Acta Parasitologica (2024) 69:1704–1716
https://doi.org/10.1007/s11686-024-00880-5

REVIEW

The Elimination Status of Visceral Leishmaniasis in Southeast Asia Region

Samiur Rahim[1] · **Muhammad Manjurul Karim**[1]

Received: 29 March 2024 / Accepted: 30 July 2024 / Published online: 20 August 2024

Abstract

Purpose Visceral leishmaniasis (VL) is caused by an intracellular parasite that is transmitted to humans by sandfly bites. It is prevalent throughout Asia, Africa, the Americas, and the Mediterranean area, where 147 million people are at risk of contracting the illness. The manifestation of heterotrophic illness relies on both *Leishmania* implicated and the host's immunological response, ranging from asymptomatic to severe leishmaniasis with potentially lethal effects.

Method We reviewed the literature (published till 31st December 2023) on the worldwide situation of leishmaniasis, standard and novel detection techniques, and traditional and modern treatment strategies and endeavors to eliminate VL. Moreover, epidemiological data was collected from the World Health Organization's publicly available databases. GraphPad Prism Version 8 was used to analyze and produce figures based on the epidemiological data.

Results Diagnosis of parasites in tissues or serology is commonly employed. Diagnosis by identifying parasite DNA using molecular techniques is becoming more popular. Despite recent findings of *L. donovani* resistance to pentavalent antimoniate medications, it continues to be the cornerstone in the medical management of VL. Amphotericin B and its lipid formulations, injectable paromomycin, and oral miltefosine are among the new therapy options being researched. The number of reported VL cases has reduced remarkably over the last decade due to human interventions made to eliminate VL. Particularly countries from the South East Asian region have experienced momentous progress in reducing VL cases and eliminating this disease from this region. Owing to the robust elimination programs, countries such as Bangladesh has eliminated VL as a public health concern. India and Nepal are on the verge of its elimination.

Conclusion Rapid diagnosis, effective and inexpensive treatment, simple access to newly discovered medications, appropriate vector control, and a well-designed vaccine are all required for the elimination of this disease burden in impoverished areas of the globe.

Keywords Visceral Leishmaniasis · Kala Azar · Southeast Asia · VL Elimination Program

Introduction

Visceral leishmaniasis (VL) also known as kala-azar (KA) is the most severe form of leishmaniasis with a fatality rate of 95% if untreated [1]. Two species under the genera *Leishmania* cause VL. In 4 countries of Southeast Asia namely India, Bangladesh, Nepal, and Bhutan, and East African countries (Ethiopia, Kenya, Somalia, South Sudan, Sudan, and Uganda), *Leishmania donovani* (LD) is the main agent causing VL, although LD from these two regions differ from each other [2, 3]. In Eastern Mediterranean countries and Brazil, *Leishmania infantum* causes VL [3, 4]. The vector for this agent is sand fly, *Phlebotomus*, although its frequency for causing VL varied across the regions: *P. argentipes* in South Asian countries, *P. orientalis* in the northern savanna (Sudan, northern Ethiopia), and *P. martini* in the southern savanna (southern Ethiopia, Kenya) [5, 6]. The sand flies breed in damp soil, cracks, and crevices of mud houses; hence people dwelling in those households, who are from lower socioeconomic status, are the vulnerable group for contracting VL.

✉ Muhammad Manjurul Karim
manjur@du.ac.bd

Samiur Rahim
samiursamit@gmail.com

[1] Department of Microbiology, University of Dhaka, Dhaka 1000, Bangladesh

The parasite exists in two stages in its life cycle involving human and sand fly: Amastigote and Promastigote stages respectively. The amastigote form, residing in the cells of the reticulo-endothelial (RE) system, like macrophage, neutrophil, and endothelial cells of the human host, multiplies by binary fission until the RE cells become enlarged. The cells are eventually ruptured liberating the parasites in the circulation that invade fresh cells; the cycle is repeated until all cells of the RE system are affected. The proliferation of RE cells leads to massive splenomegaly and hepatomegaly. The bone marrow is also involved, resulting in pancytopenia [7–10].

Clinical Manifestation and Host Response

The clinical signs and varied disease presentation of VL are influenced by both parasite characteristics including infectivity, pathogenicity, and virulence as well as host variables and reactions [11, 12]. Clinical manifestation of viscerotropic infection by *Leishmania* spp. varies from subclinical to oligosymptomatic to fully established kala-azar [13–15]. Following an incubation period of 3 to 8 months [4], the disease progresses from the oligosymptomatic stage to kala-azar over weeks to months [15–17]. In the early stage of clinically expressed VL, fever, weakness, night sweats, anorexia, and weight loss are common and progress rapidly [16–18]. In some cases, an incomplete oligosymptomatic infection resolves spontaneously [19, 20]. Lymphadenopathy, hepatomegaly, splenomegaly, pallor, anaemia, leukopenia, thrombocytopenia, and asthenia along with early-stage symptoms are typical in kala-azar [4, 17]. Chronic diarrhea and growth retardation are observed in children. Untreated VL cases can progress into multisystem disease, bleeding from thrombocytopenia, susceptibility to secondary infections, and finally death [15].

