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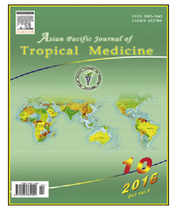

Review http://dx.doi.org/10.1016/j.apjtm.2016.06.021

Worldwide risk factors in leishmaniasis

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ARTICLE INFO

Article history:
Received 10 Apr 2016
Received in revised form 1 Jun 2016
Accepted 10 Jun 2016
Available online 29 Aug 2016

Keywords:
Leishmaniasis
Risk factors
Emergence disease
Sandfly

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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Peer review under responsibility of Hainan Medical University.

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 miltefosine in veterinary for canine leishmaniasis might also increase the development of miltefosine resistance. Combination therapy is the proposed option forward to increase efficacy of treatment, prevent the development of drug resistance, reduce treatment duration and maybe decrease treatment cost [42].

5. Travel to endemic areas

Leishmaniasis is increasingly reported among travelers returning from tropical and subtropical regions, and the broad clinical spectrum and the limited science of the disease among clinicians and travelers often lead to a wrong initial diagnosis [43]. Limited data exists on the incidence of leishmaniasis in the travelers in most developed countries, because the number of exposed travelers is often unknown, the disease is usually misdiagnosed and is self-healing. The occurrence of imported cases has increased, because more cases occur due to the increasing number of travelers to endemic countries. However, a few cases of travelers to endemic countries where leishmaniasis is prevalent that have been mentioned in the literature [44,45]. Alcais *et al.* reported that the risk of leishmaniasis was 3–10 times higher in the migrants than in the local population. Therefore, the travelers may be at a higher risk of developing leishmaniasis than the natural people [46].

While leishmaniasis has always been endemic in the Mediterranean area, this disease has been seen in northern latitudes including United States of America, Canada and Germany, from which sandfly vectors are present in very low densities [47–49]. Desjeux explained that the maximum northern latitude for sandfly survival, which is speculated to move further to the North, beyond Germany because of global warming [50]. This can be explained by dog importation or travel to the endemic countries. Nevertheless, Duprey *et al.* observed that vertical transmission of canine leishmaniasis has occurred in the eastern United States of America and Canada imported from Europe [49]. However, vertical transmission from bitch to puppy has rarely been seen [51]. Increase in the number of travels and immigration of dogs have significantly increased the incidence of this disease in the non-endemic countries [52,53]. Furthermore, in areas where the infection is not considered endemic, diagnosis may be delayed because of a low index of suggestion or by unusual presentation in immunosuppressed subjects.

6. Canine leishmaniasis

Canine leishmaniasis is a vector-borne parasitic disease of dogs, occurring in the entire world, except Oceania [54]. Transportation of dogs from areas of canine leishmaniasis endemicity has resulted in widespread of disease to areas where infection has been absent [55–57], and this topic may results in new epidemiological prevalence in the world. The risk of canine leishmaniasis transmission is dependent on sandflies, also venereal and transplacental transmission should be seriously considered [58].

7. *Leishmania*/HIV co-infection

World Health Organization reported that the incidence of human visceral leishmaniasis has displayed a sharp increase since the early 1990s in Mediterranean countries, mostly under the influence of human immunodeficiency virus (HIV) co-infection [59]. This phenomenon has occurred particularly in the coastal regions of Spain, France and Italy [60,61], where the incidence of officially reported visceral leishmaniasis cases almost doubled from 1987 up to 2004 [62,63]. *Leishmania*/HIV co-infections have worldwide distribution and have been recorded in 35 countries. Cruz *et al.* reported that there were *Leishmania* parasites in the discarded syringes [19]. Desjeux and Alvar also demonstrated that widespread needle transmission of *Leishmania infantum* was inferred in southwest Europe [64]. Gabutti *et al.* mentioned that the highest rates of worldwide *Leishmania*/HIV co-infection are from Europe, where 85% of the cases were from the southwest; 71% of which were isolated from the intravenous drug users [65]. Visceral leishmaniasis/HIV co-infection is a serious phenomenon that leads to death. Although, the highly active antiretroviral therapy for HIV has diminished the number of these co-infection cases and improved the survival rates [66,67]. The mean time from signs onset to diagnosis has been reported 3 months [68]. This delay resulted often from physicians' failure to consider the diagnosis. Malik *et al.* noted the importance of looking at rare imported diseases over a long period so that emerging risk factors can be identified [69].

The geographic distribution of leishmaniasis has prevalent in the world, and the disease has been seen in countries in which leishmaniasis was not previously endemic [50]. All form of leishmaniasis including cutaneous, mucocutaneous, visceral and recently leishmaniasis/HIV co-infection are widespread in all of the world [50]. According to the World Health Organization, visceral leishmaniasis has often been known as a disease of children [50]. However, visceral cases are recently reported in adults too. This occurrence in age groups may be explained by the increased proportion of *Leishmania*/HIV co-infected individuals and partly by increased travel activities of differently immunocompromised individuals. People traveling to endemic countries should be aware about their increased susceptibility to infection with *Leishmania*. However, travelers should be recommended to wear suitable cloths, take repellents and have mosquito nets to reduce the exposure to the sandfly, and use collars impregnated with repellents for accompanying dogs [47].

