OLD WORLD LEISHMANIASIS - A REVIEW

AJU-AMEH, Onyawoibi Celina and AGWALE, Simon Magaji
Laboratory of Leishmaniasis and AIDS, Department of Zoology, University of Jos, Jos, Plateau State, Nigeria.

Corresponding Author: Aju-Ameh, O. C. Department of Zoology, University of Jos, Jos, Plateau State, Nigeria. **Email:** celinaaju@gmail.com **Phone**: +234 8023125612

ABSTRACT

The leishmaniasis is a globally widespread parasitic diseases of multifaceted clinical manifestations (cutaneous, mucocutneous, diffuse cutaneous and visceral). They are caused by several species belonging to the genus Leishmania - a kinetoplastic flagellate transmitted exclusively by the bite of the female of the phlebotomine sandfly. The sandfly becomes infected when taking blood from reservoir hosts, which includes man or domestic and wild animals. Most leishmaniasis is zoonotic and humans are infected only accidentally when exposed to the natural transmission cycle. However in the anthroponotic forms man is the reservoir host. A Leishmania species in a given area is usually maintained by single reservoir host even if other mammals may sometimes be infected. Identification of the reservoir is a prerequisite for the selection and application of selective control methods. Leishmaniasis poses a public health threat to the people of any nation under its debilitating effects, thus the need for prompt and adequate attention. As at the time of this write up no effective vaccine has been developed to date, but results of vaccine trials are encouraging. For now the more conventional methods of control such as vector reduction, elimination of infected reservoirs, personal protection, surveillance, and treatment is the only option.

Keywords: *Leishmania,* Old World, Visceral, Cutaneous, Sandflies, Review

INTRODUCTION

The Leishmaniasis is a group of parasitic diseases with varied clinical manifestations in different parts of the old world. The parasites are several species of protozoa belonging to the genus *Leishmania*. These *Leishmania* species are kinetoplastic flagellates that are transmitted to humans by the bites of sandflies of the genus *Phlebotomus,* Diptera; Psychodidae and Phlebotominae in the old world. *Leishmania* exist in mammals as an obligate intracellular parasite. The major forms of leishmaniasis are cutaneous, mucosal and visceral and these result from multiplication of the parasites in the macrophages of the skin, oronasopharynx and visceral reticuloendothelial systems, respectively. Among the protozoan disease of humans, leishmaniasis rank second only to malaria in medical and economic importance in endemic regions. Although there are no accurate data on the incidence and prevalence of leishmaniasis, according to WHO (1990), it has been estimated that at least 400,000 new cases of leishmaniasis occur every year. This number is considered to be greatly under estimated, and by extrapolation using available data may be closer to 1.5 - 2 million cases per year. Development projects in many endemic areas of the old world may introduce non-immune individuals into the region which can result in an alarming number of new infections.

The more benign self healing lesions of cutaneous leishmaniasis caused by *L. major* and *L. tropica* limit their public health importance, but the working time lost and costs of in treatment can be significant socio-economically.

The cruel disfiguring type of diffuse cutaneous leishmaniasis, although infrequent, constitutes important social and health problems. The disease affects children and the productive age group of the population. It is fatal when left untreated and unfortunately most communities affected are usually furthest away from government infrastructures, including schools and health care delivery centers because they are mostly in remote areas. They therefore tend to receive minimal attention from responsible authorities, especially in the case of cutaneous leishmaniasis for which morbidity, rather than mortality in usually the rule. In the light of the above this review was undertaken to critical look at old world leishmaniasis. The "old world" consists of Afro-Eurasia (Africa, Europe and Asia), regarded as the part of the world known to Europeans before European contact with the Americas (Wikipedia, 2014a).

MATERIALS AND METHODS

A comprehensive internet search of literature on old world leishmaniasis was undertaken using Google Search. Literatures recovered were analyzed in pros and relevant cited tables adopted.

RESULTS AND DISCUSSION

Biological and Molecular Characteristics of Leishmania Species

Parasitic protozoa of the genus *Leishmania* (Kinetoplastida: Trypanosomatidae) are a biologically diverse group of micro-organisms. They posses a unique mitochondrial or Kinetoplastic DNA (KDNA) and appear to be among the most highly diverged eukaryotic cells known. In nature, all *Leishmania* species are transmitted by the bite of infected phlebotomine sandflies (Diptera: Psychodidae). These parasites have two distinct stages in their life cycle; a motile flagellated promastigote stage that lives extracellularly within the alimentary tract of the sand fly vector and a non-motile amastigote state that resides within macrophages of the vertebrate host (Grimaldi and Tesh, 1993).

