

Epidemiological, Biological and Clinical Aspects of Leishmaniasis with Special Emphasis on Busi Yasi in Suriname

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Received date: February 24, 2017; Accepted date: March 16, 2017; Published date: March 20, 2017

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Abstract

The parasitic disease leishmaniasis is caused by protozoa of the genus *Leishmania* which are transmitted by sand fly vectors of the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World. Transmission can either be anthroponotic (human to human) or zoonotic through mammalian reservoirs such as dogs and rodents. Leishmaniasis has three principal clinical manifestations, namely cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), and visceral leishmaniasis (VL). The cutaneous form characteristically causes skin ulcers, the mucocutaneous form manifests as lesions of skin, mouth, and nose, and the (potentially lethal) visceral form affects the internal organs such as spleen and liver and also invades the bone marrow. Leishmaniasis is endemic in about ninety-eight countries and the diverse types of the disease occur in different regions of the world. CL is most common in Afghanistan, Algeria, Pakistan, Iran, Brazil, and Colombia; MCL is mainly restricted to countries of the Amazon Basin; and VL is most frequently seen in the Indian sub-continent, the Horn of Africa (Sudan and Ethiopia), and Brazil. The current global prevalence is estimated at about 12 million, and each year, the disease in one of its forms makes about 2 million new victims and claims up to 50,000 fatalities. This paper presents epidemiological, biological, and clinical aspects of leishmaniasis throughout the world; then focuses on the disease in the Republic of Suriname (South America); addresses in more detail the species of *Leishmania* parasites in that country; and concludes with potential future directions to improve our understanding of leishmaniasis in Suriname.

Keywords: Leishmaniasis; Epidemiology; Biology; Clinical aspects; Suriname; *Leishmania* species

Introduction

Leishmaniasis is a complex of parasitic diseases caused by kinetoplastid flagellates of the genus *Leishmania* (Trypanosomatidae) [1,2] (Figure 1). These obligate intracellular protozoa are transmitted via infected female sand flies which are about one-third to half the size of a mosquito (Figure 2). There are a number of mammalian reservoir hosts including man [3,4]. Based on their location in the sand fly's gut during their development, two subgenera can be distinguished, namely the subgenus *Leishmania* (*Leishmania*) which develops in the sand fly's midgut, and the subgenus *Leishmania* (*Vianna*) which develops in its hindgut [5]. Phylogenetic studies have confirmed this distinction [6].

Leishmaniasis manifests as three principal clinical forms, namely cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), and visceral leishmaniasis (VL) [7]. These are found in more than ninety countries on every continent except Australia and Antarctica [7]. CL and VL are the main forms of the disease in the Old World (the Eastern Hemisphere), particularly in parts of Asia, the Middle East, tropical Africa, North Africa, and southern Europe [7,8]. All three forms are encountered in the New World (the Western Hemisphere), mostly in parts of Mexico, Central America, and South America with the exception of Chile and Uruguay [7,8]. *Leishmania* parasites

flourish in ecological niches ranging from rain forests to deserts [7,8] and are more common in rural areas and the outskirts of municipalities than in metropolitan areas [7,8]. Most infections occur during twilight, evening, and night-time hours, when the sand fly vectors are in general most active [7,8].

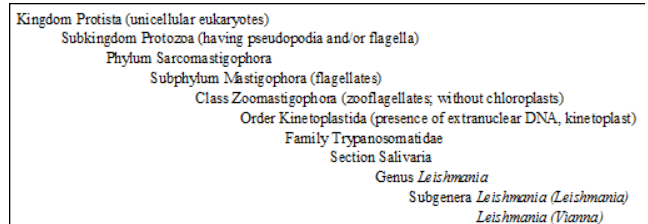


Figure 1: Taxonomic position of *Leishmania* spp. in the kingdom of the protists.



Figure 2: Female sand fly specimen.

Infections in the Old and the New World are caused by distinct *Leishmania* species [8]. For instance, CL in the Old World is caused by, among others, *L. (L.) tropica* and *L. (L.) major*, and in the New World by, among others, the *L. mexicana* species complex encompassing *L. (L.) mexicana*, *L. (L.) amazonensis*, and *L. (L.) venezuelensis*, as well as the *L. braziliensis* species complex (also known as the subgenus *Viannia*) comprising *L. (V.) braziliensis*, *L. (V.) guyanensis*, *L. (V.) panamensis*, and *L. (V.) peruviana* [8]. MCL is - as mentioned above - restricted to the New World where it is mainly caused by *L. (V.) braziliensis* [8]. VL is most frequently caused by the two members of the *L. donovani* complex, namely *L. (L.) donovani* and *L. (L.) infantum* (known as *L. (L.) chagasi* in the New World) [8].

Leishmaniasis is the second leading cause of parasite-related deaths after malaria, causing 62,500 of the total number of 1,000,700 fatalities attributable to parasitic diseases in 2013 [9]. An astonishing 350 million individuals are at risk of getting infected [10], particularly those living under poor circumstances in tropical and subtropical developing countries [11-13] and/or war-torn countries such as Afghanistan [14], Sudan [15], Iraq [16], and more recently, Syria [17]. The current global prevalence exceeds 12 million, each year more than 2.5 million new cases are diagnosed [10], and the estimated disease burden is 2.4 million disability-adjusted life years [10,18]. As a result, the World Health Organization has classified leishmaniasis as a category 1 disease - an emerging and/or uncontrolled disease - acknowledging it as a severely neglected condition and emphasizing the need of research programs to improve vector control, diagnostics, and therapeutic arsenal to contain further morbidity and mortality [10,18].

This paper gives some background on the biology, transmission, pathology, diagnosis, treatment, and prevention and control of leishmaniasis throughout the world; provides some relevant details about this disease in the Republic of Suriname (South America); addresses in more detail the species of *Leishmania* parasites as well as their sand fly vectors and mammalian reservoirs in that country with respect to the rest of South America; and concludes with a few suggestions for future lines of research.

Background

Biology

Leishmaniasis in humans can be caused by about twenty-one of the thirty *Leishmania* parasite species known to infect mammals [1,2].

Among these are the species within the *L. donovani* complex; those within the *L. mexicana* complex; *L. (L.) tropica*; *L. (L.) major*; *L. (L.) aethiopia*; and the members of the *Viannia* subgenus [5,7]. All of them have different degrees of virulence and cause distinct clinical courses [5,7]. This makes the choice of treatment regimen difficult, because different *Leishmania* (sub-) species respond differently to selected therapies [5,7]. Furthermore, certain forms of treatment are associated with significant toxicity [19], while the emergence of drug resistance is an additional reason for concern [20,21].

The different *Leishmania* species are morphologically indistinguishable, but can be differentiated on the basis of geographical, biological, molecular, and clinical features [5,7,8]. More exact species identification requires very sensitive methods which are based on isoenzyme analysis, molecular assays, and the use of monoclonal antibodies [1,6]. However, all *Leishmania* species are unicellular eukaryotes with a well-defined nucleus and other cell organelles including a characteristic kinetoplast and flagella (Figure 3) [22,23]. The kinetoplast is a unique structure that is only found in protozoa of the order Kinetoplastida [22,23]. It is formed by a mass of DNA (circles or networks) inside the single large mitochondrion, contains many copies of the mitochondrial genome and lies usually adjacent to the flagellar basal body (Figure 3; [22,23]).

