Leishmaniasis

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Leishmaniasis is a poverty-related disease with two main clinical forms: visceral leishmaniasis and cutaneous leishmaniasis. An estimated 0·7–1 million new cases of leishmaniasis per year are reported from nearly 100 endemic countries. The number of reported visceral leishmaniasis cases has decreased substantially in the past decade as a result of better access to diagnosis and treatment and more intense vector control within an elimination initiative in Asia, although natural cycles in transmission intensity might play a role. In east Africa however, the case numbers of this fatal disease continue to be sustained. Increased conflict in endemic areas of cutaneous leishmaniasis and forced displacement has resulted in a surge in these endemic areas as well as clinics across the world. WHO lists leishmaniasis as one of the neglected tropical diseases for which the development of new treatments is a priority. Major evidence gaps remain, and new tools are needed before leishmaniasis can be definitively controlled.

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See Online for appendix

Introduction

Leishmaniases are vector-borne parasitic diseases caused by at least 20 species of the genus *Leishmania,* and are transmitted between mammalian hosts by female sandflies (figure 1; appendix p 1). Leishmaniasis is primarily zoonotic with the exception of *Leishmania donovani* and *Leishmania tropica*, although there is some evidence that animal reservoirs exist for both species across Africa and Asia.[2,3]

Distinct species of *Leishmania* cause different clinical manifestations, ranging in severity from self-curing cutaneous lesions to life-threatening visceral disease (table 1; appendix p 4). The outcome is determined by the interplay of the following: parasite characteristics, vector biology, and host factors, with immune responses taking centre stage among the host factors.[4] Visceral leishmaniasis—caused by *L donovani* in Asia and Africa and *Leishmania infantum* in the Mediterranean Basin, the Middle East, central Asia, South America, and Central America—is the most severe, systemic form that is usually fatal unless treated. Post-kala-azar dermal leishmaniasis is a skin manifestation that occurs in otherwise healthy people after treatment of visceral leishmaniasis.[5] Cutaneous leishmaniasis is usually limited to an ulcer that self-heals over 3–18 months, but can also lead to scarring, disfigurement, and stigmatisation as disability outcomes. Depending on parasite species, up to 10% of cutaneous leishmaniasis cases progress to more severe manifestations. These severe manifestations are known as mucocutaneous leishmaniasis, diffuse cutaneous leishmaniasis, disseminated cutaneous leishmaniasis, and leishmaniasis recidivans. Further information about sandfly biology, parasite–vector interaction, and parasite–host interaction can be found in the appendix (pp 2, 3).

Epidemiology

Visceral leishmaniasis

In 2015, seven countries (Brazil, Ethiopia, India, Kenya, Somalia, South Sudan, and Sudan) reported more than 90% of the worldwide cases of visceral leishmaniasis. However, the disease remains endemic in more than 60 countries (figure 2). Devastating epidemics have been described in east Africa[7] and the Indian subcontinent.[8] The global incidence of visceral leishmaniasis decreased substantially in the past decade: from between 200 000 and 400 000 new cases in 2012, to between 50 000 and 90 000 in 2017.[9,10]

India, Nepal, and Bangladesh used to have more than 50% of the global burden of visceral leishmaniasis. In 2005, these countries committed to eliminate visceral leishmaniasis as a public health problem by 2015, a deadline that has been subsequently extended. The elimination target was set at less than one case per 10 000 people per year at the district (Nepal) and subdistrict (India and Bangladesh) level, an incidence rate considered to be no longer of public health concern.[11] These elimination efforts contributed to the global decline of visceral leishmaniasis, but cyclical epidemiological patterns are also common (figure 3; appendix pp 5, 6). In east Africa, the burden of visceral leishmaniasis remains steady, with shorter cyclical patterns of 6–10-year intervals (appendix p 7). Previous outbreaks were often related to forced migration of non-immune populations into endemic areas following conflict.[12] In Ethiopia, HIV and visceral leishmaniasis co-infection might have contributed to increased transmission, with up to 40% of patients with visceral leishmaniasis testing positive for HIV infection in a hospital series in 2006.[13] Brazil reports more than 99% of the estimated 3500 yearly cases in Latin America, and although case numbers remain steady, the continental distribution spreads south-westward (appendix pp 8, 9).

