Manipal Journal of Medical Sciences

Volume 4 | Issue 1 Article 6

6-1-2019

Kala-Azar elimination in India-Where do we stand

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Editorial

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Visceral Leishmaniasis (VL) is a tropical disease, which is caused by parasite *Leishmania donovani.* Female*Phlebotomus argentipes* (commonly known as sand fly) which has feasted on a human infected by Leishmania, transmits the parasite from infected to the healthy humans. Visceral Leishmaniasis (Kala-azar) is the disease of poverty and generally affects the poorest of the poor. [1]

Kala-azar is also known as the Black fever and Dumdum fever and has been endemic in India since historical times and Bengal is the oldest known Kala-azar endemic area in the world. The word 'kala' means black and 'azar' means fever in Hindi, the disease gets its name because of the peculiar darkening of the skin. If left untreated, it can lead to death in 100% of the patients within two years' time. The disease-causing organism (parasite) for the first time was identified by Dr William Leishman in Calcutta (Dumdum), India and by Dr Charles Donovan from a patient suffering from prolonged fever in Madras (Chennai) almost simultaneously in year 1903. The organism was named after both of them as '*Leishmania donovani.*' The transmission of Kala-azar in Indian sub-continent is restricted to areas with heavy annual rainfall, mean humidity above 70%, a temperature range of 15–38°C, with abundant vegetation, subsoil water and alluvial soil. The disease is commonly seen in villages where houses are constructed of mud walls, and cattle and other livestock are living close to humans.

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Manuscript received : 16/6/19
Revision accepted : 16/6/19

The patient infected by *Leishmania donovani* has presence of parasite in the organs (spleen, liver and bone marrow) involved in hematopoiesis and leads to complaints of fever, loss of weight, weakness and loss of appetite. Post Kala-azar Dermal Leishmaniasis (PKDL) is a late sequel, among those who have received treatment for VL in the past and patients usually present with painless lesion of skin that may be macular, papular and/or nodular.

The Directorate of National Vector Borne Disease Control Program (NVBDCP) recommends the following treatment modalities for VL and PKDL cases

- **Visceral Leishmaniasis:** (i) Single-dose single day treatment with Liposomal Amphotericin B injection (Treatment of choice) or (ii) capsule Miltefosine (28 days) and injection Amphotericin B (15 injections on alternate days) or (iii) combination of Miltefosine and Paramomycin injection.
- **Post Kala-azar Dermal Leishmaniasis:** (i) Miltefosine: 100mg orally per day for 12 weeks (Treatment of choice) or (ii) Amphotericin B deoxycholate: 1mg/kg over four months 60-80 doses, or (iii) Liposomal Amphotericin B: 5mg/kg per day by infusion two times per week for three weeks for a total dose of 30mg/kg. Case management of special conditions like relapse, HIV-VL co-infection and others will follow WHO treatment guidelines.

More than 147 million people are at risk of acquiring VL, in the Southeast Asian region,[2] WHO has identified VL as a major public health concern. With VL having localized geography, humans being the only host reservoirs, and Sand fly being the only vector responsible for the transmission;

How to cite this article: Roy N. Kala-Azar elimination in India-Where do we stand. *MJMS.* 2019; 4(1): 1-4.

the availability of effective tools for its diagnosis and treatment makes VL amenable to elimination. The Governments of India, Bangladesh and Nepal signed a tripartite memorandum of understanding in 2005 for reducing the incidence of VL to less than one case per 10,000 populations at the block level through intercountry cooperation and cross-border collaboration and achieved elimination of VL by 2015.

In 2014, India, Bhutan, Thailand, Nepal and Bangladesh signed a memorandum of understanding to eliminate VL from the South East Asia Region of WHO by 2017.

As per the WHO, India would achieve the elimination of VL when the annual incidence of VL declines to less than one case of VL per 10,000 populations at the block level in all VL endemic districts.

Kala-Azar is endemic in the state of Bihar, West Bengal, Jharkhand and districts of Eastern Uttar Pradesh. In the decade of 1970s, VL had almost disappeared due to the use of DDT for vector control under the Malaria Control Program. However, due to the environmental concerns regarding the use of DDT for vector control, the use of DDT was stopped as a result of which there was not only increase in the cases of Malaria but also of VL. The present strategy of National Program for Elimination of VL includes following components

- Early diagnosis and complete treatment
- Integrated vector management including Indoor residual spraying (IRS)
- Advocacy, communication for behavioural impact and inter-sectoral convergence
- Capacity building
- Supervision, monitoring and evaluation.

The National Program has made tremendous progress towards elimination through focused and data-driven decision-making facilitated by the timely availability of data for program activities.

With the introduction of rapid diagnostic test kit (rK39) and treatment with a single dose of liposomal Ambisome, the national program has accelerated early diagnosis and complete treatment of VL cases.