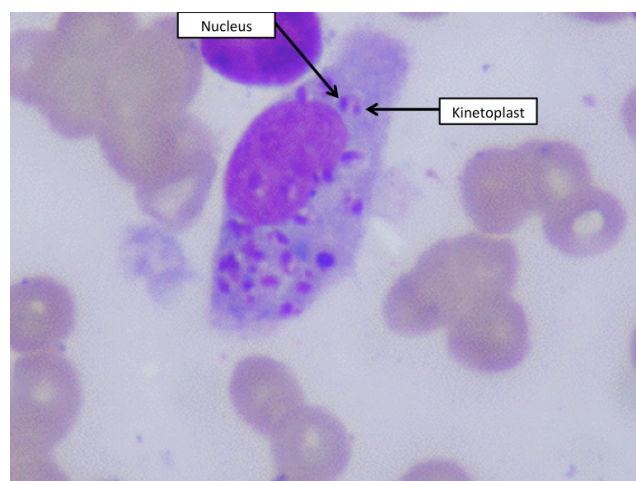


Figure 3: Macrophage infected with *Leishmania* spp. clearly showing nuclei and kinetoplasts.

As mentioned above, *Leishmania* species are digenetic or heteroxenous parasites whose life cycle involves two hosts, a (mammalian) vertebrate and an invertebrate (a sand fly) [3,4]. Mammalian reservoirs for *Leishmania* parasites include wild animals such as marsupials and opossums [24,25]; anteaters and sloths [26,27]; armadillos [28,29]; hyraxes [30]; various rodents including the spiny rat [31], the water rat [32], the agouti [33], and the climbing mouse [34]; some carnivores such as the crab-eating fox [35], the kinkajou [36], and the hog-nosed skunk [37]; primates such as the red-crested tamarin [38], the three-striped night monkey [39], and the red-faced spider monkey [40]; as well as certain bats [41]. Importantly, because of their close contacts with humans, domestic animals such as dogs [42-45], cats [46,47], and horses [48,49] can also function as mammalian reservoir for *Leishmania* spp.

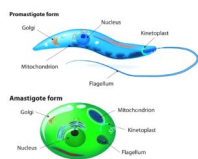


Figure 4: Promastigote (top) and amastigote forms (bottom) of *Leishmania* spp.

At least ninety-three sand fly species are proven or probable vectors of *Leishmania* parasites worldwide [7,8,35,50]. However, those that transmit *Leishmania* parasites to humans comprise about thirty species from the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World [7,8,36,50]. Depending on the stage of their lifecycle, the parasites exist as intracellular amastigotes in the vertebrate reservoir or as extracellular promastigotes in the sand fly (Figure 4; [51-53]). The amastigote forms reside in macrophages and other types of mononuclear phagocytic cells and the circulatory system of vertebrates including humans [51-53]. They are immobile, spherical to oval in shape, measure 3 to 6 μm in length and 1 to 3 μm in width, and have a short flagellum that is embedded at the anterior end without projecting out (Figure 4). The promastigote forms are found in the alimentary tract of sand flies [5,51-53]. They are motile, considerably larger than the amastigote forms, and elongated, measuring 15 to 30 μm in length and about 5 μm in width (Figure 4).

A long flagellum (with a length of about the body length) projects externally at the anterior end (Figure 4).

Transmission cycle

When a female sand fly takes a blood meal from an infected mammalian, it takes up the amastigotes in the mononuclear phagocytes from the prey's circulation [51-53]. In the sand fly's midgut (subgenus *Leishmania*) or hindgut (subgenus *Viannia*), the amastigotes develop into promastigotes which attach to the gut wall and multiply by longitudinal binary fission [51-53]. After approximately one week they transform into the infective metacyclic promastigotes which migrate forward to the sand fly's foregut and proboscis [51-53].

When the sand fly feeds again, it regurgitates the metacyclic promastigotes into the bite site, introducing them into the circulation of the new host [51-53]. There, the promastigotes are phagocytized by macrophages of the reticuloendothelial and lymphoid systems of skin, nasopharynx, or viscera, depending on the parasite species [51-53]. The parasites survive within the phagosomes, resisting digestion by lysosomal enzymes, transform into amastigotes, multiply and grow, rupture the host cell, and release their progeny to infect new macrophages including circulating monocytes, continuing the infection cycle [51-53]. Clinical disease becomes apparent within weeks to months after infection, depending on the (sub-)species of parasite and the host's immune status [51-53]. Figure 5 gives a schematic representation of the transmission cycle of leishmaniasis.

Pathology

As mentioned earlier, *Leishmania* infection can result in three main clinical manifestations depending on species, geographic region, and host immune response, namely CL, MCL, and VL [1,2,3,7,54,55]. These disease forms result from infection of macrophages in the dermis, the naso-oro-pharyngeal mucosa, and the reticuloendothelial system, respectively [51-53]. All three forms can remain silent but can cause severe morbidity, and, in the case of VL, even death [1,2,3,7]. Sometimes lesions heal spontaneously (particularly in the case of CL), conferring immunity to the host against re-infection [54].

CL (Figure 6) is the most common manifestation of the disease - particularly localized disease when compared to diffuse and disseminated CL-and is in general less severe than MCL and VL but can cause considerable mutilation [54]. The disease occurs in eighty-two countries throughout the world with the vast majority of cases seen in Afghanistan, Algeria, Iran, Iraq, Syria, Saudi Arabia, Brazil, Colombia, and Peru [56]. Most infections in the Old World are caused by *L. (L.) tropica*, *L. (L.) major*, and *L. (L.) aethiopica*, as well as *L. (L.) infantum* and *L. (L.) donovani* [7,8] and in the New World by the *L. mexicana* and the *L. braziliensis* species complex [7,8]. CL often manifests as localized disease which, however, may give rise to more than one primary lesion, satellite lesions, regional lymphadenopathy, and/or nodular lymphangitis [1,7,54]. Infected macrophages containing amastigotes are found primarily at the site of infection around the sores [1,7,54]. The lesions usually develop within weeks to months after the sand fly bite, and may persist for months or even years [1,7,54]. They typically start as papules, progress to nodular plaques, and end up as painful, volcano-shaped ulcerative lesions with a raised border and central depression [1,7,54]. The healing process commonly results in atrophic scarring [1,7,54].

