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REVIEW

Epidemiology of visceral leishmaniasis

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Paul D Ready

Disease Control Department, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

Abstract: *Leishmania* species are the causative agents of leishmaniasis, a neglected tropical disease. These parasitic protozoans are usually transmitted between vertebrate hosts by the bite of blood sucking female phlebotomine sand flies. This review focuses on the two parasites causing most human visceral leishmaniasis (VL), which leads to substantial health problems or death for up to 400,000 people per year. Except for travel cases, *Leishmania donovani* infections are restricted to the (sub-)tropics of Asia and Africa, where transmission is mostly anthroponotic, while *Leishmania infantum* occurs in the drier parts of Latin America as well as in the Mediterranean climate regions of the Old World, with the domestic dog serving as the main reservoir host. The prevalence of VL caused by *L. infantum* has been declining where living standards have improved. In contrast, infections of *L. donovani* continue to cause VL epidemics in rural areas on the Indian subcontinent and in East Africa. The current review compares and contrasts these continental differences and suggests priorities for basic and applied research that might improve VL control. Transmission cycles, pathogenesis, diagnosis, treatment and prognosis, prevention (including vector control), surveillance, transmission modeling, and international control efforts are all reviewed. Most case detection is passive, and so routine surveillance does not usually permit accurate assessments of any changes in the incidence of VL. Also, it is not usually possible to estimate the human inoculation rate of parasites by the sand fly vectors because of the limitations of survey methods. Consequently, transmission modeling rarely passes beyond the proof of principle stage, and yet it is required to help develop risk factor analysis for control programs. Anthroponotic VL should be susceptible to elimination by rapid case detection and treatment combined with local vector control, and one of the most important interventions may well be socioeconomic development.

Keywords: diagnosis, *Leishmania donovani*, *Leishmania infantum*, surveillance, transmission control, treatment

Introduction

Parasites, vectors, and disease forms

Species of the genus *Leishmania* (Kinetoplastida, Trypanosomatidae) are the causative organisms of leishmaniasis or leishmaniosis,[1] and these parasitic unicellular protozoans are usually transmitted between vertebrate hosts by the bite of blood sucking female phlebotomine sand flies (Diptera, Psychodidae).[2] Parasites of the subgenus *Sauroleishmania* are considered to be restricted to lizards, and most lizard-feeding sand flies do not usually bite humans. About 20 species of *Leishmania* infect mammals and many of them can cause human leishmaniasis. Motile infective forms of the parasite (metacyclic promastigotes with a long free flagellum) develop in the guts of competent

Correspondence: Paul D Ready
Disease Control Department, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK
Tel +44 20 7927 2164
Fax +44 20 7927 2918
Email paul.ready@lshtm.ac.uk

sand fly vectors, which inoculate them into mammalian skin. There they are ingested by cells of the mononuclear phagocyte system (formerly the reticuloendothelial system), transform into rounded amastigote forms with the loss of the free flagellum, and then can multiply in the phagolysosomes of recruited macrophages to cause a primary lesion at the site of the sand fly bite. Infections can spread, often via the lymphatic system, to cause secondary dermal lesions with forms and tissue tropisms in humans that show some parasite species specificity. Human cutaneous leishmaniasis is caused by most *Leishmania* species in the subgenus *Leishmania*, which occur in most subtropical and tropical regions (for example *Leishmania (Leishmania) major* from Africa and Asia, and *Leishmania (Leishmania) mexicana* from Central and South America), and by many species in the subgenus *Viannia*, which are restricted to Latin America (for example *Leishmania (Viannia) brasiliensis*). Any parasite causing cutaneous leishmaniasis can visceralize (for example *Leishmania (Leishmania) tropica*, which normally causes Oriental sore), but only two species of the subgenus *Leishmania* routinely do so, and these are the causative agents of most human visceral leishmaniasis (VL) worldwide.