VL can reappear as post-kala-azar dermal leishmaniasis (PKDL) which is a dermal manifestation of infection, caused by LD parasites, and mostly develops in patients who have been previously cured of VL [21]. Although this reactivation accounts only for 6 to 10% [21], the rest of PKDL patients could result without developing VL. This disease is characterized by erythematous papules, nodules, and hypopigmented macules all over the body, persisting for a long time period [22–25]. PKDL manifestation is governed by the host's poorer immune response, use of immunosuppressant drugs, or other diseases such as HIV [22, 23, 25, 26]. Histopathological studies showed a polymorphic infiltration of macrophages, plasma cells, and lymphocytes [11, 22].

Host response in viscerotropic *Leishmania* infection is a major regulatory factor in disease expression and progression. Susceptibility to VL and disease expression are governed by age, nutrition, and efficacy of both innate and acquired T-cell dependent immune responses of the host [11, 15, 27, 28]. Innate and adaptive immune responses also dictate the response to chemotherapy [29–32]. Antigen-specific T-cell reactivity, innate responses as well as other factors such as activating cytokine secretion (interleukin(IL) 12, IL-1a, TNF) are responsible for a complex host immune response in asymptomatic infections [11, 29, 30, 32, 33].

Epidemiology of Visceral Leishmaniasis

Epidemiology of VL: Global Scenario

Visceral leishmaniasis (VL) is one of the neglected tropical diseases (NTD) recognized by the World Health Organization (WHO). Affected individuals majorly hail from poor socio-economic conditions with poor housing, malnutrition, and weak immune systems. Despite being endemic in certain poverty-stricken geographic locations, VL is found globally on all continents except Oceania [4] (Fig. 1). However, estimating its global impact is difficult due to a variety of criteria such as different clinical and epidemiological presentations, focality, and data dependability.

Alvar and colleagues (2012) performed what was one of the earliest worldwide updates of empirical data for leishmaniases as part of the WHO's Leishmaniasis Control Program [1]. Between 2007 and 2010, regional meetings were hosted in 98 nations and three territories. Country representatives and researchers participated to epidemiological surveys focusing on treatment and control by providing local health data on leishmaniasis for not less than the past 5 years. After a detailed literature analyses that included worldwide incidence, distribution, surveillance, patterns, as well as potential under-reporting, the authors assembled epidemiological data using mapping technology (GIS) and estimated the potential final incidence. In 2010, the official incidence of VL was 58,000 cases per year. Surveillance, however, had severe gaps, with only two-thirds of endemic nations submitting incidence data. The final study yielded a range of incidence estimates for VL: 202,000–389,100 cases per year, worldwide. While case fatality rates (CFR) ranged from 1.5% in Bangladesh to 20% in peacetime South Sudan, yearly mortality was estimated to be 20,000–40,000 based on an overall CFR of 10%. More than 90% of VL cases were discovered in just six countries: India, Bangladesh, Sudan, South Sudan, Brazil, and Ethiopia [1]. The authors also prepared national profiles with additional information about the status of leishmaniasis. That was the first detailed look at the leishmaniasis epidemic.