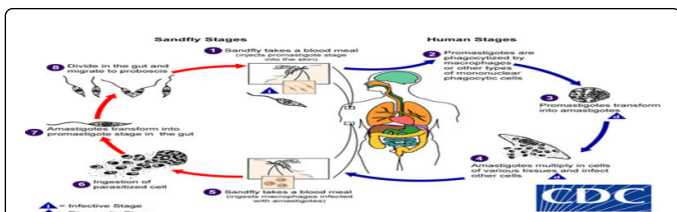


Figure 5: Leishmaniasis is transmitted by the bite of infected female phlebotomine sandflies. The sandflies inject the infective stage (i.e., promastigotes) from their proboscis during blood meals (1). Promastigotes that reach the puncture wound are phagocytized by macrophages (2) and other types of mononuclear phagocytic cells. Promastigotes transform in these cells into the tissue stage of the parasite (i.e., amastigotes (3)), which multiply by simple division and proceed to infect other mononuclear phagocytic cells (4). Parasite, host, and other factors affect whether the infection becomes symptomatic and whether cutaneous or visceral leishmaniasis results. Sandflies become infected by ingesting infected cells during blood meals (5,6). In sandflies, amastigotes transform into promastigotes, develop in the gut (7) (in the hindgut for leishmanial organisms in the *Viannia* subgenus; in the midgut for organisms in the *Leishmania* subgenus), and migrate to the proboscis (8) (from <https://www.cdc.gov/parasites/leishmaniasis/biology.html>).



Figure 6: Typical case of cutaneous leishmaniasis (from <http://www.dragonfly75.com/leish/leish.html>).

MCL (Figure 7) is a less common clinical manifestation of leishmaniasis compared to CL and VL [2,3]. It is a New-World disease that is mostly encountered in Latin America, particularly Brazil, Bolivia, and Peru [8]. It is mainly caused by species in the *L. (L.) braziliensis* complex but can also be caused by *L. (L.) amazonensis* [1-3,5,7]. MCL occurs as a sequela of untreated or sub-optimally treated CL, enabling parasites to spread from the skin, progressively destroying the mucous membranes of the nasopharynx and surrounding tissues leading to severe facial disfigurement [1,7,54]. MCL has an incubation period of anywhere between one month and twenty-four years [1,7,54]. The initial infection is a small red papule that ulcerates in a few weeks, giving flat and often exuding lesions [1,7,54].



Figure 7: Severe case of mucocutaneous leishmaniasis (from <http://www.parasiteswithoutborders.com/about/>).

VL (Figure 8) is a slow but progressive illness and the most severe form of leishmaniasis that is invariably fatal if left untreated [3,54,55]. This disease is prevalent in seventy countries throughout the world with more than 90% of cases (about 300,000 per year) occurring in India, Bangladesh, Nepal, Sudan, and Brazil [56]. The worldwide

mortality due to VL has been estimated at 20,000 to 40,000 [9]. VL is usually caused by *L. (L.) donovani* and *L. (L.) infantum* and develops following invasion of the parasites and congregation of infected macrophages into the lymphatic tissues including bone marrow and viscera (particularly liver and spleen), producing hepatosplenomegaly, edema, and anemia [2,5,7,55]. Other characteristic symptoms are fever, cachexia, pancytopenia, a high total protein level and a low albumin level with hypergammaglobulinemia, as well as lymphadenopathy [2,5,7,55]. VL often develops within months of the sand fly bite [2,5,7,62], but asymptomatic infection can become clinically manifest years to decades after the exposure, particularly in immunocompromised individuals [2,5,7,55].



Figure 8: Child with visceral leishmaniasis with hepatosplenomegaly (from <http://www.emedmd.com/content/leishmaniasis>)

Post kala-azar dermal leishmaniasis (PKDL) is a sequela of VL characterized by macular, maculopapular, and nodular eruptions that may develop mainly on the face, arms, and upper part of the trunk of patients who apparently had successfully been treated for VL [57]. PKDL is mainly seen in Sudan [58] and India [59] in patients who had recovered from infection by *L. (L.) donovani*, the principal causative agent of VL in these countries [8]. In Sudan, it develops in about 50% of these patients within 0 to 6 months after their recovery but most cases heal spontaneously [58]. In India, on the other hand, PKDL occurs in 5 to 10% of former VL patients, manifests two to three years after their recuperation, and in general requires treatment [59]. In both

cases, the patients—even though completely cured from VL—may play a role in the transmission of the disease [60].

Diagnosis

The diagnosis of leishmaniasis is based on clinical features (supported by epidemiological data) and laboratory testing. Numerous diagnostic methods have been described with a large variation in diagnostic accuracy, including direct parasitological examination (microscopy, histopathology, and parasite culture) and/or indirect testing with serology and molecular diagnostics.

The laboratory diagnosis of CL (and MCL) is largely based on the direct microscopic demonstration of *Leishmania* parasites or DNA in skin scrapings or biopsy specimens (Figure 9; [61-63]). In the case of suspected VL, usually a physical exam for signs of an enlarged spleen or liver is first performed which, if positive, is followed by microscopic examination of a bone marrow biopsy or a blood sample for the presence of *Leishmania* parasites or DNA [64,65]. Examination of a bone marrow sample is more accurate than most serologic assays which do not reliably distinguish between active and past infection [64,65].

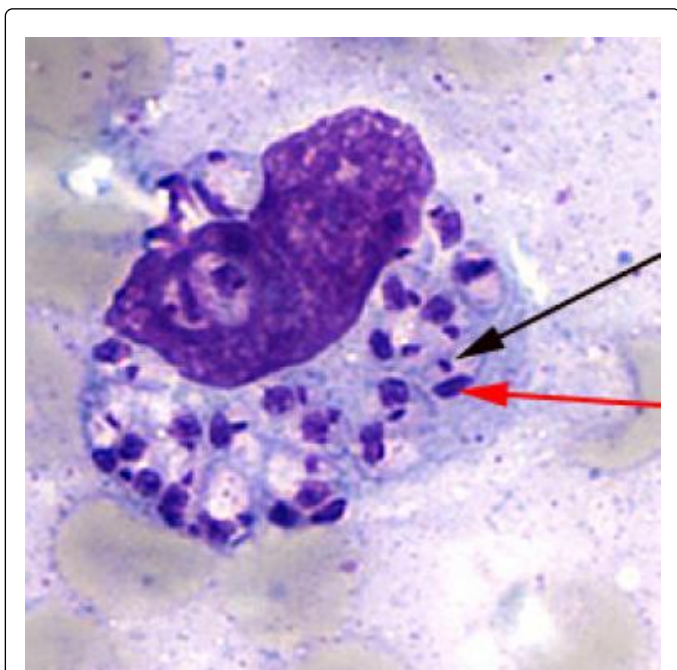


Figure 9: Light-microscopic examination of a stained bone marrow specimen from a patient with VL showing a macrophage containing multiple *Leishmania* amastigotes. The red arrow indicates the amastigote's nucleus, the black arrow its kinetoplast (from http://www.cdc.gov/parasites/leishmaniasis/health_professionals/).

Parasite culture in tubes containing Novy-MacNeal-Nicolle medium from clinical samples [66,67] is difficult, requires significant technical expertise, is prone to contamination, and is time-consuming. The sensitivity of culture also tends to be low and highly variable [66,67].

