

## Epidemiology and Control of Leishmaniasis

Leishmaniasis refers to a diverse spectrum of clinical syndromes caused by infection with protozoan parasites of the genus *Leishmania*.

The clinical syndromes and manifestations of leishmaniasis vary widely but are often divided into the three clinically distinct syndromes of visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucosal leishmaniasis (ML). Cutaneous leishmaniasis is also divided into Old World cutaneous leishmaniasis and New World cutaneous leishmaniasis, referring to the Eastern and Western Hemispheres, respectively.

### Worldwide distribution

The leishmaniasis are widely distributed across the tropical, subtropical, and temperate regions in 88 countries, 72 of which are in developing areas of the world. Three-hundred fifty-million women, men, and children are at risk in widely scattered areas. An estimated 12 million people suffer from leishmaniasis, with 500,000 new cases of VL per year and 1 to 1.5 million new cases of CL per year, with 2.4 million disability-adjusted life-years. Approximately 90% of all cases of VL are found in three areas: the drainage basin of the Ganges river in eastern India and neighboring areas of southern Nepal (the "Terai") and areas of Bangladesh that share the same ecology; the Sudan, where a large epidemic has occurred among displaced people; and Brazil, where VL is endemic in rural areas and large periurban outbreaks have been reported from cities in the northeast.

VL has also emerged as an important opportunistic disease in persons with acquired immunodeficiency syndrome (AIDS) in southern Europe and other areas of the world where the two diseases coexist, in persons who have had organ transplants, and in association with other conditions in which cell-mediated immunity is compromised.

Approximately 90% of the world's CL cases occur in Iran, Saudi Arabia, and Syria in the Middle East; in Afghanistan in Central Asia; and in Brazil and Peru in Latin America. CL is an important problem for residents, settlers, travelers, and military personnel visiting endemic areas. More than 2000 cases of CL have been reported among American troops serving in Iraq and Afghanistan since 2001. Other cases occur among North American civilians after exposure in endemic regions. Finally, 90% of the cases of ML occur in three Latin American countries: Bolivia, Brazil, and Peru.

## Vector(Sandfly)

Female sand flies of the genus *Lutzomyia* in the Americas and *Phlebotomus* elsewhere transmit *Leishmania* spp. The sand flies are modified pool feeders, meaning that they feed on pooled blood from their bite. They breed in cracks in the walls of dwellings, in rubbish or rubble, or in rodent burrows. They are weak fliers and tend to remain close to the ground near their breeding sites. Promastigotes in the sand fly gut replicate and differentiate to metacyclic promastigotes over a period of approximately 1 week. Saliva from the sand fly enhances the infectivity of promastigotes through the effects of maxadilan, a potent vasodilator and immunomodulator, and possibly other factors. Depending on the *Leishmania* sp., the sand fly genus, and the geographic location, the major reservoirs are canines, rodents, or humans.

### Other routes of transmission

Although most transmission is by sand fly bites, *Leishmania* can be transmitted by blood transfusions, sharing of needles by intravenous drug abusers, occupational exposures, congenital transmission, and rarely by sexual transmission. Leukodepletion effectively reduces or eliminates transfusion-associated risk of *Leishmania* infection.

## Visceral Leishmaniasis

Parasites in the *Leishmania donovani* complex are responsible for most cases of visceral leishmaniasis. *Leishmania chagasi*, once considered a separate species causing VL in the Americas, is now considered the same as *L. infantum*, which is endemic in the Mediterranean and was probably introduced into the New World by early explorers.

Transmission depends on the sand fly vector, the presence of a suitable reservoir, and susceptible humans. In the Indian subcontinent, humans serve as the reservoir, and transmission is by *Phlebotomus argentipes* and other anthropophilic *Phlebotomus* spp. Persons with post-kalaazar dermal leishmaniasis (PKDL) may serve as the reservoir during interepidemic periods. VL caused by *L. infantum* also occurs in Central Asia and historically in southern China, where dogs and other canines are reservoirs.

In East Africa, VL occurs in Eritrea, Ethiopia, Kenya, Somalia, Sudan, and Uganda. *L. donovani* has been responsible for a very large epidemic among displaced persons in southern Sudan. VL is endemic and sporadic in other areas of East Africa. Putative reservoirs include rats, gerbils, other rodents, and small carnivores. Humans may also be a reservoir during epidemics. Although all

visceralizing *Leishmania* parasites from East Africa are now considered to be *L. donovani*,<sup>53</sup> molecular methods demonstrate a very high degree of strain heterogeneity.

