Leishmaniases in Bolivia: Comprehensive Review and Current Status

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Abstract. The leishmaniases are protozoan, zoonotic diseases transmitted to human and other mammal hosts by the bite of phlebotomine sandflies. Bolivia has the highest incidence of cutaneous leishmaniasis (CL) in Latin America (LA), with 33 cases per 100,000 population reported in 2006. CL is endemic in seven of the country’s nine administrative departments. Visceral leishmaniasis (VL) is comparatively rare and is restricted to one single focus. Most CL cases are caused by *Leishmania* (*Viannia*) *braziliensis* (85% cases); VL is caused by *L. (L.) infantum*. Seven sandfly species are incriminated as vectors and *Leishmania* infections have been detected in several non-human mammal hosts. Transmission is associated with forest-related activities, but recently, cases of autochthonous, urban transmission were reported. Because most cases are caused by *L. (V.) braziliensis*, Bolivia reports the greatest ratio (i.e., up to 20% of all cases) of mucosal leishmaniasis to localized CL cases in LA. Per national guidelines, both CL and VL cases are microscopically diagnosed and treated with pentavalent antimony.

INTRODUCTION

The leishmaniases are a group of protozoan diseases transmitted to mammals including humans by phlebotomine sandflies. They are characterized by a spectrum of clinical manifestations: disseminated visceral infection (visceral leishmaniasis [VL]) to various manifestations of cutaneous leishmaniasis (CL), including ulcerative skin lesions developing at the site of the sandfly bite (i.e., localized cutaneous leishmaniasis [LCL]); multiple non-ulcerative nodules (i.e., diffuse cutaneous leishmaniasis [DCL]); and destructive mucosal inflammation (i.e., mucosal leishmaniasis [ML]).

Globally, ~350 million people are thought to be at risk of infection and disease. It is estimated that an annual 1.5–2 million new cases occur and 70,000 deaths are caused by the disease, with associated morbidity and mortality causing 2.4 million disability-adjusted life years.

The leishmaniases have been endemic in Latin America for centuries, as evidenced in ceramic pottery from the pre-Incan Moche and Chimú eras. They were first described in Bolivia in 1876 and then again in 1903, when several cases of CL were reported in the region of the Mapiri River and the Colónias territory during the *Campaña del Acre*. Since these early reports, several detailed studies on the leishmaniases have been carried out in Bolivia investigating the clinical, epidemiologic, genetic, and immunologic aspects of the disease. Thus, although VL only occurs in one isolated focus, Bolivia has probably the highest incidence of LCL and ML in Latin America (e.g., whereas the LCL incidence per 100,000 population in Brazil was 11.9 in Brazil in 2006, it was 32.7 in Bolivia).

Also, an increasing number of patients (e.g., tourists) contracting leishmaniases in Bolivia have been reported.

Although some of these studies have been summarized previously in a review of CL in Colombia, Peru, Venezuela, and Bolivia published in 2000, studies that have been published since then have yet to be comprehensively reviewed, together with the latest national case notification data available. Additionally, we describe operational aspects of leishmaniases’ case management, prevention, and control and discuss approaches that could be undertaken in Bolivia to 1) significantly contribute to the knowledge of the leishmaniases; 2) develop a comprehensive leishmaniases prevention and control strategy; and 3) assist in managing patients that have contracted the disease.

MATERIALS AND METHODS

We conducted a comprehensive literature search of medical databases (Medline, Global Health, and Cochrane library) and non-medical search engines using several keywords: leishmaniasis, leishmaniosis, *Leishmania*, cutaneous, mucosal, mucocutaneous, diffuse, and Bolivia. If appropriate, we contributed our personal knowledge on the subject.

Given the previous review by Davies and others and given the country-specific burden of CL compared with VL, our review primarily focused on studies undertaken or published in the past 10 years and on CL. Where relevant or where there are clear differences in case management, prevention, or control of CL versus VL, VL-specific data are reviewed and discussed.