A particular diagnostic approach for CL is the use of the *Leishmania* intradermal skin test (LST) or Montenegro skin test (MST), a marker of cellular immune response [72]. The LST is occasionally used in CL diagnosis (for instance, in epidemiological surveys and vaccine studies)

because of its relative simplicity and high sensitivity [73]. Its main disadvantages are the requirement of culture facilities to produce the MST antigen, the different impact of different antigen preparations on test sensitivity, and the failure to distinguish between past and present infections [74].

Current serological tests for leishmaniasis are mainly based on formats such as indirect fluorescent antibody (IFA; [71]), enzyme-linked immunosorbent assay (ELISA; [72]), western blotting [73], lateral flow assay [74], and direct agglutination test (DAT; [75]). These tests are not widely used for the diagnosis of CL, but particularly the DAT is considered the serological standard for VL [76].

Many molecular diagnostic tests have been developed for the diagnosis of leishmaniasis, as these have excellent sensitivity and specificity and may allow for the use of less invasive sampling for diagnosis [61-64]. In particular PCR has been widely exploited, either as a single test [77], in a nested format [78], or as a quantitative assay [79].

As there are no defined generally accepted protocols and almost each laboratory applies its own in-house method, a head-to-head comparison of the different PCR methods would be required for the general implementation of this technology in routine diagnosis. Furthermore, PCR requires adequate research infrastructure (equipment, electricity) and technically skilled operators, making this diagnostic platform less suitable for resource-restricted laboratories in disease-endemic countries [61-64].

Application of isothermal diagnostic platforms that have been developed in the last years could circumvent these requirements. For example, nucleic acid sequence-based amplification (NASBA), an isothermal reaction targeting parasite RNA, has been developed for leishmaniasis [80]. Combined with oligo-chromatography (OC) for post-amplification analysis further avoids the use of complex equipment while preserving appropriate diagnostic performance characteristics [81]. Furthermore, loop-mediated isothermal reaction (LAMP) that is performed at 60 and 65 °C, has a very high specificity, because it uses six primers and the end-product can be directly visualized using simple detection methods [82].

Treatment

Some cutaneous infections do not require medication and lesions heal spontaneously [54,83,84], but all cases of MCL and VL should be treated [1,2,62,63,65,85]. However, there are no universal medical protocols for managing the various clinical manifestations of leishmaniasis [1,2,62,63,65,85]. Rather, treatment is often individualized, the choice depending on the infecting parasite species, the status of the patient's immune system, and the geographic location the infection has been acquired [1,2,62,63,65,85]. Notably, even therapeutic approaches found effective against a certain *Leishmania* species in a particular area do not always function in other situations [1,2,62,63,65,85]. For example, data from clinical studies of therapy for VL in a certain geographical area are not necessarily directly applicable to VL caused by the same *Leishmania* species in other regions, to VL caused by other *Leishmania* species, or to treatment of CL and MCL [1,2,62,63,65,85].

The variation in clinical responses is probably partially attributable to the differences in the sensitivity of different *Leishmania* species to available therapies [86]. The mechanisms involved in this phenomenon are still unclear, largely because of our incomplete understanding of the mechanisms that enable *Leishmania* parasites to evade or exploit

host immune defenses and to persist in host cells incomplete [87]. Contributing to the variation in clinical responses is the emergence of drug resistance due to the use of inefficacious drugs, sub-therapeutic drug dosages and/or drug administration schedules, and/or poor patient compliance [1,2,85,88]. Complicating the treatment of leishmaniasis even more is the realization that special groups such as young children, elderly persons, pregnant/lactating women, and immunocompromised individuals and those suffering from other comorbidities may need adjusted or entirely different medications or dosage regimens [1,2,85,88]. Unfortunately, however, many endemic areas lack the financial means to acquire a broad inventory of useful drugs and develop an efficient healthcare infrastructure to effectively manage all the different clinical variants of leishmaniasis [7,12].

The treatment approach of CL is mainly governed by the risk for mucosal dissemination as well as the number, size, location, evolution, and other clinical characteristics of the patient's skin lesions [1,2,62,85]. The options that are available include local therapy involving heat and cryotherapy, as well as systemic parenteral and systemic oral therapy. The drugs of first-choice in most countries are pentavalent antimonials such as sodium stibogluconate and meglumine antimoniate. Frequently used alternatives are miltefosine and pentamidine isethionate. As these drugs cause substantial toxicity and side-effects [1,2,62,85] and the majority of cases of CL heal spontaneously [72], the potential risks and benefits of treatment must be balanced by an experienced dermatologist for each CL patient [1,2,62,85].

Local therapy involves cryotherapy using liquid nitrogen [89,90], thermotherapy using localized current field radiofrequency heat [91,92], intralesional administration of pentavalent antimonials [93,94], and/or topical application of a paromomycin ointment [95,96], either alone or at certain combinations [62,85,89,90,97]. Local treatment modalities are applicable in cases of CL of a few (less than five) lesions or without risk to develop into mucosal disease [86]. These cases comprise CL caused by Old World species such as *L. (L.) tropica* and *L. (L.) major* [91,92], CL caused by New World species that do not cause MCL such as *L. (V.) naiffi*, *L. (L.) chagasi*, and *L. (L.) mexicana* [98,99], as well as uncomplicated cases of CL caused by *L. (V.) guyanensis*, *L. (L.) panamensis*, and *L. (L.) amazonensis* [86].

Systemic treatment of CL can be considered for disfiguring facial lesions, lesions at sites that make topical treatment less desirable, multiple lesions, and lesions caused by *Leishmania* species associated with MCL [62,85,97]. For the latter reason, systemic pentavalent antimonials are the gold standard treatment for New World CL which, with the exception of CL caused by *L. (L.) mexicana*, carries the risk of mucosal involvement [1-3,7]. Thus, these compounds are the drugs of choice for treating CL caused by *L. (V.) braziliensis*, in addition to MCL caused by *L. (L.) panamensis*, *L. (L.) amazonensis*, and *L. (V.) guyanensis* [86]. Alternative systemic treatments for New World CL are oral miltefosine and parenteral amphotericin B, but these compounds have important drawbacks. The clinical efficacy of miltefosine shows geographic variations [100-102] and this compound is, due to the existence of resistance, even not active against CL caused by *L. (L.) mexicana* [103]. The latter compound causes considerably more serious side-effects and is quite expensive [104]. In the Old World, parenteral antimonials are considered second-line systemic treatment for multiple or complicated CL lesions, caused by, for instance, *L. (L.) major* [62,85,97]. Instead, such patients are given (oral) miltefosine [105,106].

Systemic pentamidine isethionate is regularly used for treating CL in South America [107,108]. This compound is also the treatment of choice for the cutaneous lesions caused by *L. (V.) guyanensis* in French Guiana and Suriname [35,109,110]. In Suriname, pentamidine isethionate is in use since 1994 and is the only treatment option for CL by *L. (V.) guyanensis* [109]. It is given as 3 intramuscular injections of 300 mg in 7 days [109] but is not effective in about 25% of CL patients [109,111,112]. The possibility that the unsatisfactory responses were attributable to infections by unresponsive variants of *L. (V.) guyanensis*, unresponsive *Leishmania* species other than *L. (V.) guyanensis*, and/or poor therapy compliance needs to be verified.

