REVIEW ARTICLE

Kala-azar in India: Current Status and Future Prospects

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Abstract

Kala-azar or visceral leishmaniasis (VL) is a deadly disease if left untreated. It is caused by the protozoal parasite, Leishmania donovani and spread by the bite of infected sandflies, primarily Phlebotomus argentipes. There are two other types of leishmaniasis, namely, cutaneous leishmaniasis and mucocutaneous leishmaniasis. After recovery from kala-azar, a condition known as post-kala-azar dermal leishmaniasis (PKDL) occurs. Kala-azar is endemic in India, mainly in four states. There are several diagnostic approaches and treatment modalities for the disease. However, a safe and effective vaccine against kala-azar is still not available. The crux of the problem with this disease lies in the fact that it affects the poorest of the poor, who lack access to the life-saving medical tools due to their dismal financial condition. Hence, it is suggested that more political will, coupled with other strategies are likely to get the ball rolling, so that availability, accessibility, and affordability of the life-saving medical tools is increased so that those who need them most are benefitted.

Introduction

Kala-azar, which is medically known as visceral leishmaniasis (VL), is a zoonotic disease caused by the protozoal parasite, Leishmania donovani, of which there are more than 20 species that reside in various animal reservoirs. Kala-azar is fatal in 95% of infected patients, if left untreated and is the most severe form of leishmaniasis. Kala-azar gets its name from the greyish-black colored dry skin patches on the hands, feet, and abdomen of infected patients (1). That's why kala-azar is known as black fever ("kala" means "black" and "azar" means "fever" in Bengali). Kala-azar or VL affects the internal visceral organs, especially the liver and spleen and is characterized by their inflammation, which is medically termed as hepatosplenomegaly. Other symptoms include erratic bouts of fever, dark patches on the skin, fatigue, weakness, hypergammaglobulinemia, anemia, and weight loss, among others (2).

Other major forms of leishmaniasis are cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis (MCL). In case of CL, localized infection in the form of nodules can be observed on the skin, which may turn into skin ulcers. This disease can recur repeatedly, even with continuous treatment. In case of MCL, primarily the mucosal lining of the nose, mouth, and throat are destroyed. It should be kept in mind that CL is the most common form, MCL is the most debilitating form, and VL is the most severe form of leishmaniasis. The main focus of this review is India-centric and therefore, will primarily discuss various aspects of kala-azar.

Discovery of Leishmania donovani

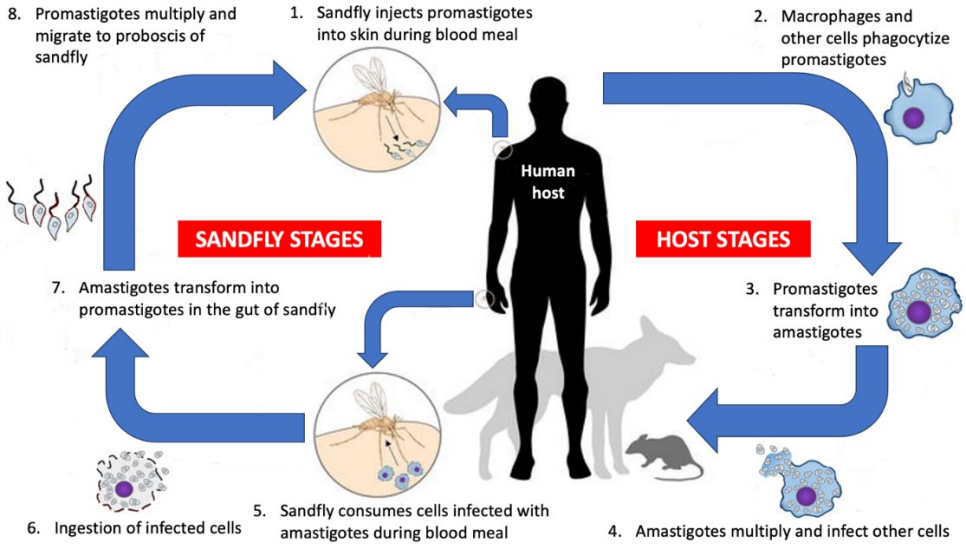
Leishmania donovani was independently discovered by Charles Donovan at the Government General Hospital, Madras (now Chennai) and William Leishman in Netley, England (3). In the latter case, the parasite was isolated from the enlarged spleen of a soldier, who had been posted in Dum Dum, Calcutta (now Kolkata) and subsequently died at the Army Medical School in Netley. Leishman identified these parasites using a stain that he had recently developed and which was subsequently named after him. Since the soldier was infected in Dum Dum, kala-azar is also as Dum Dum fever. Since both Donovan and Leishman discovered the parasite at the same time, a controversy arose on who should receive the credit for the discovery. After much debate and deliberation, the problem was resolved by Sir Ronald Ross who was then working at the Liverpool School of Tropical Medicine, England. Ross opined that the parasite should be named *"Leishmania donovani"*, thereby resolving the controversy once and for all by giving credit for the discovery to both William Leishman and Charles Donovan.