RESULTS

Disease distribution. Notification and incidence. In Bolivia, the leishmaniases are a notifiable disease. The leishmaniases are endemic in seven of nine of the country’s departments (Figure 1A); the two departments without notified cases are Oruro and Potosí, largely because their high average altitude limits the geographic habitat of sandfly vectors. According to data of the Ministry of Health (MoH) National Program of Leishmaniasis Control (NPLC), in the last 24 years (1983–2006), 31,095 cases of LCL and 4619 cases of ML have been reported. Over the same time period, LCL incidence has steadily risen from 2.1 per 100,000 in 1986 to 32.7 per 100,000 in 2006 (Figure 2). Although this increase is partly because of better disease notification, it is probably also because of changes in land use and internal human migration into endemic areas, resulting in the mass exposure of (susceptible) humans to zoonotic *Leishmania* life cycles.

Of all LCL and ML cases reported in 2006, 48%, 28%, and 13% occurred in La Paz, Beni, and Pando departments, respectively; thus, almost 90% of CL cases are reported in...
only three of the country’s nine departments. Based on the recent data from 2006, the NPLC has stratified municipalities according to leishmaniases risk, with 20, 12, and 18 of the country’s 314 municipalities classified as having high (i.e., incidence is > 3.0 per 1,000), medium (i.e., 1.0–2.9) and low (i.e., 0.1–0.9) risk of *Leishmania* transmission, respectively (Figure 1B). Based on this stratification, the Pando department has 10 municipalities with high transmission risk, whereas the La Paz department has 9, and the Beni department has 1. In contrast to LCL, during the 1983–2006 time period, only 10 and 4 cases of VL and DCL were reported, respectively. All VL cases were reported from the Yungas region in the La Paz department. DCL cases were reported from Beni and La Paz departments.

Similar to many other leishmaniases-endemic areas in Latin America, it is likely that the passively collected MoH data grossly underestimates true burden of the disease in Bolivia. It is likely that many cases are never seen, because of limited access (e.g., in many rural areas where the leishmaniases are endemic, health facilities are disparate) or use of public health facilities (e.g., especially if these lack materials to diagnose and treat the disease). Such cases may self-cure over time or may attend private and non-government organization (NGO) health services; cases diagnosed and treated outside of the public sector are not recorded and added to the MoH data and cases.

**Etiology and parasite distribution.** As in much of Latin America, the clinical spectrum of the leishmaniases observed in patients in Bolivia mirrors the complexity of the leishmaniases’ epizology, with several *Leishmania* species having been reported as causing disease and a multitude of sandfly and mammal species having been incriminated as vectors and reservoir hosts, respectively.

In Bolivia, CL is mostly caused by *L. (Viannia) braziliensis* (up to 85% cases), *L. (Leishmania) amazonensis* and *L. (V.) lainsoni*; recently, some cases have also been found to be caused by *L. (V.) guyanensis* (Table 1). All parasite isolates that have been characterized to species have primarily been reported in the north, center, and east of the country (i.e., Departments of La Paz, Beni, Pando, Santa Cruz, and Cochabamba) (Figure 1). A co-infection of *L. (L.) amazonensis* and *L. (L.) infantum* [syn. *L. (L.) chagasi*] was reported in one case of DCL.

**Figure 1.** Map of Bolivia. Administrative departments (A). Stratification of municipalities according to incidence of leishmaniases in 2006 (B). This figure appears in color at www.ajtmh.org.

**Figure 2.** Number of localized cutaneous leishmaniasis cases in reported in Bolivia 1983–2006.
Leishmania (L.) infantum, the causative agent of VL, was isolated from or detected in patients,31-33 dogs,34,35 and the insect vector Lutzomyia longipalpis36 in the Yungas region in the Department of La Paz. To our knowledge, VL remains rare in Bolivia and is restricted to this unique focus in the Yungas region in the Beni department, where the first autochthonous case was diagnosed in 1984.31

Unlike in many other endemic areas in Latin America, co-infection of Leishmania with HIV is not described in the literature; however, recently HIV infection was detected in an adult male with ML caused by L. (L.) braziliensis in Cochabamba (Parrado and others, unpublished data).