VL is always treated systemically, along with adequate supportive care involving, for instance, therapy for malnutrition, anemia and bleeding, inter-current infections [1,2,85,88], and sometimes also HIV co-infection [1,2,85,88]. As there is no effective vaccine available, the clinical management of VL is solely based on chemotherapy using mainly pentavalent antimonials; amphotericin B and its analogues, particularly liposomal amphotericin B; oral miltefosine; and paromomycin [1,2,85,88]. Similarly to their use against CL, most of these drugs are not ideal for treatment of VL, causing serious side-effects, evoke resistance, are very costly, require prolonged treatment, and/or must be prepared and administered by complicated procedures [1,2,85,88].

For many years, systemic therapy with the pentavalent antimonials sodium stibogluconate and meglumine antimonate was similarly to that of CL—the treatment of choice for VL [1,2,85,88]. These compounds are given parenterally and cause serious side-effects including high cardiotoxicity, joint and muscle pain, pancreatitis, and nephrotoxicity [1,2,85,88]. Nevertheless, they have proven successful for treating VL in endemic areas in Africa, South America, and Asia [1,2,85,88]. The notable exception is VL caused by *L. (L.) donovani* in parts of India and Nepal, where up to 65% of cases are highly resistant to pentavalent antimonials [113,114]. This has been attributed to inadequate dosing and treatment duration, poor patient compliance [113,114] as well as the anthroponotic transmission of VL infection which increases the chances for the rapid spread of resistant parasites among humans [115]. Antimonials are still widely used for treating VL, but require four weeks of hospitalization for daily IM injections and monitoring the severe adverse events [1,2,85,88]. Of note, low rates of antimonial resistance have also been reported in other endemic areas such as Sudan [116].

Amphotericin B deoxycholate is a highly effective alternative for pentavalent antimonials in the treatment of VL [117]. However, this compound is highly toxic, causing among others, infusion reactions, nephrotoxicity, hypokalemia, and myocarditis [118]. These adverse effects can be partially circumvented by careful and slow intravenous administration [118]. Amphotericin B deoxycholate is also recommended for the treatment of PKDL in the Indian subcontinent [118].

Lipid amphotericin B formulations for treating VL with improved bioavailability and pharmacokinetic properties and less toxicity when compared to amphotericin B deoxycholate [119-121] are liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B colloidal dispersion. However, these compounds displayed considerable geographical variation in their total dose requirements for clinical efficacy: from 10 mg/kg in India [122] to 18-21 mg/kg in the Mediterranean and South America [123-125] and 30 mg/kg in East Africa [126]. Nevertheless, liposomal amphotericin B has become an approved treatment for VL with less toxicity, a better half-life, and a

high level of efficacy (a 90% cure rate) when compared to the parent compound [119,120]. In the Mediterranean basin, for instance, it is the treatment of choice for immunocompetent VL patients [127]. Its main limitations are its high cost, the necessity of slow IV administration, and its lack of stability at high temperature (cold chain is needed).

Miltefosine was the first effective oral treatment for VL [128], showing efficacy in both antimony-responding and -non-responding patients [129]. Oral miltefosine is the first choice for treating VL in various endemic regions in Africa and Asia [128], has been recommended as first-line drug for childhood VL [130], and is also efficacious against PKDL [131,132]. The most notable side-effects of this compound are gastrointestinal manifestations, hepatotoxicity, and nephrotoxicity which are, fortunately, manageable [133]. However, its potential teratogenicity is an important problem, while its very high price prohibits its widespread use in the populations most in need [133]. The combination of miltefosine with amphotericin B or with paromomycin may be helpful against antimony-resistant VL infections [134].

Paromomycin sulphate was approved in India for the treatment of VL in August 2006 [135]. Subsequent clinical trials in Kenya, Sudan and India showed that this drug, either singly or in combination with sodium stibogluconate was highly efficacious against VL [136-139]. Its manageable side-effects (mainly pain at the injection site, reversible ototoxicity, and reversibly raised hepatic transaminases) and its relatively low cost (about US \$10 per case) represent important advantages [140,141]. However, its parenteral administration make its broad use in control programs of a developing country unfeasible [140,141], while its use as a single agent may lead to the development of resistance [140,141]. Despite limited experience with paromomycin sulphate for VL in the Mediterranean and Latin America-where *L. (L.) infantum* is the causative agent [7,8] - it is an accepted alternative against VL that is resistant to the above-mentioned antileishmanial drugs [88,142].

Pentamidine isethionate was originally used as second-line drug in India to treat refractory VL [1,2,87,90] but was discontinued because of declining efficacy due to the emergence of resistance [114,143] as well as the occurrence of serious toxicities such as insulin-dependent diabetes mellitus [144]. However, PI is still used in combined therapies for VL [145].

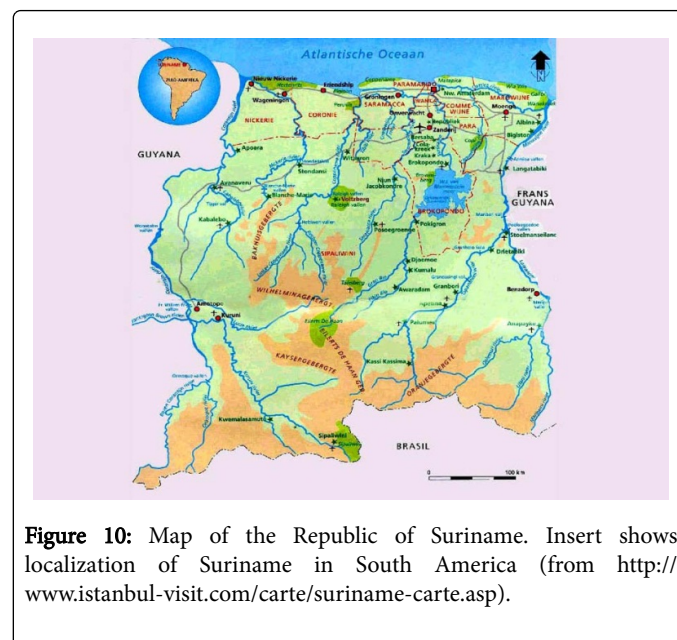
Prevention and control

In various urban endemic areas where the transmission cycle is zoonotically maintained by dogs, reducing the size of these reservoirs has been attempted as a means to contain further spread of the disease [146]. However, this approach has not always proven effective and may be considered unethical [147]. In forested areas away from human habitation, the reservoir hosts are wild animals, and prevention of sand fly bites is even more difficult. Preventive measures may include protection from sand fly bites, for instance, by avoiding nocturnal outdoor activities as much as possible, wearing protective clothing, and applying insect repellent to exposed skin, and insecticidal sprays in residences [148,149]. The use of bed nets impregnated with long-lasting insecticides may also be helpful [150]. In areas with anthroponotic transmission, early detection and effective treatment of individual patients can help control the spread of the parasite [150]. Importantly, suboptimal treatment must be avoided at all costs, as this can lead to the development and spread of drug resistance [150]. Spraying houses with insecticides and using impregnated bed nets is also recommended [148,150].

