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Is Leishmaniasis donovani elimination feasible in Bhutan? A review of current prevention and control mechanisms in Bhutan

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ABSTRACT

Introduction: Leishmaniasis is a neglected tropical disease with an annual estimated 700,000 to 1 million new cases globally. The diseases affect the rural community and people living in poverty. It is transmitted by female phlebotomine sand-fly; a tiny 2–3 mm long insect vector. Along with the regional countries, Bhutan has embarked on the elimination goal. However, several challenges lies ahead on its path to elimination. There is no elimination strategy and actions. The reporting, surveillance system, control and prevention mechanisms are inadequate. Further, there is lack of knowledge among the health care providers that impedes elimination goals. Therefore, if Bhutan is serious about its elimination goal, all the gaps and current challenges needs to be addressed appropriately.

Keywords: Bhutan; Elimination; Leishmaniasis.

INTRODUCTION

Leishmaniasis is a neglected tropical disease with an annual estimated 700 000 to 1 million new cases globally[1]. Leishmaniasis is caused by protozoan parasites that belong to more than 20 Leishmania species[2]. These parasites are transmitted to humans by the bite of an infected female phlebotomine sand-fly; a tiny 2–3 mm long insect vector[3]. There are three main forms of leishmaniasis, namely; cutaneous leishmaniasis (CL), visceral leishmaniasis (VL), also known as kala-azar, and mucocutaneous leishmaniasis (MCL). VL is the most severe form and is prevalent in Brazil, East Africa and the Indian subcontinent including Bhutan. The Indian subcontinent accounts for nearly 70% of world's VL burden[4,5]. Most of the cases go unreported[1]. Cutaneous leishmaniasis (CL) causes skin lesions, mainly ulcers, on exposed parts of the body, leaving life-long scars and serious disability. It is prevalent mostly in the Americas, the Mediterranean basin, the Middle East and Central Asia. Mucocutaneous leishmaniasis leads to partial or total destruction of mucous membranes of the nose, mouth and throat and mostly reported in Bolivia, Brazil, Ethiopia and Peru. The Indian Sub-continent region has set the elimination target to achieve less than one case per 10 000 populations annually, at the district or sub-district level[6]. A Memorandum of Understanding (MoU) was signed in 2014, and the countries agreed to collaborate to eliminate VL[7]. While the region has started with an ambitious goal to eliminate leishmaniasis from the region, unfortunately, implementation of actions in the field were inadequate to ensure the success of the initiative and to prevent its further resurgence[8]. The regional elimination goal was unrealistic without a clear direction on the process and stepwise elimination pathways[9]. Even the elimination deadline has been extended to 2020 with initial deadline being 2015[10]. Recently, India has taken lead for the regional elimination drive, with other countries falling in line for elimination[4]. Although, Bhutan has been a front runner in eliminating many diseases that are of public health concern, Bhutan's focus on leishmaniasis has been rather feeble. This review article reports the current status of leishmaniasis in Bhutan and its tryst towards elimination.

METHODS

The bulk of the information of this review article was generated through review of available literature, expert opinions, and government documents. We searched the available literature using the terms Bhutan, leishmaniasis, kala-azar and combination of these terminologies. Google Scholar, PubMed and google search were used to find the relevant articles, reports and electronic information including personal communication with relevant

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officials. We also searched various web publications and reports maintained in the Ministry of Health website http://www.health.gov.bt/ and unpublished reports including guidelines. Consultant reports and other reports that are maintained with the Vector Borne Disease Control Program (VDCP) were provided by the program for review.

RESULTS AND DISCUSSIONS

Epidemiology

There is very limited data on the epidemiology of leishmaniasis in Bhutan. First published literature occurred in 2006 with report of six cases who were confirmed as VL[11]. Following this report, a thorough investigation was conducted in 2011. The investigation noted nineteen cases[12]. Parasite typing yielded two novel microsatellite sequences, both related to Indian strain of L. donovani. Also, the investigation confirmed the vector status of both Phlebotomus species and Sergentomyia species sand flies[13]. Over the period, sporadic cases were reported from different areas. In 2019, eleven cases were reported[12]. Of these, one case of post-kala-azar muco-cutaneous leishmaniasis that resulted in severe disfigurement[14].