Seroprevalence data shows high endemicity in some European countries [70,71]. On the other hand, the evidently potent associations between *Leishmania* seropositivity and traveling to endemic countries, as risk factor is clearly associated with prolonged residence in an endemic country. Migration, climate change, contact with dogs and *Leishmania*/HIV co-infection are the main factors driving the increased incidence and prevalence of leishmaniasis [30,50].

Climate changes might affect natural transmission of *Leishmania* spp. by the bite of sandflies. On other hand, the temperature and climate changes might affect on parasite reproduction and proliferation and the abundances of the sandflies and eventually on distribution of leishmaniasis [72]. A strong association between the cycle and the annual incidence of visceral leishmaniasis has been reported by Franke *et al.* in Brazil [73]. Spatio-temporal modeling of the distributions of the leishmaniasis and their vector in relation to climate change has previously been mentioned [74].

8. Household level

Whilst some reports have indicated that leishmaniasis is associated with climate change, HIV/*Leishmania* co-infection, environmental factors and domestic animals, little is known about other household characteristics that associated with this disease. Household design and construction material including number of floors, number of rooms, dirt floor, damp earthen floors and houses with cracked mud or thatched plastered house walls are the common risk factors of leishmaniasis. Other risk factors of the disease include presence of domestic animals such as dogs, pigs and rodent and proximity to forested areas and other regions where sandflies are aggregated [75–77].

Reithinger *et al.* indicated that household construction materials including brick walls and design such as number of rooms or number of windows per person can significantly influence anthroponotic leishmaniasis risk. Household level and human behavior may ultimately increase or decrease sandfly exposure. However, greater density in terms of household members per room and increasing the individual household members, in contrast to increased number of household rooms with inside walls and doors more likely increase and reduces exposure of the household members' to sandflies respectively [78]. Thus, the transmission risk of *Leishmania* is strongly dependent on the presence of disease in other household members in the same region, which is indicative of the short flight range of sandflies [79] and it is likely that a household with a high proportion of people with leishmaniasis is ‘infectious’ to its inhabitants from an epidemiological point of view.

Finally, it has been shown that reduction in vector exposure can be highly successful in reducing the risk of leishmaniasis. Screening of household windows and ceilings is effective in reducing leishmaniasis [78]. The previous studies have interestingly shown that this approach has been effective in reducing malaria and other mosquito-borne infectious disease too [80]. Intervention strategies to reduce sandfly vector contact and implementation of provisional treatment modalities are recommended to reduce leishmaniasis risk.

9. Social condition

Leishmaniasis, especially the visceral form, tends to affect the poorest people and marginalized societies [81] particularly those people that are close to water resources, live in humid houses, and are in vicinity of accumulated rubbish, sewerage and farms of livestock. Individuals in under-developed houses for example mud or thatched rooms with cracked walls and low socio-economic status have been found at risk for leishmaniasis [82,83]. The recent risk factors contribute to the growth and multiplication of sandfly. Other studies have shown that the risk of leishmaniasis has been associated with mud house, cattle density, presence of rodent, dog, other leishmaniasis cases and poor socio-economic status [82,83] which may have difficulties in accessing treatment [84]. However, infected individuals may play an important role in sustaining transmission in these areas and result in endemicity of leishmaniasis in poor communities [85]. The role of domestic animals mainly cattle in proximity of the houses has been emphasized as a risk factor for leishmaniasis [86].

The risk of disease in those individuals which are living in close contact to the asymptomatically infected individuals and leishmaniasis cases in the neighboring houses is significantly high [87]. A worse socio-economic status is associated with an increased risk of seroconversion. It has also been confirmed that seroconversion and leishmaniasis are strongly associated [87]. In addition, a strong association between the occurrence of a new leishmaniasis case and the presence of asymptomatically infected persons in the surrounding houses has been indicated. Many studies have shown the use of bednets to be protective against *Leishmania* infection [87,88]. Some sleeping habits such as using bednet, sleeping under a cover and spraying inside have been found protective [88]. However, seroconversion has significantly been found that it associated with household spraying. Finally, investigation of the risk factors for this disease is complex because of the leishmaniasis with unstable transmission and because of the high number of latent infections and infected animals for which validated markers is not present.

10. Environmental factors

The prevalence and development of leishmaniasis are largely dependent on environmental factors and natural conditions. In addition to the economic, social and cultural conditions, prevalence of leishmaniasis is influenced by ecological factors too [89]. Vegetation area and climatic factors have important roles in proliferation and growth process of sandflies and subsequent outbreak of leishmaniasis. Also, improving vegetation types and climate condition for growth and proliferation of rodents that can transmit the disease could be suitable in declining the leishmaniasis outbreaks [90]. It has been reported that deforestation has led to an increase in leishmaniasis [74,91]. The forest has been shifted to other types of cultivation, dispersed with patches of forest. With growth of the dog, fox and rodent populations as reservoir hosts of this disease, the prevalence of leishmaniasis has increased and the sandfly vectors have become peridomestic [92].