Although it seems that most cases are caused by L. (V.) braziliensis, data on Leishmania parasite distribution in Bolivia are very fragmented. Culture and characterization of isolates is only being done routinely by a couple of laboratories (i.e., the Universidad Mayor de San Simón in Cochabamba and the Instituto Nacional de Laboratorios de Salud in La Paz), with most data coming from a few long-term and specific research projects37-39 rather than nation-wide surveillance.

Transmission epizoology, vectors, and reservoirs. Traditionally, the leishmaniasis were considered a sylvatic disease, with data typically showing that both CL and VL in Bolivia are associated with sex, age, living in close to the forest, or pursuing labor in forested areas.16,25,33,40,41 Although this still holds true for much of the Bolivian territory, in the past few years, an increasing number of reports emerged of LCL in children and cases contracting the disease in an urban environment rather than in forested areas.22,23 For better epidemiologic leishmanias’ surveillance in Bolivia, multidisciplinary studies will have to investigate these trends in the future, studying the extent of peridomestic transmission and determining risk factors for infection and disease.

The distribution of the leishmaniases is greatly related to the distribution of sandfly vector species. According to the computer-aided identification of phlebotomine sandflies of the Americas (CIPA) database, 86 Lutzomyia species occur in Bolivia,42 in a wide diversity of ecosystems from very humid tropical forest to dry tropical forest or to the high altitude Andean cordillera. Of these species, only seven have conclusively been incriminated as Leishmania vectors, based on 1) the presence of the species at the site where infections and disease have been reported in humans; 2) the species’ anthropophilic behavior; 3) the identification of Leishmania promastigotes in the sandfly guts either microscopically or by polymerase chain reaction (PCR)-based methodology; and 4) the isolation of the same Leishmania species and/or strain circulating in humans and sandflies. The species incriminated as Leishmania vectors in Bolivia are as follows: Lu. carreraui, Lu. llanosmartinsi, and Lu. yucumensis [vectors of L. (V.) braziliensis]43,44; Lu. nuneztovari anglesti [L. (V.) braziliensis, L. (L.) amazonensis, and L. (V.) lainsoni]47,48; Lu. shawi [L. (V.) braziliensis and L. (V.) guyanensis]45; and Lu. longipalpis [L. (L.) infantum].46 Several other sandfly species are possible vectors based on their presence in foci of disease and based on their highly anthropophilic behavior, and these include Lu. ayrozai, Lu. flaviscutellata, and Lu. neivai.44,46-50

Natural Leishmania infections have been found in a range of non-human mammal hosts (principally marsupials, rodents, edentates, and carnivores).34,35,51-53 However, their importance in the Leishmania transmission cycle in Bolivia is difficult to assess, because their role as reservoirs was not specifically

### Table 1

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* Mention of twenty additional isolates characterized as L. (V.) braziliensis.
† One isolate studied using MLEE had ‘marked’ variation in 6 of the evaluated enzymes.
‡ Not primary report, mention of eight isolates that have been characterized as L. (L.) amazonensis using MLEE.
¶ Only two of 14 PCR positive samples tested positive for L. (L.) infantum-specific rk39 RDT.
studied. As previously shown in other eco-epidemiologic settings, reservoir incrimination is difficult because it often is specific to the local epizootic context and depends on a range of parameters (e.g., host abundance and distribution, infectiousness to the sandfly vector). Thus, these data stem from small non-reservoir studies that assessed the prevalence of infection in animals suspected of being *Leishmania* reservoir hosts. *Leishmania* parasites have been detected and isolated from the following mammals: *Conepatus chinga rex* \([L. (V.) braziliensis\) and *L. (L.) amazonensis\] 52; *Akodon* sp. \([L. (L.) amazonensis]\) 52; *Oligoryzomys* spp. \([L. (L.) amazonensis]\) 52,53; *Orizomys capito* \([L. (L.) amazonensis, unpublished results\]; *Sciuris vulgaris* \([L. (L.) amazonensis]\) 52; *Canis familiaris* \([L. (V.) braziliensis and L. (L.) infantum\] 34,35; and *Coendu prehensilis* \([L. (L.) infantum]\). 51 Further epidemiologic studies will have to determine these host species’ role in the *Leishmania* transmission cycle.

