

# Toward Eliminating Leishmaniasis as a Public Health Problem in Yemen: Advocating for a One Health Approach

Rashad Abdul-Ghani <sup>1</sup>, Ahmed A Azazy<sup>2</sup>

<sup>1</sup>Department of Medical Parasitology, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen; <sup>2</sup>Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Al Baha University, Al Baha, Saudi Arabia

Correspondence: Rashad Abdul-Ghani, Department of Medical Parasitology, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen, Tel +967 775005239, Email rashadqb@yahoo.com

**Abstract:** Leishmaniasis is among the most neglected tropical diseases in Yemen, where both cutaneous and visceral clinical forms represent a public health challenge. *Leishmania tropica* is the main cause of cutaneous leishmaniasis, whereas *L. donovani* and *L. infantum* cause visceral leishmaniasis in the country. Although leishmaniasis has been recognized for decades, its actual burden in Yemen remains poorly defined, largely due to weak surveillance, constraints in diagnostic services, and the lack of a national control program. Conflict-related disruptions in healthcare, poverty, poor housing, and malnutrition further contribute to continued transmission. Surveillance of potential vectors and reservoirs is extremely limited, and access to effective diagnosis and treatment remains inadequate, particularly in rural areas. In the absence of integrated vector management and intersectoral coordination, disease control primarily relies on case management. This paper reviews the historical, epidemiological, clinical, and ecological aspects of leishmaniasis in Yemen, with attention to the diversity of *Leishmania* species, as well as their vectors and potential animal reservoirs that sustain transmission. Because there are no reliable baseline estimates on the national or subnational incidence of leishmaniasis, its elimination as a public health problem has been defined operationally in line with World Health Organization guidance as achieving a reduction in reported cases exceeding 90%, along with no mortality from visceral leishmaniasis, following implementation of strengthened active surveillance and systematic risk mapping. To advance such elimination, this paper also proposes a “One Health” approach integrating human, animal, and environmental health sectors through coordinating surveillance, mapping national risks, engaging communities, and strengthening diagnostic and treatment strategies. This collaborative framework is essential for informing targeted interventions, mobilizing resources, and ultimately eliminating the disease as a public health problem.

**Keywords:** leishmaniasis, elimination, one health, Yemen

## Introduction

Leishmaniasis is a vector-borne disease caused by several *Leishmania* species and transmitted by the bites of numerous species of female sandflies, primarily belonging to *Phlebotomus* in the Old World and *Lutzomyia* in the New World.<sup>1</sup> This neglected tropical disease (NTD) disproportionately affects populations living in resource-limited settings, including Yemen. Clinically, leishmaniasis may present as localized cutaneous or mucocutaneous lesions or as a systemic disease involving reticuloendothelial tissues with potential skin involvement.<sup>2</sup> Disease severity can vary from mild self-healing skin lesions to severe and potentially fatal visceral involvement, with each type caused by several distinct *Leishmania* species.<sup>2</sup>

Cutaneous leishmaniasis (CL) represents the most common form of the disease and is characterized by skin lesions or ulcers on exposed skin, often resulting in permanent scarring and, in some cases, social stigmatization.<sup>1</sup> Approximately 95% of cases occur in Latin America, the Middle East, the Mediterranean region and Central Asia, with an estimated annual incidence between 0.6 and 1 million cases.<sup>1</sup> In the Old World, CL is caused by *Leishmania tropica* (mainly in the Mediterranean region, Middle East, and Africa), *Leishmania major* (mainly in North and West Africa, Middle East, and

Central Asia), *Leishmania aethiopica* (mainly in Ethiopia and Kenya), and *Leishmania infantum* (mainly in the Mediterranean region).<sup>2</sup> In the New World (Central and South America), it is caused by *Leishmania mexicana*, *Leishmania braziliensis*, *Leishmania guyanensis*, *Leishmania amazonensis*, and *L. infantum*.<sup>2,3</sup> Immunosuppression increases the risk of developing diffuse CL (DCL) and disseminated CL (DsCL).<sup>4</sup> DCL is a chronic form characterized by multiple extensive non-ulcerative skin nodules containing large numbers of parasites resulting from an absent or reduced cellular response.<sup>2</sup> In the Old World, this form is caused by *L. aethiopica*, whereas in the New World, it is caused by *L. mexicana* and *L. amazonensis*.<sup>2</sup> However, DsCL is characterized by the presence of ten or more mixed-type lesions containing a few parasites that occur in two or more body sites with frequent mucosal involvement.<sup>2</sup> It is commonly caused by *L. mexicana*, *L. amazonensis*, and *L. guyanensis* in the New World and by *L. aethiopica* in the Old World.<sup>2</sup> Leishmaniasis recidivans is an unusual recurrent form that typically occurs because of reactivation of dormant *L. tropica* after resolution of CL in immunocompetent individuals with a good immune response and manifests as new lesions around the scar of the original ulcer.<sup>5</sup>

Mucocutaneous leishmaniasis (MCL) causes destructive lesions that involve the oronasal and pharyngeal mucous membranes as a result of lymphatic or hematogenous metastasis from skin lesions, leading to permanent disfigurement.<sup>2,3</sup> MCL mainly occurs in the New World and is typically caused by *L. braziliensis* (known as espundia), *L. panamensis*, and *L. guyanensis*.<sup>2,3</sup> Other *Leishmania* species can cause MCL in immunocompromised patients,<sup>6</sup> with Brazil, Bolivia, and Peru accounting for over 90% of cases worldwide.<sup>1</sup>

Visceral leishmaniasis (VL), also referred to as kala-azar, is the most serious and deadly form of the disease if left untreated. It is caused by the *Leishmania donovani* complex, which includes *L. donovani* in Asia and East Africa, and *L. infantum* in the Mediterranean, Western and Central Asia, and Central and South America.<sup>3,7</sup> VL is typically characterized by intermittent febrile episodes, hepatosplenomegaly, progressive anemia, pancytopenia, and weight loss and can be complicated by secondary infections.<sup>1</sup> Most cases occur in Brazil, East Africa, and India, with an estimated annual incidence of up to 90,000 cases worldwide.<sup>1</sup>

Although leishmaniasis has long been endemic in Yemen, comprehensive data on its epidemiology, parasite diversity, potential vectors, animal reservoirs, and transmission dynamics remain limited. Disease control efforts have been further constrained by fragmented interventions, insufficient resources, and weak coordination between human and veterinary health sectors. Therefore, this review consolidates fragmented historical, epidemiological, clinical, and ecological data on leishmaniasis in Yemen. It aims to unveil the complex interplay of disease drivers, identify key deficiencies in current control paradigms, and lay the groundwork for evidence-based interventions under a One Health framework, particularly in a conflict-affected setting where such an integrated approach is particularly needed.