Prevention and control strategies

Bhutan has committed to the leishmaniasis elimination. However, currently, there is no specific leishmaniasis prevention and control strategy that the country has approved or adopted. Except for one descriptive epidemiology study[12], no studies have been conducted. The draft treatment guideline developed by MoH outlines the components of prevention and control[15]. The main pillars of leishmaniasis prevention and control is the vector control (adult sand flies) through use of insecticides (mostly pyrethroids) for indoor residual spraying (IRS) of dwellings and animal shelters, use of insecticide-treated nets (LLINs), and insect repellents. In Bhutan, IRS and LLINS are mainly deployed for malaria elimination and these interventions are focused only in high-risk malaria endemic areas. IRS and LLINs are not deployed in malaria free areas of Bhutan. Anecdotal evidence based on Leishmaniasis cases notification suggested that almost all cases were reported from malaria free areas. Only very few cases were reported from malaria endemic areas even though sandflies abundance have been reported. This suggested that IRS and LLIN may be effective for controlling leishmaniasis. There are also evidences in other countries[16] where leishmaniasis cases have increased after malaria control have stopped or scaled down following malaria elimination. LLIN also needs continuous supply to reach and keep good coverage of population at risk. It is imperative that understanding vector bionomics is essential for any long-term vector control measures to be implemented. An effective and focused vector control is essential and this requires understanding of vector bionomics. The phylogenetic analysis together with sequences from other L. donovani complex strains showed that Bhutanese isolates are closely related to Indian isolates belonging to the ITS type H(13). The vector of VL in India is Ph. argentipes var annandale which is anthropophilic in nature[17].

The sandflies are known to breed in places with suitable humidity such as crevices in the stone or mud walls, animal burrows and loose soil around tree roots[17]. The adults rest in dark and undisturbed places during the day time and become active in the evenings. More than 60% of the Bhutanese population are farmers and live in villages where houses are constructed of wood and stone or mud wall. Cattle and other livestock are housed in close proximity of human dwellings. A review of studies focused on Indian subcontinent found that VL occurrence in South Asia are determined by the interplay of factors affecting sand fly abundance, infection rate, feeding behavior, proximity of infectious person and determinants of human exposure to infected person[8]. Poor socio-economic conditions, poor nutrition, poor housing condition, lack of waste management, crowded housing has also been a high-risk factor for leishmaniasis transmission[18].

The life cycle of the leishmania parasites is an essentially a transformation of the amastigotes (Diagnostic stage) to promastigote (Infective stage). This occurs within the mid-gut of the female sandflies. The infection is transmitted to a new host when these infective female sand flies take their next blood meal. Therefore, effective control of human leishmaniasis could only be achieved through integration of patient management, prevention of infections and control of the vector. It is very important that Bhutan adopts a comprehensive interventions including early detection and treatment of clinical VL and PKDL cases and active surveillance as part of the elimination strategy. Further, Bhutan needs to strengthen the capacity for epidemiological surveillance, and carrying out focused prevention and control measures.

Diagnosis and treatment

In Bhutan, a case of VL is defined as a person with prolonged fever (> 2 weeks), splenomegaly, anaemia and weight loss with serological (rK39) and/parasitological diagnosis[15]. The diagnosis of Leishmaniasis is only possible in few district hospitals where rapid rK39 strip test is available. Microscopy confirmatory test with samples from spleen, bone marrow or lymph node aspirates is done only at the regional and national referral hospitals. The current rapid diagnostic test detects only antibodies against rK39 antigen and usually not very specific unless interpreted in conjunction with clinical features of fever for more than two weeks and enlargement of spleen. Although such rapid test has been vital in control phase, its role in elimination phase has been limited due to low positive predictive value in the elimination or post elimination phase. More specific tests are being developed and would become very important in the elimination phase[10].

Until 2005, the injectable sodium stibogluconate (SSG) was the only medicine available to treat Kala-azar and PKDL cases. By 2005, miltefosine was registered. However, miltefosine has its drawbacks with gastrointestinal side-effects and teratogenicity. Currently, liposomal Amphotericin B is the first-line regimen. Bhutan has also adopted treatment regimen with these drugs[15]. Other medicines such as paromomycin-miltefosine combination is not available in Bhutan. Pharmacovigilance to monitor the adverse

effects and monitoring of drug resistance needs to be strengthened[11].

A systematic review conducted in Bangladesh, India and Nepal, found that high prevalence of asymptomatic visceral leishmaniasis. Review also found that 3.8-28.6% of PKDL had no past history of natural infection of VL, showing a vast variability of disease progression[7]. About 5-10% of patients develop post –kala-azar dermal leishmaniasis 6 months or more after apparent cure, which further complicates the infection[10]. Untreated VL and PKDL patients are considered as the main reservoirs of parasites in the Indian subcontinent[19]. Early case detection and epidemiological surveillance is the cornerstone as the program moves towards the elimination of Leishmaniasis. As the parasite infection and clinical cases decline, awareness on knowledge of disease targeting both patients, community and health workers should be enhanced. Current case notification and surveillance needs to be redesigned and strengthened. People with leishmaniasis infection often comes late to seek health service from the hospital. Delay is further added by health workers' inability to properly diagnosis the case or misdiagnosis[14].