Life Cycle of Leishmania donovani

In India, *Leishmania donovani* generally resides in cattle, goats, and dogs, which are its natural reservoir. It is transmitted from the reservoir hosts to humans by the bite of sandflies, scientifically known as *Phlebotomus argentipes*, which are the vectors of leishmaniasis. There are two distinct stages in the life cycle of the parasite. One is the sandfly stage involving promastigotes, which occurs in sandflies and the other is the host stage involving amastigotes, which occurs in humans and other mammals (4).

The promastigotes are injected into the skin of humans while the sandfly takes a blood meal. Then these promastigotes are phagocytized primarily by macrophages and are eventually transformed into amastigotes. While multiplying and developing in the reticuloendothelial system, the amastigotes may produce various symptoms of kala-azar. During the recovery stage, the most common manifestation is post-kala-azar dermal leishmaniasis (PKDL). A very recent study has established that there are some *Leishmania* RNA viruses (LRV1), which can cause mucosal damage and infection through Toll-like receptors (5). The life cycle of *Leishmania donovani* is depicted in Figure 1.

Figure 1: Life cycle of *Leishmania donovani*



Epidemiology of Visceral Leishmaniasis

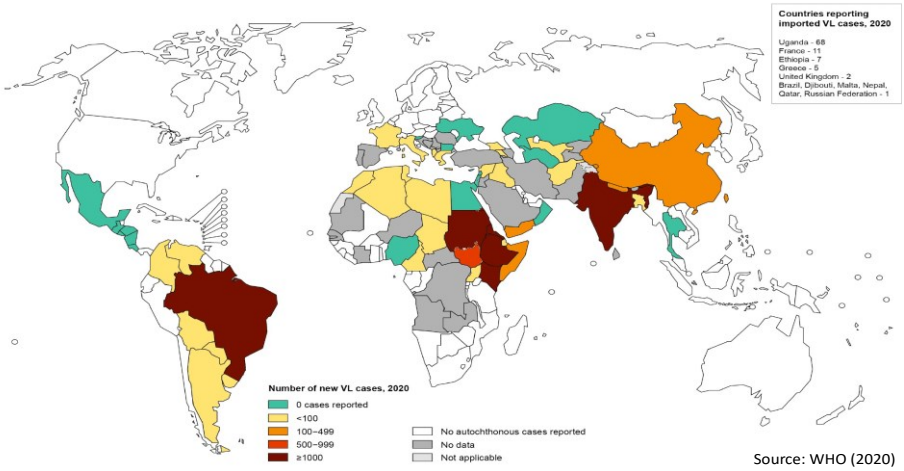
Leishmaniasis affects the poorest of the poor, as the disease is often associated with malnutrition that severely cripples the immune system, so that the infected individuals are unable to fight the disease and become immunocompromised. Other aspects of poverty also go hand-in-hand with disease-

severity, namely, mass displacement due to natural calamities associated with climate change (droughts, heatwaves, floods, cyclones), poor-quality living conditions, and lack of hygiene, sanitation, and safe drinking water, to name a few.