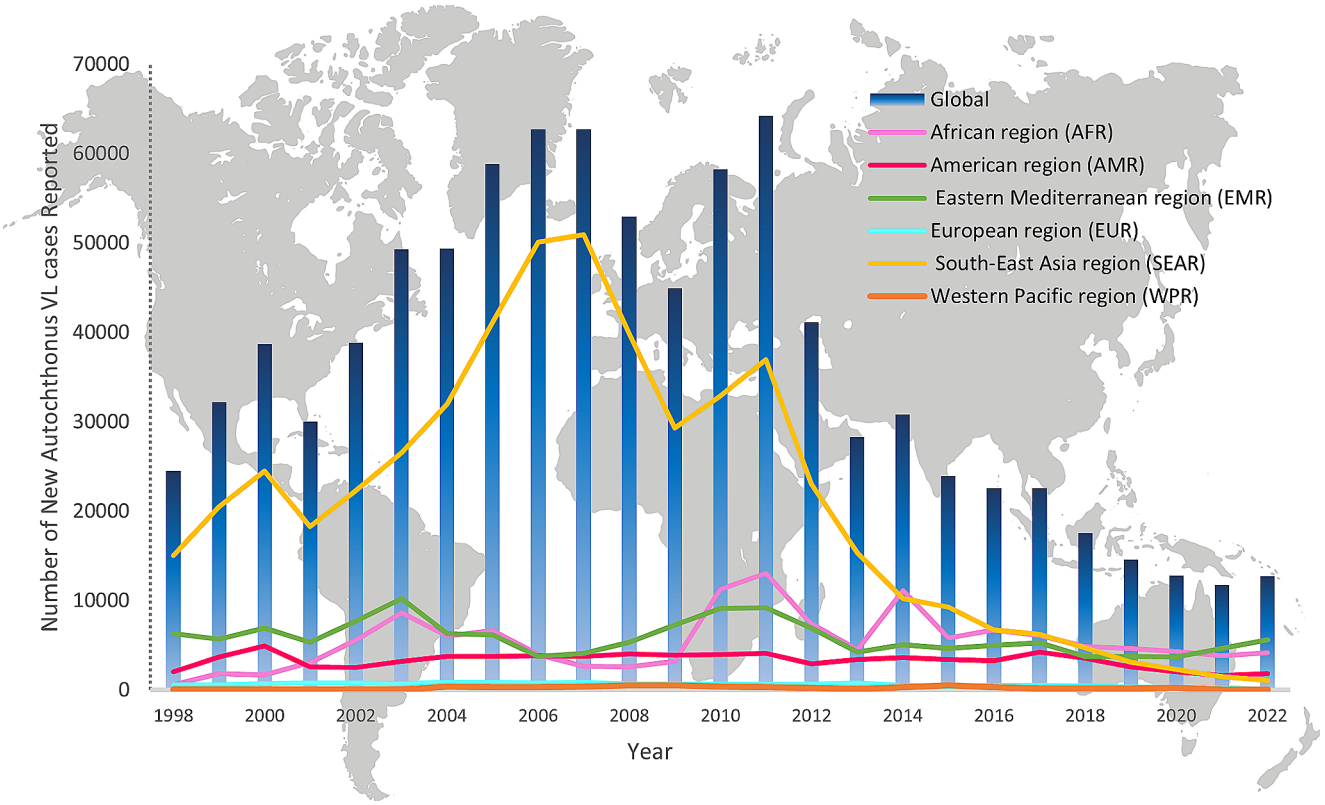

Fig. 1 Incidence of VL cases in WHO region, 1998 – 2022

Global VL incidence has seen a remarkable reduction in the last decade from an estimated 200,000 to 300,000 in 2008 to 12,773 reported cases in 2022 [1, 34–36]. According to the Global Leishmaniasis Surveillance by WHO, 78 out of 200 countries were considered as endemic for VL [34]. Around 90% of new VL cases are limited to ten countries namely Brazil, Ethiopia, India, South Sudan, Sudan, Bangladesh, Kenya, Nepal, China, and Somalia [1, 34].

Since 2011, Southeast Asia has observed a remarkable decline in VL burden which has been one of the major improvements in public health (Fig. 1). WHO estimated 147 million people at risk with 100,000 new cases appearing each year in India, Bangladesh, Nepal, and Bhutan [37]. Although 80% of global cases of VL once were reported in this region in 2006, the situation improved to 57% in 2011, then to 28% of total global VL cases (< 5,000 cases) in 2018 [34]. In 2022, only 8.3% of VL cases were reported by SEAR, thanks to the launching of the regional kala-azar elimination program initiated by the governments of Bangladesh, India, and Nepal, supported by WHO in 2005 [35–38].

Among the 3 major eco-epidemiological hotspots for VL, the hotspot of East Africa which includes countries from the African Region (AFR): Ethiopia, Kenya, South Sudan, and Uganda; and Eastern Mediterranean Region (EMR): Sudan and Somalia have the highest number of reported VL cases, constituting 72% of all cases worldwide in 2022 [36]. The American region (AMR) has the second-highest prevalence of VL. Caused by *Leishmania infantum* [3], Brazil, another hotspot, housed 13% of total global cases of VL in 2022 [36]. Like AMR, *L. infantum* is also the causative agent of VL in the EMR that recorded 44% of global cases (5,633 cases) in 2022 and this region is currently the major contributor of global VL burden [3, 36]. On the contrary, the SEAR, housing the last eco-epidemiological hotspot; the Indian Subcontinent, showed less VL burden than AFR and EMR for the fifth and fourth consecutive years respectively [36].

Since 2014, WHO increased surveillance of PKDL, a frequent complication of VL and a possible source of infection. A total of 840 PKDL cases were reported from six countries globally, with 92% (773/840) coming from India, 5% (37/840) from Bangladesh, 2% (16/840) from Sudan, and just under 1% from South Sudan, Ethiopia, and Kenya [35]. Although a spike in PKDL cases has been observed in 2017 (2322 cases), the number of reported PKDL cases has remained just over 700 [34].

Epidemiology of VL: Southeast Asia

Southeast Asia region comprises of 11 countries and hosts one of the major 3 eco-epidemiological hotspots for VL, the

Indian subcontinent (India, Bangladesh and Nepal). 12% of all reported VL cases globally and 97% (810 cases) of global PKDL cases in 2021 occurred in SEAR particularly in the Indian subcontinent. In the last ten years, SEAR has seen a remarkable decline, estimated 96% in the VL cases, from 36,920 cases in 2011 to less than 1,500 in 2021 (Fig. 2) [35].

Historically, VL has century-old relationship with the Indian subcontinent. The earliest suspected incidence of VL dates back to 1824 in Jashore, India (now Bangladesh) [39]. After that, Kala-azar first came to the attention of Western doctors, where it was initially thought to be a form of malaria or anemia. Later, the agent of the disease was first isolated by Scottish doctor William Leishman in Dumdum, Calcutta, India [40]. In the 19th and early 20th centuries, epidemic outbreaks of VL with CFR of over 95% occurred every 15–20 years in a wide range of districts in Bengal and Assam giving it a new name, *Assam fever* [41, 42]. A 4-year epidemic outbreak from 1824 to 1827 in Jashore had been suspected of killing 75,000 people, and between 1931 and 1943, more than 1 million VL cases were reported in former Bengal [39]. The death rate, on the other hand drastically decreased after the discovery of urea stibamine, a less toxic antimonial drug for VL treatment by Upendranath Brahmachari [43].