## Narrative Review Method

This narrative review synthesized published and gray literature on CL and VL in Yemen by searching for relevant articles and reports in three databases (PubMed, Scopus, and Google Scholar), in addition to WHO documents, national reports, and reference lists of retrieved publications. The search covered literature published from the early 20<sup>th</sup> century to April 2025 and employed the core search Boolean combination (leishmaniasis OR *Leishmania*) AND Yemen. There were no strict language or study type restrictions applied during the search; however, the majority of publications were available in English. Studies conducted outside Yemen were included only when necessary for contextual interpretation or comparative analysis. All retrieved records were screened, and articles relevant to the epidemiology, transmission, clinical features, diagnosis, vectors, reservoirs, and control of leishmaniasis in Yemen were included in the review.

## Overview of Leishmaniasis in Yemen

Yemen has long been known to be endemic for both CL and VL, particularly in rural areas with poor living conditions and limited access to healthcare. The protracted conflict in Yemen since 2015 has likely exacerbated the burden of leishmaniasis through widespread disruption of healthcare infrastructure and disease control activities. Internal displacement brought on by the conflict may have raised the risk of transmission through several mechanisms, including housing disruption, malnutrition, outdoor sleeping, and limited access to healthcare. A recent global ecological analysis across 52 countries<sup>8</sup> supports this hypothesis by showing that leishmaniasis incidence increased with conflict intensity, with

population displacement serving as a mediating factor. Evidence at the community level from Yemen's conflict-affected regions also shows a high prevalence of CL linked to unfavorable living circumstances, like sleeping outside and having structurally damaged housing.<sup>9</sup> Disease control has been further constrained by fragmented interventions, limited resources, and weak coordination between human and veterinary health authorities. Addressing these challenges will require strengthening surveillance systems, improving diagnostic capacity, and expanding access to healthcare services to better quantify and reduce the burden of leishmaniasis in Yemen.

Leishmaniasis epidemiology in the country exhibits marked geographic and ecological heterogeneity, with both CL and VL documented in various governorates, mainly in rural areas. The transmission patterns in the western highlands and coastal/lowland areas have shown some differences. For instance, in the western and central highlands and escarpment zones, leishmaniasis is predominantly cutaneous, with *L. tropica* identified as the principal causative species and transmission largely following an anthroponotic pattern.<sup>9–15</sup> However, the lowland and coastal regions display a more complex epidemiological pattern, with the occurrence of both CL and VL and mixed or zoonotic transmission cycles.<sup>16,17</sup> The heterogeneity in transmission patterns may be attributed to differences in environmental and ecological conditions, *Leishmania* species and sandfly vectors, underscoring the importance of geographic and ecologic contexts in shaping leishmaniasis epidemiology in the country. Because of diversity, uniform national strategies are unlikely to be effective in eliminating the disease, reinforcing the need for geographically tailored One Health interventions.

Anthroponotic CL caused by *L. tropica* is the most common form of leishmaniasis in the country,<sup>11,12</sup> whereas zoonotic CL is caused by *L. major*, with small mammals such as gerbils serving as reservoir hosts.<sup>18</sup> *L. donovani* and *L. infantum*, which typically cause VL, have been found to cause CL in some endemic areas of the country.<sup>11,19</sup> Since 2005, CL cases reported to the World Health Organization (WHO) from Yemen have generally remained below 5,000 annually, with the exception of 2016 when 9,120 cases were reported.<sup>20</sup> However, limited healthcare access and resources, limited diagnostic capacity, and conflict-related disruptions can result in underreporting and underdiagnosis, and the actual number of cases may be much higher. Furthermore, it is challenging to compare incidence-based data with other endemic countries due to the absence of accurate population denominators, surveillance coverage, and complete reporting. *Phlebotomus sergenti* has been found to be a vector of the anthroponotic *L. tropica*,<sup>21</sup> for which no reservoir hosts have been identified. On the other hand, three *Phlebotomus* species (*P. bergeroti*, *P. duboscqi*, and *P. papatasi*) have been identified as potential vectors of the zoonotic *L. major*.<sup>21</sup>

VL has been on the rise in Yemen,<sup>22</sup> but few cases have been reported over the last decade, with the highest number of reported cases in 2020 (450 cases), followed by 286 cases in 2021 and 214 cases in 2022. Notably, no cases were reported in certain years, such as 2016.<sup>20</sup> Nevertheless, the actual number of cases may be higher because of underreporting or misdiagnosis resulting from limited healthcare access and resources. Notably, the absence of reported cases in certain years probably reflects underreporting due to the disruption of surveillance, limited diagnostic capacity, and restricted access to healthcare during the ongoing conflict in the country, rather than a true interruption of transmission. Both *L. donovani* and *L. infantum* have been identified as the causative species of VL in the country.<sup>17,23</sup>

## Historical and Epidemiological Insights into Cutaneous Leishmaniasis

### Early Reports of Endemic Foci and Potential Vectors

While early reports provide foundational insights, it is crucial to acknowledge that diagnostic tools and surveillance capabilities often limit their scope and methodologies, potentially underestimating the true disease burden and diversity of parasite species and vectors. In 1933, Sarnelli<sup>24</sup> used the Italian term “leishmaniosi muco-cutanee” to describe CL in five cases with nose and lip lesions containing numerous amastigotes in Sana'a, northern Yemen. Three decades later, skin biopsies taken from ten British Royal Marines near Aden led to the first confirmation of CL in the country's south.<sup>25</sup> The patients had been bitten by small flying insects while sleeping outside a few weeks before the lesions appeared at the bite sites on exposed body surfaces. However, at that time, the country lacked information regarding sandfly vectors. In the early 1970s, *Phlebotomus* species were identified among collections of sandflies from northern parts of the country.<sup>26</sup> In the late 1970s, CL was shown to be endemic in Taiz governorate, southwest of the country,<sup>27</sup> accounting for approximately 0.6% of all dermatoses in the local population.

