The increase in risk factors for leishmaniasis worldwide

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Abstract
Economic development leads to changing interactions between humans and their physical and biological environment. Worldwide patterns of human settlement in urban areas have led to developing countries to a rapid growth of mega-cities where facilities for housing, drinking-water and sanitation are inadequate, thus creating opportunities for the transmission of communicable diseases such as leishmaniasis. Increased risk factors are making leishmaniasis a growing public health concern for many countries around the world. Certain risk factors are new, while others previously known are becoming more significant. While some risk factors are related to a specific eco-epidemiological entity, others affect all forms of leishmaniasis. Risk factors are reviewed here by entity.

Keywords: leishmaniasis, Leishmania, epidemiology, risk factors, review.

Introduction
The paper describes the increase in risk factors for leishmaniasis worldwide in the context of 4 epidemiological situations. Some risk factors are clearly man-made, such as migration, deforestation, urbanization, or changes in the human host's susceptibility to infection such as immunosuppression and malnutrition. However, others are due to natural environmental changes. Human infection with Leishmania parasites is dependent on the ecological relation between human activity and reservoir systems. Any change in the environmental factors is likely to lead to a change in the distribution of the parasite (ASHFORD, 2000).

Leishmaniasis includes 4 major eco-epidemiological entities: zoonotic and anthropoontic visceral leishmaniasis, zoonotic and anthropoontic cutaneous leishmaniasis. In anthropoontic forms, humans are considered to be the sole source of infection for the sandfly vector; in zoonotic transmission cycles, animals are reservoirs which maintain and disseminate the Leishmania parasites.

Leishmaniasis is endemic in 88 countries (66 in the Old World) and 22 in the New World) with an estimated yearly incidence of 1-1.5 million cases of cutaneous leishmaniasis and 500,000 cases of visceral leishmaniasis. The population at risk is estimated at 350 million people, with an overall prevalence of 12 million (DEJEUX, 1996).

Currently, leishmaniasis has undoubtedly a wider geographical distribution than before; it is now reported in areas that were previously non-endemic such as western Upper Nile in southern Sudan. However, it is sometimes difficult to differentiate between a real and an artificial increase in incidence due to better awareness, better detection, improved reporting and/or improved accessibility to treatment. Trends revealing an increase are more frequently available than actual figures. Unfortunately, official data are often obtained through passive detection only and do not include data from private practitioners and non-governmental organizations.

Zoonotic cutaneous leishmaniasis (ZCL): risk factors
The main foci of ZCL are located in Latin America, south-western and central Asia and North Africa. In the New World, ZCL is due to Leishmania species belonging to L. (Viannia) braziliensis and L. (Leishmania) amazonensis complexes. Vectors are extremely diverse and animal reservoirs are small rodents or big mammals located mainly in primary forests, secondary forests and, less frequently, in peri-domestic areas. In the Old World, ZCL is due to L. (L.) major, the main vector is Phlebotomus papatasi and reservoirs are restricted to small rodents (gerbils) living in rural areas.

The main risk factors related to ZCL are: urbanization, deforestation and new settlements, domestication of the transmission cycle and agricultural development with the building of dams and new irrigation schemes leading to new crops.

In the New World a prime example is the city of Manaus, Amazonas State, Brazil, where planned and unplanned urbanization has taken place over the past 10 years with the construction of several new suburbs on the outskirts of the primary forest. The occupation of these newly urbanized areas brought many people into contact with the zoonotic cycle of L. (L.) guyanensis. As sylvatic reservoirs (mammals) and vectors (Lutzomyia umbratilis) maintain the L. guyanensis cycle in the remnants of the forest, a correlation between the risk of transmission to humans and the proximity of the forest has been clearly established (BARRETT & SENKA, 1989).

According to recent estimates, the world at present loses some 20 million hectares of forest annually, of which half is in developing countries. Unprecedented widespread deforestation in recent decades was supposed to reduce ZCL incidence but has in fact frequently led to a domestication of transmission throughout Latin America, increasing the per- and intra-domestic transmission. Continuing deforestation and spread of colonization, together with the biodiversity and adaptability of Leishmania parasites and sandflies, will result in this complex of diseases remaining a public health problem (WALSH et al., 1993) (Fig. 1).

