Sand Flies: Medical Importance

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Phlebotomine sand flies (Diptera, Psychodidae, Phlebotominae) are small Diptera that appeared in the Cretaceous, approximately 120–135 million years ago (Hennig 1972; Azar et al. 1999); they represent a group of approximately 1000 known species around the world, of which 530 were found in the Americas (Shimabukuro et al. 2017). They carry trypanosomatid protozoans, including species from the *Leishmania* genus. These can affect human health, contaminate domestic animals, and make wild mammals into reservoirs for infectious diseases (Shaw et al. 2003; Brazil and Brazil 2014). It is estimated that 98 species of phlebotomine sand flies are possible natural vectors of *Leishmania* spp. (Killick-Kendrick 1999; Galati 2003; WHO 2010a). This is due to specific characteristics of their biology such as anthropophilia; being naturally infected by the same *Leishmania* that circulates among humans; and their spatial distribution, which coincides with likely places of infection.

These Diptera are holometabolous insects. The adult forms are considered to be cryptozoans because of their thin integument (exoskeleton) and their being extremely sensitive to variations in temperature and humidity. Natural shelters for adults include hollow spaces in tree trunks, fallen leaves, grottos or animal holes, and large treetops. In environments with human occupation or interference, artificial shelters include shaded and humid areas, other than domestic animals shelters such as hen houses, pigsties, and barns. The interior of houses can also be cited here (Aguiar et al. 1987; Killick-Kendrick 1999; Brazil and Brazil 2003). Immature phlebotomine forms develop in decomposing organic matter, particularly vegetable matter.

Both males and females feed on carbohydrates, especially aphids' nectar and secretions. They normally leave their natural shelters to feed at night and/or at dusk. Hematophagic activity, however, may take place throughout the night period, from

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dusk to dawn. Only females are hematophagous, a required condition for their ovaries to mature. Because of their feeding habits, females are infected when they bite *Leishmania* spp. reservoirs and may later transmit infectious forms of the disease by biting humans and other mammals (Ministério da Saúde do Brasil 2017; Brazil and Brazil 2003).

In Brazil, as in the whole Every American, South, Central and North Continent, the species of phlebotomines that are responsible for spreading *Leishmania* spp. belong to the following genera: *Bichromomyia*, *Lutzomyia*, *Migonemyia*, *Nyssomyia*, *Pintomyia*, *Psychodopygus* and *Trichophoromyia* (Galati 2003; Marcondes 2007).

Current policies in Brazil establish that the control of leishmaniasis is the responsibility of the country's public health system (*Sistema Único de Saúde* [SUS]). According to the Health Surveillance Department's 'National Program of Leishmaniasis', Municipal Health Secretariats supported by State Health Secretariats are responsible for organizing the basic network of patient care and for implementing actions to combat the disease's vector (Ministério da Saúde do Brasil 2014, 2017).

The success of vector surveillance and control actions for leishmaniasis as planned by the Ministry of Health remains a great challenge in Brazil. These are illnesses with a complex eco-epidemiology, with different transmission cycles, unique links in their epidemiological chain and which can occur in various Brazilian biomes.

Considering this context and the diversity of *Leishmania* spp. vectors, entomologic surveillance will still need to collect more precise data on phlebotomine sand flies, including information for their correct identification and on their incidence in likely places of infection. Regarding incidence, both home and wild environments should be considered in order to obtain a full understanding of the local epidemiology. Another relevant factor to take into account is behavioral change in local vectors provoked by environmental changes. Important gaps in knowledge on phlebotomine vectors still exist, and they need to be addressed.

Leishmaniasis

Leishmaniasis is among the diseases with a higher impact on human health. Contributing to this scenario are environmental changes, which can be related to global climatic changes and impact on specific ecosystems. This context, however, becomes more complex as alterations in the environment can also be aggravated by the socioeconomic and living conditions of populations in risk areas for leishmaniasis. These conditions are important determinants in the process of disease transmission (Ministério da Saúde do Brasil 2017; Rangel et al. 2014).

The different forms of leishmaniasis are distributed worldwide, with an estimated 350 million people living in endemic regions. These illnesses are among the six most important infectious diseases in the world, which can be explained by their high detection coefficient, high number of related deaths and deformities, as well as their presence in 98 countries. Approximately 15 million people around the world

are infected by leishmaniasis and endemic areas include the Americas, Africa, Asia and Southern Europe (Desjeux 2004; Malafaia 2009; WHO 2010a; Alvar et al. 2012; Ministério da Saúde do Brasil 2014, 2017).