Two *Phlebotomus* species, *P. sergenti* and *P. saevus*, have been recognized as potential vectors of *L. tropica* in Taiz.<sup>16</sup> An entomological survey conducted in Hajjah governorate identified six *Phlebotomus* species, with *P. alexandri* being the most abundant, followed by *P. arabicus*, with other species including *P. bergeroti*, *P. orientalis*, *P. sergenti*, and *P. papatasi*.<sup>28</sup> Although *Leishmania* DNA was not detected in the examined female sandflies, the authors suggested *P. arabicus* as a vector of *L. tropica* and rock hyraxes as reservoir hosts, as previously demonstrated in experimental work.<sup>29</sup> However, it should be noted that conventional polymerase chain reaction (PCR) was used in these investigations, and the absence of detectable *Leishmania* DNA in examined sandflies may reflect limited assay sensitivity rather than the true absence of infection, underscoring the need for more sensitive molecular assays such as real-time PCR.<sup>30</sup> Moreover, *P. alexandri* and *P. orientalis* have been proposed as likely vectors of VL in this region.<sup>28</sup> These findings emphasize the ecological diversity and epidemiological relevance of sand fly species in Yemen, highlighting the need for further investigation of their vector competence and seasonal patterns.

### Parasite Characterization and Genetic Diversity

Beyond vector identification, understanding the genetic makeup of parasites is crucial. To this end, isoenzyme electrophoresis identified *L. tropica* as the causative agent of CL among humans in Hajjah governorate and adjacent areas in northern Yemen.<sup>10</sup> However, there remains a paucity of studies exploring the range of potential reservoir hosts and vectors for *Leishmania* species or investigating the transmission routes and spread of parasite strains in the country. Zymodeme analysis is an essential epidemiological tool for identifying potential reservoir hosts and vectors of *Leishmania* species, as well as for understanding the transmission dynamics of specific parasite strains.<sup>31,32</sup> However, such studies are largely lacking in Yemen, limiting our understanding of specific parasite strains and their spread. Zymodeme analysis of four isolates from the northern part of the country identified one strain as MON-137 and three strains as belonging to two novel zymodemes closely related to MON-71,<sup>10</sup> suggesting genetic diversity among *L. tropica* circulating in the country. The identification of the zymodeme MON-137 for the first time in Yemen in a patient who had not travelled outside the country<sup>10</sup> suggests an autochthonous origin.

Molecular characterization using PCR-restriction fragment length polymorphism (RFLP) revealed that *L. tropica* was responsible for 85.8% of CL cases in northwestern Yemen<sup>11</sup> and confirmed it as the species causing CL in Hajjah.<sup>13</sup> In the early 1990s, CL caused by *L. donovani*, as characterized by starch gel electrophoresis, was reported in a French visitor to Yemen, who experienced repeated sandfly bites during their stay in the country.<sup>19</sup> Later, *L. donovani* and *L. infantum* were detected in 3.2% and 11% of patients with CL in northwestern Yemen, respectively, using PCR-RFLP analysis.<sup>11</sup> Notably, *L. donovani* has been associated with CL in several other countries.<sup>33–36</sup>

### Recent Reports and Outbreaks

In Yemen, recent prevalence estimates are often derived from localized studies published in literature or passive surveillance, making national-level extrapolation challenging and unlikely to reflect the full spectrum of disease incidence, especially in remote or conflict-affected areas. Leishmaniasis data are primarily generated through passive reporting from health facilities and sporadic localized research studies, with case notifications collected by focal points in health facilities. However, thorough data aggregation and timely interpretation of national trends are hampered by the lack of systematic active surveillance, limited integration between public health authorities and research institutions, and fragmented data-sharing mechanisms across institutions. A 2015 survey of 1,165 children in Utmah district in Yemen's western highlands, using the leishmanin skin test and physical examination, revealed a CL prevalence of 18.5%, with hyperendemicity in the escarpments (37%), comprising 5.5% for active lesions and 31.5% for scarring.<sup>15</sup> A community-based study of 612 participants in Utmah district reported that 33% had active lesions and/or scars consistent with CL, with a confirmed prevalence of 8.7% for *L. tropica* based on molecular diagnosis. Age  $\leq 10$  years, female sex, poor housing conditions, household contact with suspected cases, and sleeping outdoors were significant risk factors, whereas keeping livestock on the ground floor appeared to be protective.<sup>9</sup> These findings point to ongoing local transmission that disproportionately affects children and females and is associated with poverty-related factors. Subsequent molecular detection of *L. tropica* DNA in 16.4% of 122 examined domestic and wild animals, including goats, dogs, cattle, a donkey, a rabbit, a rat, and a bat, in this district provided the first evidence of potential reservoirs of zoonotic CL in

Yemen.<sup>37</sup> These findings suggest potential reservoir involvement; however, studies confirming that these animals can transmit the parasite and sustain the transmission cycle have not yet been conducted in the country. Overall, CL in western Yemen may involve a complex transmission cycle that is influenced by behavioral, environmental, and zoonotic factors. In a previous study on humans, the authors found that households that kept livestock on the ground floor showed a protective effect,<sup>9</sup> possibly because of sandfly zoophylaxis or altered vector-feeding behavior.