In Andean countries massive migration from the high plateaux to the low tropical areas has been encouraged by the government and has led to numerous new settlements and much human activity. In situ natural reservoirs as well as human reservoirs such as entering the forest after sunset, hunting, and tree felling, which create frequent contacts with the sylvatic cycle, were the major risk factors for transmission (DEDET et al., 1989). However, as the primary forest close to settlements is progressively disappearing, the number of cases related to professional activities is decreasing accordingly. Nevertheless, transmission is simultaneously moving from sylvatic to peri-domestic areas. The plantation of new crops and the presence of rodents, attracted by the new source of food, have created a new and major risk of transmission in and around houses.

In Venezuela, the sharp increase in the number of ZCL cases in recent decades, from 600 per year in 1955 to 2600 per year in 1998, is believed to be partly due to the spread of L. braziliensis transmission from sylvatic to peri- and intra-domestic environment (FELICIANGELI, 1997).

In Brazil, the annual ZCL incidence has increased from 6000 in 1984 to 12,000 in 1985–86, 20,000 in 1998 and over 30,000 in 1999. In north-eastern Brazil a 10-fold increase of ZCL transmission has been reported during the past 12 years (BRANDAO-FILHO et al., 1999).

The records of the National Health Foundation (FUNASA) and the Ministry of Health show that ZCL incidence increased in Mato Grosso State from 2283

An increasing domestication of ZCL (L. braziliensis) transmission by either Lu. utricularia or Lu. intermedia has been reported from areas with a long history of colonization and relatively little remnant rain forest (Tuleczko, 1994; Rosales & Pacheco, 1994; Fuentes et al., 1996). However, while creating new problems such as a global increase of cases, a wider age distribution and frequent family cases, the gradual domestication of the transmission cycle has simultaneously increased the possibilities for vector control in and around houses.

In the Old World, urbanization is also a major risk factor: even residential suburbs located in the outskirts of the towns have intruded on the terrain that was formerly inhabited only by the sandfly vector, P. poppei, and the main reservoir, the rodent Progonomys obsetus. This situation has led to an increased transmission to humans as observed in some cities of eastern Saudi Arabia such as Hefat, Al Hassa (Peters, 1988).

Another important risk factor in the Old World is the building of dams, with corresponding new irrigation schemes and new crops, which in turn have frequently provoked a sharp change in the reproduction patterns of the animal reservoirs (giraffe) (Fig. 2). For example, following the construction of a large dam in Sidi Saad, central Tunisia, a large area was planted with Atriplex, a well-known food plant for sheep. Unfortunately, Atriplex is also a plant of the Chenoportocaceae family, the toxin source for Ps. obstetrix, the main animal reservoir for ZCL in this area. Consequently, there was a sudden and exponential increase in the giraffe population followed by an epidemic of ZCL (Ben Ammar et al., 1984; Ben Kamal et al., 1986). A similar situation occurred in Djeriss Zor, north-eastern Syria, where the geographical extension of irrigated areas near the Euphrates River led to an increase in the animal reservoir (Nasokia indica) population, followed by an epidemic of ZCL in the city and neighbouring villages. The records of the Ministry of Health indicate that there were 60 cases in 1993, 810 in 1994 and 2609 in 1995.

In Senegalese climate variability seen in extended rainy seasons as well as the implementation of counter-season cultures for export to Europe have helped to increase the availability of food for the giraffe reservoirs of ZCL and their patterns of reproduction. As a result, their number increased, followed by an unusually high number of ZCL human cases (Dejeux & Dedet, 1982).

Zoanotic visceral leishmaniasis (ZVL): risk factors

ZVL occurs mainly in Latin America, the Mediterranean Basin and Asia. The parasite is L. (L.) infantum, called L. infantum/chagasi in the New World. The name in the Old World is L. longipalpis but in the Old World several species are involved. Dogs are the main domestic animal reservoirs, foxes and jackals are the sylvatic ones. One of the main risk factors is again migration from rural to urban areas. A prime example is the massive migration which has been occurring in north-eastern Brazil where, due to climatic changes (drought) and socioeconomic factors, many have had to abandon their rural location and settle in the shanty towns of cities such as Fortaleza, Natal, João Pessoa, Sao Luis and more recently Salvador do Bahia. The records of the National Health Foundation (FUNASA) and the Ministry of Health show that ZVL global incidence has more than doubled from 2154 in 1998 to 3892 in 1999 but more specifically in north-eastern States, which report 82% of the total cases. The incidence has risen from 1840 in 1998 to 3260 in 1999. A possible association was observed between human infection and the presence of dogs in and around human dwellings (Cunha et al., 1995).

