. Treatment drugs are not ideal, and supplies of these drugs are irregular as well.

Conclusion: Achievement of elimination of *Kala azar* from Indian sub-continent is still unpredictable. To improve the elimination of *Kala azar* it should be classified as a notifiable disease. There is a need to refocus current strategies and monitor the program more closely. Furthermore, there is a need to assess alternative vector control methods. Policies to control *Kala azar* will have to include health education and behaviour change. *Kala azar* may not affect the national economy or the national GDP, but it devastates the

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families affected.

Keywords: *Kala azar*; visceral leishmaniasis; neglected tropical diseases; black fever.

1. INTRODUCTION

Visceral Leishmaniasis (VL), also known as *Kala azar* or *black fever*, is a vector-borne parasitic disease [1]. *Kala azar* is one of the World's most neglected and poverty-related diseases, affecting the poorest people in developing countries associated with malnutrition, weakness of the immune system, displacement, poor housing, illiteracy, gender discrimination, and lack of resources [2]. *Kala azar* is spread over a large geographical area across the globe with estimated yearly incidence of *Kala azar* of 500,000 cases, which lead to loss of nearly 2.4 million disability-adjusted life years (DALYs) each year [3]. Since the last century several outbreaks of *Kala azar* have affected South-East Asia. Various programmes to control the disease have failed despite considerable efforts being done for prevention and control of the disease [4].

This review was done to analyze the bottlenecks in achieving the elimination of *Kala azar* and to identify the additional strategies towards faster achievement of the Goal in Indian Subcontinent. Information was collected from PubMed, Google Scholar and the WHO database using the key words *Kala azar*, Visceral Leishmaniasis, Neglected tropical diseases, and Black fever. A manual search of the literature was conducted in the B.B. Dikshit library and National Medical library, New Delhi. Further criteria included: community-based studies of *Kala azar* in the South-East Asia Region, available for free and in the English language. No date restrictions were applied to the search. On initial search of key words and manual search identified 48 articles of which 22 met our additional criteria. Main findings are summarized in the present article.

2. WHY IS VISCERAL LEISHMANIASIS A CANDIDATE FOR ELIMINATION?

Currently several factors have made a smooth road for achieving the goal of eliminating *Kala azar* from the South East Asia Region (SEAR) [5]. In SEAR, the only causative agent is protozoan parasite *Leishmania Donovanii*, the only known vector is the female Sandfly of genus *Phlebotomus Argentipes* and the only reservoir is human [6,7]. Availability of effective and relatively safer drugs like Miltefosine and liposomal Amphotericin for treatment, indoor residual spray and availability of a rapid diagnostic test (rk39) makes *Kala azar* a candidate for elimination [8,9]. India, Bangladesh and Nepal have demonstrated strong political will and commitment towards elimination of *Kala azar* by signing a Memorandum of Understanding (MoU) during the World Health Assembly in Geneva in 2005 [9]. The goal of Tripartite MoU was to contribute for improving the health status of vulnerable groups and at-risk population living in *Kala azar* endemic areas of Bangladesh, India and Nepal by the elimination of *Kala azar* so that it would no longer be a public health problem [3,10].

3. EPIDEMIOLOGY OF *Kala azar*

Kala azar is endemic in 88 countries, particularly in Africa, Latin America, South and Central Asia, the Mediterranean basin and the Middle East with over 200 million people at risk [2,11]. In the South-East Asian Region *Kala azar* is prevalent in India, Bangladesh and Nepal and with few foci in Bhutan [6]. It is endemic in 115 districts spread over this four countries

namely India (52), Bangladesh (45), Nepal (12) and Bhutan (6) [11]. In India *Kala azar* cases are concentrated in Bihar, Uttar Pradesh, West Bengal and Jharkhand with over 165.4 million people at risk [10]. In India there is a resurgence of *Kala azar* in last few years, but overall deaths are declining [10,11]. (Fig. 1) Epidemiologically, *Kala azar* follows an epidemic cycle resurging almost every 15–20 years [12]. The population at risk is nearly 65 million, 6 million, and 2.5 million in Bangladesh, Nepal and Bhutan respectively [11,13]. Regardless of lots of strategy for elimination estimated annual incidence of *Kala azar* cases are varying from 20 – 25 in India, 5 – 8 in Nepal and 13 –31 in Bangladesh per 10,000 population [8].