Forest fragmentations, climatic variables, vegetation indices and land surface temperature are important candidate predictors for vector-borne diseases such as leishmaniasis [93–97]. Changes in land coverage such as deforestation and continually replace by farmland has an increasing risk for leishmaniasis [98]. Feliciangeli *et al.* indicated that risk of leishmaniasis has traditionally been associated with working in or near forest [99]. Recent studies in Latin American countries have shown that transmission of leishmaniasis has been shifting from sylvatic and forestial areas to domestic and rural settlements [100,101]. Risk of cutaneous and visceral leishmaniasis has been found to be associated with environmental factors such as land use, temperature and vector density [98,102–104].

Kassiri *et al.* showed a correlation between the gender and incidence of leishmaniasis and the disease was seen more in men than women [105]. Occurrence of higher prevalence in men than women is logic, because the men work or sleep in populated and infected environments and is exposed to the infected vectors more than women [106]. Many investigations have found that gender difference, attributable to hormonal effects, has been observed in some other parasitic diseases too [107]. It is more likely that men are exposed to sandflies in fields and other open areas more than women; probably this issue equally or more importantly than the sex hormones may affect the establishment and the course of parasitic diseases [108,109].

11. Vaccines

Leishmaniasis, especially its visceral form, affects poor countries, generally in remote rural areas. The disease is mostly endemic in the poorest and least developed countries in the world [110]. The high direct and indirect costs of the disease such as the costs of diagnosis, treatment and loss of household income, should be paid by patients [111–113]. The commitment of the governments of the developing countries to precede a regional visceral leishmaniasis elimination program is necessary. The existing methods of vector or reservoir control cannot be used effectively by poor countries due to their high cost and problems with their operating and administrative programs [114,115]. Furthermore, toxicity of the available drugs including pentavalent antimonials, the current drugs of choice in these countries, and increasing parasite resistance underline the need for an effective preventive vaccine that would protect the susceptible subjects against leishmaniasis and could also interrupt the transmission cycle of parasite [42,111,115].

Table 1

Risk factors of emergence and re-emergence leishmaniasis and their effects.

Risk factor	Effects
Organ transplant	Prescription immunosuppressive drugs/prevent T-cell activation and proliferation of parasite/reduce the defense mechanisms against intracellular parasites
Resistance of drugs	Widespread veterinary use of visceral leishmaniasis drugs/use antimonials in poor countries/increasing use of miltefosine for canine leishmaniasis
Travel to endemic areas	Increasing travel to tropical and subtropical countries (endemic area)/dog importation to non-endemic regions
Canine leishmaniasis	Transportation of dogs from regions of canine leishmaniasis endemicity to non-endemic area/infecting sandflies and venereal and transplacental transmission in dogs in non-endemic area
Leishmania/HIV co-infections	Prevalence of human immunodeficiency virus (HIV)/existing *Leishmania* in discarded syringes of addict persons/incidence visceral leishmaniasis in adults in addition to children
Climate change	Temperature and environmental variation on the abundances of the sandflies
Household level	Design and type of construction material of house/presence of domestic animals and proximity to forested areas
Social condition	Worse socio-economic status of people in the marginalized societies and proximity to water bodies, rubbishes, sewerage and farms and increasing exposure to sandfly/difficulties accessing treatment
Environmental factors	Role of vegetation area and climatic factors in proliferation and growth process of vector and reservoir/change in land coverage, deforestation, forest fragmentations, climatic variables and temperature
Vaccines	Increase in the disease incidence in immunocompromised subjects/the difficulties of epidemiological control

The need for safe prophylactic vaccines for human and dogs has became more important for the following reasons: 1) the drug resistance, 2) toxicity of chemotherapy, 3) the increase of the disease incidence in immunocompromised subjects 4) the difficulties of epidemiological control based upon sacrifice of seropositive dogs [116]. In spite of many vaccine candidates identified, the poorly developed biotechnology industry and lack of expert scientists in regulatory agencies of poor countries contribute to the continuous use of chemotherapy.

12. Conclusion

Leishmaniasis becomes an important and opportunistic parasitic disease after toxoplasmosis and cryptosporidiosis [64]. Risks of emergence or re-emergence of leishmaniasis are associated with several main scenarios. The exotic *Leishmania* species and strains are introduced via the increasing worldwide travelling of humans to endemic areas and importing domestic dogs [50,52]. The cutaneous and visceral leishmaniasis spread naturally in the endemic regions and are transmitted to neighboring temperate areas where there are vectors without disease [74,117]. The re-emergence of disease has increased in some areas such as Mediterranean region of Europe due to increase in *Leishmania*/HIV co-infections cases that have been observed during the recent decades (Table 1) [118]. However, for control and prevention, concise instruments and methodologies and expert physicians are necessary to develop surveillance and monitoring of each risk factor.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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