The incidence of VL declined and was thought to be eliminated in the 1970s as a collateral effect of the DDT-spraying campaign of the National Malaria Eradication Programs in India as well as in East Pakistan (now Bangladesh). VL became apparent again in the late 1970s in India and in the early 1980s in Bangladesh owing to the suspension of DDT-spraying in both countries due to its toxicity [44]. Since 1998, the reported incidence of VL has gradually increased from 15,036 in 1998 to an estimated 50,900 cases in 2007[38,39]. However, the last two decades saw a remarkable decline of VL cases in this region, owing to the launching of the regional kala-azar elimination program by the governments of Bangladesh, India, and Nepal in 2005, ably supported by WHO [37, 38]. In 2022 only 1069 cases of VL were reported in SEAR [36].

Diagnosis and Treatment

Diagnosis

Kala azar is a progressive disease and the mortality rate in untreated cases ranges from 75 to 95% and death usually ensues within 2 years [4]. If diagnosed earlier, patients can be cured by successful treatment. Several laboratory-based methods including parasitological, immunological, and molecular methods are available for diagnosis of Kala Azar.

Microscopy and Culture

The classical method for diagnosis of VL is confirmation by microscopy of the presence of the parasite in macrophages, stained with Giemsa or Wright, collected from aspirates of lymph nodes, bone marrow, spleen, and liver with a varying sensitivity of 53–58%, 53–89%, 95–97%, 40% respectively [7, 45, 46]. Though spleen aspirate gives a high sensitivity, it is controversial due to the high risk of fatal hemorrhage that may lead to death. It also requires a trained physician not suitable for the field as well as mass screening. Intracellular *Leishmania* can also be cultured using spleen, lymph node, and liver aspirates in Novy–McNeal– Nicolle medium (N-N-N medium) followed by demonstration using microscopy. The culture-based technique has a sensitivity of 85%

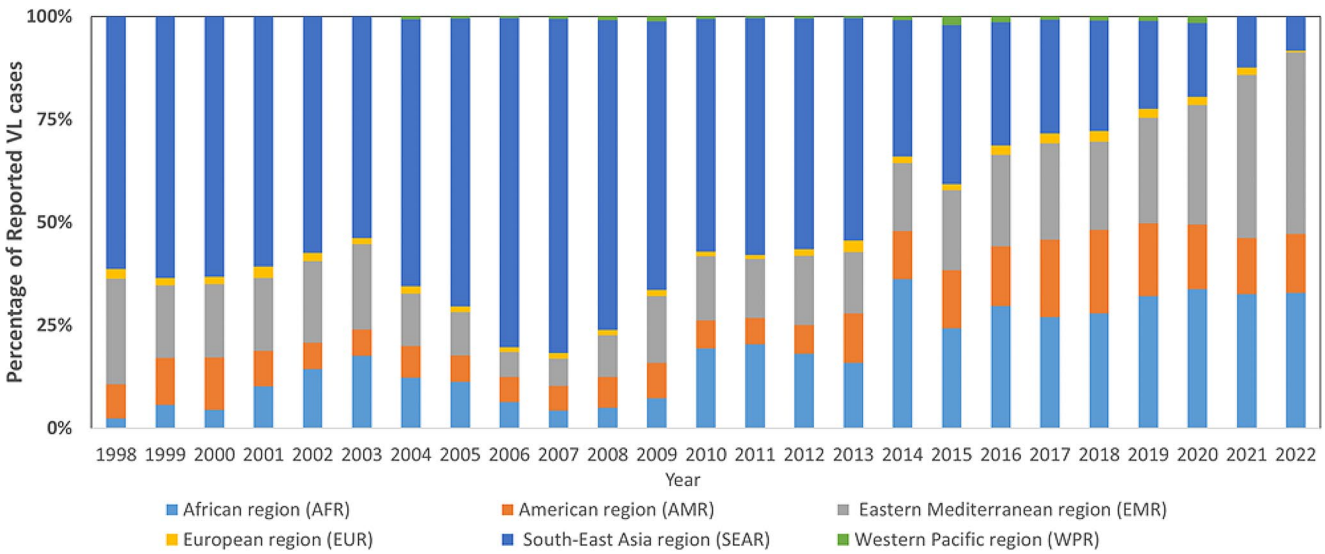

Fig. 2 Percentage of reported VL cases during 1998 – 2022 in the WHO region

[15]. This method is lengthy because the flagellated form of LD appears in the second culture in most cases. The culture of the aspirates (bone marrow, spleen) might improve the sensitivity; but it is expensive, time-consuming, and needs expertise and sophisticated equipment [47, 48].