Sophisticated laboratory models involving well-characterized cell life, cloned parasites, genetically defined animals and colony-reared sand flies are now been used for studying experimental leishmaniasis (Qureshi *et al.,* 1996). Many of these parasites can also be grown *in vitro* in defined or semi defined liquid media as either promastigotes or axenic amastigotes. Consequently, considerable progress in defining the molecular and biological characteristics of these micro-organism as well as the immunological mechanisms involved in host protection are being presently done.

The following aspects of parasite virulence are now recognized: (i) infectivity varies even among clones of a given *Leishmania* strain, (ii) amastigotes are generally more infective than promastigotes, (iii) actively motile promastigotes in the stationary phase of growth are more infective than the longer and slender forms in log-phase growth, (iv) promastigotes often lose infectivity after long periods of in vitro cultivation, (v) changes in virulence that are observed in different growth phases or after prolonged cultivation parallel the development of biochemical and antigenic changes in the parasites and (vi) during the differentiation process from infective (metacyclic) promastigote to amastigote, there is an increase in the expression of certain genes that probably pre-adapts the parasite to survive in the hostile environment of the macrophage phagolysosomes (Grimaldi and Tesh, 1993; Santos-Gomes and Abranches, 1996).

Leishmania species multiply asexually by binary fission in both their invertebrate and vertebrate hosts; however, a sexual reproduction may also exist in this genus. Although it is generally believed that *Leishmania* species depend primarily on mutation for their variability, there is recent evidence of hybrid formation, gene amplification detection, and possible genetic recombination may also be involved in the evolution of these parasites.

Genetic studies have revealed many interesting aspects of the molecular biology of leishmanial parasites (Grimaldi and Tesh, 1993). A number of genes are potential drug or vaccine targets and they appear to be responsible for parasite virulence of developmentally regulated adaptation in the vertebrate host. The *Leishmania* genome is relatively, small, approximately 50,000kb and is diploid at most loci. The various *Leishmania* species contain 25 to 30 small chromosomes that are readily separated by pulsed field electrophoresis. Molecular karyotypic analyses among leishmanial stocks have demonstrated chromosome size polymorphisms and a high degree of plasticity in the genome. In addition, current data suggest that a variety of chromosomal alteration involving amplification of certain genes may be a common characteristic among *Leishmania* species. Several repeated gene families also have been demonstrated among Leishmania species. These and other examples of gene amplification may play an important role in shaping the parasite's genome and providing new substrates for its evolution (Grimaldi and Tesh, 1993).

Taxonomic Status of the Old Word *Leishmania* Parasites

Since the discovery of the genus *Leishmania* taxonomic studies of leishmanial isolates indicated a tremendous diversity within the genus. Until recently, the taxonomy of *Leishmania* was based largely on clinical and epidemic logical features of the diseases that they produce in humans, and on biological characteristics of the parasites in laboratory animals and sandflies. But these criteria are no longer relied upon because the features tend to overlap a great deal. As a result, this system of classification has now been supplemented by a variety of biochemical, immunologic and molecular biology methods. Agwale (1994) reported that the old concept of three of four species of *Leishmania* each causing a separate clinical disease, has been disproved, at least 20 species of *Leishmania* are pathogenic for humans. There is no absolute correlation between *Leishmania* taxon and the clinical disease produced. This diversity has vast implications for the control and treatment of the disease and requires the identification of the parasite in each focus. There are about 35 species in this genus. The status of several of these species is disputed and for this reason the final number may differ from this estimate. Briefly Wikipedia (2014b) reported that there are (at least) three subgenera: *Leishmania*, *Sauroleishmania* and *Viannia* (Table 1). The division into the two subgenera (*Leishmania* and *Viannia*) was made by Lainson and Shaw (1987) on the basis of their location within the insect gut. The species in the *Viannia* subgenus develop in the hind gut: *L. (V.) braziliensis* has been proposed as the type species for this subgenus, this division has been confirmed by all subsequent studies.

Host Response and Immunity to Leishmaniasis Infection

The evolution, outcome and character of an established infection is largely determined by the immune response of the host, that is the breakdown of host protective cellular immune responses; and the ability of some strains of *Leishmania* species to resist the microbicidal effect of activated macrophages. *Leishmania* species are flagellates which live within the cell of various tissues of the host. As obligate intracellular parasite, they have evolved complex strategies for evading host defence mechanisms that occur before (the complement-mediated killing process), during (the toxic effect of oxygen metabolites produced during the macrophage-induced respiratory burst), and after the non oxidative killing effect of lysosomal hydrolases or nitric oxide from L-arginine) entry into host cells. Studies of several membrane surface enzymes and other macromolecules synthesized by leishmanial parasites have provided new insights about their functions in the establishment of infection. However, the various mechanisms developed by leishmanial parasites for evading host defenses are still not well defined. New evidence suggests that parasite virulence determinants which are responsible for evasion of such defenses are often developmentally regulated, allowing these organisms to survive in