**Clinical disease and diagnosis.** *Clinical presentation.* Although many different *Leishmania* species can cause the leishmaniases in Bolivia, many infections probably remain asymptomatic, e.g., recent active case detection for VL detected no VL cases but 15 subclinical infections of *L. (L.) infantum*. 33 Whether an infection remains subclinical, progresses to overt disease, or spontaneously cures is dependent on a number of parasite and host-specific factors, and essentially, the clinical picture of the leishmaniases in Bolivia is similar as to the one found in other endemic areas in Latin America and elsewhere. 1,2,12 Nonetheless, several points are of note. First, because most LCL cases are caused by *L. (V.) braziliensis*, arguably the most virulent of *Leishmania* species, 55 cutaneous lesions seen in clinical practice tend to be larger and more aggressive than in other settings (Figure 3). Also, most lesions are found in body areas exposed to sandfly vectors, i.e., upper and lower limbs. Second, it is well known that patients infected with *L. (V.) braziliensis* are at greater risk of developing ML (Figure 3). 1 Of all countries in Latin America, Bolivia reports the lowest LCL:ML case ratio. National case notification data for 2006 showed a ratio of 6:1 LCL cases for every ML case. 10 Also, of 828 CL cases seen in the Universidad Mayor de San Simón in Cochabamba between 2002 and 2005, 225 (37%) were ML cases (Garcia and others, unpublished data), and one study in La Paz department reported that, on average, 20% (range, 11–57%) of LCL patients developed ML. 56 There is some evidence that this increased risk varies with geographic location, 56 may be dependent on ethnic origin, 57 and has a human genetic basis. 58,59 It remains to be established whether it is also dependent on parasite virulence and/or the molecular composition of the saliva of local sandfly vectors. Reported LCL:ML ratio has to be interpreted with caution, however, because it may reflect the poor health service coverage and/or the quality of the lesion, microbial contamination from over-infected ulcers, or even untrained staff.

**Figure 3.** Clinical spectrum and diagnosis of leishmaniases cases in Bolivia. Cases can be either localized cutaneous (**A**), mucosal (**B,C**), diffuse cutaneous, or visceral leishmaniasis. This figure appears in color at www.ajtmh.org.

**Diagnosis.** In Bolivia, CL and VL diagnosis relies on clinical manifestations or, where available, on microscopic examination of parasites in smears of tissue samples (i.e., CL) or aspirates (i.e., VL). 13,60 Although clinical diagnosis is very sensitive, it is not very specific (e.g., a multitude of conditions of non-*Leishmania* etiology have a similar clinical appearance to CL). 13 In contrast, although the specificity of microscopic examination is high (i.e., > 95%), the sensitivity is low to moderate (i.e., 35–70%; Parrado and others, unpublished data) and varies because of the chronicity of the lesions, microbial contamination from over-infected ulcers, or even untrained staff.
Parasite cultures (i.e., in Novy-MacNeal-Nicolle [NNN] with different modifications of medium components and antibiotic concentrations) have successfully been used in Bolivia to confirm clinical diagnosis and isolate parasite strains, with sensitivity as high as 80–90% (Parrado and others, unpublished data). However, it is only performed by specialized laboratories (see above) that have the infrastructure and the financial and technical human resources to successfully carry out parasite culturing.

A number of different PCR assays have been developed and used for diagnosis and *Leishmania* typing in Bolivia.\[^{22,28,29,33,62-44}\]

The sensitivity varies according to the PCR protocol used, but in all cases, PCR proved to be more sensitive and specific in detecting *Leishmania* parasites compared with culture, microscopy, or clinical diagnosis (especially for ML). Similar to parasite culture, however, the use of PCR in Bolivia is limited to research purposes or epidemiologic studies because of the cost and need for specialized laboratory infrastructure and technically trained staff. The implementation of more simple assays such as PCR-oligochromatography might constitute a promising alternative in the future.\[^{65}\]