Serological Diagnosis

An array of serological techniques is used in the field for the diagnosis of VL including direct agglutination test (DAT), enzyme-linked immunosorbent assay (ELISA), and IgG-based rapid diagnostic tests (RDT). In DAT, whole promastigotes are stained in Coomassie brilliant blue and incubated with sera of the patients for 24 to 48 h to observe the agglutination [49]. In a study in Sudan, the sensitivity of DAT was 94%, specificity 72%, and predictive values of positive and negative tests were 78% and 92% respectively [50]. However, the high cost of the antigen, lengthened incubation time, and the possibility of producing false positive results due to past infection are its major drawbacks.

ELISA is used for serodiagnosis of VL but its specificity and sensitivity depend on the antigen used. Antigen rk29-based ELISA has demonstrated the highest sensitivity and specificity of 100% and 96% respectively [51]. Its main advantage is the antibody titer to the antigen rk29 directly correlates with active disease, thus the improvement of the patient receiving the treatment can be monitored. On the contrary, recombinant *L. donovani* gene B protein (rGBP) and a peptide sequence of *L. donovani* gene B protein (GBPP) showed 92% and 55% sensitivity respectively [7].

Indirect Fluorescent Antibody Test (IFAT) is a very sensitive technique that detects the presence of antibodies, developed in the very early stages of infection, and becomes undetectable six to nine months post-convalescence. Though its sensitivity (96–100%) and specificity (98–100%) are very high, IFAT cannot be applied on a regular basis due to the requirement of sophisticated laboratory conditions [52, 53].

Immunochromatographic (ICT) strips using rK39 antigen is a rapid diagnostic test. It has become popular in recent years due to its ease of use in the field and rapid detection. This method is suitable for various types of biological samples including blood, urine, and saliva [54, 55]. In early clinical evaluation, this technique showed promising results of 100% sensitivity and 98% specificity for blood serum [56]. Later in a meta-analysis, this method reproduced similar results (sensitivity 98.4–100% and specificity 81.2–96.4%) [57]. To name a disadvantage, ICT remains positive long after remission of illness like DAT; and in endemic areas, healthy individuals may appear positive.

Molecular Diagnostic Techniques

PCR as well as real-time PCR-based diagnosis of VL are available with primers targeting several genes, e.g., rRNA genes, and kinetoplast DNA (kDNA) [58–60]. These techniques can be applied to blood, BMA, spleen, lymph node aspirate, and urine, from where parasites can be detected even at sub-species level [59–61]. PCR-based diagnosis has high sensitivity and specificity [62], for example, the method produces a sensitivity ranging from 70% [63, 64] up to 100% [62, 65–67] depending on the primer used for probing the DNA collected from blood samples of suspected VL patients. In a comparative study in Italy, PCR analysis of blood demonstrated higher sensitivity than bone marrow [68]. In another study in Brazil, PCR-based diagnosis of VL using urine demonstrated promising results (96.8% sensitivity and 100% specificity) [60, 69]. An overview of sensitivities and specificities of various PCR-based diagnostic assays based on primers targeting different regions of *Leishmania* genome is hereafter presented (Table 1). Real-time PCR-based diagnosis system using various samples including blood, urine or bone marrow have also demonstrated high specificity and sensitivity both being around 100% [70, 71].

Recently developed loop-mediated isothermal amplification (LAMP) assay and Reverse transcriptase-loop-mediated isothermal amplification (RT-LAMP) assay showed high accuracy and can be used as a point-of-care diagnostic tool. LAMP can detect parasite DNA as little as 1 fg/mL concentration [75]. When using blood as a specimen, the sensitivity of LAMP is 80% [75], and RT-LAMP is 83% [76].

Table 1 Sensitivities and specificities of different primers for PCR-based diagnosis of VL

Target for conventional PCR	Sensitivity (%)	Specificity (%)	Reference
kDNA (204 bp): *L. donovani*	82.3	100	Singh 1999 [72]
kDNA (600 bp): *L. donovani*	96	96	Salotra et al. [73].
kDNA (790 bp): *Leishmania* spp	100	100	Pal et al. [74].
kDNA (600 bp): *L. donovani*	99	100	Maurya et al. [62].
kDNA (104 bp): *L. donovani*	98	100	Khatun et al. [67].
kDNA (104 bp): L. donovani (qPCR)	100	100	Rahim et al. [71].
REPL repeats (66 bp): LD complex (qPCR)	100	100	Hossain et al. [70].
SSU-rRNA (nr): *Leishmania* spp SSU-rRNA	70	100	Osman et al. [63].
MedRNA (180 bp): *L. donovani*	96.8	100	Adhya et al. [64].

Treatment

Therapeutic drugs used for the treatment of VL have drawbacks of toxicity, high cost, and long-term administration [77], therefore the treatment aim is to kill the parasite efficiently without harming the patient at a low cost. Normally, it takes a long-term administration of drugs ranging from 30 to 35 days according to the WHO guidelines [78, 79]. In most cases, a follow-up until 6 months is recommended [78–80].