A survey conducted in 2012 and 2013 among 525 villagers aged 1–60 years in Shara'b District of Taiz revealed a CL prevalence of 18.9%.<sup>14</sup> This prevalence is markedly higher than most previously reported prevalence estimates from other endemic areas in Yemen, where CL prevalence has typically ranged from approximately 6% to 8.7% in community-based surveys,<sup>9,15</sup> underscoring the presence of localized hyperendemic foci within the country. Infection was significantly associated with poor housing (mud or cracked walls), the presence of domestic animals, and lack of household protection,<sup>14</sup> indicating the role of environmental and socioeconomic factors in sustaining transmission. In 2018, an outbreak of 30 CL cases was reported in Kuhlan Affar district, Hajjah governorate.<sup>38</sup> Of these, seven were under the age of five years. The attack rate was seven per 1,000 people for those aged <5 years and one per 1,000 for those aged >15 years. Female sex, malnutrition, poor household hygiene, plantations around houses, and raising animals were independent predictors of CL, possibly contributing to disease endemicity.<sup>38</sup> According to an analysis of national surveillance data from January 2019 to June 2020, 6,416 CL cases were reported in Yemen, with an incidence rate of 19.6 per 100,000 population.<sup>39</sup> The incidence was higher among under-five children, males, and residents of six governorates; namely, Lahj, Al-Jawf, Amran, Dhamar, Sa'adah, and Rayma.<sup>39</sup> The higher incidence observed among young children is consistent with long-established epidemiological patterns of leishmaniasis globally,<sup>40,41</sup> where children often bear a disproportionate burden of disease due to increased vulnerability and exposure.

### Clinical Perspectives

Clinically, most patients with CL in the northern and northwestern parts of Yemen present with a single, dry, noduloulcerative lesion on the face.<sup>10,11</sup> The dissemination of lesions to different exposed and unexposed parts of the body<sup>10,11</sup> and involvement of the mucosae of the nose and lips have also been observed in Yemeni patients with CL.<sup>10,24</sup> The clinical features were found to be similar irrespective of the causative species.<sup>11</sup> An investigation of 143 CL cases from 18 villages in Hajjah found that 98.6% of patients exhibited localized dry-type lesions and 1.4% exhibited wet-type lesions, mainly among children aged 5–15 years, with amastigotes detected in 74.1% of these lesions.<sup>13</sup> In Taiz, lesions are predominantly of the dry type, most often affecting the hands and face, with single lesions constituting the majority of cases.<sup>14</sup>

A study of 145 patients with CL from central and southwestern Yemen showed considerable clinical variations, with single lesions in 67% and multiple lesions in 33% of cases.<sup>42</sup> Localized ulcerative lesions were the most frequent (35%), mostly affecting the face and limbs. Atypical lesions, including the lupoid, verrucous, and eczematous forms, some of which resemble granulomatous dermatoses, have also been documented. Mucosal involvement has been identified in approximately 10% of lesions, whereas chronic and relapsing forms of leishmaniasis recidivans and satellite papular lesions have been documented in only a few cases.<sup>42</sup> These findings underscore the clinical heterogeneity and diagnostic difficulties in Yemen, emphasizing the need for clinician awareness to prevent misdiagnosis and minimize disfigurement.

## Historical and Epidemiological Insights into Visceral Leishmaniasis

### Early Reports of Endemic Foci, Causative Species, and Incriminated Vectors

VL was first documented in Arabia in 1904 when two Egyptian patients who had worked in Saudi Arabia and Yemen,<sup>43</sup> suggesting the presence of the disease in Yemen. Later, in the 1980s, *L. donovani* and *L. infantum* complexes were identified as the causative agents of VL in Taiz,<sup>17</sup> with two *Phlebotomus* species, *P. orientalis* and *P. arabicus*, suggested as potential vectors for both species.<sup>16</sup> *L. infantum* was also detected in a 10-year-old child near Bayt al-Faqih district in the western coastal plain of Tihama, who subsequently died of VL.<sup>17</sup> Eco-epidemiologically, no co-circulation of *L. infantum* and *L. donovani* complexes has been detected in the coastal plains of Tihama.<sup>17</sup> Moreover, species causing VL and CL have been documented to co-circulate in endemic areas of Taiz, with the absence of the visceral form when the cutaneous form is uncommon.<sup>17,44</sup>

To better understand the seroepidemiology of VL, an indirect fluorescent antibody test was employed to detect antibodies to *Leishmania* in serum samples of 104 rural children aged 6–15 years in southern Yemen, with rates of 43.8% in the lowlands and 39.3% in the highlands.<sup>45</sup> However, the small sample size of children did not accurately reflect the disease seroepidemiology in the entire population. Furthermore, serological tests may have limited sensitivity and specificity, which could affect the accuracy of seroprevalence estimates. In this regard, a study aimed at developing a serodiagnostic method for VL using sera from Yemeni patients found a sensitivity of 68% for indirect enzyme-linked immunosorbent assay (ELISA) for detecting antileishmanial IgG antibodies and capture ELISA for detecting *Leishmania* antigens.<sup>46</sup> In addition, the specificity was 67% for indirect ELISA and 64% for capture ELISA.<sup>46</sup> These findings highlight the wider challenge of suboptimal VL diagnosis in endemic settings.<sup>47</sup> The limitations in diagnostic performance, in particular for serological tests, contribute to underdiagnosis and delayed case detection, which underscore the need for improved, sensitive and locally validated diagnostic tools to improve case detection and surveillance. Another study found that dot-ELISA with anti-amastigote IgG antibodies was 100% sensitive for detecting circulating *Leishmania* antigens in the sera of Yemeni patients and demonstrated a high level of specificity, with only one case of *Plasmodium vivax* showing cross-reactivity.<sup>48</sup>

### Parasite Characterization

*L. donovani* zymodemes in Yemen are similar to those isolated from patients in eastern Ethiopia,<sup>17</sup> suggesting that the same zymodeme is prevalent from Arabia in the west to Africa in the east along the Red Sea. Sequencing-based molecular characterization of *Leishmania* isolates from bone marrow specimens of Yemeni children confirmed the presence of both *L. donovani* and *L. infantum*.<sup>23</sup>