Serologic diagnosis is not used in CL diagnosis in Bolivia. Sensitivity and specificity of tests can be variable, with tests suffering from cross-reaction with *Trypanosoma cruzi*, which is sympatric in many leishmaniases-endemic areas.\[^{62}\]

The Montenegro skin test is occasionally used in diagnosing cutaneous disease (e.g., in epidemiologic surveys),\[^{41}\] because of its simple use and high sensitivity and specificity; however, it fails to distinguish between past and present infections. Although not mandated by the NPLC, for VL case detection, the rk39 rapid diagnostic test has recently been used.\[^{33}\]

**Treatment.** Detection and case treatment are the cornerstones of Bolivia’s NLCP. The standard therapy is meglumine antimonate (Glucantime, Sanofi Aventis, Paris, France) by intravenous or intramuscular injections at a dosage of 20 mg SbV/kg/day (20 days for LCL, 30 days for ML and VL).\[^{10}\] Therapy is usually given on an outpatient basis. In a large operational program in the Department of Cochabamba, clinical efficacy for LCL ranged from 75% to 94% (Garcia and others, unpublished data). A randomized controlled clinical trial on the safety and efficacy of generic sodium stibogluconate (SSG) in Bolivian LCL patients showed 93% and 82% per protocol and intention-to-treat cure rate, respectively.\[^{46}\]

Another trial using SSG confirmed these results, reporting a cure rate of 94% and 73% for LCL and ML, respectively.\[^{27}\] Recently a study reported 7% of patients unresponsive to SbV.\[^{48}\]

Unresponsiveness could be caused by the use of subtherapeutic doses and substandard drugs, patient non-compliance with the treatment regimen, immunosuppression (e.g., because of HIV infection), and, of course, the real emergence of drug-resistant parasite strains. Of note is that, whereas SbV-resistant strains of *L. (V.) braziliensis*, *L. (V.) guyanensis*, and *L. (V.) lainsoni* were encountered in Peru, only *L. (V.) braziliensis* strains have been shown to be SbV-resistant in Bolivia (Dujardin and others, unpublished data).

For patients unresponsive to antimony (e.g., ML patients), amphotericin B deoxycholate (Fungizon, Bristol Myers Squibb, New York, NY) is the second-line drug in Bolivia. Similar to antimony, this drug can have severe side effects (e.g., pancreatitis, renal failure, hepatotoxicity)\[^{1}\] and has to be given under medical supervision. In a small clinical study, the efficacy of treating ML with amphotericin B was shown to be 90%; combining amphotericin B with itraconazole did not improve efficacy.\[^{69}\]

Another drug that has been tested for its efficacy in treating CL in Bolivia is miltefosine, with reported cure rates of 88–91% and 58–83% for LCL and ML, respectively.\[^{70,71}\]

Several anecdotal reports describe the use of folk medicine to treat the leishmaniases in Bolivian communities,\[^{72}\] and many local Bolivian plants have been found to have anti-leishmanial activity *in vitro*\[^{75-74}\] and *in vivo*.\[^{74}\] However, to date, there has been no controlled study to establish whether these plants have a potential application in clinical medicine.

Although government policy is to provide free drug therapy for the leishmaniases, it has rarely been fully operative because of the drugs’ high cost (e.g., US$250–300 for a full course of therapy using branded antimony). Thus, treatment is often facilitated by NGOs or by specific research studies. The recent World Health Organization–negotiated preferential pricing of antimony for the public sector and the availability of generic SSG may improve drug availability at health facilities in the future. Non-availability of treatment of LCL patients may result in the development of more severe lesions, including DCL and ML (particularly if *L. (V.) braziliensis* is the infecting parasite species). VL patients are almost certain to die if no treatment is administered.

**Prevention and control.** The NPLC was established in 1989 and is being implemented by the Disease Prevention and Control Unit of the Bolivian MoH.