The same phenomenon of urbanization of ZVL has been reported in Colombia and Venezuela (Agullar et al., 1998). In poor suburbs, the sandfly vector is everywhere, dogs are very common, sanitary conditions are poor and malnutrition is a significant risk factor. Consequently, ZVL is increasing quickly among the population of shanty towns.

In southern Europe, ZVL was initially purely rural but is now becoming more and more suburban. Significant foci are located on the periphery of cities where dogs are present and small gardens encourage the presence of sandfly vectors (P. perniciosus and P. arcan). Because of its present alarming, the maximum northern latitude in Europe for sandfly survival could move further to the north and as a result more countries could become endemic for VL (Killkic Kandik, 1996).
Fig. 1. Slash and burn in the Amazonian Forest, Brazil.

Fig. 2. Irrigated crops in southern Morocco.

Fig. 3. Shanties with poor sanitary conditions, Kabul, Afghanistan.

Fig. 4. Visceral leishmaniasis case with malnutrition in India.

Fig. 5. Sandfly breeding sites, India, in cowsheds near houses.

Source of photographs: P. Desjeux.
and other immunosuppressive conditions increase the risk of Leishmania-infected people developing visceral illness. The overlapping geographical distribution of VL and AIDS is increasing owing to the spread of the AIDS pandemic from rural to urban areas on the one hand and the simultaneous spread of VL from rural to urban areas on the other. Thirty-three countries around the world have already reported cases of Leishmania/HIV co-infections. The appearance of Leishmania/HIV co-infections in southern Europe, considered as a real threat, has increased the incidence among the main population at risk: the intravenous drug users (IVDU). The cumulative number of cases in western Europe reported to WHO up to June 1998 was 1446 and up to December 1999: 1027. The cumulative immunosuppression (CD4 cells < 200/ mm$^3$) explains the frequency of new opportunistic infections in these patients (DESJEUX et al., 2000). Moreover, owing to the presence of numerous Leishmania parasites in organs outside the reticuloendothelial system such as peripheral blood, these patients become real reservoirs and sources of infection for the vector. Transmission among the IVDU through the syringes has also been demonstrated (ALVAR et al., 1997). WHO has recently set up a worldwide surveillance network which includes 28 institutions.

**Anthropogenic visceral leishmaniasis (AVL): risk factors**

AVL is primarily restricted to East Africa and the Indian subcontinent (Bangladesh, India and Nepal). The parasite is L. (L.) donovani; sandfly vectors are from several species. Priority for control is based on early detection followed by prompt treatment. As humans are the sole reservoir, unremitting cases and especially post-kala azar dermal leishmaniasis (PKDL) cases are those who house and disseminate the parasite. AVL epidemics are frequent with high death rates.

In East African countries, migration has played a major role in the dissemination of AVL and in the upsurge of severe epidemics. An accumulation of returnees, refugees and seasonal workers in areas where AVL is endemic, such as northern-western Ethiopia, represents a major risk. Moreover the temporary migration of people from non-endemic to endemic areas is a potentially high risk factor, as, on their return, these people can import the disease into a non-immune population. This has occurred in southern Sudan and has led to one of the most severe AVL epidemics, with 100,000 deaths among a population of less than one million (SIAMAN et al., 1996). Other risk factors such as civil war, malnutrition and disruption of health services have amplified the problem.

In the Indian subcontinent, cross-border migration is also an important risk factor for AVL dissemination. For example, there is a permanent movement of population between India (Bihar and Uttar Pradesh States) and Nepal (Morang District in Terai) and vice versa as AVL patients frequently cross the border looking for available drugs.