Zoonotic VL occurs sporadically in the Mediterranean littoral and the Middle East, where rodents, such as the black rat, and dogs are reservoirs for *L. donovani* and *L. infantum*, respectively. The importance of asymptomatic infection in humans as a reservoir of *L. infantum*, for parasite transmission by blood donation and for development of clinical disease in immunocompromised individuals is increasingly recognized.<sup>56</sup> Clinically apparent cases are typically encountered among infants, young children, and immunocompromised persons. VL emerged as an important opportunistic disease among persons with AIDS in southern Europe in Spain, France, and Italy.<sup>57,58</sup> Sharing of contaminated needles and syringes by intravenous drug users was implicated in artificial anthroponotic transmission of *Leishmania* in Spain.

In Latin America, *L. infantum/L. chagasi* is endemic and broadly distributed. Most areas have focal disease risk with a background of asymptomatic or subclinical infection with sporadic clinical cases in rural areas. The clustering of cases in households suggests that humans may also be reservoirs in these settings. Children are most frequently affected. *Lutzomyia longipalpis* is the major vector. Domestic dogs and wild foxes are reservoirs of infection. Major periurban outbreaks of VL have been reported from cities in northeastern Brazil, where suburbs have extended into endemic areas.

On occasion, *Leishmania* spp. that usually cause CL, such as *L. amazonensis*, *L. tropica*, or other *Leishmania* spp., are isolated from persons with visceral disease. For example, a small group of American military personnel who served in the Persian Gulf War acquired a “viscerotropic” form of *L. tropica* infection.

#### Post–Kala-Azar Dermal Leishmaniasis

PKDL follows the treatment of VL caused by *L. donovani* in 5% to 10% of persons within 2 to 4 years after treatment in India and approximately 50% of persons within 0 to 6 months of treatment in the Sudan. PKDL is rarely seen after treatment of VL in Latin America or in the Mediterranean when the infection is with *L. infantum/L. chagasi* and, when reported, has been seen in patients with

concurrent AIDS. Patients with PKDL are thought to be infectious and serve as reservoirs for continued anthroponotic infection. Treatment of PKDL patients, at least to render them noninfectious to sand flies, is likely an important part of a future successful control strategy.

### Cutaneous Leishmaniasis

Cutaneous leishmaniasis (CL) is endemic in widely scattered areas throughout the world. The classic form of Old World CL is the “oriental sore,” also known by a variety of colorful local expressions, such as *bouton d’orient*, *bouton de Crete*, *bouton d’Alep*, *bouton de Biskra*, *Aleppo evil*, *Baghdad boil*, and *Delhi boil*, in various regions of the Middle East, the Mediterranean littoral, Africa, India, and Asia. Old World cutaneous leishmaniasis is most frequently caused by *L. major*, *L. tropica*, or *Leishmania aethiopica*, but *L. donovani* and *L. infantum/L.chagasi* can also cause simple cutaneous leishmaniasis. The resulting skin lesions range from troublesome and unsightly to severe and complicated, but they generally are not life threatening. Severe cases and facial lesions are very stigmatizing. DCL caused by *L. aethiopica* infection is reported from Ethiopia and adjacent areas of Africa.

New World CL is endemic in widespread areas of Latin America. The causative species include *L. braziliensis*, *L. mexicana*, *L. panamensis/L. guyanensis*, and many others. *L. infantum/L.chagasi* is associated with simple nodular CL in Central America. Depending on the clinical presentation and geographic location, New World CL is variously known as *pian bois* (bush yaws), *uta*, or *chiclero’s ulcer*.

In the Old World, CL is usually a sporadic disease in endemic areas, but on occasion it occurs in an epidemic pattern, particularly when large groups of susceptible persons are exposed during road construction, refugee movements, or military activities. *L. major* is an infection of desert rodents, primarily gerbils, and affects humans in arid and rural regions of the Middle East, North Africa, and Central Asia. CL caused by *L. major* has been a major problem for Western military personnel operating in endemic regions in the Middle East. The lesions tend to be larger and “wet” with an overlying exudate. *Phlebotomus papatasi* and other *Phlebotomus* spp. are the vectors.

*L. tropica* infects dogs and humans in urban areas of the Middle East, such as Baghdad, Teheran, Kabul, and Damascus, as well as cities in the Mediterranean littoral, India, and Pakistan. The lesions tend to be crusted and “dry.” The vectors include *Phlebotomus sergenti* and *P. papatasi*. On occasion, *L. donovani* and *L. infantum/L. chagasi* cause simple CL.

New World CL is usually a rural zoonosis.<sup>3</sup> The main reservoirs are forest rodents, except in the case of *Leishmania peruviana*, for which dogs are the primary reservoir. The vectors are ground-dwelling or arboreal *Lutzomyia* spp. Disease is common in persons working at the edge of the forest and among rural settlers. Outbreaks occur when areas of forest are cleared for roads, villages, or farms, or when military personnel or tourists enter endemic regions.