Table 1: Species checklist for Leishmania, Sauroleishmania and Viannia

Subgenus Leishmania	Subgenus Sauroleishmania	Subgenus Viannia
Leishmania aethiopica	*Leishmania adleri*	*Leishmania braziliensis*
Leishmania amazonensis	*Leishmania agamae*	*Leishmania colombiensis*
Leishmania arabica	*Leishmania ceramodactyli*	*Leishmania equatorensis*
Leishmania donovani	*Leishmania deanei*	*Leishmania guyanensis*
Leishmania enrietti	*Leishmania garnhami*	*Leishmania lainsoni*
Leishmania gerbilli	*Leishmania gulikae*	*Leishmania naiffi*
Leishmania hertigi	*Leishmania gymnodactyli*	*Leishmania panamensis*
Leishmania infantum	*Leishmania hemidactyli*	*Leishmania peruviana*
Leishmania killicki	*Leishmania hoogstraali*	*Leishmania pifanoi*
Leishmania major	*Leishmania nicollei*	*Leishmania shawi*
Leishmania mexicana	*Leishmania senegalensis*	*Leishmania utingensis*
Leishmania siamensis	*Leishmania tarentolae*	
Leishmania tropica		
Leishmania turanica		

the immunologically hostile environment of the host (Awasthi *et al.,* 2004). Cell mediated immunity rather than humoral immunity, is considered the main protective immune response in leishmaniasis, although a number of antibody-mediated effects against leishmanial infection have been demonstrated. The innate or acquired capacities of macrophages for killing intracellular parasites appear ultimately to eliminate or control leishmanial infection. The current hypothesis is that T-cell mediated macrophage activation is the major protective mechanism against leishmanial infection. After having contact with the parasite antigen that is delayed in the infected host cell membrane, T-cells are stimulated to secrete IfN-Y. This substance together with other cytokines elaborated by T-cells or macrophages e.g. Interleukin-2 [IL-2] granulocyte-macrophage colony-stimulating factors and tumor necrosis factor [alpha] leads to the local activation of macrophages activating co-induction of resistance to infection mediated by nitric oxide from L-arginine. Although macrophage functions are necessary for the immunological control of leishmaniasis, the suppressive responses of these cells of their parasite-induced functions can also play important roles in determining the susceptibility to infection (Grimaldi and Tesh, 1993). The use of murine models and other defined animals for immunological studies of leishmanial infections has greatly improved the understanding of the regulation of the immune response and of the cellular immune mechanisms involved in host resistance and susceptibility to leishmanial infections (Grimaldi and Tesh 1993; El-Shoura *et al.,* 1995; Shiddo *et al.,* 1995; Kausalya *et al.,* 1996; Awasthi *et al.,* 2004; Nylén and Eidsmo, 2012).

The Human Leishmaniasis

Clinical forms and etiology: The currently recognized *Leishmania* species associated with human disease in the old world are listed in Table 2. A wide variety of clinical manifestations have been associated with most of the old world *Leishmania* species; many of the parasites are capable of producing in human host a spectrum of disease rather than a single clinical form as was thought previously. The leishmaniasis of the old world can be grouped into two broad clinical categories: (i) the human visceral leishmaniasis and (ii) the human cutaneous leishmaniasis.

The human visceral leishmaniasis (VL) of the old world is usually caused by *L. infantum* which is zoonotic and *L. donovani.* Cutaneous leishmaniasis (CL) is caused by *L. major* and *L. aethiopica* which are both zoonotic while *L. tropica* causes the anthroponotic form. The visceral leishmaniasis or Kala-azar is a disease of the reticuloendothelial system and is widely distributed in the old world (Basu and Mallick, 1995; Hailu *et al.,* 1996; Mohareh *et al.,* 1996; Rathore *et al.,* 1996; Chappuis *et al.,* 2007; WHO, 2011). The human cutaneous leishmaniasis result from the primary skin lesion, it is a disease of the reticuloepithelial cells of the skin and is commonly