Elimination feasibility and challenges

Singh et al. highlighted both technical and operational feasibility and summed up that it is technically and operationally feasible as long as mitigation to address current challenges are addressed through concerted efforts[19]. Another review article also highlighted the challenges and the need to revamp the elimination strategy and approaches[5]. The scanty information available from the South Asian countries, such as Bhutan, makes estimation of the true disease burden difficult. It also acts as a stumbling block for effective control and elimination of this disease from the region. A detailed understanding of epidemiology is critical for both the development and evaluation of interventions and for the successful implementation of leishmaniasis surveillance and control programs. Knowledge on leishmaniases at both individual and population levels, identification of disease hotspots and understanding the biological, behavioral, and environmental factors that influence leishmaniasis transmission are especially important as the global community strengthens control and elimination efforts. Likely role of animal reservoirs including primates can be another challenge and studies into this field is required.

With the current elimination targets, reduction of cases has been achieved in some countries. However, resurgence and flare up of cases is eminent with the current relaxed mode of leishmaniasis interventions. The ongoing leishmaniasis research program supported through financial assistance from the National Institute of Health, USA implemented in Sri-Lanka and Bhutan has provided the framework and facilitated investigation of detailed epidemiology and risk factors of leishmaniasis and vector abundance dynamics in the hotspot areas. It also has triggered programmatic approach towards the elimination of VL by MoH. Even with extensive reaching out to the health workers to enable reporting of suspected cases, the information flow of reported cases has been abysmal. This could be due to the lack of awareness on leishmaniasis and diagnostic capacity of health workers to appropriately diagnose and report leishmaniasis cases. The data reported to the MoH is hardly verified and often it is either over or under reported. Therefore, it is very important to train the health workers on proper diagnosis of the cases and reporting mechanisms. Furthermore, as there are only few cases reported, Bhutan needs to move further towards zero indigenous cases reporting rather than striving to achieve one case per 10,000 population[6]. Delayed treatment, asymptomatic individuals and PKDL cases can also pose a significant challenge towards its elimination goal[20]. There is evidence of high burden of asymptomatic leishmaniasis relative to active VL cases in the Indian subcontinent[7] which could be valid for Bhutan as well although not studied. Progression of VL to PKDL is poorly understood. There is paucity of information on the disease progression of leishmaniasis. Lack of research capacity, case definition and lack of appropriate markers are some of the reasons highlighted for poor information[7]. Increasing recognition of atypical leishmaniasis has added to the hurdles of elimination from Bhutan[2,14]. Further, more than 90% of Indian VL cases occur in the state of Bihar[8]. Bihar host one of the most famous pilgrimage site, Bodh Gaya, where thousands of Bhutanese visits every year. This poses extra threat of case importation, off tracking the efforts towards its elimination.

CONCLUSIONS AND RECOMMENDATIONS

For Bhutan to successfully declare elimination of leishmaniasis, the country needs to address the current gaps in diagnosis, treatment, vector control, implementation and those within the health systems. To identify the gaps, there should be an urgent external review of the current status of leishmaniasis elimination in Bhutan. The review should focus on current epidemiology, institutional capacity to diagnosis, treat, prevent and control activities and also systems to prevent resurgences. Further, the country needs to invest in operational and implementation research. Early diagnosis and effective treatment of both VL and PKDL is important to decrease the infection reservoir and contain the spread of infection. The current medicines employed for the treatment, considering the side effects, requires strengthening of pharmacovigilance systems and monitoring of drug resistance. Importance of addressing the sub-clinically infected people is important. Further research is required to comprehend its prevalence and its impact on elimination in Bhutan. Bhutan needs to develop a comprehensive vector surveillance and control strategy encompassing both proactive and reactive surveillance strategies. Better knowledge on the vector prevalence and its bionomics would provide a foundation to build up such strategies. The strategy should also include interventions for housing improvement, environmental interventions and community engagement. Lessons from malaria in actively utilizing community action groups can be leveraged. In addition, focused coverage of LLIN and IRS within the communities where leishmaniasis cases are detected should be enhanced. For Bhutan to leverage on the

current success and to prevent further re-surgence, continued vigilance is required and country needs to invest substantially into research, training of health workers, realigning strategies and developing elimination tools. Then only leishmaniasis elimination in Bhutan can be achieved and elimination status sustained.

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