*L. mexicana* is responsible for New World CL from northern Argentina to Texas, where a small number of autochthonous cases have been reported. New World CL is an occupational hazard of gum (chicle) collectors in Central America as well as persons living, working, or touring in endemic areas. Lesions typically appear on exposed areas of the extremities, face or ears (known as chiclero's ulcer when lesions involve the ear.). A number of sylvatic rodents are reservoirs. *Lutzomyia* species are the vectors.

*L. amazonensis* produces a spectrum of disease in South America that includes simple cutaneous, diffuse cutaneous, and visceral leishmaniasis. The vectors are *Lutzomyia* spp., and the reservoirs are forest animals.

*L. braziliensis* is found in widely scattered areas of Central and South America. It is responsible for cutaneous as well as ML. CL caused by *L. braziliensis* has been diagnosed among American tourists returning from Belize and other Latin American areas. *L. panamensis* is found in Panama and adjacent countries. It was an important problem for U.S. military personnel training in jungle areas of Panama. *L. guyanensis* is responsible for *pian bois* or *bush yaws* in the northern Amazon basin. *L. peruviana* is the cause of *uta* in Peru. It typically causes dry lesions.

### New world Mucosal Leishmaniasis

About 2% to 5% of persons infected with *L. braziliensis*, or, rarely, a related *L. panamensis*, *L. guyanensis*, or *L. amazonensis* develop mucous membrane involvement of the nose, oral cavity, pharynx, or larynx months to years after their skin lesions have healed. The percentage of patients infected with *L. braziliensis* who develop mucosal disease is relatively small. Mucosal involvement usually occurs after a resolved primary ulcer but occasionally is concurrent. The time between the primary lesion(s) and mucosal involvement may be as short as 1 month or as long as 2 decades. Mucosal involvement is seen on occasion because of the contiguous spread of cutaneous lesions caused by *L. tropica* or other *Leishmania* spp. In this setting, it has been referred to as mucocutaneous leishmaniasis.

Mucosal involvement has also been described with *L. infantum* in the Mediterranean and is usually seen in male patients, is not associated with prior cutaneous lesions, and is often associated with immunocompromised patients but can be seen in otherwise healthy immunocompetent individuals.

## Prevention

There are several approaches to prevention for individuals and communities as public health interventions. For the individual, there is no form of chemoprophylaxis or active (vaccine) or passive (immunoglobulin) immunoprophylaxis for travelers. Standard personal protective measures, such as *N,N*-diethyl-meta-toluamide (DEET)-based insect repellents and permethrin or other insecticides applied to clothing and insecticide-impregnated fine-mesh bed nets all provide protection against sand flies if used correctly.

For community-based efforts in endemic areas, vector control and reservoir control are effective, depending on local sand fly behavior and transmission dynamics. Residual insecticides applied in houses and other buildings have yielded good results in sites where peridomestic transmission occurs. Unfortunately, spraying is necessary at intervals, sand flies may become resistant, and there is concern about the environmental impact. Of note, the cessation of dichlorodiphenyltrichloroethane (DDT) spraying for malaria in Peru, India, Bangladesh, and southern Iran was followed by major epidemics and a resurgence of leishmaniasis.

In areas where transmission occurs away from dwellings, residual insecticides are obviously of no benefit. The efficacy of impregnated bed nets to reduce human–sand fly contact in at-risk populations living in endemic transmission areas is less certain and variable, with some studies showing an impact and others minimal or no impact. The efficient use of bed nets to prevent leishmaniasis will depend on an understanding of both human behaviors and sand fly biology.

Reservoir control is another option in areas with domestic animal or human reservoirs. In *Leishmania infantum*/*L. chagasi* areas, domestic and wild dogs are thought to be the primary reservoir. Immunizing dogs, preventing infection through insecticide dog collars, and culling feral dogs should interrupt transmission and reduce human disease.

In northeastern Brazil, infected domestic dogs have been identified by mass serologic testing and exterminated, but the efficacy of the program has been debated, and it is poorly accepted. Recent studies suggest that insecticide-impregnated collars may protect dogs from sand fly bites and reduce the risk of human disease. In sites where leishmaniasis is a zoonosis involving sylvatic mammals, reservoir control is rarely possible. In areas of anthroponotic (person–sand fly–person) transmission, case identification and treatment is important in control. Persons living in the same household as active cases and the existence of asymptomatic human infections in the community are a transmission risk. In countries such as Spain, where VL has been spread among intravenous drug users, needle exchange programs might limit transmission.