Table 2: Visceral Leishmaniasis of the old world

Leishmania Species	Clinical Features	Epidemiology	Vectors	Reservoirs	Geographical Distribution
Leishmania infantum	VL	ZVL	*Phletotomus asiari*	Dog/Fox	Southern Europe
Leishmania infantum	CL∂	ZVL	*Phletotomus perfiliewi*	Dog/Fox	North Africa
Leishmania infantum	CL∂	ZVL	*Phletotomus perniciosus*	Dog	North Africa
Leishmania infantum	CL∂	ZVL	*Phletotomus major*	Dog/Fox/ Jackal	Eastern Mediterranean, South Western Asia
Leishmania infantum	CL∂	ZVL	*Phletotomus langeroni*	Dog	Egypt
Leishmania infantum	CL∂	ZVL	*Phletotomus chinensis*	Dog/ Raccoon	China
Leishmania infantum	CL∂	ZVL	*Phletotomus longiductus*	Dog/Fox	Azerbaijan
Leishmania infantum	CL∂	ZVL	*Phletotomus longiductus*	Jackal	Georgia
Leishmania infantum	CL∂	ZVL	*Phletotomus longiductus*	Jackal	Kazakhstan, Tajikistan, Turkmenistan, Ukraine, (Crimea), Uzbekistan, Pakistan
Leishmania infantum	CL∂	ZVL	*Phletotomus smirnori*	Badger	Kazakhstan
Leishmania donovani	VL/PKDL	AVL	*Phletotomus martini*	Man	East Africa
Leishmania donovani	VL/PKDL	AVL	*Phletotomus orientals*	Rodent, Carnivores	East Africa
Leishmania donovani	VL/PKDL	AVL	*Phletotomus agentipes*	Man	Indian Sub-Continent
Leishmania donovani	VL/PKDL	AVL	*Phletotomus alexandri*	Man	China
Leishmania major	CL	ZCL	*Phletotomus cluboscqi*	Rodent	Arabian, Peninsula, Africa
Leishmania major	CL	ZVL	*Phletotomus cluboscqi*	*Arvicanthis* species	Kazakhstan
Leishmania major	CL	ZVL	*Phletotomus papatasi*	*Meriones* species	Tajikistan
Leishmania major	CL	ZVL	*Phletotomus salehi*		India, Pakistan, South Western Asia
Leishmania tropica	CL	ACL	*Phletotomus sergenti*	Dog	Eastern Mediterranean
Leishmania tropica	VL∂	AVL	*Phletotomus sergenti*	*Rattus rattus*	Greece, India, Pakistan
Leishmania tropica	VL∂	ACL	*Phletotomus sergenti*	*Rattus rattus*	North Africa, West Asia
Leishmania aethiopica	CL, DCL	ZCL	*Phletotomus longipes*	Hydrax	East Africa
Leishmania aethiopica	CL, DCL	ZCL	*Phletotomus pedifer*	*Dendrohyrax* species	East Africa
Leishmania aethiopica	CL, DCL	ZCL	*Phletotomus pedifer*	*Heterohyrax* species	East Africa
Leishmania aethiopica	CL, DCL	ZCL	*Phletotomus pedifer*	*Procavia* species	East Africa

Key: *VL = Visceral Leishmaniasis, CL = Cutaneous Leishmaniasis, ∂ = Rare manifestation, AVL = Anthroponotic Visceral Leishmaniasis, ACL = Anthroponotic Cutaneous Leishmaniasis, DCL = Diffuse Cutaneous Leishmaniasis, ZCL = Zoonotic Cutaneous leishmaniasis.* **Source:** Modified from Agwale (1994)

called oriental sore. It is also widely distributed in the old world (Abouel-Ela *et al.,* 1995; Sharquie, 1995; Mohareh *et al.,* 1996; WHO, 2011). In summary, it is becoming increasing apparent that the clinical expressions or features of leishmanial infections are dependent upon a host of factors amongst which are the parasite species, the immune status of the host and other external factors.

Immunological features: It is been considered that if human infection is analogous to the immune model the genetic or racial differences also may play a role in determining some of the variations among patients in the course of leishmanial infection. Both cell-mediated immunity and humoral immune responses are induced by leishmanial infections in humans (Grimaldi and Tesh, 1993; Awasthi *et al.,* 2004; Nylén and Eidsmo, 2012). In the various forms of leishmaniasis a spectrum of immune response can be described (Al-Diwany *et al.,* 1995; Chatterjee *et al.,* 1995; El-Shoura *et al.,* 1995; Eesa *et al.,* 1995; Schaefer-Kurtzhals *et al.,* 1995; Singh *et al.,* 1995; Santos-Gomes and Abranches, 1996; Berhe *et al.,* 1995; Kausalya *et al.,* 1996; Rafati *et al.,* 1997; Awasthi *et al.,* 2004; Nylén and Eidsmo, 2012). Grimaldi and Tesh (1993) reporting on studies on the clinical immunology of leishmaniasis stated that, although strong DTK may coexist with some non healing forms of the disease, such as mucocutaneous leishmaniasis (ML), healing does not occur in its absence. On the other hand, there are available data that clearly exclude essential protective role for humoral antibody response. A lymphocytic response to *Leishmania* antigen usually develops during CL and ML but is absent in diffuse cutaneous leishmaniasis (DCL).