Sodium stibogluconate (SSG), a pentavalent antimoniate compound remains the cornerstone in the treatment of both VL and cutaneous leishmaniasis (CL) all over the world [81, 82]. WHO recommended its dosage as 20 mg/kg/day (MKD) through an intramuscular route for 20 days up to 6 months [78, 79, 83]. Resistance to SSG is observed in Behar, India [84]. Again, SSG showed renal toxicity and cardiotoxicity [85]. Due to the toxicity and long-term treatment cycle, SSG is considered as 2nd line treatment in Bangladesh [79].

Therapy with liposomal amphotericin B (AmBisome) has shown promising results in children aged less than 5 and elderly people [86], 90–100% of cases can be cured [87], thanks to its presence in the body for a longer period with minimal side effects. In a study in Sudan, AmBisome monotherapy resulted in 83% cure among PKDL patients. A trial in Fulbaria, Bangladesh showed that 90% of PKDL patients responded to treatment and 34% were completely cured [88, 89], hence was considered as the 1st line treatment for both VL and PKDL [79]. On the contrary, amphotericin B deoxycholate is a second-line drug to treat leishmaniasis at a dosage schedule of 1 MKD for 20 days through infusion [79, 86]. The drug showed both acute and chronic side effects including fever, chill, nephrotoxicity, hypokalemia, myocarditis, thrombophlebitis, in some cases even death [86, 90].

Miltefosine (hexadecyl choline) is the first effective oral treatment for VL, which is equally active in treating antimony-resistant infections [15, 91]. A phospholipid derivative compound, miltefosine was found effective at 2.0–2.5 MKD for 4 weeks with a cure rate of 83 to 94% [21, 92, 93]. A phase 4 trial showed an 85% cure rate for both adults and children in Bangladesh [92]. Due to its ease of administration with some mild effects, this drug has been used in VL elimination programs in Bangladesh, India, and Nepal [21, 79].

Post Kala-azar Dermal Leishmaniasis (PKDL) Diagnosis and Treatment

PKDL is a dermal manifestation of infection, caused by LD parasites, and mostly develops in patients who contracted VL earlier and were cured [21]. Though it is considered a complication of VL, in several cases, PKDL develops without developing VL. Only 6 to 10% of VL patients develop PKDL [21].

In the nodular form of PKDL, the LD body can be demonstrated under a microscope in 90% of cases but in macular cases, the sensitivity of this technique can be as low as 3% [23, 94]. Again, serological techniques are inappropriate for PKDL diagnosis, as antibodies remain in the human body for years after remission [21]. On the contrary, PCR-based molecular diagnosis using dermal specimens is very sensitive [23, 94], recorded 87% sensitivity [23] in a study on PKDL patients of Bangladesh. qPCR-based method using skin specimens proved promising for the diagnosis of PKDL [70].

Treatment of PKDL is a challenging task that requires higher doses of drugs and a longer period for the remission [88]. The choice of drugs for PKDL are Miltefosine, liposomal amphotericin B (AmBisome®), paromomycin, and a combination of any two [89]. The outcome of the therapy with AmBisome® varied in different studies. In Sudan, AmBisome monotherapy at a dose of 2.5 MKD for 20 days produced an83% cure rate in PKDL patients [95]. In Bangladesh, this drug therapy showed a poor outcome, only 34% after 12 months [88]. Miltefosine, on the other hand, was reported to produce an 81% cure rate after a 12-week treatment in India [96]. This drug manifested mild side effects and was found relatively a safer drug for children and elderly patients. In Bangladesh, Miltefosine is recommended as 1st line treatment of PKDL [79].

Progress of the Elimination Program in SEAR

The hallmark of global public health is the eradication of an infectious disease, which calls for the convergence of biological, political, and economic variables [97]. The WHO assessed in 2005 that several of these circumstances were favorable for initiating a VL eradication program in the Southeast Asia region, notably in Bangladesh, India, and Nepal [98]. For example, the disease was focalized in 109 borderline districts (45 Bangladesh, 52 India, and 12 Nepal) where an intercountry collaboration and availability of highly effective diagnostics and treatments were required to eliminate VL from this region [98]. The VL elimination target was defined as the reduction to less than one case per 10,000 inhabitants in these districts by 2015. Furthermore, this goal requires 100% assurance of detection and treatment of all VL cases [89]. Achieving this milestone would ensure that the disease would no longer be a public health concern.

The VL elimination program in SEAR resulted in major progress with Bangladesh achieving elimination status in

2023 [99]. For three consecutive years (2020 to 2022), Bangladesh reported less than 1 case of visceral leishmaniasis per 10,000 people and this led to the recognition by the WHO [36, 99]. While concentrating towards VL elimination, India contributes to more than 80% of the total VL burden in 2022 (Fig. 3). This figure accounts only 777 cases reported to the WHO, a decline of 97% of reported cases since 2005 [36]. Provisional cases in 2019 from India's National Vector Borne Disease Control Program (NVBDCP) were 3,122 in 4 states (Bihar, Jharkhand, Uttar Pradesh, and West Bengal) with Bihar and Jharkhand carrying 77.4% and 17.3%, respectively [100]. Although the Ministry of Health's VL elimination strategy has initiated the 2017 Accelerated Plan for Kala-azar Elimination through the NVBDCP, the challenges to reach elimination in India were needed to be overcome. A significant 83% reduction in the incidence of VL cases has been observed in Nepal compared to 2005. Despite achieving elimination targets in all 12 VL-endemic districts in 2013, one previously non-endemic district surpassed the elimination target in 2017 [101]. A 2019 survey identified VL cases in four non-endemic districts where patients had no history of visiting endemic areas [102, 103]. This study indicates a geographical expansion of VL towards previously VL-free hilly districts in Nepal. The most crucial thing to keep in mind is that, to sustain the disease's eradication status in Bangladesh and Nepal, there will be a lot of effort required in the future in terms of monitoring, pharmacovigilance, and engagement with policymakers [104].