Objectives

This review focuses on the two most important causative agents of VL, namely *Leishmania (Leishmania) donovani* and *Leishmania (Leishmania) infantum*, the ones responsible for causing substantial health problems in up to 400,000 people and up to 40,000 deaths per year.[1,3] They are not always well distinguished in the medical literature, being closely-related members of the *L. donovani* species complex,[4,5] but this disguises some important epidemiological differences. Except for travel cases,[1] *L. donovani* is found only in the Old World, where it is notoriously associated with VL (kala-azar or black death) of the rural poor in the northeast of the Indian subcontinent and with VL of displaced persons in East Africa.[1,6] Most transmission is believed to be anthroponotic, from human to human, and this contrasts with the zoonotic transmission of *L. infantum*, from canine reservoir hosts to humans, not only in the Mediterranean region where it may have originated, but also in many of the drier regions of Latin America where it was probably introduced historically.[5]

The incidence of VL associated with the transmission of *L. infantum* has been declining in many foci where living standards have improved; but, in contrast, VL epidemics continue to kill thousands of people infected with *L. donovani* on the Indian subcontinent and in East Africa. Therefore, the main aims of the current review are to compare and contrast these continental differences, and to suggest priorities for basic and applied research that might improve VL control. Leishmaniasis is a neglected tropical disease,[1,6] and it is possible that the recent increases in the direct or indirect funding of applied research will not be sustained unless research priorities are well founded.[1,2]

Methods: literature search

This review is based on expert knowledge, wide-ranging reviews published in 2010–2013,[1,2,6] and other, sometimes more recent, literature found in PubMed by using the search terms "visceral leishmaniasis", "kala-azar", "*Leishmania donovani*", "*Leishmania infantum*", and key words in the following section titles.

Transmission cycles: geographical variation in eco-epidemiology

The key elements are set out in Table 1. VL caused by *L. donovani* is usually considered to be an anthroponosis,[2] but this should be challenged where control fails. Zoonotic transmission has been suspected because parasites or circulating antibodies have been detected in domestic animals on the Indian subcontinent[7] and in the mongoose and other wild mammals in East Africa.[1] The landscape epidemiology is very different on the two continents.[2] *Phlebotomus (Euphlebotomus) argentipes* is the vector in humid (sub-) tropical regions on the Indian subcontinent, where it is attracted to domestic cattle and water buffalo kept in and around rural villages near the flood plain of the River Ganges, in Sri Lanka and perhaps in Bhutan.[8] In contrast, *Phlebotomus (Larroussius) orientalis* and *Phlebotomus (Synphlebotomus)* species are the incriminated vectors in two distinctive bioclimatic regions of East Africa,[2,9] which share a savanna landscape and transmission habitats both inside and outside rural villages. Most foci on the Indian subcontinent are in long-established villages with sedentary populations, whereas migratory populations are also at high risk in East Africa, including cattle herdsmen and villagers displaced by drought and warfare. Post-kala-azar dermal leishmaniasis (PKDL) is characterized by lesions rich in parasites, and these might favor anthroponotic transmission in Africa as well as in India.[3]

VL caused by *L. infantum* is usually considered to be a zoonosis, although congenital infections have been reported even in Europe.[10] Most foci in the Old World have a Mediterranean climate and sand fly vectors that can hibernate – usually *Phlebotomus (Larroussius)* species – and so there is a risk of the disease spreading from southern

Table 1 Disease types and transmission cycles of visceral leishmaniasis worldwide

Causative parasites	Disease	Countries (suspected)	Landscapes	Reservoir hosts	Incriminated vector[a]	Suspected vector[a]
L. donovani	VL, DL, CL	Northeast India, Nepal, Bangladesh, (Bhutan), Sri Lanka	Rural, peri-domestic	Human anthroponosis	*P. (Eu.) argentipes*	None
L. donovani	VL	People's Republic of China	Rural, peri-domestic	Unknown	None	*P. (Pa.) alexandri*; *P. (Ad.)* species
L. donovani[b]	VL, DL	Sudan, Ethiopia, (Chad), (Yemen)	Rural, *Acacia–Balanites* forest	Human anthroponosis; possibly mongoose?	*P. (La.) orientalis*	None
L. donovani[b]	VL, DL	Sudan, Ethiopia, Kenya, (Uganda)	Rural, savanna termite mounds	human anthroponosis?	*P. (Sy.) martini*	*P. (Sy.) celiae*, *P. (Sy.) vansomerenae*
L. infantum	VL, CL	Med Europe, North Africa, Southwest Asia, People's Republic of China	Rural, peri-domestic	Domestic dog, wild canids, domestic cat	*P. (La.) ariasi*, *perniciosus*	*P. (La.)* species; *P.(Ad.)* species
L. infantum[c]	VL, CL	Latin America: not Peru or Guianas	Rural, peri-domestic	Domestic dog, wild canids	*Lu. (L.) longipalpis*	*Lu. (Lu.)* species; *Lu. (Pf.) evansi*