Conversely, that anti *Leishmania* antibody titers are generally low in the sera of patients with CL or ML but moderate to high in patients with DCL, These data suggest that TH1- and TH2- like immune profiles may exist in human leishmaniasis. Thus recovery and the development of long lasting resistance to re-infection appear to be the rule in CL. Some observations suggested that immunity conferred by prior self-resolving leishmanial infection may not be complete. This is the reason for the re-occurrence into the mucocutaneous forms. Furthermore in their report, VL is associated with antigen-specific immunosuppression during the acute phase of the disease that appears to be induced by a cell-mediated response. The mechanism of this immunosuppression is still unclear and there are lots of suggestions to that effect. Also common amongst patients with the disease are a contrasting depression of the cellular immune response, with a marked humoral response during active disease with elevated nonspecific immunoglobulin levels, mostly of the immunoglobulin G and M classes, thereby causing a reversal of the albumin/globulin ratio There is also a relatively high titers of anti *Leishmania* antibodies, along with hypergammaglobulinemia, rheumatoid factors and circulating immune complexes, suggesting polyclonal R-cell activation as characteristic feature of VL.

Pathology: Successful mammalian infection by *Leishmania* species depends on the abilities of the parasite to evade nonspecific host defenses, to attach to and be ingested by the host cell, and their ability to survive within the phagolysosome of macrophages. The intracellular parasitism of macrophages by *Leishmania* species can stimulate different types of inflammatory reactions and in this manner it gives rise to the various clinical and pathological patterns of the disease. Basically there is a histopathologic spectrum ranging from anergic forms of infection with heavily parasitized macrophages (e.g. DCL and VL) to hypersensitive or allergic forms (e.g. ML) with scanty organisms and a tuberculoid response. In addition, the last two forms may develop immunopathological alterations (e.g. fibrinoid necrosis of vascular walls or of the connective matrix) that produce extensive tissues damage. Although little is known about the immunopathology of the progressive and destructive form of ML, some underlying causes of its hyperergic response might include the following factors: (i) the resistance of some parasite strains to elimination and the persistence of "allergic" antigen that evokes hyperergic hypersensitivity inflammatory

responses and (ii) autoimmune phenomena related to antigens cross-reaction between leishmanial parasites and host tissues. The various geographically distinct groups of CL were histologically compared to determine whether the nature and intensities of tissue responses gave any indication of the likely outcome of infections. There was however no simple or unified pattern (Grimaldi and Tesh, 1993).

Epidemiology

Epidemiologic features of old world leishmaniasis: The leishmaniasis is far more prevalent and of greater medical importance for public health than previously recognized. The epidemiology of leishmaniasis is extremely complex partially because, firstly its taxonomy is still in a state of flux and secondly it is difficult to get accurate figures for the number of leishmaniasis cases in the old world as a whole because in many endemic areas; the patients have no access to health services and many cases thereby remain unreported. There are about 10 distinct *Leishmania* species that are recognized as causing human illness. Each of these parasites has a unique life cycle, different sand fly vectors, different animal reservoirs and a different geographic distribution. These various leishmaniasis have some common epidemiologic features such as: (i) different species of the sand fly vector have been incriminated for transmission, (ii) having a wide range of reservoir host, man being a dead-end host, (iii) most of them occurring in the rural areas in persons residing in rural areas or having contact with the sylvan habitats and, (iv) because of their zoonotic nature, changes in the environment and human behaviour or both can have a major impact on their prevalence and transmission patterns (Dye, 1992; El-Hassan *et al.,* 1995; Strelkova, 1996).

Prevalence and geographic distribution: WHO (1990), Ali and Ashford (1993) and Agwale (1994) reported world wide annual incidence of 600,000 newly reported clinical cases of leishmaniasis and an overall prevalence of 12 million cases and an estimated at risk population of about 350 million. It is however difficult to provide realistic estimates of those infected against those at risk and there's probably and even greater difference between the number of cases actually occurring and the number usually reported due to several factors amongst which are the following: (a) the distribution of transmission sites within endemic areas is often discontinuous, with separate, widely scattered foci and (b) numerous cases are undiagnosed, misdiagnosed or unreported. Especially when patients have no access to medical facilities, when diagnostic capabilities are scarce or absent, when drugs are not permanently available or when only passive case detection is used. The number of people infected but asymptomatic is much higher than the number infected and presenting with clinical illness-clinical cases been only the proverbial tip of the iceberg. In Kenya it is reported that one out of five children were infected every year and in Ethiopia, one out of seven, and in India one out of ten. Leishmaniasis is not a noticeable disease in 52 out of the 82 endemic countries. According to the same report by Agwale (1994), it is not because the health authorities concerned are not aware of the gravity of Leishmaniasis, some may be reluctant to make the disease noticeable since official recognition is accompanied by the implicit need to solve or at least alleviate the problem. Table 1 listed the *Leishmania* species currently recognized as human pathogens in the old world as well as their proven or suspected vectors, animal reservoirs, and geographic distribution.