Many poor countries in Asia, Africa, Middle East, Central and South America are affected by leishmaniasis. It is estimated that 600,000 to 1 million new cases of CL occur annually worldwide, of which only 20% is reported to the World Health Organization (WHO). With regard to MCL, the major chunk of the cases (> 90%) are reported from Bolivia, Ethiopia, Peru, and Brazil. With regard to VL, the lion's share is reported from India, Brazil, Kenya, Sudan, and Somalia. Besides these, it is also reported, to a lesser extent, from China and Nepal. Approximately 50,000 to 90,000 new VL cases are reported annually worldwide. However, these numbers are a gross underestimate, as only 25-45% of cases are officially reported to WHO (6). The geographical distribution of VL is presented in Figure 2.

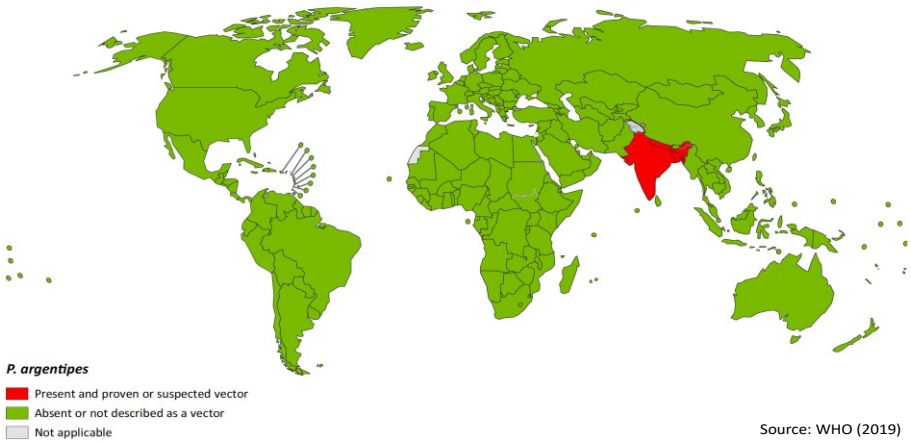
Although sandflies are distributed widely across the globe, phlebotomine sandflies, in particular, *Phlebotomus argentipes* is of relevance in the Indian context, as it is exclusively found in India (Figure 3).

Figure 2: Geographical distribution of visceral leishmaniasis



Source: WHO (2020)

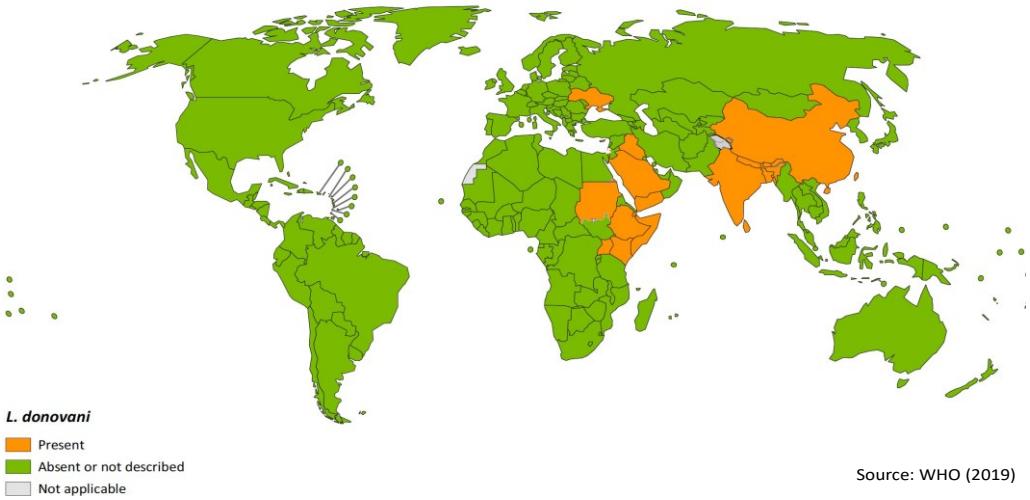
Figure 3: Geographical distribution of the sandfly *Phlebotomus argentipes*