Notes: [a]Vectorial status based on number of criteria met;[2] [b]some strains formerly named *L. archibaldi*; [c]sometimes named *L. chagasi*.
Abbreviations: *Ad.*, *Adlerius*; CL, cutaneous leishmaniasis; DL, diffuse or dermal leishmanoid leishmaniasis; *Eu.*, *Euphlebotomus*; *L.*, *Leishmania*; *La.*, *Larroussius*; *Lu.*, *Lutzomyia*; Med, Mediterranean; *P.*, *Phlebotomus*; *Pa.*, *Paraphlebotomus*; *Pf.*, *Pifanomyia*; *Sy.*, *Synphlebotomus*; VL, visceral leishmaniasis.

to northern Europe with climate change.[2] All vectors of *Leishmania* in the New World are *Lutzomyia* species, but only one of these is believed to be an important widespread vector of *L. infantum*. Diverse populations of *Lutzomyia (Lutzomyia) longipalpis* are abundant peridomestically in the yards of rural villages and the low-rise suburbs and shanty towns of many of the drier tropical regions of Latin America, and, unlike most sand fly species, they are competent to transmit a wide range of *Leishmania* species[2] including *L. infantum*. This parasite is believed to have been introduced in domestic dogs from Portugal and Spain during the last 500 years.[5]

Molecular taxonomy has not identified *Leishmania archibaldi* as a species separate from *L. donovani* in Africa or *Leishmania chagasi* as a species separate from *L. infantum* in Latin America, and the diverse groupings of the strains of *L. donovani* and *L. infantum* identified by neutral (or nonadaptive) genetic markers[4,5] have not been associated with phenotypes of medical importance. Similarly, there is little or no evidence that the diverse forms of the vectors *P. argentipes* and *Lu. longipalpis*, identified as cryptic sibling species based on neutral genetic markers, have distinctive epidemiological roles.[2]

Pathogenesis

The incubation period is usually from 2 weeks to 18 months,[11] with gross inflammatory reactions within the viscera often developing 2–8 months after infection and any initial skin lesions, but VL symptoms can take years to appear.[12] The disease is progressive and a symptomatic infection that is untreated is generally fatal,[12] with a mortality rate of 75%–95%.[11] Death usually occurs within 2 years, although spontaneous cures may occur.[11] Parasites proliferate wherever there are cells of the mononuclear phagocyte system, most often in macrophages. These are most abundant in the spleen and liver and, consequently, infection leads to an enlargement of both of these organs.[11–13] Bone marrow cells become infected, and patients develop pancytopenia (namely, depressed production of red blood cells, white cells, and platelets) and immunosuppression, making them susceptible to superinfections.[11,13]

PKDL or dermal leishmanoid[11] is a condition in which dermal lesions can be heavily parasitized in a subset of patients successfully treated for VL, and it occurs mainly in India and Sudan in patients infected by *L. donovani*.[13,14] They remain asymptomatic for months to years and then develop a progressive proliferation of parasites within the skin, giving rise to diffuse macular, maculopapular, or nodular lesions.[13] Lesions appear anywhere on the body, but they often occur on the face.[12]

Diagnosis

Clinical symptoms and microscopic diagnosis

Most infections are diagnosed clinically. The patient has an irregular fever, anemia, and leukopenia; hepatosplenomegaly and bone marrow suppression are characteristic (see above); and HIV coinfections often produce atypical presentations.[11–13] Rates of PKDL vary regionally, arising within 6 months in up to 50% of treated VL patients in parts of Sudan, but within 2–3 years in only approximately 5%–10% of patients in India.[12–14]