Leishmaniasis in Suriname

Brief background on Suriname

The Republic of Suriname is located on the north-east coast of South America and borders the Atlantic Ocean to the north, French Guiana to the east, Brazil to the south, and Guyana to the west (Figure 10). Despite its location in South America, Suriname is culturally considered a Caribbean rather than a Latin American country and is a member of the Caribbean Community (CARICOM) [151]. The climate is tropical with abundant rainfall, a uniform temperature of on average 27°C, and a high relative humidity of 81% in the capital city of Paramaribo [152]. There are four seasons, namely the long rainy season (April through July), the long dry season (August through November), the short rainy season (December through January), and the short dry season (February through March) [152].



Suriname's surface area of roughly 165,000 km² can be distinguished into a northern urban-coastal and rural-coastal area as well as a southern-rural interior (Figure 10) [153]. Approximately 80% of the population of almost 570,000 lives in Paramaribo and other cities in the relatively narrow urban-coastal part of the country [153]. The remaining 20% of Suriname's inhabitants populates the rural-coastal and southern-rural areas [153]. The latter region is referred to as the hinterland, encompasses more than three-quarters of the country's land surface, and consists largely of sparsely inhabited savanna and dense, pristine, and highly biodiverse tropical rain forest [153]. It is furthermore, together with segments of Bolivia, Brazil, Colombia, Ecuador, Guyana, Peru, and Venezuela, part of the Amazon Basin, the area of South America that is drained by the Amazon River and its tributaries and that encompasses about 7,500,000 km² (i.e., roughly 40%) of that continent [154]. As a result, Suriname is one of the most forested countries in the world [154,155].

The urban-coastal region is characterized by a 'western' lifestyle, modern health-care facilities, and an economy that is mainly based on commerce, services, and industry [156]. The rural-coastal and southern-rural societies have a more traditional way of living, lack comprehensive public health services, and have agriculture, forestry,

crude oil drilling, bauxite and gold mining, as well as ecotourism as major economic activities [156]. These activities have been growing in scale and economic importance in recent years and are, together with agriculture and fisheries, the country's most important means of support, contributing substantially to the gross domestic income of US\$ 5.297 billion and the average per-capita income of US\$ 9,583 in 2014 [156,157]. This positions Suriname among the upper-middle income economies of the World Bank's ranking [156,157].

Suriname uses around 6% of its gross domestic product for health expenditures [159] which corresponds to US\$ 589 per capita in 2014 [158]. The Minister of Health and the Director of Health (the Chief Medical Officer) are responsible for all aspects regarding health care in the country [158]. Important subdivisions of the ministry are the Bureau of Public Health which is in charge of, among others, eradicating parasitic and microbial diseases; the Regional Health Service and the Medical Mission which are responsible for primary health care in the coastal area and the hinterland, respectively; and the Dermatology Clinic that provides services for sexually transmitted diseases, HIV/AIDS, and skin conditions including leishmaniasis [158]. Secondary and specialist care are provided by two private and two government-supported public hospitals in Paramaribo and one public hospital in the western rural-coastal district of Nickerie [158].

Occurrence of leishmaniasis in Suriname

CL is the most common form of leishmaniasis in Suriname [159] where it is generally known as 'bosyaws' or 'busi yasi' (meaning 'disease from the jungle') [160]. The first cases of CL in the country were reported in 1911 [160]. Since then, CL has become an increasing public health problem in Suriname and is generally considered an endemic disease [109,159,161]. The incidence has been estimated at 5.45 per 1,000 for the hinterland and 0.68 per 1,000 for the entire country [159] but no reliable epidemiological data are available. This is due, among others, to the lack of information about risk groups such as infected Brazilian gold miners who work (illegally) in the hinterland, and infected Amerindians and Maroons in the hinterland who treat themselves [162,163].

CL in Suriname is maintained by a zoonotic cycle in which the sand fly vectors exist in close association with the *Leishmania* parasites and a variety of wild mammals believed to serve as reservoir hosts including the two-toed sloth, the anteater, and several species of marsupials and rodents [35]. Although domestic animals such as cats, horses, and dogs may also assume the role as reservoir host [43,46], most infections occur in the forested hinterland when the victims (like tribal people, personnel from gold mining, bauxite mining, and logging companies; eco-tourists; as well as recreational fishers and hunters) intrude into the vectors' habitats [159].

For many years, *L. (V.) guyanensis* was believed to be the only *Leishmania* species that caused CL in Suriname [159,161]. However, in the past decades, a number of patients presented with clinical forms of the disease that behaved differently from that associated with this parasite species. The presumption that there were other *Leishmania* species present in Suriname was confirmed by PCR-based methods identifying a few cases of leishmaniasis caused by *L. (V.) lainsoni* [159], *L. (V.) naiffi* [164], *L. (V.) braziliensis* [165], and *L. (L.) amazonensis* [159,166]. At the same time, sand fly species associated with the transmission of CL by all the above-mentioned *Leishmania* species were detected in high-transmission areas of CL in Suriname [167,168]. Hereunder, the various *Leishmania* species identified in Suriname are addressed in more detail.

Leishmania species in Suriname

L. (V.) guyanensis

L. (V.) guyanensis is most probably the principal *Leishmania* species in Suriname [109,159,160], being responsible for more than 90% of CL cases in the country and claiming roughly 200 victims per year [159,165,166]. *L. (V.) guyanensis* is also highly prevalent in French Guiana and Northern Brazil and is, furthermore, found in various other South America countries such as Guyana, Peru, Colombia, and Ecuador [35,169-175]. In all these regions-but particularly in Suriname, French Guiana, and Northern Brazil-infection by this parasite is an important cause of CL [35,169-175]. In Columbia and French Guiana, for instance, *L. (V.) guyanensis* has been held responsible for more than 95% of cases of CL [35,174]. And in areas south of the Amazon River in Brazil it has also been associated with MCL [176].

Several sand fly vectors have been implicated in the spread of CL (or MCL) by *L. (V.) guyanensis* in Suriname, including *Lu. umbratilis*, *Lu. anduzei*, *Lu. migonei*, and *Lu. whitmani* [168]. *Lu. umbratilis* and *Lu. anduzei* are proven vectors of the parasite in other parts of the Amazon Basin such as French Guiana [35] and several areas in Brazil [177]. *Lu. anduzei* is, in addition, a suspected vector of *L. (V.) guyanensis* in French Guiana, Guyana, Suriname, and Venezuela [178]. *Lu. migonei* has been reported as a putative vector of *L. (V.) guyanensis* in Venezuela [178]. And *Lu. whitmani* may function as a vector of this *Leishmania* species in the state of Amapá, Brazil [179]. *Lu. ayacuchensis* has been found in Peru naturally infected by *L. (V.) guyanensis* promastigotes [175] but has not been encountered in Suriname.