Sand fly vectors and vertebrate reservoirs: The human pathogenic *Leishmania* species are all transmitted by the bites of infected phlebotomine sandflies (Diptera: Psychodidae). The phlebotomine vectors of the old world leishmaniasis are usually included in the genus *Phlebotomus,* and at the sub-genus level in the old world, the taxonomic distribution of vectors is more widespread with species from most of the sub-genera of *Phlebotomus* incriminated as *Adlcrius, Phlebotomus, Larroussius* and *Kuphlebotomus*. However there is a tendency for species of *Phlebotomus* (s.s) to transmit *L. major* and for *Larroussius* species to transmit *L. donovani* (except in

Ethiopia). The remaining sub-genera have too few species with "proven vector status (Agwale, 1994). These sand flies are 2 – 3 mm varicoloured insects, differentiated by pointed velvet wings, arched back and big dark eyes. They are abundant all year round in tropical areas. More than 500 species and sub-species are known throughout the world but less than 35 have been proved to be vectors of human leishmaniasis. The haematophagous sand fly females feed all through the night but especially at dusk. However, they can also bite during the day when disturbed in their resting places. The insect absorbs the *Leishmania* parasite with the blood from an infected host. The parasite life cycle in the sand fly is 4 – 7 days, after which the parasite can be inoculated in another animal or human when the fly takes a blood meal. The gadfly breeding sites remain unknown, although some have been identified, such as rodent burrows, tree trunks and organic debris. Leishmaniasis is caused by a wider range of parasite than any other human parasitic disease. The difficulties in the taxonomy of the phlebotomine sandflies pose special problems in deciding with certainty which sandfly is responsible for the transmission of one or other species of *Leishmania* in a given locality. Advances in the biochemical and molecular typing of the parasites and the sandflies have clarified the roles of many vectors (Agwale, 1994; Agwale *et al.,* 1995). Most of the leishmaniases are zoonoses of wild or domestic animals. Visceral leishmaniasis involves canines (dogs, jackals and foxes) where as cutaneous leishmaniasis depends on rodents, sloths, marsupials, hyraxes, primates and other mammals. *Leishmania* species in a given area is usually maintained by single reservoir host, even if other mammals may sometimes be infected. Identification of the reservoir is a prerequisite for the selection and application of selective control methods; in case of anthroponotic forms, man is the reservoir (Agwale, 1994; Ikeh *et al*., 1995; Acedo-Sanchez *et al.,* 1996; Morsy *et al.,* 1996; Githure *et al.,* 1996).

Management of Leishmaniasis

Agwale (1994) reported that leishmaniasis can be controlled by specific intervention directed against vulnerable pathways in the transmission cycles. The control measures are however dependent on the specific epidemiological characteristic of each focus. In all foci of leishmaniasis, passive case detection followed by treatment and case reporting should constitute the basis of a control programme and the first step towards a national strategy for control. Active medical surveillance involving regular systematic screening of clinically suspected cases through serological testing and parasitological diagnosis is needful. Additional control strategies (vector or reservoir host-control) depending on up-to-date information on the local epidemiology; identity of vector species, animal reservoir hosts, type of disease (cutaneous or visceral, anthroponotic or zoonotic) and the anticipated severity of the problem should be employed.

Vector control: Attempts at vector control have focused mainly on adult sandflies, since the larval breeding sites of most species are unknown. Insecticides are quite useful in controlling these insects in domestic and peri-domestic situations, and to date resistance has not been a serious problem. In contrast, the use of insecticide in forested areas, by either local application or aerial spraying, has not been very effective. The clearing of forests around villages and settlements has been useful in reducing the abundance of some fly vectors by eliminating their breeding and daytime resting sites. Sandflies have a relatively short flight range and do not travel long distances, so local insecticide application or environment management can be helpful in controlling the insects in defined areas. However, until more is learned about the biology and natural history of some of the important vector species, attempts to control sandflies and the disease associated with them will have only limited success (Dye, 1992; Grimaldi and Tesh, 1993; Agwale, 1994).

Elimination of reservoir hosts: Control of leishmaniasis by elimination or reduction of its reservoir host has been recommended for zoonotic leishmaniasis.