Parasites are usually identified to the genus *Leishmania* by light microscopy.[11,12] The amastigote form is usually detected microscopically after Giemsa staining. Blood examinations are the easiest to perform, but frequently there are very few circulating parasitized cells in buffy coat films.[11,12] Spleen aspirates are a rich source of parasites,[11] but biopsy should be performed only by trained personnel because there is the risk of rupture or bleeding.[12] Liver biopsy is safer, although finding amastigotes is certain only in very heavy infections.[11,12] Bone marrow aspiration (from the sternum) is frequently used,[11] but it is a specialized technique with lower sensitivity.[12] Detection of parasites in nodular forms of PKDL is easier than in macular forms.[13,14] Inoculation of biopsy materials into culture media or laboratory rodents can be sensitive but slow.[1]

Biochemical diagnosis

Until recently, isoenzyme analysis has been the gold-standard method to identify both phylogenetic species and strains (or zymodemes) of *Leishmania*, which usually reproduce asexually.[1,5] However, it requires growing many parasites, and promastigote cultures can fail because of contaminating bacteria and fungi, or strain-specific temperature and nutrient requirements.

Serological diagnosis

Serological tests provide the most widely used indirect methods of diagnosis.[1] The indirect fluorescence antibody test, the enzyme-linked immunosorbent assay, and the Western blot[12] are widely used in Africa, Asia, Europe, and Latin America, but they all require equipment that has not been optimized for field conditions[12] and there is often a lack of standardized protocols, antigens, and other reagents.[15] The Montenegro or leishmanin skin test has the same drawbacks and may not even be specific to *Leishmania* species.[1] It is negative in active kala-azar, and then usually becomes positive within 2 months after successful treatment.[11]

In contrast, two other types of tests have proved to have high sensitivity and specificity, at least regionally, and have translated to peripheral health centres.[12,16] These are the direct agglutination test and immunochromatographic tests (ICTs) using the recombinant (r) K39 antigen, which is encoded by a fragment of a kinesin-related gene. The rK39 ICTs have the advantage of using convenient formats (often a dipstick) and a standardized recombinant antigen. However, the kinesin-related gene fragment derives from a Brazilian strain of *L. infantum*, and the kinesin genetic diversity among strains of *L. donovani* in East Africa and between there and Asia is extensive enough to influence the performance of the rK39 ICTs.[17] Even in Brazil, the diagnostic performance of rK39 ICTs was found to be only reasonable for confirmation of infection in suspected cases of canine VL, and the sensitivity to detect infected dogs was too low for large-scale epidemiological studies and operational control programs.[18]

Serological tests have limitations because some antibodies are detectable years after cure.[12] A latex agglutination test detecting a heat-stable carbohydrate in the urine of VL patients has promise as a field-adapted antigen test; it showed good specificity but low-moderate sensitivity.[19]

Molecular diagnosis

The polymerase chain reaction is more sensitive than microscopic examination and, therefore, it is often the primary test in referral hospitals and research centers, with quantitative polymerase chain reaction permitting accurate diagnosis using venous blood samples instead of bone marrow aspirates.[12,16] *Leishmania* species and their strains causing VL can now be identified by the comparative DNA sequence analysis of five of the polymorphic metabolic enzymes routinely used for isoenzyme analysis,[20] by restriction fragment length polymorphism analysis of the heat-shock 70 gene,[21] and by microsatellite DNA analysis.[4]

Conclusion: integrated diagnosis

Molecular tests in hospitals and research centers permit strain identification and diagnosis using venous blood samples. However, many primary health teams rely on clinical symptoms together with rK39 ICTs for rapid diagnosis prior to chemotherapy. A combination of molecular and serological tests demonstrated significant numbers of asymptomatic infections in endemic areas of Bihar State, India.[16] The selection of the best combinations of rapid diagnostic tests might be improved by meta-analyses of Phase IV studies performed in target populations, and Bayesian methods could improve estimates of sensitivity and specificity.[22]