### Serosurveys and Bone Marrow Investigations

Seroprevalence studies of VL are important for understanding the disease epidemiology and transmission dynamics, identifying risk factors, and evaluating control efforts. However, studies on disease seroprevalence in endemic areas are lacking. In the late 1990s, antibodies against *Leishmania* species were reported among 34.7% of schoolchildren in Sana'a and Hajjah governorates in the north of the country.<sup>49</sup> Moreover, 50% of feral dogs in the study areas tested positive for antileishmanial antibodies.<sup>49</sup> A prospective study conducted at a tertiary care hospital in Sana'a City between 2010 and 2014 confirmed 47 cases of VL (59.6% adults and 40.4% children) by bone marrow examination.<sup>50</sup> Most patients originated from rural areas of Hajjah (27.7%), Taiz (14.6%), Amran (12.8%), Dhamar (12.8%), and Al-Hudaydah (8.5%) governorates,<sup>50</sup> highlighting these as endemic foci of VL.

A recent study in Sana'a reported a 6% seroprevalence of anti-*Leishmania* antibodies among adults aged 18–65 years attending four health facilities using the rK39 immunochromatographic test (ICT).<sup>51</sup> The study identified male gender, presence of domestic and peri-domestic animals (dogs, rats, and goats), garbage accumulation around houses, presence of sand flies, sleeping outdoors, and population displacement as significant factors associated with VL seropositivity.<sup>51</sup> It is noteworthy that seropositive individuals might have been non-permanent residents of the city, suggesting possible exposure to infection in other endemic areas. Another concern is that the sensitivity and specificity of rK39 ICTs have yet to be validated in Yemen. Although this test is simple, rapid, and field-adapted, it cannot distinguish between active and past infections, necessitating its interpretation in conjunction with clinical criteria.<sup>52</sup> A Cochrane meta-analysis showed that rK39 ICTs had high sensitivity and specificity (>90%) for diagnosing suspected cases, particularly in the Indian subcontinent, although the performance was comparatively lower in East African settings, possibly due to regional strain variations and host immune differences.<sup>53</sup> Given the documented regional variability in rK39 performance and the absence of country-specific validation data, there is an urgent need to evaluate and standardize the use of rK39 RDTs in Yemen's specific epidemiological context.

### Clinical Perspectives

Clinically, fever, fatigue, and abdominal distention were found to be the most common symptoms of VL in pediatric patients in Hajjah governorate.<sup>54</sup> In addition, anemia was observed in all cases, leukopenia in over 80%, and thrombocytopenia in over half of the cases.<sup>54</sup> In Aden city, fever and splenomegaly were consistently observed in all children hospitalized with VL. Additionally, hepatomegaly was present in more than 80% of cases, and peripheral pancytopenia

was observed in 70% of children, with varying degrees of anemia detected in all children.<sup>55</sup> Furthermore, weight loss and abdominal distension were also common in approximately two-thirds of children, while lymph node enlargement was observed in 17.2% of them.<sup>55</sup> A study on confirmed VL cases at a tertiary care hospital in Sana'a revealed that fever, pallor, splenomegaly, and hepatomegaly were the predominant clinical manifestations among Yemeni patients, with notably uncommon lymphadenopathy (<10%).<sup>50</sup> This clinical pattern is consistent with that reported from the southern region of Saudi Arabia.<sup>56</sup>

A hematological investigation of 47 Yemeni adults and children with bone marrow-confirmed VL at a tertiary care hospital demonstrated that anemia was present in all cases, with leukopenia (87%), neutropenia (89%), thrombocytopenia (94%), eosinopenia (89%), and pancytopenia (72%) being the most frequent abnormalities. Notably, marked bone marrow eosinopenia has been identified in over 90% of cases.<sup>57</sup> Bone marrow eosinopenia has been highlighted as a potential diagnostic indicator of VL, particularly among patients presenting with splenomegaly and cytopenias, even in non-endemic settings.<sup>57</sup> VL was identified as the leading cause of pancytopenia among children aged 2 months to 15 years admitted to the hospital in Hadhramout governorate, eastern Yemen, accounting for 37.9% (39/103) of cases,<sup>58</sup> underscoring the substantial contribution of VL to pediatric morbidity in endemic areas of the country. These findings emphasize the importance of early diagnosis of VL to avoid unfavorable outcomes, especially in febrile children with pancytopenia and hepatosplenomegaly who do not respond to standard treatment. Improving diagnostic capabilities and raising clinician awareness in both peripheral and tertiary healthcare facilities are crucial to help reduce disease burden and mortality among children in endemic areas of the country.

The difficulty in diagnosing VL remains a major challenge in Yemen, where several parasitic infections with overlapping clinical presentations coexist. For instance, an eight-year-old boy with concurrent malaria and schistosomiasis presented with persistent fever, hepatosplenomegaly, and weight loss, but he failed to respond to standard antimalarial and antischistosomal therapy.<sup>59</sup> However, VL was subsequently confirmed by bone marrow examination and successfully treated with sodium stibogluconate.<sup>59</sup> This case exemplifies how co-endemic infections may obscure VL and delay diagnosis, emphasizing the need for clinical vigilance and parasitological confirmation in patients with fever and splenomegaly unresponsive to conventional therapies in endemic areas of the country.