Approximately 1.6 million new cases of these diseases are estimated to emerge each year, of which 500,000 are visceral leishmaniosis and 1.1 million are cutaneous or mucocutaneous leishmaniasis. Ninety percent of the cases of visceral leishmaniosis are concentrated in Bangladesh, Brazil, Ethiopia, India, Nepal and Sudan, 90% of the cases of cutaneous leishmaniosis can be found in Afghanistan, Saudi Arabia, Algeria, Brazil, Iran, Peru, Syria and Sudan, and 90% of the mucocutaneous cases are from Bolivia, Brazil and Peru. Only 600,000 of this total estimated number of 1.6 million cases are reported (Alvar et al. 2012; WHO 2010a). Every year, 500,000 new cases of leishmaniasis emerge, 60,000 related deaths occur and 200 million individuals are found to be at risk of developing the disease. Thus, the actual global leishmaniasis-related mortality is likely to be even higher than this estimate (de Oliveira et al. 2012).

Leishmaniasis presents a range of clinical manifestations, which are associated with infection from different types of *Leishmania*. In the Americas, they are distributed from the southern United States to the north of Argentina (Ministério da Saúde do Brasil 2014, 2017; WHO 2010a).

In Latin America, the disease has been described in at least 12 countries, although 90% of the cases are concentrated in Brazil. These cases generally occur in rural and peri-urban areas, commonly affected by elements of vulnerability, such as lack of basic sanitation services and garbage collection. These factors feed upon themselves, and generate a poverty–disease cycle (Alvar et al. 2012; WHO 2010a).

In Brazil, the leishmaniases are considered emerging endemic diseases in clear territorial expansion. They are included in the Ministry of Health's "System of Diseases with Compulsory Notification" and cases have been reported in all states of the country. Brazil is considered to have the biggest prevalence of leishmaniasis in the Americas, both for visceral and cutaneous forms (Ministério da Saúde do Brasil 2014, 2017; WHO 2010a). The importance of the national public health context for the spread of these diseases has increased significantly over recent years. This is mainly due to urbanization processes and to changes in the natural habitats of the species involved in the transmission cycle of leishmaniasis. The scenario for these illnesses in Brazil is therefore complex, and difficulties related to their control and the elimination of risk factors should always be taken into account (Toledo et al. 2017).

Migration flows should also be considered as an important social component influencing on the epidemiology of leishmaniasis. These phenomena have been observed in the north-east, center-east, south-east and south regions of the country, including cases of in-house transmission and cases in urban environments (Rangel 1995; Rangel and Lainson 2009; WHO 2010a).

American cutaneous leishmaniasis (ACL) is associated with a range of dermotropic leishmania (of the sub-genera *Leishmania* and *Viannia*) and manifests itself clinically through localized skin lesions, multiple lesions, cutaneous–mucosal and cutaneous–diffuse lesions. The latter tends to be very aggressive and it mainly develops in immunosuppressed patients (Ministério da Saúde do Brasil 2017; WHO 2010a).

Combined infection by *Leishmania* and HIV is an emerging problem that requires urgent attention (Lainson and Shaw 1972; Silveira et al. 1987; Lainson and Shaw 1989; Grimaldi et al. 1989; Lainson et al. 1994; WHO 2010a).

Throughout several regions in Brazil, the transmission of ACL occurs in deforested areas (Ministério da Saúde do Brasil 2017). This has mainly been concentrated in sites where houses are close to secondary forests (Lima et al. 1988; Sabroza 1981).

In the case of American visceral leishmaniasis (AVL), the parasite mainly develops in cells of the mononuclear phagocytic systems of the spleen, liver, bone marrow and lymphoid tissues. If the disease is not treated, it may lead to death (WHO 2010a), with cases concentrated in Venezuela, Bolivia and Brazil (Ministério da Saúde do Brasil 2014).

This disease has moved from being endemic in exclusively rural areas to, in recent decades, important numbers of AVL being recorded in urban sites, including state capitals, and both large- and medium-sized cities (Ministério da Saúde do Brasil 2014; Vilela et al. 2014; WHO 2010a). Today, the main challenge to fighting AVL lies precisely in the urbanization of its main vector: *Lutzomyia longipalpis*.