Treatment and prognosis

Travel cases, indigenous cases, and health care

Few travel cases of VL are usually recorded in North America and Europe,[1,9,23] and a recent review alerts clinicians to the range of clinical syndromes, treatments, and prognoses, including the development of PKDL seen in patients with HIV/AIDS undergoing highly active antiretroviral therapy (HAART).[13] Treatment and prognosis for indigenous cases are determined by regional health care practices and

budgets, with fewer uncomplicated cases being resolved in East Africa and India than in southern Europe and Brazil.[1,6] Malnutrition is one of the important risk factors for VL, and a fall in disease incidence in southern Europe during the last 50 years coincided with better nutrition.[1,6]

Drug resistance and alternatives to pentavalent antimonials

Much research is focused on the resistance mechanism to pentavalent antimonials, which have been the standard drugs despite their toxicity.[12] They are now nearly obsolete in Bihar State, India, because of drug resistance, but sodium stibogluconate (Pentostam [GlaxoSmithKline UK Ltd] and a generic brand) and meglumine antimoniate (Glucantime; Sanofi S.A., Paris, France) are useful elsewhere.

AmBisome (Gilead, Foster, CA, USA), a liposome formulation of amphotericin B, is now a standard treatment for VL, especially against *L. donovani* in Bihar, and a single dose treatment has been successfully trialed in rural public hospitals in Bangladesh (http://www.who.int/tdr/news/2013). However, clinical studies indicate that it is less effective against *L. donovani* in East Africa and *L. infantum* in Latin America and, therefore, further research is required.[12] Similarly, paromomycin is efficacious in the Indian subcontinent, but not in East Africa.[12] Miltefosine, a phospholipid derivative, provides an oral treatment for VL, and it has been used in the VL Elimination Programme for the Indian Subcontinent.[12] However, it is potentially teratogenic, requires a long oral treatment (28 days) that can lead to poor compliance and relapses, and drug resistance is a concern.[12]

Novel drug combinations

Drug combinations can shorten therapy as well as reducing toxicities and the selection of resistant mutations, and so there have been some promising Phase III trials of combinations of AmBisome, miltefosine, and paromomycin in India and of sodium stibogluconate with paromomycin in Sudan.[12] Barrett and Croft[12] noted that new drugs might target parasites in the low pH phagolysosomes of macrophages.

Prevention

Vaccine development

Vaccination is probably the best way of controlling a rural vector-borne disease like leishmaniasis.[1,2,24] Unfortunately, no vaccine is likely to be deployed in the short-term against VL, partly because of the complexity of the cellular immune response and the immunomodulatory effects of antigens from sand fly saliva.[1,2] Salivary peptides could also be vaccine components.[2,24] Vaccines against canine leishmaniasis have been trialed in Brazil and Europe with mixed results,[1,10,18] and this could be an effective way of reducing the transmission of *L. infantum* to people.

Vector control

Unlike for mosquitoes, source reduction is not an option because the terrestrial sites of sand fly larvae are largely unknown. The spraying of residual insecticides, often dichlorodiphenyltrichloroethane (DDT), to control *Anopheles* mosquitoes was a key component of the malaria eradication campaign of the mid-20th century, and it is credited with having greatly depressed the transmission of *L. donovani* in India and *L. infantum* in southern Europe by the untargeted killing of peri-domestic adult sand flies.[1,25] VL resurgence followed the cessation of DDT spraying, but this could have been coincidental. Since then, a range of vector control approaches have been tested, but there is little evidence that the results of experimental trials have informed public health approaches.

Indoor residual spraying with DDT or pyrethroids has been the mainstay of VL vector control on the Indian subcontinent and in Brazil,[1,25,26] but it is unknown whether or not the insecticide reaches or remains for long on the surfaces favored by the adults of *P. argentipes* and *Lu. longipalpis*, many of which may spend more time on cattle or chickens, respectively, than on the inner or outer walls of houses and animal shelters.[27,28] Insecticide-treated (mosquito) nets have been tested on the Indian subcontinent and in East Africa,[8] occasionally as long-lasting insecticidal nets,[26,29] and sometimes they have been shown to be better than indoor residual spraying for reducing the local abundance of vectors, as in Bangladesh.[30] Little or no insecticide resistance has been detected in VL foci,[1] and this is consistent with only a small fraction of the vector populations being exposed to insecticides.