## Leishmaniasis Control in Yemen

There is currently no independent leishmaniasis control program in the country. Instead, there is a unit for leishmaniasis control under the supervision of the NTD Directorate, a dedicated unit within Yemen's MoPHP responsible for coordinating prevention, surveillance, and control activities for NTDs, but no sandfly control has been implemented as part of the control strategies. Moreover, there is no national strategic plan for the control and elimination of leishmaniasis. A report outlining the action plan for leishmaniasis in 2013 indicated that implementing vector control interventions for malaria could potentially decrease the sandfly population in certain areas where both diseases are endemic.<sup>60</sup> This effect is most likely attributable to indoor residual spraying (IRS), a key component of malaria control efforts in the country, which primarily targets indoor-resting *Anopheles* mosquitoes through the application of long-lasting insecticides to indoor surfaces. IRS may incidentally affect sandfly populations, particularly species that rest indoors, and has been reported to achieve short-term reductions in indoor sandfly densities and VL incidence elsewhere.<sup>61</sup> Nevertheless, further investigations are necessary to determine the specific impact of malaria vector control on sandfly populations. In 2014, Yemen conducted its first vector control needs assessment (VCNA) to identify gaps, priorities and opportunities in vector control and to guide the development of the country's 2015–2020 Integrated Vector Management (IVM) strategy. In December 2014, a workshop was conducted to develop an IVM strategic plan in collaboration with the WHO Regional Office for the Eastern Mediterranean (EMRO) in Cairo and the National IVM Steering Committee, with representatives from key ministries, the community, and other relevant stakeholders. However, the IVM strategic plan 2015–2020 has not been implemented because of a lack of sufficient funding and weak commitment to national strategies and plans, in addition to the eruption of armed conflicts and humanitarian crises since 2015. In 2018, the country's VCNA was updated following the humanitarian crisis and war.

An action plan was developed in 2014 to establish the Leishmaniasis National Control Program,<sup>62</sup> with the overarching goal of reducing the number of cases and the spread of the disease. Specifically, the plan aimed to strengthen the

infrastructure, establish a data collection system, ensure a system for early detection and prompt treatment of cases, and enhance community awareness and engagement. The strategy outlined in this plan involves establishing vector control.

Leishmaniasis control in Yemen relies mainly on case management (diagnosis and treatment). However, vector control has not been prioritized as an intervention. Because the disease mostly affects impoverished communities in rural areas, the cost of diagnosis and treatment poses a significant barrier for the most vulnerable individuals, preventing them from seeking necessary medical care. Access to treatment with pentavalent antimonial compounds is limited through the central pharmacy of the Ministry of Public Health and Population (MoPHP) and is present in some Yemeni governorates, with a few patients who can afford treatment in the private sector. Consequently, traditional treatment methods, such as the application of corrosive chemicals, poultices made from plants, and direct heat, are commonly used to treat CL in many regions of the country.

Epidemiological data at national and subnational levels are critical for planning intervention needs and effective resource allocation. There is no functioning system for routine surveillance of leishmaniasis in the country. While reporting cases of leishmaniasis has become mandatory, active detection of human cases is not regularly conducted. Instead, surveillance and rapid response to outbreaks are the main functions of the leishmaniasis control unit. In 2022, leishmaniasis data collected by focal points were integrated into the Electronic Disease Early Warning System (eDEWS), an initiative implemented to enhance disease surveillance and early detection of outbreaks in the country, and expanded to include 2,379 health facilities in the public and private health sectors in all districts of all 23 governorates.<sup>63</sup>

Inadequate capacity for surveillance and diagnosis, particularly at the peripheral level in rural areas, poses a challenge to leishmaniasis control in Yemen. Therefore, efforts should be made to strengthen disease surveillance, enhance diagnostic capabilities, and improve access to healthcare services to capture and address the disease burden in the country accurately. On the other hand, the entomology staff responsible for sandfly surveillance and control is nearly nonexistent because vector control is not included in the disease control interventions. Although leishmaniasis transmission is predominantly vector-borne, non-vector routes, including vertical transmission, should not be entirely disregarded as potential contributors to pediatric infections in highly endemic settings. Congenital VL has been reported, including cases where infants were infected by asymptomatic mothers,<sup>64</sup> highlighting the potential for vertical transmission in human populations. Therefore, understanding vertical transmission dynamics is crucial for developing targeted public health interventions in endemic areas, as it may significantly impact infection control strategies.<sup>65</sup> However, occurrence of congenital transmission of VL has not been documented in Yemen, and its epidemiological role remains uncertain locally.

In 2013, the International Society of Dermatology sponsored a community initiative called “Eradication of Leishmaniasis from Yemen Project” as the first community-based initiative contributing to reducing disease burden in the country.<sup>66</sup> As part of the project, the Regional Leishmaniasis Control Center (RLCC) was established in Sana’a in 2014 as a charitable nongovernmental organization (NGO). The RLCC operates with the support of a network of volunteers, including physicians, scientists, technicians, health workers, community leaders, and patients. It provides free diagnosis and treatment for leishmaniasis and conducts awareness-raising and educational campaigns, as well as surveillance, control, and research activities. The RLCC also collaborates with the MoPHP to organize free medical camps for the detection and treatment of leishmaniasis. These camps also serve to raise public awareness of disease prevention and control. However, the available information does not state the specific role of RLCC in sandfly control.

## Need for a “One Health” Approach

“One Health” is defined by WHO as “an integrated, unifying approach to balance and optimize the health of people, animals and the environment.”<sup>67</sup> This collaborative and multidisciplinary approach considers the complex relationship between these three domains to address the associated health challenges by engaging public health, veterinary, and environmental sectors.<sup>67</sup> Several studies have advocated for a One Health approach to effectively control and eliminate leishmaniasis by managing the health risks shared among humans, reservoir animals, and ecosystems, while also considering the social factors involved.<sup>68–71</sup> In the Yemeni context, where diverse *Leishmania* species co-circulate, potential animal reservoirs remain largely unidentified, and control efforts are fragmented across human, animal, and

environmental sectors, a siloed approach is demonstrably insufficient. The dynamic interplay among human populations, domestic and wild animals, and the changing environment necessitates the integrated perspective offered by One Health.