Indoor residual spraying of households with insecticides, insecticide-impregnated materials (e.g., bed nets, curtains, clothes, or bed sheets), and repellents have been shown to be effective in protecting people from infection and disease.\[^{1}\] We are only aware of one small study investigating one such intervention (i.e., residual spraying) against the leishmaniases in Bolivia.\[^{75}\]

Even though prevention and control is part of the NPLC strategy, implementation of such activities has been done sporadically at best, often after mediatized outbreaks or public and political pressure. Limited implementation is caused by the lack of resources of the NPLC and the scarce evidence that prevention and control activities may actually be effective in the Bolivian setting. Thus, until recently, most evidence on sandfly behavior seemed to indicate that *Leishmania* transmission is sylvatic or, perhaps, peridomestic, with sandflies being mostly exophilic and exophagic. In such environments, interventions focusing on the household (e.g., indoor residual spraying or insecticide-treated nets) will have limited efficacy.\[^{1,75}\]

Thus, the NPLC strategy has mainly focused on case management rather than the reduction of human–vector contact, but even this approach has been fraught with operational challenges. Patients are usually seen at MoH facilities, many of which have neither the human (e.g., trained health care personnel) nor laboratory (e.g., microscopes for parasitologic diagnosis) resources to diagnose attending patients; additionally, poor health facility coverage means that patients do not have access to diagnosis and treatment services. Although several diagnosis and treatment guidelines do exist, and treatment is (officially) free of charge, the reality on the ground is that guidelines are not implemented systematically (e.g., training of health workers in case management is variable and no quality assurance/quality control system exists to confirm collected patient data) and that treatment is rarely available, with
patients having to wait for treatment to become available. In fact, in certain endemic areas, the burden of disease and the unavailability of services are such that communities formed self-help groups or cooperatives to facilitate patient timely diagnosis and treatment.36

Ideally, to be sustainable in the long term and especially if new evidence corroborates recent reports of domestic transmission of Leishmania spp. in Bolivia,22,23,33 leishmaniases case management, prevention, and control should be—inasmuch as possible—integrated in the MoH’s overall strategy for other vector-borne diseases, including malaria and Chagas disease. Unfortunately, even these programs suffer from poor funding support and implementation.

**DISCUSSION AND CONCLUSION**

Despite its local and regional public health importance, little is known about the leishmaniases in Bolivia. Here we summarize the latest up-to-date case notification data information available for Bolivia and review and discuss past studies. Based on our review, we highlight the following gaps in surveillance, case management, prevention, and control for operational programming, as well as potential necessary operational research (Table 2). Addressing these gaps in the future will be of critical importance should the NPLC aim to reduce the morbidity and mortality of the leishmaniases in Bolivia.

**Table 2**

Plan of action for leishmaniases’ case management, prevention, and control in Bolivia

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<tr>
<th>Surveillance</th>
<th>Case management</th>
<th>Prevention and control</th>
<th>Operational research</th>
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<td>• Inclusion of clinical disease (i.e., LCL, ML, DCL, VL), sex, age in case notification data collected at health facilities</td>
<td>• Ensure provision of laboratory reagents and anti-leishmanial drugs for effective management of cases at health facility level</td>
<td>• Promotion of health education activities informing the population about the risk of the leishmaniases and about approaches to minimize sandfly exposure (e.g., through use of repellents or bednets)</td>
<td>• Implementation of community-based prevalence studies to estimate the burden of CL and VL as well as to determine the level of disease under-reporting</td>
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<td>• Random sampling of aspirate and tissue samples at health facility level, with samples to be processed for direct species characterization, so that a more complete picture about the parasite distribution in Bolivia can be obtained</td>
<td>• Health education activities should be implemented to increase access of health facilities for timely diagnosis and treatment, and thus minimize risk of death (i.e., VL) or development of more chronic or severe disease (i.e., LCL developing into DCL or ML)</td>
<td>• Determination of risk factors for VL and CL in Bolivia to quantify those variables important in disease transmission (e.g., should household level risk factors be important, use insecticide-treated bednets or indoor residual spraying of households with insecticide could be considered as approaches for vector control)</td>
<td>• Investigation of sandfly ecology should be carried out in several transmission foci, to incriminate sandfly vectors and determine sandfly behavior (i.e., host preference, abundance and species composition) to plan comprehensive vector control activities</td>
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**REFERENCES**