Insecticidal sprays, roll-ons, and collars are widely used for protecting dogs in southern Europe and the wealthier areas of Latin America, but this may provide only individual protection, not the community-wide control that would reduce transmission from dogs to humans.[27] N, N-diethyl-meta-toluamide (DEET) has been the repellent of choice for the individual protection of people, and cheaper natural products have started to be tested.[2] Integrated control has occasionally identified avenues of applied research that should be further explored, including environmental modification by plastering the walls of village houses with mud or lime to reduce the number of sand fly resting sites in VL foci on the Indian subcontinent.[25]

Surveillance, transmission modeling, risk factors, and predictive modeling

Routine surveillance is usually too insensitive to assess accurately any changes in the prevalence or incidence of VL,[15,27] with most case detection being passive.[6] Also, it is not usually possible to estimate the human inoculation rate of parasites by the sand fly vectors[2] because most sand fly surveys use light and sticky traps that do not target host-seeking female flies, and the reports often mention only the relative abundances of species without distinguishing males from females.[25,26] Consequently, transmission modeling is not commonplace, although research projects have provided proofs of principle models for VL transmission in Asia[31] and for canine leishmaniasis in Europe.[32] Better transmission modeling is required to underpin risk factor analysis, which is more likely to be applied in control programs. Risk factor analysis has been carried out for foci on the Indian subcontinent,[28] in Ethiopia,[33] and in Brazil,[27] frequently identifying poverty, malnutrition, and proximity of parasite or vector hosts to dwellings as high risk factors. Spatial modeling has usually only predicted the presence or absence of disease and vectors based on rather broad measures of climate and environmental variation,[2,15,32] providing resolution that is little better than descriptive landscape epidemiology.

Prevalence and incidence

This topic is considered late in this review because it depends on an understanding of the different disease forms associated with geographically-isolated transmission cycles and regional differences in surveillance. The disease burden will strongly influence the regions chosen for sustainable integrated control of VL, which is discussed in the next section.

A major review of the incidence of leishmaniasis worldwide was led by the World Health Organisation (WHO) Leishmaniasis Control Programme, and the findings were published in 2012.[6] This review concluded that leishmaniasis had often been ignored in discussions of tropical disease priorities because of the paucity of current incidence data. Disease burden is often expressed as disability-adjusted life years, but the accuracy of this measure depends on the reliability of the incidence, duration, severity, and mortality data for a condition, which are difficult to extrapolate from official data sources because of the focal distribution of leishmaniasis in remote locations.[6] The 2012 review concluded that the majority of VL deaths are unrecorded, and case fatality rates may be 10%–20% even with treatment access. However, the authors did produce regional tables of reported and estimated VL incidence based on the expert opinions of national program managers and professionals;[6] these are summarized in Table 2. Among the few published empirical

Table 2 Reported and estimated incidence of VL worldwide

Region	Country	Reported cases per annum	Report years	Estimated annual incidence
America	Brazil	3,481	2003–2007	4,200–6,300
	Others	187	2004–2008	300–500
	Total	3,668		4,500–6,800
Mediterranean	Spain, Italy, Albania	365	2003–2008	440–660
	Morocco, Algeria, Tunisia	352	2004–2008	540–970
	Others	158	2002–2008	220–370
	Total	875		1,200–2,000
East Africa	Sudan	3,742	2005–2009	15,700–30,300
	South Sudan	1,756	2004–2008	7,400–14,200
	Ethiopia	1,860	2004–2008	3,700–7,400
	Somalia	679	2009	1,400–2,700
	Others	535	2004–2008	1,200–1,400
	Total	8,569		29,400–56,000
Middle East to Central Asia	Iraq	1,711	2004–2008	3,400–6,800
	People's Republic of China	378	2004–2008	760–1,500
	Others	407	2004–2008	840–1,700
	Total	2,496		5,000–10,000
Indian subcontinent and Southeast Asia	India	34,918	2004–2008	146,700–282,800
	Bangladesh	6,224	2004–2008	12,400–24,900
	Nepal	1,477	2004–2008	3,000–5,900
	Others	4	2005–2010	21–40
	Total	42,623		162,121–313,640