Each situation in the control of zoonotic leishmaniasis would depend on the local conditions and on the resources and knowledge available. While reduction of the reservoir of infection, in the case of anthroponotic cutaneous leishmaniasis, depends on the detection and treatment of all cases. In the case of visceral leishmaniasis, treatment of patients and destruction of infected animals are required, for zoonotic cutaneous leishmaniasis, control of the wild animal reservoir host is required (WHO, 1990). Besides the fact that reduction of the wild rodent population is easier said than done, it has grave implications from the ecological point of view. Also canine surveillance programme are not feasible because they are not only labour intensive but are expensive and require constant surveillance to be effective. Agwale (1994) reported that between 1980 and 1983 in Iraq, it was decided to restrict contact between jackals and dogs by burning dead animals around the chicken farms and slaughter houses; as a result, the incidence of infantile VL in these areas decreased by over 75% compared to a control area where it fell by only 40% during the time of observation and in Kenya an integrated control programme included the killing of infected dogs.

Surveillance and treatment of human cases: Leishmaniasis affects millions of people in the world especially in the tropics and subtropical regions. The fact is that man is only an incidental host, that is, man maybe involved in the maintenance of the cycles, therefore treating infected people does little to Interrupt parasite transmission in nature. But surveillance, detection and early notification of the disease to the appropriate health authorities for treatment help to keep the prevalence of the disease in check. Although this manner of approach will not reduce the incidence of new cases much. At least it will save people a lot of misery and socio economic loss. This therefore encourages an integrated approach for the control of leishmaniasis including health education, besides vector, reservoir and human control methods. Health education control programme using leaflets and broadcasting media, usually employs the co-operation of the local population. This is aimed at educating the people on the relevant aspects of the transmission of the disease and also disabuses their minds against some of their traditional belief and practices (WHO, 1990).

Personal protection: Personal protective measures by individual can be very effective. They can be achieved by the use of repellants such as diethyltoluamide or trimethyl pentanediol and by staying out of forested areas or their defined habitats. Other useful measures are the use of fine mesh, screens or sandfly net, bed nets, mosquito coils, treated curtains, electrically heated fumigation and fumigant canisters, thick clothing to reduce man-vector contact. The only disadvantage with this is the reduction in ventilation of screened houses as well as for the individual with thick clothing or sleeping in a fine sand fly net especially in hot areas. Repellants could be used either directly to the skin or impregnated into clothing or Wire-mesh and bed nets. But some traditional methods of treating the disease such as the application of local preparation of vaccine types including battery acid, tar and toxic herbal concoctions, may cause further suffering. Owing to the limited flight range of sandflies, a little change in the sitting of construction camp for example may considerably affect the rate of exposure to infected flies (WHO, 1990).

Immunization: Grimaldi and Tesh (1993) reported that, to date, no vaccine against any form of leishmaniasis has been shown conclusively to be effective. Nonetheless, current research suggests that the development of unit vaccines against leishmaniasis may be feasible. Two approaches to developing immunoprophylactic methods against the disease have been adopted. One approach is the induction of protection by using whole parasites (attenuated, killed or disrupted). The other approach is subcellular fractionation of the parasites with the aim of identifying, isolating and inducing protection with purified antigens. CL caused by *L. major* has been the target of most human vaccination attempts. A live - promastigote vaccine has been evaluated with clinical form of the disease. Although the vaccine confers resistance to infection, a significant percentage of persons receiving it developed cutaneous lesions.

Further more, this type of immunization can be used only with *Leishmania* species that produce benign self-healing lesions. Killed vaccines are still only in the experimental stage of development. Preliminary vaccination trials against old world CL have also given inconclusive or negative results. Nonetheless, complete or appreciable levels of protection against CL and VL have been achieved in mice by using more defined antigens such as the major promastigote surface glycoprotein gp63, either incorporated into liposomes or expressed in *Salmonella* species and other glycoconjugates in conjunction with adjuvants. According to the same report although all of these are still at very preliminary stages, the results so far are encouraging and suggest that it may e possible to develop safe protective vaccines against leishmaniasis.

Laboratory diagnosis: A presumptive diagnosis of leishmaniasis can be made on the basis of results of laboratory tests in conjunction with clinical and epidemiologic data. This does not however completely rule out the need for definitive diagnosis of the disease through the demonstration of the parasite. Sometimes in chronic cares of CL and ML a definitive diagnosis is difficult due to the paucity of parasites in lesions. A definitive diagnosis of VL depends on detection of parasites by examination of smears of bone marrow, lymph node, or spleen aspirate. The classical methods used for direct demonstration of the parasite in tissues or skin lesions include the following: (i) examination of stained smears or histological sections, (ii) inoculation of hamsters with aspirates from infected tissues or with triturated tissues fragments, and (iii) *in vitro* culture of tissue homogenates or aspirates in biphasic media. Combinations of these methods are still the most commonly used method for the diagnosis of leishmaniasis especially the cutaneous form. However, newer immunologic and molecular techniques are now available. *In situ* detection of amastigotes with characterization of the infecting parasite species can be done in CL by immunocytochemical procedures using either polyclonial or monoclonial antibodies. Rapid in Situ diagnosis of leishmaniasis is also possible by examining dot blots of fluid aspirates or touch blots of infected tissues on nitrocellulose paper The dot blots are subsequently tested, employing monoclonial antibodies or KDNA or genomic DNA-labeled probes.