So far, only a few studies on reservoir mammalian species of *L. (V.) guyanensis* have been conducted in Suriname. In one of these studies, indications have been obtained to implicate the dog in the transmission of CL-causing *Leishmania* species in Suriname [44]. However, these data were not conclusive [44], even though evidence is accumulating that dogs and other domestic animals may serve as reservoirs of CL caused by *L. (V.) guyanensis* in other parts of the Americas [180,181]. Wild mammals believed to be important hosts of *L. (V.) guyanensis* [29,35] such as sloths - including the two-toed sloth *Choloepus didactylus* - are present in Suriname, but also have not conclusively been identified as reservoirs of the parasite in the country. Remarkably, certain New World tree sloths are parasitized by another vector of *Lu. umbratilis*, the intra-erythrocytic flagellate *Endotrypanum*, which may complicate the diagnosis of leishmaniasis [182].

Pentamidine isethionate is since 1994 the first-line drug and the only treatment option for CL caused by *L. (V.) guyanensis* in Suriname [109,165]. It is given as three intramuscular injections of 300 mg on days 1, 4, and 7 [109,165]. The infection responds in general favorably to pentamidine isethionate [109,110] if not resolving spontaneously [54,83,84], but, as mentioned above, accomplishes cures in only about 75% of patients [112,165]. This suggests that some of the infections may be caused by *Leishmania* species other than *L. (V.) guyanensis* which do not respond to pentamidine isethionate [159,164-166]. It is also possible that the infections are caused by distinct populations of *L. (V.) guyanensis* which behave differently from each other with respect to severity and dissemination of cutaneous lesions as well as response to pentamidine isethionate. This has been reported for Suriname's neighboring country French Guiana, where CL may be caused by two

dissimilar populations of *L. (V.) guyanensis* which have a different disease course and require different forms of treatment [183].

It is also possible that the unfavorable responses to pentamidine isethionate are attributable to poor therapy compliance [184] or the emergence of drug resistance [185,186]. Obviously, these factors may lead to incomplete healing and therapy failure [184-186]. Clearly, these issues must further be investigated. Meanwhile, in order to improve response rates and compliance, a comparative clinical trial has assessed the standard regimen of pentamidine isethionate IM 300 mg on days 1,4, and 7 with respect to a shorter but more dose-intensive regimen of 7 mg/kg on days 1 and 3 [165]. The results from this study showed that the former regimen was not non-inferior to the latter, but less toxic when compared to the latter [165]. For this reason, the 3 day-regimen is still the mainstay in Suriname for treating CL caused by *L. (V.) guyanensis*.

L. (V.) lainsoni

CL in Suriname caused by infection with *L. (V.) lainsoni* was first reported in 2006 [159]. Using PCR-RFLP analysis of skin biopsies from thirty-three patients with microscopically and/or PCR-confirmed CL, one patient appeared infected by this parasite [159]. This *Leishmania* species is probably endemic in Suriname, as the infected patient had never traveled outside the country [159]. Nevertheless, to our knowledge, no other cases of CL caused by *L. (V.) lainsoni* have been reported in Suriname, suggesting that this species has relatively little clinical relevance.

Still, *L. (V.) lainsoni* is probably widely distributed in South America. After its original identification in samples from infected humans in the state of Pará in the Brazilian Amazon region [187], *L. (V.) lainsoni* was detected in CL patients from other parts of Brazil [188], the sub Andean regions of Peru [189] and Bolivia [190,191], French Guiana [35], and the Ecuadorian Amazon [192] besides Suriname [159].

Consistent with the identification of *L. (V.) lainsoni* in Suriname is the identification of *Lu. ubiquitalis* in the country [168], a proven sand fly vector of *L. (V.) lainsoni* in Pará state, Brazil [33,193-195]. In Yungas, Bolivia, *Lu. nuneztovari anglesi* has been implicated in the transmission of this parasite [191,196], but it has so far not been encountered in Suriname. In the Brazilian Amazon region, the rodent Agouti paca has been implicated as a reservoir host of *L. (V.) lainsoni* [33]. Although this mammalian is also present in Suriname its involvement in the transmission cycle of CL by *L. (V.) lainsoni* in this country Suriname remains to be verified.

L. (V.) naiffi

The first cases of CL caused by *L. (V.) naiffi* in Suriname - three Dutch male military who had been infected during jungle training in the country - were reported in 2010 [164]. The infecting *Leishmania* species was identified in patient biopsies by microscopy of Giemsa-stained smears, culture, and mini-exon repeat PCR [164]. The identification in Suriname of a confirmed reservoir host (the nine-banded armadillo *Dasybus novemcinctus*) as well as sand fly vectors implicated in the transmission of *L. (V.) naiffi* (*Lu. paraensis* [25,200], *Lu. ayrozai* [168], and *Lu. squamiventris* [168]), provided support for *L. (V.) naiffi* as a cause of CL in the country.

Of note, *Lu. ayrozai* is a proven vector of *L. (V.) naiffi* in Brazil [35,201], and *Lu. squamiventris* is generally considered a vector of *L. (V.) naiffi* in both French Guiana [35] and Brazil [29]. Furthermore, *L. (V.) naiffi*, first described as a parasite of *D. novemcinctus* in the

northern Brazilian state of Pará [28], was later confirmed to represent a reservoir of this *Leishmania* species [25,29]. These and other studies also implicated the above-mentioned sand fly species in the transmission of CL in the Brazilian Amazon [25,29,202-204], French Guiana [35], and the central Amazonian area Arajuno in Ecuador [205].

In addition to Suriname, *L. (V.) naiffi* was identified as a cause of CL in particularly Amazonian Brazil [25,29,188,203,206] as well as various other Latin American and Caribbean countries [25,35,99,188,205-208]. These observations suggest that *L. (V.) naiffi* is widespread in South America [99], which is consistent with the presence of both hosts and vectors in a wide geographical area in this continent [25]. Nevertheless, as reported for other endemic parts of South America and the Caribbean [25,29,35,188,203,205-208], *L. (V.) naiffi* also seems an uncommon cause of CL in Suriname when compared to CL caused by other *Leishmania* species [164].

L. (V.) braziliensis

The first case-and so far the only one-of CL in Suriname due to infection with *L. (V.) braziliensis* dates from 2012 [165]. The patient was a 26 year-old male who had probably contracted the disease three years before while on a hunting trip in Suriname's hinterland [165]. A PCR restriction fragment length polymorphism assay and nucleotide sequencing confirmed that *L. (V.) braziliensis* was the causative agent [165]. However, the infection showed no signs of mucosal involvement and responded favorably to treatment with pentamidine isethionate [165].