Note: Alvar J, Vélez ID, Bern C, et al. Leishmaniasis worldwide and global estimates of its incidence. *PLoS ONE*. 2012;7:e35671.[6]
Abbreviation: VL, visceral leishmaniasis.

assessments of under-reporting in surveillance data, two from Bihar, India, compared VL case numbers estimated by house-to-house surveys with official data, which were 4.2-fold and 8.1-fold lower.[6]

The incidence of VL associated with the transmission of *L. infantum* by sand flies has been declining in many foci where living standards have improved, with better nutrition believed to mitigate the progression of debilitating or fatal infantile visceral leishmaniasis.[6] Also, there has been a decline or stabilization in the incidence of VL resulting from the transmission of *L. infantum* by needles or blood transfusion through better awareness and drugs to combat coinfecting HIV.[6]

International collaboration for sustainable integrated control of VL

The paradigm for controlling vector-borne diseases should be prevention at source using an integrated set of intervention measures,[34] not detection and response. There are many lessons to be learned from malaria control,[35] including the realization that the aim of sand fly control should not be to reduce the relative abundance of a vector species, but to reduce the contact of its blood feeding females with humans and to reduce their lifespans so that fewer survive long enough to transmit *Leishmania* parasites.

The VL Elimination Programme for the Indian Subcontinent was set up as an international collaboration between Bangladesh, India, and Nepal in 2005.[36] This required a clear set of aims and objectives, which prompted the standardization of experimental trials aided by European and North American researchers and funding agencies. There continues to be a need to assess by appropriate randomized trials the efficacy of some of the common intervention tools, including the residual activity of insecticides on bednets.[37]

Conclusion: priorities for applied and basic research

It has been argued that leishmaniasis research has focused too much on descriptive eco-epidemiology at the expense of transmission modeling and integrated control.[2] For example, it does not really matter whether the causative agents of VL are classified by molecular taxonomists as two species (*L. donovani* and *L. infantum*) or as four species (with *L. archibaldi* and *L. chagasi* also recognized), if these taxa are not associated with specific sets of symptoms, treatments, and interventions in each endemic region. It is surely more important to understand what determines the distributions of parasite phenotypes of importance for treatment and control within each regional anthroponosis or zoonosis. Basic research on drug resistance and development underpins the applied aims of chemotherapy, but priorities are less clear for basic research for vector control and vaccine development. Predictive spatiotemporal modeling of VL should focus more on where and when disease incidence is likely to change, not on the presence or absence of species of parasites and vectors. A recent review of preventative measures against human leishmaniasis infection concluded that more research is needed to investigate human infection as the primary outcome measure, as opposed to intermediate surrogate markers.[38]

VL on the Indian subcontinent and in many African foci is believed to be an anthroponotic disease, and, therefore, it should be susceptible to elimination by rapid case detection and treatment combined with local vector control. However diagnosis of early infections can be problematic.[6,17,19] The economic cost benefits of control are being explored on both continents,[39,40] and one of the most important interventions against VL may well be socioeconomic development, as it is for malaria.[41] Applied research on leishmaniasis must continue to be prioritized in order to ensure that it continues to benefit directly or indirectly from the support of the Bill and Melinda Gates Foundation (http://www.gatesfoundation.org), Drugs for Neglected Diseases initiative (http://www.dndi.org), Médecins Sans Frontières (http://www.msf.org), TDR-World Health Organization (http://www.who.int/tdr), and other bodies. The combat against VL might be assisted by the proposal to combine groups already working on chemotherapy into a single organization, the VL Global R&D and Access Initiative.[42]

Disclosure

The author reports no conflicts of interest in this work.

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