Source: WHO (2019)

Each type of *Leishmania* parasite has its own specificity with reference to predilection, host factors, tropism, and symptoms, among others. For example, in case of *Leishmania donovani,* its prevalence is highest in in South Asia (Bangladesh, India, Nepal, Sri Lanka) and East Africa (Sudan, Somalia, Ethiopia, Kenya) (Figure 4). Other types, such as *Leishmania infantum* is mainly found in Brazil, Pakistan, Iran and the Middle East. In this context, it should be mentioned that *Leishmania donovani* and *Leishmania infantum* are the so-called Old World species, whereas *Leishmania chagasi* and *Leishmania amazonensis* are the New World species.

Figure 4: Geographical distribution of *Leishmania donovani*



Source: WHO (2019)

Data from 2020 shows that 18% of VL cases were reported from India that year. Mostly four Indian states are affected by VL. These include Bihar, West Bengal, Jharkhand, and Uttar Pradesh. This disease has become endemic in 633 blocks of these four states. However, in other states, sporadic cases have been reported (7). In India, between 1992 and 2021, VL cases have decreased by 98%. However, WHO's target is to bring down the number of cases even lower to 1 case per 10,000 population by 2030 in line with the Sustainable Development Goals (SDGs) (8).

Pathogenesis of Visceral Leishmaniasis

Knowledge about the mechanisms involved in the pathogenesis of VL is limited. So far, it is known that asymptomatic infections can confer prolonged immunity to infected individuals and only a minority progress to develop full-blown clinical VL. This occurs only when the parasites overcome immune defences. When this occurs, the parasites multiply primarily in the macrophages and gradually target the liver, spleen, and bone marrow. Rapid multiplication of the parasites in the spleen and liver causes hyperplasia, which results in hepatosplenomegaly. Systemic inflammation can also occur that is mediated by various cytokines, which in turn trigger the release of acute phase proteins from the liver. The cytokines can penetrate the brain, causing fever. These also induce cachexia and vomiting. Also, overexpression of tissue factors can give rise to disseminated intravascular coagulation (DIC), as occurs in case of sepsis (9).

The acute phase proteins that were released by cytokine-stimulation, give rise to hypergammaglobulinemia, anemia, and edema. Active disease is characterized by marked immunosuppression, a negative Montenegro or Leishmanin skin test (LST), delayed type hypersensitivity, and non-responsiveness of the peripheral blood mononuclear cells (PBMCs) upon *in vitro* stimulation with leishmanial antigens. Subsequently, the inflammatory response, coupled with the depletion of lymphocytes increase the risk of opportunistic bacterial infections, which, combined with DIC, eventually leads to death (10).

Diagnostics for Visceral Leishmaniasis

Visceral leishmaniasis can be diagnosed by a variety of diagnostic tests, but the gold standard is still the demonstration of the amastigote stage of the parasite in tissue biopsy samples or bone marrow aspirates (11). However, splenic aspirates are more sensitive, but the procedure is more invasive and requires highly skilled clinicians to carry out the aspiration. Serological tests, such as the rapid immunochromatographic test (ICT), rK39, is indicative of VL, especially when combined with clinical findings. However, one shortcoming is that this test cannot differentiate between past and active infections (12). A similar rapid diagnostic test (RDT) that resembles rK39 is the rK28 test, which uses a urine sample instead of blood

sample and is therefore more acceptable to patients, as there is no need for invasive methods. This test has been evaluated in South Asian countries, including Bangladesh (13). There are also other diagnostic tests, including the enzyme-linked immunosorbent assay (ELISA), indirect fluorescent antibody test (IFAT), indirect hemagglutination assay (IHA), and direct agglutination test (DAT). Nowadays, molecular diagnostic tools are also available for diagnosing VL that utilize the polymerase chain reaction (PCR), PCR coupled with restriction fragment length polymorphisms (PCR-RFLPs), real-time PCR, and loop-mediated isothermal amplification (LAMP), among others.