Challenges in Kala-Azar Elimination

Implementation of Improved Diagnostic Tools for Diagnosis and Surveillance

The current rapid diagnostic test is based on the detection of antibodies against the rK39 antigen. To confirm the diagnosis and start treatment, a positive result must be interpreted along with clinical signs and symptoms that included fever for two weeks and a palpable spleen. Although, on its own, this rapid test is not specific for the acute stage of the disease and is also positive in latent carriers and in cured patients, due to its ease of use and low cost, all three endemic countries of SEAR have implemented this diagnosis test for mass use [37, 79]. The combination with a clinical case definition induces a delay of two weeks before the patient is diagnosed. Decreasing the time between onset of symptoms and diagnosis might help reduce transmission [105].

This rapid diagnostic test for VL detection has been very helpful for the Kala-Azar eradication programs in Indian subcontinent. However, the test has become inadequate in the post-elimination phase in Bangladesh and Nepal, and the near elimination phase in India as the probability of its false positive diagnosis may increase rapidly when near elimination is achieved. Many patients with a false positive result risk being given treatment for kala-azar while the actual cause of their persistent fever (brucellosis, rickettsiosis, tuberculosis, etc.) is not dealt with. A more specific test will be required, preferably based on antigen detection or molecular detection. More specific test will be helpful for

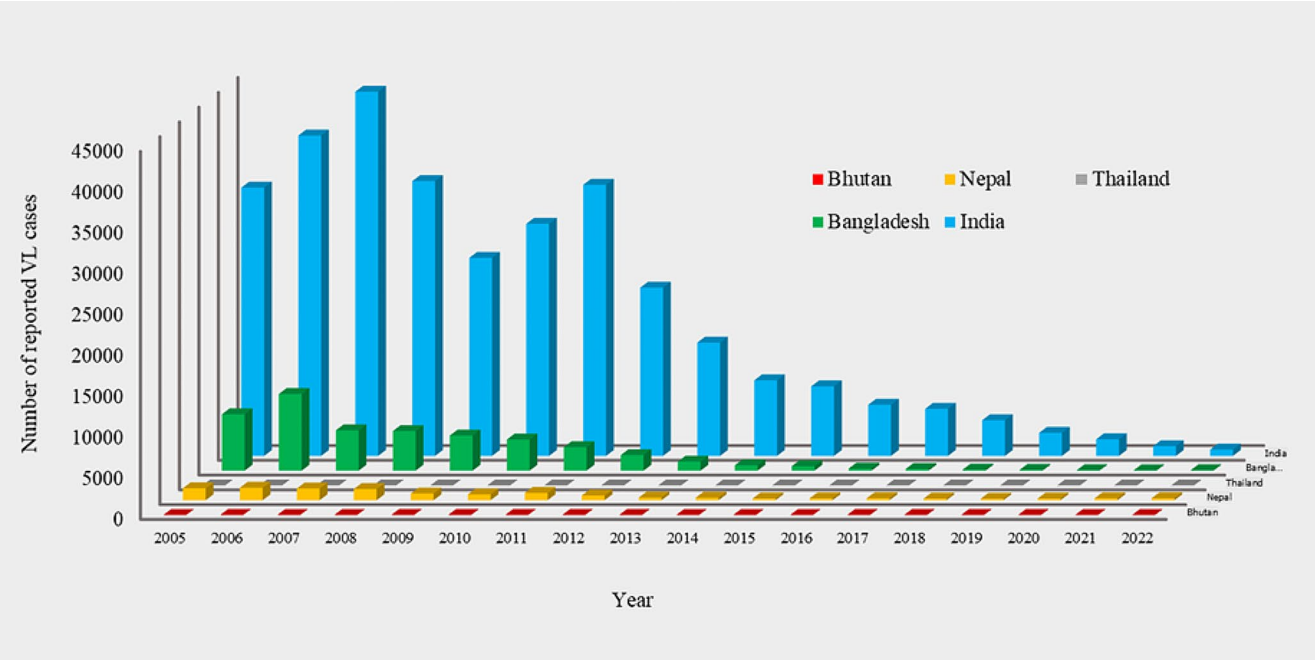

Fig. 3 Number of reported VL cases during 1998 – 2022 in SEAR

both ruling out the false positive diagnosis in this endemic region and for surveillance of new outbreaks.