## A Proposed One Health Approach to Eliminate Leishmaniasis in Yemen

Given the absence of comprehensive national or subnational incidence estimates in Yemen, “elimination of leishmaniasis as a public health problem” is operationally defined as achieving a reduction of more than 90% in reported leishmaniasis cases and zero mortality from visceral leishmaniasis, following the implementation of strengthened active surveillance and systematic risk mapping. This definition is framed as an aspirational target and is consistent with the WHO strategic framework for the elimination of visceral leishmaniasis as a public health problem in eastern Africa,<sup>72</sup> which specifies elimination benchmarks of approximately a 90% reduction in new cases at the country level relative to baseline averages and a case-fatality rate below 1%. Elimination metrics will be assessed relative to the baseline data generated after strengthening surveillance and systematic risk mapping across endemic districts, where cases are expected to increase as a result of strengthened surveillance rather than a real increase in transmission. To advance a One Health approach to eliminating leishmaniasis as a public health problem in Yemen, several strategies should be integrated to tackle various aspects related to public health, veterinary public health, and the environment, together with the social determinants of infection. These strategies include:

### Establishment of a National Working Group on Leishmaniasis

Existing leishmaniasis control efforts are fragmented and lack a clear coordination mechanism, with the NTD Directorate and RLCC operating almost independently. Therefore, the establishment of a national working group on leishmaniasis, jointly led by the Ministry of Health and Environment and the General Directorate of Veterinary Services, is the first step toward the One Health approach. The working group should involve a variety of stakeholders, including relevant health and non-health programs, pertinent ministries, academic and research institutions, NGOs, and international partners such as WHO. It will serve as a central coordinating entity that brings together human, animal, and environmental health initiatives within a unified framework. Table 1 outlines the major stakeholders in the proposed working group and their key roles in the One Health approach.

**Table 1** Expected Key Roles of Major Stakeholders to Be Involved in the Proposed One Health Approach to Leishmaniasis Elimination in Yemen

Stakeholder	Key Roles
<b>Ministry of Health and Environment</b> and its relevant health programs	<ul style="list-style-type: none"> <li>• Establish a national working group on leishmaniasis.</li> <li>• Prepare and update strategic plans and policies, and mobilize funding.</li> <li>• Lead human health interventions, surveillance integration, and case management.</li> <li>• Coordinate health facility reporting through eDEWS and district health offices.</li> <li>• Map risk zones and identify environmental risk factors.</li> <li>• Supervise environmental health aspects of vector control and pesticide use.</li> <li>• Train personnel and share data.</li> </ul>
<b>General Directorate of Veterinary Services</b>	<ul style="list-style-type: none"> <li>• Conduct animal surveillance (especially canine and rodent reservoirs).</li> <li>• Confirm zoonotic <i>Leishmania</i> infections and maintain the animal reservoir database.</li> <li>• Support zoonotic leishmaniasis monitoring and outbreak investigation.</li> </ul>
<b>Local authorities</b>	<ul style="list-style-type: none"> <li>• Facilitate community engagement and raise awareness of leishmaniasis prevention and control through district and governorate councils.</li> <li>• Integrate vector control into local sanitation and waste management programs.</li> </ul>
<b>Academia and research institutions</b>	<ul style="list-style-type: none"> <li>• Conduct operational research, GIS risk mapping, molecular xenomonitoring, and vector and reservoir identification.</li> <li>• Train local teams on various aspects of leishmaniasis surveillance and control.</li> </ul>
<b>Private sector</b>	<ul style="list-style-type: none"> <li>• Report cases via eDEWS</li> <li>• Provide diagnosis and treatment services</li> </ul>
<b>Nongovernmental organizations</b>	<ul style="list-style-type: none"> <li>• Provide free diagnosis, treatment, and community outreach.</li> </ul>
<b>International partners</b>	<ul style="list-style-type: none"> <li>• Provide technical support for surveillance, diagnostics, and the One Health framework design.</li> <li>• Provide financial support to implement surveillance, treatment, and community-based vector control.</li> </ul>

**Abbreviations:** GIS, Geographic Information System; eDEWS, Electronic Disease Early Warning System.

## National Risk Mapping of Leishmaniasis

Risk mapping is crucial for effectively allocating resources, developing targeted control strategies, and prioritizing interventions for high-risk areas. Given the absence of a national risk map for leishmaniasis in Yemen, disease epidemiology in the country remains unclear. The distribution of leishmaniasis in the country is mostly based on either a limited number of studies published in the literature or a consensus on the presence of leishmaniasis cases observed in a certain locality. Although these sources provide an initial agreement on the presence of leishmaniasis, there is a need to integrate data on disease prevalence and distribution of *Leishmania* species, potential reservoirs and vectors of these species, and environmental factors facilitating disease transmission. Community screening and targeted investigations in hotspots accelerate the identification of symptomatic and cryptic infections and are recommended where underreporting or hotspots are suspected.<sup>73</sup>

Spatial and spatiotemporal modeling of leishmaniasis, considering environmental risk factors, vectors, and reservoirs, can assist in generating risk maps and identifying high-risk areas using GIS-based surveys.<sup>74–77</sup> For this purpose, a multidisciplinary team comprising parasitologists, entomologists, epidemiologists, environmental health professionals, geospatial statisticians, and experts from other relevant disciplines is required.

## Case Management and Awareness Raising

Early diagnosis, standardized treatment, and post-treatment follow-up should be adopted and linked with notification systems. Knowledge gaps and misconceptions regarding leishmaniasis and its transmission may contribute to sustained endemicity and persistent transmission, suggesting the importance of community-based health education and awareness programs. In this context, a community-based survey among residents of a rural endemic district in Taiz revealed limited knowledge and negative attitudes toward CL,<sup>78</sup> with only 14.8% recognizing sandflies as vectors and nearly half having negative attitudes toward the disease.

## Identification of Potential Reservoir Hosts

Potential reservoir hosts for zoonotic leishmaniasis in the country are largely unrecognized. For instance, antileishmanial antibodies were detected in the sera of feral dogs in the northern parts of the country,<sup>49</sup> however, their role as reservoir hosts for zoonotic VL has not been confirmed. The detection of *L. tropica* in domestic and wild animals in the country's western highlands provided the first confirmed evidence of natural infection in animals,<sup>37</sup> indicating that animal reservoirs may contribute to the transmission cycle of CL in the country and underscoring the need for studies to clarify their reservoir competence and role in sustaining endemic transmission. While canine reservoirs are well established in several endemic regions globally, evidence in Yemen remains limited to serological and molecular detection studies without definitive reservoir confirmation.