In Bangladesh, India and Nepal, where 50% of worldwide VL reported cases occur, socioeconomic and cultural factors are crucial and contribute greatly to the maintenance of the disease. AVL is associated with low socioeconomic status and AVL patients are among the poorest of the poor (in Bihar State of India 75% of VL patients have a daily income of < US$ 1 and 88% < US$ 2). Even when drugs are available, patients cannot afford the costs of transportation and hospitalization. In hyperendemic areas of India, no more than 9% of those affected by AVL seek medical advice for diagnosis or treatment; also women have less access to treatment than men. Owing to the lack of resources and health education, compliance for treatment is extremely low. Consequently, interruptions are frequent and the lack of response to the first-line drug, pentamidine antimonials, has been increasing sharply in India (in > 90% of the patients). Malnutrition, a consequence of poverty, is frequent and contributes to an increased severity of the disease by impairing the immune response (THAKUR, 2000) (Fig. 4). Environmental factors also play an important role, such as the proximity of houses to cattle sheds (78% within 15 m) and the presence of organic debris which facilitates the breeding sites (Fig. 5). Moreover, the numerous ponds and the high sub-soil water level keep the soil moist and the high humidity high; they thus encourage the survival of P. argentipes, the proven sandfly vector of L. donovani in India and Nepal (THAKUR, 2000). India is among the few places in the world where sandfly breeding sites have been clearly visible at the base of the walls of cowsheds.

In Bangladesh, a case-control study has shown that people living in villages protected from floods by the embankment of the river had an 18-times greater risk of developing AVL than those living outside the embankment. One explanation is that the embankment impedes the flood's ability to wash out organic remnants and facilitates the persistence of the breeding sites for sandflies' larvae (ISPAN, 1993).

In addition, cracks and crevices in the walls of houses made of mud and dried grass provide resting places for adult sandflies. However, the presence of cattle (cows and buffaloes) can be protective as these animals probably divert some sandflies from biting humans; the protective effect could be also related to the better nutritional status of cattle owners (C. Bern, personal communication).

**Conclusion**

There is a permanent worldwide risk of a resurgence of leishmaniasis not only because of the appearance of new risk factors but also because of a sudden and significant increase in previously identified ones. Permanent awareness based on continuous health education and strict surveillance including early warning systems are crucial to reduce this risk. New methodological advances, such as geographical information systems and remote sensing, can make a positive contribution to these efforts.

Some risk factors can be decreased by applying control strategies tailored to each eco-epidemiological entity, ensuring continuity, adjusting these strategies to any new environmental change and improving them through specific research. However, this requires a strong political and financial commitment from all stakeholders involved. Efficient multidisciplinary coordination between health and other governmental sectors, such as education, agriculture, water, forestry and other natural resources, is also crucial for the prevention and control of major risk factors.

**References**


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The book is available by direct order from Blackwell Science: fax +44 (0) 1861 206026, e-mail meddirect@blackwcl.co.uk

**Book Review**


The new fourth edition of Lecture Notes on Immunology has a new colour Figure giving an overview of the immune system, and new coverage of topics such as HIV and AIDS and susceptibility to immunological disease. This book is based on years of experience in teaching medical students, for whom the book was designed, and this bias is evident in the later chapters which contain useful clinical examples, but also some medical terms that might be less clear to biologists.

Part 1 covers immunity and the immune system. Chapter 1 gives a clear overview of the immune system. Interestingly, this is followed by antigen recognition, and lymphocytes and cytokines precede antibodies. Complement and phagocytes come next, and this section ends with mast cells, basophils and eosinophils, and killer cells. Part 2 is called immunopathology; there are good chapters on immunity to viruses, including 22 ways in which pathogens evade the immune response, and HIV infection and AIDS. Immunodeficiency disorders and allergies come next, and then chapters on real mechanisms of immunopathology, and susceptibility to immunological disease (with a very clear introduction to genotype nomenclature and how relative risks are calculated). The chapter on lymphoproliferative disease covers topics often not included in basic texts, and the book ends with a brief coverage of transplantation.

Overall, this book provides an introduction to immunology that is ideal for medical students. I have a few quibbles, mostly about Figures and terminology. It is a pity that I and I cannot be distinguished as this produces TT-1, not TT-1 (T independent type 1) antigen. Some of the labelling in the Figures is confusing—numbers (sometimes over the nucleus of the cell) can depict CD numbers in one Figure, or refer to footnotes in another. Sometimes the authors' attempts to make immunology simple have introduced unnecessary complexity—a Figure illustrating recognition and defence has the receptor labelled as recognition (R) and the cell labelled as defence (D), as if the lymphocytes, macrophages, mast cells and more were not enough for medical students. I have a few quibbles with the odd statement in the text too: can antigens really be divided into immunogens and tolerogens? And it is a pity that only one Figure is in colour, although this policy has presumably helped to keep the price down. But these are minor points; all in all, this is a remarkable concise and informative coverage of immunology, with a focus on human immune response and disease.

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