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Worldwide risk factors in leishmaniasis

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ABSTRACT

Recently, vector-borne parasitic diseases such as leishmaniasis have been emerged or re-emerged in many geographical areas and resulted in global health and economic concerns that involve humans, domestic animals and wild life. The ecology and epidemiology of leishmaniasis are affected by the between host, reservoir and vector (human, animal and sandfly) and the environment. Important drivers for the emergence and spread of leishmaniasis include environmental factors such as alterations in temperature and water storage, irrigation habits, deforestation, climate changes, immunosuppression by HIV or organ transplant, development of drug resistance, increase traveling to endemic regions and dog importation. War, poor socio-economic status and low level household are also major contributors to the spread of this disease. Health education via the public media and training should be implemented by international organizations and governmental agencies in collaboration with research institutions. Fully protection during transmission season, using bednets and insecticides and reservoirs' control should be also mentioned in the planning. Based on the findings of the recent studies and high prevalence of leishmaniasis, it is concluded that serious public health monitoring should be considered.

1. Leishmaniasis

Leishmaniasis, a vector-borne disease that is caused by several species of obligating intra-macrophage protozoan parasite [1,2]. This neglected disease is endemic in large areas of the tropics, subtropics and the Mediterranean basin. The vector-borne parasitic disease is characterized by diversity and complexity [3]; it is caused by about 20 *Leishmania* species and is transmitted to humans by more than 30 different species of phlebotomine sandflies [4,5]. This infectious disease has diverse clinical manifestations, including cutaneous, diffuse cutaneous, mucocutaneous (espundia), visceral (kala-azar), post kala-azar dermal leishmaniasis (PKDL) and recidivans [6]. Leishmaniasis is a public health problem in more than 88 countries [7,8]. The estimated world prevalence of all forms of the disease is 12 million, with 1.5–2 million added new cases annually of cutaneous, and 500 000 cases of visceral leishmaniasis and about 50 000 deaths from the disease each year [9,10], a death toll that is surpassed between the parasitic diseases only by malaria [11].

So far, leishmaniasis research has considered only a single or a limited number of parameters, and has majority been conducted in *Leishmania*-endemic areas. There is thus an urgent that needs to conduct more ambitious researches on the clinical, environmental, co-infections and resistance predictors of *Leishmania* in endemic areas. In these times leishmaniasis shows a wider geographic distribution than before; it is still one of the world's most neglected diseases affecting largely the poor and developing countries.

The increase in leishmaniasis incidence and prevalence is mainly attributed to several risk factors that are clearly man made and the most important factors have been mentioned in this review. Generally, environmental conditions, socio-economic status, demographic and human behaviors pose major risks for human leishmaniasis [12,13]. Also increase in the worldwide incidence of leishmaniasis is mainly attributed to the increase of several risk factors that are clearly man made and such as great migration, deforestation, urbanization and immunosuppression. The environment and the population movements, probably lead to alterations in the number, range and density of the vectors and reservoirs and consequently, may increase human exposure to infected sandflies [14].

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Leishmaniasis affects the rural poor community and usually outbreak occurs during harvesting seasons [15]. Following agricultural development in the area, a large number of labor migrants from the highlands were moved to the endemic areas in the late 1970 for crop harvesting. This led to spread of visceral leishmaniasis, which resulted in high morbidity and mortality [16].

2. Vector distribution

Approximately, 600 species of *Phlebotominae* are known, most of which belong to the genera *Phlebotomus* in the Old World and *Lutzomyia* in the New World. Less than 10% of these species act as disease vectors and only 30 species of these are important in the public health. *Phlebotomus* is the dominant genus in the Palearctic. It includes the earthly ecoregions of Europe, Asia, northern Africa, the northern and central parts of the Arabian Peninsula and extending to other regions of the Old World. *Phlebotomus* are of little importance in North America but *Lutzomyia* is the main genus in Latin America and is found over large regions [17]. The spread and distribution of sandflies largely determines the occurrence of leishmaniasis. In general, *Phlebotomus* (the Old World sandfly species) is seen in desert or semi-arid ecosystems [18]. Some of the species breed in peridomestic situations and enter human housing; whereas *Lutzomyia* (the New World sandfly species) transmit the leishmaniasis in forest habitation and occur in humans near the forest. Usually, sandflies are seen around human dwelling and breed in specific organic wastes including to dung, feces, rodent holes, leaf litter and the cracks and crevices in the walls having high temperature and humidity. It is noted that the distribution pattern of sandflies and leishmaniasis appears to be changing [17].