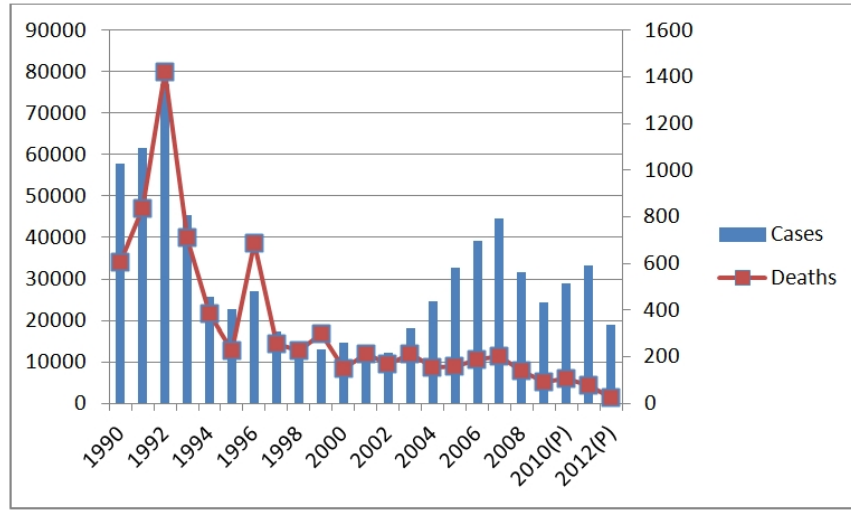


Fig. 1. Showing the trend of cases and death due to Kala azar in India (as updated on 08. January. 2013)

4. STEPS AND STRATEGIES TOWARDS ELIMINATION

In India, first step that decreased the incidence of *Kala azar* was residual insecticide spray under National Malaria Control Programme in the 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 the year 1990 [15]. The program merged with National Rural Health Mission in the 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 Leishmaniasis (PKDL) to less than one per 10,000 population at the district (or sub-district) level by the end of the 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 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 the 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 commences 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 until no increase in the incidence rate of *Kala azar* occurs at the 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 it possible to track all the 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 two weeks not responding to antibiotics and antimalarials [15]. The disease usually presents 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 the demonstration of parasite in bone marrow, spleen, lymph node aspiration or in the culture medium [10].

For almost six decades pentavalent antimonials were used for treatment of *Kala azar* until drug resistance emerged in 1970. Newer drugs that are effective and long lasting are Miltefosine and Amphotericin B [17,18]. *Kala azar* has more than 80 percent mortality if not treated [4]. Subsequently early diagnosis and treatment is extremely valuable to reduce case fatality.

In India the mainstay of vector control is through indoor residual spraying (IRS) of DDT up to six feet height from the ground done biannually [3]. IRS 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 under the National policy. Another available option is the 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. New Drugs will be required as Amphotericin B is an injectable preparation whose compliance is poorer as compared to a newer oral preparation and also in India the drug Miltefosine is not freely available [23].

5. 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-reliance 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 the health system with a consequent delay in treatment and sustaining the human reservoir. Besides this unavailability of noninvasive rapid diagnostic test aggravates the delay the diagnosis [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 stop in between due to high cost, leading to prolonged transmission [18]. Strategies are 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 notifiable disease [24]. This will not only help to estimate the true burden of *Kala azar* but also hasten the treatment of patients identified with better monitoring. There is a 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 a need to strengthen the 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 was reported for DDT indoor residual spraying and uses of insecticide treated nets are inconclusive, so there is a need to assess alternative vector control methods. Governmental indoor residual spraying was not in operation in Bangladesh until 2010 and sub optimum in India and Nepal during the 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 have an impact on the incidence, prevalence and spread of infectious diseases [24].

Post Kala Azar Dermal Leishmaniasis (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 families affected. 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 annum 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]. Supports from international agencies and non-governmental organizations need to be achieved to overcome the economic constrains.

6. FUTURE COURSE TOWARDS ELIMINATION

To combat the problem of treatment failure in *Kala azar* and to reduce the 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. Over the counter, sale of anti leishmanial drugs should be restricted. This could be a major step towards preventing the emergence of resistance against anti-leishmanials. 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. Improved detection

of PKDL cases by health workers would be useful. The PCR should be promoted for the diagnosis of PKDL. Supervised treatment could be a way for improving treatment compliance by patients.

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

A vaccine against leishmaniasis for general human use is still under trial. Presence of an effective vaccine is one of the pillars for achieving elimination. One major factor for a vaccine not being in use is the lack of perception of a market for human leishmaniasis vaccines. Moreover, leishmaniasis is a regional problem and not global one [30]. Endemic country of SEAR needs to conduct active case detection to estimate the correct burden of disease. This could include house to house surveillance also known as blanket screening, the index case approach using snowballing, a camped base approach or an incentive-based approach.

Nearly 50% of the problem of *Kala azar* is in the districts located on international borders. The porous border between India and Nepal accentuate the problem through population movements, including migration. Regular exchange of information at the local level across borders, 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. A number of strategies and tools exist to improve global health that can be applied to *Kala azar*. Improved information systems need to be constructed so that the epidemiology, transmission and burden of *Kala azar* and PKDL is accurately assessed. Effective behaviour change communication is needed to sensitize the people. Various forms of local advertisement like street plays, health talks, hoardings and other methods, along with electronic media will prove to be a powerful tool for this. Public-private partnership and involvement of NGOs need to be strengthened in order to provide better services to *Kala azar* patients. Public-private partnership is essential to boost funding and support. Political commitment and development of accountability is the need of the hour. Though three endemic countries have three more years to achieve the set targets, we are still far from our targets.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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