The national program has bolstered the vector control measures through introduction of Synthetic Pyrethroid and replacement of stir-up pumps with Hudson pumps for indoor residual spraying. A threefold decline in the number of VL cases was recorded from 2013 (13,869) to 2018 (4,380). By beginning of 2019, among the 633 endemic blocks endemic for Kala-azar, 91.6% (580) blocks have achieved the annual incidence required for elimination. Among the 53 blocks, which continue to have annual incidence of VL more than 1 case per 10,000 population at the block level, 35 blocks are from Bihar, 17 from Jharkhand and 1 from Uttar Pradesh. The villages from where cases of Kala-azar were reported halved between 2013 and 2018. The success of the National Kala-Azar Elimination program can be attributed to the following

1. Enhanced data analytics and data-backed decision-making process
2. Enhanced monitoring of the program activities
3. Intensification of elimination activities in the blocks with persistent transmission
4. Enhanced incentive for the patient for completing treatment
5. Intensification of post-treatment follow-up of cases for identification of cases of relapse
6. Capacity building of frontline workers for early identification and referral of suspected cases of VL and Post-Kala-Azar Dermal Leishmaniasis (PKDL)
7. Leveraging on the existing national program for the elimination of Leprosy for confirmation of diagnosis of PKDL at the level of districts.
8. Integration with the National AIDS Control Program and the National Tuberculosis Control Program for mandatory screening of patients of VL for HIV and Tuberculosis.

Although National VL elimination program has made impressive progress and the disease has now been limited to a small number of blocks, there are still concerns, which need attention. The National Program for Elimination of Visceral Leishmaniasis should address the following challenges to sustain the progress towards elimination-

Roy N: Kala-Azar elimination in India-Where do we stand

Sustaining elimination: The 1970s resurgence of Kala-azar became evident; when the use of DDT for Malaria control activities was discontinued owing to its potential environmental impacts. The global initiative for elimination of VL has not envisioned 'elimination' of the pathogen, which will warrant low-level transmission to continue. With the country achieving elimination of VL, it would mean decline in the number of cases and consequently it is likely that there would be complacency in the level of awareness among the health care providers and decreased availability of resources for diagnosis, treatment and vector control. Post Kala-azar, dermal Leishmaniasis and VL cases with HIV co-infection have demonstrated to serve as reservoirs of Leishmania parasite and may have a role to play in sustaining transmission at low levels and facilitating resurgence of Kala-azar in post-elimination phase. Hence, it is imperative that surveillance activities are adjusted to the post-elimination phase to maintain continued detection of Kala-azar cases.

Improved diagnostic tools: The early case detection has improved manifold with the introduction of antibody-based rapid diagnostic test (RDT) kits (rk16 and rK39) for Kala-azar. These rapid diagnostic kits are very useful for detecting cases of visceral leishmaniasis who have acquired the infection for the first time. These RDT's are based on antibody detection; hence even the treated cases of Leishmania continue to give a false positive test as the antibodies developed for Leishmania persist for many years. This inherent problem with the RDTs makes the identification of cases of re-infection difficult. The clinical features of PKDL are difficult to differentiate from other skin conditions like leprosy and fungal infections, hence requiring an invasive test like slit skin smear or skin biopsy for confirmation. The invasive tests for confirming diagnosis of PKDL are not usually present at the level of primary health centres, therefore, delaying their diagnosis and treatment. It is essential to develop a diagnostic test, which is not only more specific and sensitive for identifying the cases of VL and PKDL but can be used as a test for cure after treatment.

Newer drugs: With the introduction of Liposomal Ambisome, the duration of treatment for VL has reduced from 28 days to one day. In cases of VL with HIV co-infection, a higher dose of Ambisome has been recommended. The treatment of VL cases is now dependent on a single drug that is manufactured by one company globally. Relapse of VL is known to occur in patients treated with Ambisome; hence it will be prudent to identify other possible combinations of drugs, which may be used for treatment of VL cases. Miltefosine is recommended for the treatment of PKDL and it has to be consumed daily for 12 consecutive weeks. The long duration of treatment with Miltefosine is a probable reason for non-compliance among the patients; hence new shorter and efficacious treatments' regimens need to be explored.

Vector control measures to reduce transmission: Indoor residual spray for control of sand flies is critical for reducing the transmission of VL. The national program for elimination of VL moved from use of DDT to synthetic pyrethroid as insecticide of choice. The insecticide needs to be changed based on the results of insecticide sensitivity tests. Testing of sand flies for resistance to insecticide needs to be conducted diligently and data generated should be used for guiding choice of insecticide for vector control measures.

Strengthening the surveillance and early cases' detection: There has been an impressive improvement in the early detection of cases of VL and now lesser numbers of cases are missed from getting tested for VL. This achievement needs to be sustained and consolidated, so that all cases of VL and PKDL are identified and treated at the earliest. It is expected as the number of cases will decline the awareness and knowledge about Kala-azar will fall among the clinicians, front line workers and the community, therefore it is critical that strategy should be devised to sustain the level of awareness among all the stakeholders.

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