3. Organ transplant

Natural transmission of the *Leishmania* species is occurred by phlebotomine sandflies of the genus *Phlebotomus* or *Lutzomyia*. However, different forms of leishmaniasis could also be transmitted by organ transplantation and blood transfusions by needle sharing among intravenous drug addicts [19]. *Leishmania* species are obligated intracellular parasites in the mammalian host, where they exist as multiplicative "procyclic" promastigotes and infective "metacyclic" promastigotes and they are living mainly in the phagolysosome of macrophages. Cell-mediated immunological mechanisms are responsible to control the infection in the infected cells of host [20]. Acquired resistance to leishmaniasis is mediated by T cells. $CD4^+$ lymphocytes are crucial for resistance and $CD8^+$ are more involved in memory than as effector cells. The immunosuppressive drugs prevent T-cell proliferation and activation, therefore alter the defense mechanisms against *Leishmania* species in transplant recipients [21,22].

Although leishmaniasis is a rare disease among transplant patients, it requires clinical evaluation for several reasons. Many organ transplantations are performed annually in the world, while the transplant recipients often travel to endemic leishmaniasis countries. Thus, the risk of developing leishmaniasis among the transplant recipients that travel to an endemic region following transplantation, which has been reported in several cases [23,24]. Moreover, there is limited information about leishmaniasis among physicians. Leishmaniasis usually occurs as a late complication after transplantation, with a median delay of 18 months between transplantation and onset of disease [25,26]. Diagnosis of the clinical signs of leishmaniasis in the transplanted recipients can be delayed for several months or it might be misdiagnosed [27–29]. Visceral leishmaniasis should be considered in the differential diagnosis from other symptoms occurring after organ transplantation including fever and pancytopenia, especially in endemic regions and in organ recipients who travel to regions where the disease is endemic.

4. Drug resistance

The current control strategies for leishmaniasis rely on reservoir and vector control, active case detection and treatment of their disease and the use of insecticides [7,30] and the anti-leishmanial vaccines are still to be developed. Treatment strategies of the infected dogs are not effective control manners, because relapses of disease are seen frequently and dogs can regain infectivity weeks after treatment, despite being clinically cured [31]. Moreover, the extensive veterinary use of leishmaniasis drugs might lead to resistance in parasites. Gavgani *et al.* demonstrated that a new control approach was the use of deltamethrin-treated collars which reduced the risk of infection in dogs by 54% and in children by 43% [32].

Early detection, diagnosis and treatment are crucial for individual patients and for the community. Untreated leishmaniasis patients are as reservoir for parasites and therefore provide disease transmission in anthroponotic leishmaniasis regions [9,30,33]. The sodium stibogluconate, meglumine antimoniate and pentamidine have been the first-line drugs for human leishmaniasis in many countries of the world for more than 70 years [34]. Pentavalent antimonials are toxic drugs with frequent adverse side effects, such as cardiac arrhythmia and acute pancreatitis and they are life-threatening in some cases. Patients under the age of two and age over 45 years with symptoms of advanced disease and with severe malnutrition are at higher risk of death during treatment with antimonial compounds owing to drug toxicity, slowness of drug action or a combination of these factors [35].

However, miltefosine, paramycin and liposomal amphotericin B, alone or in combination became the drug of choice in recent decades to prevent the emergence of resistance [36]. In reality, antimonials are still applied in many poor countries. Conventional amphotericin B has changed antimonials as the first-line treatment for disease in some countries that treatment failure rates are high [37]. Fever, chills and rigor are almost universal adverse effects following treatment with conventional amphotericin B, and life-threatening side effects including hypokalemia and nephrotoxicity. In the first-dose of this drug, anaphylaxis is not uncommon. Moreover, conventional amphotericin B is costly and requires a complicated regimen (15 slow infusions on alternate days). Liposomal amphotericin B is considered by many experts as the best existing drug against visceral leishmaniasis, and is used as the first-line choice in the United States and Europe. Until recently, its use in the developing countries was prevented by its high market price [38,39].

Miltefosine is a teratogenic drug and its use is thus strictly forbidden in pregnant women or in women who could become pregnant within two months of treatment. It has been seen that miltefosine has a long half-life and parasite resistance is easily induced [40]. Non-adherence to the recommended regimen could lead to prevalent parasite resistance [41]. The increasing use of

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