Another approach is the *in situ* hybridization, using KDNA probes for the detection of individual parasites in imprint smears of aspirates from lesion. KDNA hybridization can also be employed for identification of *Leishmania* species within shadflies or alternatively both the sandfly and species can be confirmed in the vector by using double probes on squash blots. More recently the polymerase chain reaction technique is a rapid and highly sensitive method for the diagnosis of visceral leishmaniasis and appears to be capable of distinguishing between past and current infections. Also there are indirect methods based on serologic techniques which include the ELISA, direct agglutination test and the *Leishmania* skin test (Dye, 1992; Grimaldi and Tesh, 1993; Ali and Ashford, 1993; Agwale, 1994; Tiwari *et al.,* 1995; Shiddo *et al.,* 1995; Schaefer *et al.,* 1995: Hailu *et al.,* 1996; Kumar *et al.,* 1996; Senaldi *et al.,* 1996; Rafati *et al.,* 1997).

Treatment: Treatment of the disease is usually based on the use of leishmanicidal drugs, principally injections of pentaralent antimony (Sb5) compounds, which despite their toxic properties still remain the treatment of choice. The biochemical basis for the anti leishmanial activity of antimonial drugs is still not well understood although it may involve inhibition of ATP synthesis. The two Sb5 compounds in common use, sodium stibogluconate (Pentosan; Burroughs Wellcome) and meglumine antimoniate (Glucantime; Rhone-Poulenc), give similar therapeutic results. Treatment trials of these drugs in cases of CL, ML and VL have been done in diverse patient populations with different parasite infections and different dosage regimens consequently, the results and recommended therapies have been variable. In the 1980s use of 20mg of Sb5 per kg per day was recommended for treating VL. Subsequently, this does was recommended for CL and ML as

well, but a maximum daily dose of 850mg was specified. Treatment data indicated that the response to Sb5 is better with higher daily doses of the drug and with longer treatment but the side effects (arthralgias, myalgias and hepatic, cardiac and renal toxicity) are also greater considerations in using the higher and longer dosage schedule in areas of endemicity, other may include cost and logistics of administration. A regimen of 20 mg of sodium stibogluconate per kg per day, without an upper limit on the daily dose is now recommended; CL cases are treated for 20 consecutive days while 28 days of continuous therapy are re commended for ML and VL.

Furthermore, on the report by Grimaldi and Tesh (1993) due to the increase in antimony refractoriness in the various clinical forms of leishmaniasis, therapeutic regimens have been modified in both dose and duration of therapy and by the addition of other anti leishmanial compounds. Other systemic drugs with proven efficacy in human leishmaniasis are amphoterin B, pentamidine, itraconazole or miconazole and the orally administered agent allopurinol ribonucleoside. It was also found that most of the reported studies supporting the use of these various alternatives were preliminary; consequently, there are insufficient data to select one drug over another. Besides these alternative drugs may not be equally effective with all *Leishmania* species. Also the associated high toxicity with some of these alternative drugs is a limiting factor in their systemic use in CL. There are also in addition to systemic therapy, several forms of local treatment that have been tested with the cutaneous forms of the disease these include: (i) topical application of drugs, (ii) curettage, (iii) irradiation, (iv) heat and (v) freezing (Mebrahtu *et al.,* 1992; Sharquie 1995; Nyakundi *et al.,* 1995; Seaman *et al.,* 1995; Thakur *et al.,* 1996).

Conclusion: The global importance of human leishmanial infection has been realized in recent years. Ikeh *et al.* (1996) reported that it is ranked second to malaria in medical and economic importance in endemic areas of the world. It is therefore now a public health threat especially to the labour force of any nation due to its debilitating effects. Agwale (1994) reported that leishmaniasis affects mainly people from developing countries (72 out of 82) of which 13 are among the least economically developed. Within countries, the affected classes of the population are those of the lowest socio-economic status, who have minimal political influence and very limited capacity to afford the costs of the disease diagnosis, hospitalization, treatment etc. Vaccination may prove to be the easiest and most effective intervention method for the prevention of leishmaniasis at the population level but, since it is still in the experimental stage, an integrated control approach that uses more traditional methods of vector reduction, elimination of infected reservoirs, personal protection, surveillance and treatment is recommended option. Finally, there is a need for more research into the biological, molecular and immunologic features of the sandfly, the parasite and the reservoir host. Priority being given to the vector and the pathogen with the hope that better understanding will yield insight into new and improved control methods.

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