Infections by *L. (V.) braziliensis* are also encountered in other South American countries in and around the Amazon Basin as well as most of Central America [209,210]. In Ecuador, for instance, *L. (V.) braziliensis* is probably the dominant CL-causing species besides *L. (V.) guyanensis*, and the number of infections by this *Leishmania* species is increasing in the Pacific coast areas of this country [171]. And although *L. (V.) guyanensis* is, similarly to Suriname, the main cause of CL in French Guiana, cases due to *L. (V.) braziliensis* are occasionally encountered [35]. Importantly, in many countries in the New World, *L. (V.) braziliensis* infections not only manifest as CL but also as MCL [211,212], causing more cases of MCL than any other *Leishmania* species in these parts of the globe [214]. In the Amazon region, for instance, *L. (V.) braziliensis* is the predominant cause of MCL [169,210].

Several sand fly vectors associated with the transmission of CL or MCL by *L. (V.) braziliensis* have been detected in Suriname [168]. These include *Lu. ayrozai*, a proven vector of *L. (V.) braziliensis* in Bolivia [177]; *Lu. whitmani*, a putative vector of *L. (V.) braziliensis* in various parts of Brazil [214-216]; *Lu. davisii*, found infected by *Leishmania* spp. in regions in Brazil considered endemic for *L. (V.) braziliensis* [25,204]; *Lu. migonei*, incriminated in the transmission of CL by *L. (V.) braziliensis* in endemic areas in Brazil and Venezuela [201,217-219]; and *Lu. intermedia*, considered the principal vector of *L. (V.) braziliensis* inside houses and in peridomestic premises in Southeast Brazil [220-222].

The armadillo *Euphractus sexcinctus* and *A. paca* are presumed mammalian reservoir hosts in the sylvatic cycle of *L. (V.) braziliensis* in Espírito Santo, Brazil [223]. Dogs and possibly horses are believed to be the most important vertebrate hosts in the peridomestic cycle of this parasite [42]. The latter findings may support the possible involvement of the dog in the transmission of CL in Suriname [44]. However, in an earlier study on the sand fly fauna in high-transmission areas of CL in

Suriname [168], only one of the 2,743 captured sand fly specimens (belonging to 34 different species)-a female specimen of *Lu. squamiventris* (s.l.) - was naturally infected with *L. (V.) braziliensis*. Future studies should determine whether this sand fly specimen was an incidental or a secondary vector of the parasite.

L. (L.) amazonensis

L. (L.) amazonensis was first detected as a cause of CL in Suriname in 2006, together with *L. (V.) lainsoni* [159]. To the best of our knowledge, this is the only case in Suriname of CL caused by this *Leishmania* species. Nevertheless, *L. (L.) amazonensis* is probably, together with *L. (V.) braziliensis*, among the most common *Leishmania* species in the Amazon region [169,211,224-227], being responsible for about 8% of cases of human CL in Brazil [224]. *L. (L.) amazonensis* has also been encountered in various sub-Andean regions of Bolivia [228-229].

Sand fly species implicated in the transmission of *L. (L.) amazonensis* are *Lu. flaviscutellata*, *Lu. withmani*, *Lu. nuneztovari anglesi*, and *Lu. migonei*. *Lu. flaviscutellata* is a proven vector of *L. (L.) amazonensis* in the Amazon basin [35] as well as other parts of Brazil and South America [201,230,231]. Importantly, specimens of this sand fly species which were experimentally infected by *L. (L.) amazonensis* amastigotes produced infections in hamster skin [232]. *Lu. withmani* and *Lu. nuneztovari anglesi* are suspected vectors of this parasite in the state of Mato Grosso do Sul, Brazil [231], and Bolivia [233,234], respectively. And *L. (V.) amazonensis* amastigotes developed normally to promastigotes in experimentally infected *Lu. migonei* sand flies, after which the latter were able to transmit the infection to vertebrates [235]. Up to now, there are no indications for any of these vectors transmitting *L. (V.) amazonensis* in Suriname.

Mammalian reservoirs of *L. (L.) amazonensis* are probably small rodents, marsupials, primates, and carnivores [226] including rice rats and grass mice in Bolivia [228,233,234], and in Brazil, domestic dogs [236]. The latter assumption is based on a case of canine leishmaniasis caused by *L. (V.) amazonensis* in the Brazilian state of Paraná which is considered endemic for CL in humans [2].

The identification of all four above-mentioned sand fly species in Suriname [168] and the possible involvement of the dog as a host reservoir in the country [44], raise the possibility that *L. (L.) amazonensis* may also be more abundantly present in Suriname. Surinamese health authorities should be aware of this possibility, because this parasite has not only been associated with spontaneously healing cutaneous and diffuse cutaneous CL [234], but also with disseminated disease [234] and MCL [2,3,7,8]. In the State of Bahia, Brazil, for instance, infection with *L. (L.) amazonensis* was associated with various different clinical presentations including CL (20/49 cases), MCL (5/13 cases), and VL (11/46 cases), as well as four cases of PKDL [242].

Future directions

CL is the main manifestation of leishmaniasis in Suriname [109,112,159,165] and *L. (V.) guyanensis* is most likely the principal species causing this disease in the country [109,159,160]. However, a few cases of CL caused by *L. (V.) braziliensis* and *L. (L.) amazonensis* have emerged in Suriname [159,165,166]. As both parasite species have also been associated with more serious forms of leishmaniasis [35,176,211-213,235], it is necessary to develop and implement proper measures for diagnosing and treating cases of MCL that may emerge in the country.

L. (V.) lainsoni and *L. (V.) naiffi* have also been identified as additional causes of CL in Suriname [159,164]. Even though there were also only a few cases up to now [159,164], the wide presence of these parasite species in South America [29,35,172, 187-194,203,205-208] raises the possibility that they may contribute more to the burden of CL in Suriname than one might think at first sight. Indeed, infections by these *Leishmania* species may remain undetected - similarly to those caused by *L. (V.) guyanensis* [87,90] - because they respond to parenteral antimony drugs and pentamidine isethionate or heal spontaneously [1,2,87,159,164,203,207]. For these reasons, a series of comprehensive studies should be initiated to identify the full spectrum of *Leishmania* species present in Suriname and to determine their impact on CL in the country.

Although previously suggested [44], it is not certain whether the dog plays a role as a reservoir host in the transmission of CL in Suriname. It is also not certain whether and which other domestic animals [42-49] and wild animals [24-41] play a role in this phenomenon in Suriname. Clearly, such efforts will both improve our understanding of leishmaniasis in Suriname and contribute to programs to combat this disease in the country. For the same reasons, efforts following up the first and so far the only comprehensive study on the sand fly fauna in high-transmission areas of CL in Suriname [168] should be dedicated to identify the sand flies operating as vectors of CL in Suriname.

These surveys are all the more important when considering the expanding geographical distribution of CL in Suriname as a result of the growing economic activities and increasing deforestation in the sand flies' habitats in the country's hinterland [156,157]. Given the absence of efficacious drugs other than pentamidine isethionate in [109,165], and the limited financial resources of Suriname [156,157], elimination of the disease poses a huge challenge for the country. Therefore, priority should be given to establishing effective control programs based on extensive comprehension of the biology of CL. Hopefully, these will help in the design of strategies to effectively target the breeding and resting sites of the sand fly vectors and successfully control domestic and sylvatic mammalian reservoirs near human dwellings.

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