## Establishment of an Integrated Leishmaniasis Surveillance and Reporting System

WHO recommends establishing a national integrated surveillance system for all NTDs, including diseases of major public health importance such as leishmaniasis.<sup>79</sup> However, a notable shortcoming in leishmaniasis control in Yemen is the absence of an effective surveillance and reporting system. Therefore, the establishment of an independent or integrated leishmaniasis surveillance system is imperative to allow early case detection and better tracking of disease trends. An effective surveillance system should combine active and passive approaches to allow a comprehensive assessment of leishmaniasis burden and transmission patterns. This involves periodic community-based surveys in endemic areas to identify cases that may not reach health facilities. At present, passive surveillance in Yemen depends largely on case reporting from health facilities through the eDEWS platform; however, the completeness and timeliness of reporting remain suboptimal. Strengthening reporting mechanisms is therefore essential to improve the accuracy, timeliness, and use of surveillance data. The adoption of digital reporting tools, including mobile applications and web-based platforms, could facilitate real-time data submission and early outbreak detection, particularly for emerging zoonotic forms of leishmaniasis.<sup>80</sup> In parallel, systematic reporting of canine cases through veterinary health services is critical to support integrated surveillance efforts.

Entomological surveillance and monitoring of potential animal reservoirs remain largely absent and require systematic implementation. To date, no structured surveillance activities targeting sandfly populations or animal reservoirs have

been conducted, limiting the understanding of local transmission dynamics. Molecular xenomonitoring has increasingly been applied in leishmaniasis-endemic settings, as it enables the sensitive and specific detection of *Leishmania* DNA in pooled sandfly samples and supports the identification of vector species involved in parasite transmission.<sup>81–83</sup> However, it has not yet been implemented in Yemen, resulting in limited data on *Leishmania* infection rates in sandfly vectors and the species involved in transmission.

### Vector and Reservoir Control

Effective control of *Leishmania* vectors and reservoirs is driven by surveillance data and requires IVM, reservoir control, and community engagement. However, vector and reservoir control remains one of the weakest programmatic components for controlling leishmaniasis in the country. Vector control is largely achieved indirectly through the efforts of the National Malaria Control Program, which conducts indoor residual spraying, distributes insecticide-treated nets, and implements environmental management to reduce malaria transmission. However, these activities have had a limited impact on leishmaniasis, mainly because the country lacks a dedicated sandfly control program and has a minimal entomological capacity. In the context of the One Health approach, vector control should adopt IVM principles, encourage cross-sectoral collaboration and community engagement, and integrate human, animal and environmental health components. Establishing sandfly sentinel sites in known transmission hotspots—ideally in partnership with university entomology departments—would allow routine monitoring of vector abundance, species composition, and insecticide susceptibility, thus providing the evidence base needed for targeted and effective interventions.

In view of the concerns raised in the country regarding dogs as potential reservoirs of CL and VL,<sup>37,49</sup> it is essential to implement canine surveillance, vaccination, and screening in areas where dogs are primary reservoirs of infection, guided by serology and molecular tools.<sup>84</sup> Integrated animal health surveillance is recommended to address this gap through cooperation between veterinary services, research institutes and public health authorities. The One Health approach should focus on routine screening of domestic dogs, elimination of feral dogs, community education on responsible dog management and vaccination, as appropriate, and the use of insecticide-impregnated collars.<sup>68,85</sup>

### Evidence Gaps Limiting One Health Implementation

Beyond the proposed One Health framework, important research gaps persist in Yemen and require urgent attention. Priority areas include molecular epidemiological studies to characterize *Leishmania* species and strains across diverse ecological zones; entomological surveys to map vector distribution, understand their bionomics, and assess insecticide resistance; investigations to verify and quantify the reservoir capacity of suspected animal hosts; and socioeconomic and behavioral studies that explore community knowledge, health-seeking challenges, and acceptance of proposed control measures. Filling these gaps would provide the evidence needed to better tailor and strengthen the One Health approach within Yemen's unique ecological and social context.

### Conclusions and Perspectives

Leishmaniasis continues to pose a major public health challenge in Yemen, with both CL and VL persisting in a context of fragile health services, poverty, and conflict. Current control efforts are largely focused on case management, with relatively little emphasis on vector control, reservoir surveillance, or environmental determinants of transmission. Beyond vector control, leishmaniasis control in the country should also consider non-vector routes of transmission, recognizing that vertical transmission and blood-transfused infections, although limited, should not be entirely disregarded in highly endemic settings. In this context, exclusive reliance on vector-borne transmission models may overlook less common but epidemiologically relevant transmission pathways. Although these transmission modes have been reported in other endemic settings, their epidemiological contribution in Yemen remains undocumented and requires further investigation. Accordingly, the magnitude of the disease remains underreported and inadequately addressed, reflecting the shortcomings of surveillance, reporting, and control. The diversity of *Leishmania* species, vectors, and possible animal reservoirs further complicates transmission dynamics and underlines the need for a unified evidence-driven approach to disease elimination. The lack of an independent national control program, along with fragmented prevention and control measures, undermines progress toward elimination. The inclusion of veterinary and environmental

components is essential for advancing disease elimination within a One Health approach, offering a practical pathway to address existing gaps and strengthen control efforts. In the short term, progress toward eliminating leishmaniasis as a public health problem in Yemen will require a small set of pragmatic actions that are feasible even in the current context. Key actions include establishing sentinel surveillance in selected high-burden governorates, local validation and standardization of diagnostic RDTs to enhance case detection and reporting, and initiation of minimal entomological monitoring through partnerships with academic and research institutions. Together, these actions would generate vital data to guide targeted interventions while laying the foundation for a more comprehensive One Health framework. In the longer term, sustained funding will be required to develop comprehensive GIS-based national risk mapping, establish a fully integrated national surveillance system, expand systematic reservoir and entomological surveillance, and implement a formal national sandfly control program.

## Disclosure

The authors declare no conflicts of interest in this work.

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