Treatments for Visceral Leishmaniasis

Nowadays, there are several drugs that work effectively against VL. One of the first ones was urea stibamine, which was developed by the renowned Indian physician-scientist, Sir Upendranath Brahmachari in 1920. This drug is the urea salt of para-amino phenyl stibnic acid and was found to be highly effective against VL and exhibited >90% cure rate. In this context, it should be mentioned that Sir U.N. Brahmachari was the first to describe PKDL (14). Urea stibamine was the first drug to be developed that belonged to the class of pentavalent antimonials (SbV). Other notable drugs in this class include sodium stibogluconate and meglumine antimoniate. Unfortunately, SbV has become widely resistant across India (15). These have been replaced by other classes of drugs, including miltefosine and amphotericin B. The former belongs to the class of alkylphosphocholine drugs, while the latter belongs to the polyene class.

Amphotericin B is recommended for use in immunocompromised individuals. Liposomal amphotericin B (LAmB) and miltefosine are US-FDA approved drugs that can be used for the treatment of VL and have a good safety profile. In India, miltefosine and paromomycin are normally used for monotherapy, while LAmB is used as a combination therapy with miltefosine and paromomycin.

However, the major disadvantage of these drugs is that they're very expensive and largely out of reach of the poor, who need them most. Moreover, it has been reported that amphotericin B has also developed drug resistance in certain places in India (16).

Vaccines for Visceral Leishmaniasis

Vaccination is the most cost-effective medical intervention ever invented to prevent infectious diseases. With regard to VL, various vaccine platforms have been explored. These include the first-generation vaccines that use the inactivated or live-attenuated platforms. These are traditional vaccine platforms that have been used for over a century and therefore have a good safety record and physicians have more confidence with these vaccines. Second generation vaccines, like recombinant protein subunit vaccines and third generation plasmid DNA vaccines have also been studied. These have been combined in a heterologous prime-boost strategy in a bid to increase the immunogenicity of the vaccine formulation and have yielded promising results. A few of these have been licensed for canine VL, including Leishmune®, Leish-Tec®, and CaniLeish® (17). Progress in the development of vaccines for human VL has been slow. Studies are ongoing in many parts of the globe, but these are few and far between. One such study involves the use of a specific T-cell epitope-containing chimeric protein as the vaccine antigen (18). However, till date a safe and effective vaccine for human VL still eludes us.

Future Prospects and Way Forward

Kala-azar still continues to plague us, despite the untiring efforts of scientists to develop new, improved diagnostics, therapeutics, and vaccines. The crux of the problem lies in the fact that the disease disproportionately affects the poor, who lack the purchasing power to access these life-saving medical interventions. As a result, the pharmaceutical companies also lack the incentive to manufacture these medical tools. Hence, the onus lies with the Indian government to troubleshoot this problem by incentivization, subsidies, and other mechanisms. The primary health centers

(PHCs) will be instrumental in reaching out to the poor rural folk to increase access. Since these marginalized populations lack a voice in their own health matters, more advocacy is required to ensure that they are heard. This will help in demand generation, which is of the utmost importance when vaccines for human VL become available. It is clearly evident that greater political will is required for framing actionable policies, which will accelerate things. This will greatly facilitate in enhancing the availability, accessibility, and affordability of these medical interventions for the poor. It should be remembered that "if we miss the poor, we miss the point"!

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Conflict of Interest
There are no conflicts of interest.

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