Kala-azar-HIV Co-infection

The chance of developing visceral Leishmaniasis clinical manifestation of disease accompanied by high relapse and high death rates is very high in Kala-azar comorbid conditions like HIV, tuberculosis, or any immunocompromised condition. Kala-azar-HIV co-infected cases are especially of concern and have important immunological implications since they affect the cellular responses in charge of parasite control. After an initial report from southern Europe, notably Spain in 1980, KA-HIV co-infection has spread in many kala-azar endemic countries [106]. As of 2021, this co-infection has been reported in 45 countries, of which Brazil, Ethiopia, and India had the highestrates [16]. For example, in Bihar, India's most endemic state for VL, an estimated 2–7% of VL patients are HIV co-infected, albeit this is most likely an underestimate of the total incidence [100].

Drug Resistance

One of the major threats to kala-azar elimination from SEAR is the insurgence of drug resistance in *Leishmania donovani*. Drug resistance to antimonial drugs was reported in India and Nepal in early 1980s. The first report of drug resistance came from North Bihar, about 30% of patients were not responding to the prevailing regimen of the pentavalent antimonial drug, which had a small daily dose (10 mg/kg; 600 mg maximum) for a short duration (6 to 10 day). Within 10 years, the cure rate went down to 71% at a higher dose of the drug 20 mg/kg up to a maximum of 850 mg for 20 days [107]. Spread of antimonial resistance to the Eastern Nepal was reported in 2003 with a cure rate of 90% [108].

Antileishmanial drug resistance developed due to the improper use of the drug which was evident in India. There it was observed that only 26% were treated according to the WHO guidelines, 42% did not take the drug regularly and 36% stopped the drug on their own initiative [109]. This suggests the importance of the monitoring of the patients during treatment. Furthermore, monitoring parasite resistance is preferable to tracking relapses or poor responses. Additionally, it will make it possible to identify important intracellular targets and parasite defense mechanisms, which may then be used to rationally build analogs of current medications that won't interfere with the majority of defenses.

Global Climate Change

Environmental factors are also playing an important role in influencing the complexity of VL transmission. A variety of biological factors can influence biology, such as rainfall patterns, temperature patterns, soil types and vegetation types [110]. There are many ways in which leishmaniasis is being affected by the phenomenon of global climate change, just as there are several other vector-borne diseases. As a result of global climate change, it has been demonstrated that the distribution of vectors, including vectors of sandflies, has expanded worldwide.

The Southeast Asian region, for instance, has been observed to have vector competency as the temperature varies between 15 and 38 degrees Celsius [111]. This means that climate change alters vegetation patterns, rainfall patterns, and the behavior of vectors and humans alike. The WHO has developed the "Global Vector Control Response 2017–2030" to effectively address the growing threat of vector-borne diseases caused by climate change, population movement, and urbanization. Through its implementation, the WHO hopes to reduce the risk of VL.

Vector Control

Indoor residual spraying of insecticides in endemic communities reporting kala-azar cases in the previous years has been the primary vector control measure. Within the kala-azar eradication effort, a toolset for monitoring and evaluating entomological treatments was created in India, Bangladesh, and Nepal [112]. In well-controlled tests, pyrethroid spraying was proven to be successful in eliminating sand flies [113]. However, field studies indicate that the number of vectors in villages treated with indoor residual spraying has not decreased much [114]. Spraying also necessitates a large amount of equipment, is costly, and is sometimes unpopular with communities, making it unsustainable in the long run.

In light of these disadvantages, researchers sought less expensive alternatives that had a longer time of efficacy, and were simple to use and maintain. Sandfly density was reduced in trials in Bangladesh, India, and Nepal using reimpregnated commercial bed nets and long-lasting insecticide-treated bed nets [115]. They did not, however, protect against VL in a cluster randomized study conducted in India and Nepal [116]. A research in endemic areas in Bangladesh found a larger reduction in the prevalence of VL in one region when individuals slept under bed nets impregnated with a delayed-release of an insecticide, KO Tab, compared to the control area [117]. Although the upfront expense is high, durable wall lining has shown potential in lowering sand fly population. Wall paint containing three insecticides

and an insecticide repellent combination for canine leishmaniasis are also being tested [118].

Conclusion

Through strategic human resource planning in the health system, strengthening Kala-azar monitoring is a critical component of the Kala-azar eradication campaign. The last step of Kala-azar elimination must be conducted in mission mode. Bottom-up and top-down management techniques are both possible. Bangladesh, India and Nepal have some of the best national guidelines for eliminating Kala-azar; nevertheless, converting it into actual ground application with the necessary resource mobilization would be a main requirement. To make an evidence-based choice, reliable epidemiological data must be used. In keeping with the spirit of national health policy, health systems must resist the urge to administer the Kala-azar control program as a vertical program rather than integrating it with primary health care. Sandfly vector management must adopt a holistic approach using integrated vector control technologies.

Funding The authors did not receive support from any organization for the submitted work.

Data Availability The datasets generated during and/or analyzed during the current study are available in the World Health Organization repository.

Declarations

Ethical Approval The authors declare that this review article does not involve human participants or animals and complies with ethical standards.

Conflicts of Interest Statements The authors declare that they have no known conflicts of interest that could have appeared to influence the work reported in this paper.

Competing Interests The authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper.

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