Leishmaniases as Neglected Diseases

Neglected diseases affect the lives of 1 billion people around the world and threaten the health of millions of others. They generate a substantial burden in terms of health, economic and social conditions. Neglected diseases represent a group of old illnesses that have afflicted humanity for centuries which proliferate in impoverished environments within tropical areas of the world. In many cases, these diseases remain hidden, concentrated in remote rural environments, but also in urban communities (Araújo-Jorge et al. 2014).

As a part of the group of neglected diseases, not only do leishmaniases prevail in contexts affected by poverty, but they also contribute to maintaining inequalities. A notable geographic spread of these diseases can be observed, which is related to numerous environmental, social, political and historic conditions. With these changes, the relationship between the components of the diseases' transmission chain in urban environments has become much more complex (WHO 2010b; Ministério da Saúde do Brasil 2014, 2017; Rangel et al. 2014).

Due to global climatic and environmental changes, uncertainties regarding nature and its impact on the scale of local ecosystems add to the complexities of the new reality of urban Brazil. In that sense, new barriers to fighting leishmaniasis appear (Costa 2016).

Considering the epidemiologic scenario for these diseases, vector control through an integrated program—one that contemplates the interface between health and the environment—should be a priority measure. A program with this approach would focus on local communities' quality of life, aiming to mitigate social inequalities.

This approach to vector control—where epidemiologic surveillance can subsidize more targeted action—requires rational decision-making processes that optimize the use of available resources. These actions should be undertaken under the perspective of public health, using integrated interventions that are based on disease control tools, aiming to prevent mortality, reduce morbidity and interrupt the transmission cycle of the disease (WHO 2010b).

Bartonellosis

Bartonellosis, which has not yet been reported in Brazil, and is largely unknown by Brazilian health professionals, is also transmitted by phlebotomine sand flies. However, it has been observed near the Brazilian border and its impact might be aggravated by the development model adopted in the Amazon forest. The infection is caused by the bacteria *Bartonella bacilliformis*, the only known vectors of which are phlebotomines from the *Lutzomyia* genus (Alexander 1995). Townsend (1913, 1914) was the first to suggest that phlebotomines could act as vectors for *B. bacilliformis*, based on evidence derived from the presence of phlebotomine sand flies in areas where the disease occurred. Also known as "Carrion disease", Bartonellosis was originally observed in the inter-Andian valleys of Peru, Colombia and Ecuador. The following species of phlebotomines are suggested as potential vectors: *Lutzomyia (Helcocyrtomyia) peruensis*, *Pintomyia (Pifanomyia) columbiana* and *Pi. (Pif.) verrucarum* (Sherlock 1962; Vargas and Perez 1985; Gray et al. 1990; Galati 2003; Marcondes 2007).

Studies have presented evidence that *Pi. verrucarum* is the most likely vector of *B. bacilliformis* in the Rimac Valley in Peru, although there are other species of anthropophilic phlebotomine sand flies in the area, such as *Lu. noguchii* and *Lu. peruensis*, which could also be involved in the local epidemiology.

Pi. verrucarum does not seem to exist in Ecuador and the identification of a possible vector is still pending (Alexander et al. 1992; Young and Duncan 1994; Maroli et al. 2013).

The most likely vector in Colombia is *Pi. columbiana*, which is intimately related to *Pi. verrucarum*. This species is highly anthropophilic and can be found in all areas of Colombia in which Bartonellosis outbreaks have occurred (Gamarra 1964). Outbreaks continue to be notified in areas in which *B. bacilliformis*, and not *Lu. Verrucarum*, is endemic. This leads to the conclusion that other phlebotomines, or even other arthropods, might be acting as vectors in this coastal region (Alexander 1995; Maroli et al. 2013).

The possibility of Bartonellosis entering Brazil through the Amazon forest raises many concerns. The spread of the disease could be accelerated by the process of increased anthropic action that is occurring in the region. The south-western portion of the Brazilian Amazon possesses favorable conditions for the emergence of Bartonellosis, with environmental changes and migration flows affecting the region (http://www.pragas.com.br/noticias/destaques/infeccao_bacteriana.php). Due to

environmental impact, some species of phlebotomine sand flies from Brazil could become apt to transmission.

For a better understanding of the epidemiology of Bartonellosis, it is essential to improve surveillance of this disease in countries that share a border with Brazil. Because Bartonellosis is directly related to deforestation and migration, the surveillance tools used need to be the most precise available, such as modelling for complex systems in which phlebotomine sand flies and possible reservoirs are included, and the environment being seen as a socio-natural, dynamic and complex element. The results of these studies may point to possible phlebotomine vectors, as well as assisting in strategic planning for border surveillance.

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