Search strategy and selection criteria

The literature research for this Seminar started from standard works and recent reviews. We searched PubMed for publications written in English with the search terms "leishmaniasis" OR "kala-azar". We limited the results to those published between June 1, 2005, and June 31, 2017, filtering by "human". From the 6304 references generated, we prioritised those reporting applied epidemiology and clinical research; and, where necessary, we searched secondary references until we found the original record. Additional key references were retrieved from the personal databases of all coauthors.

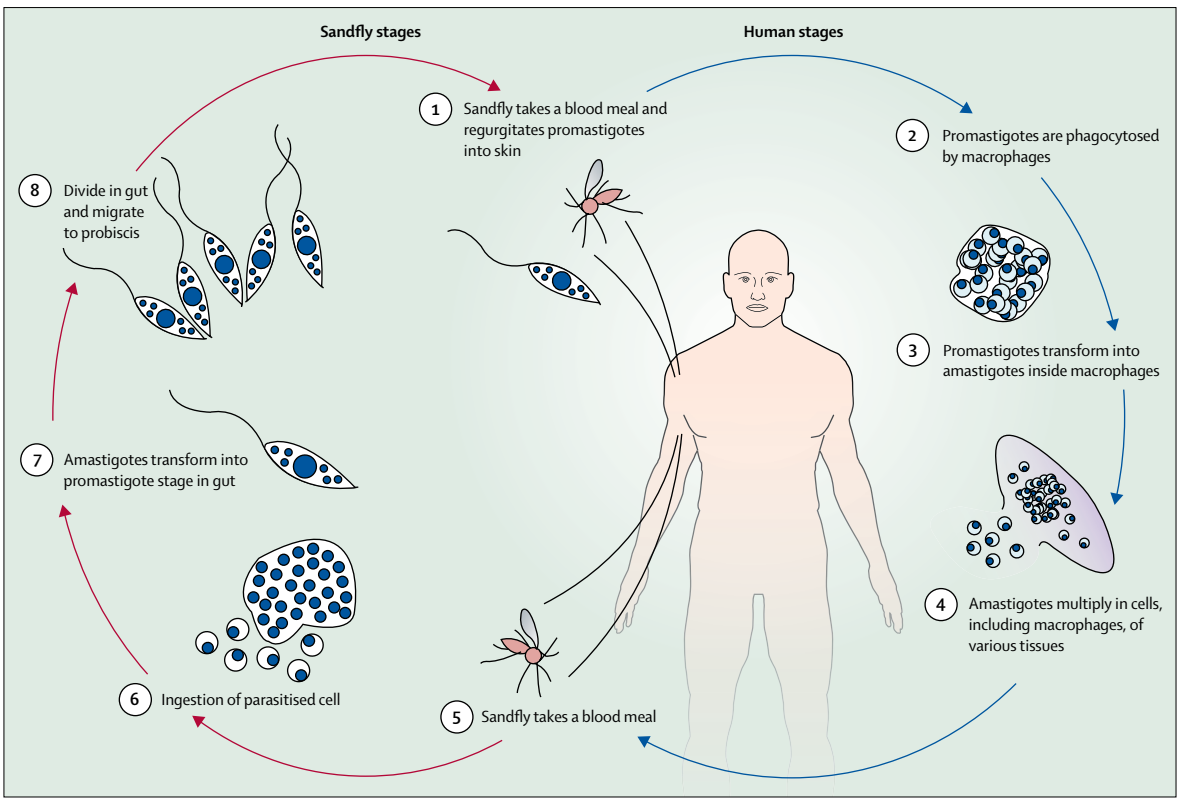

Figure 1: **Leishmania life cycle**
Reproduced from Reithinger et al,[1] by permission of Elsevier.

Asymptomatic infection is common in endemic areas; the seroprevalence ranges from 7% to 63% for *L donovani* in the Indian subcontinent,[14] and from 29% to 34% for *L infantum* in Brazilian children.[15] A recent Ethiopian study reported nearly 17% PCR positivity in a cohort of more than 4000 asymptomatic people.[16] Incident asymptomatic infections outnumber symptomatic infections by a factor of between four and 17 in cohort studies done in the Indian subcontinent,[17] 5·6 in Ethiopia,[18] and four in Kenya.[19] Between 2% and 23% of people with asymptomatic infections described in India developed symptoms within a year.[17,20–27] High antibody titres are a risk marker for progression to disease.[20]

Humans are the main reservoir for visceral leishmaniasis due to *L donovani*. In the Indian subcontinent, transmission occurs peridomestically in the alluvial plains of the Ganges river, typically an altitude below 700 m.[28] These areas have heavy monsoon rains, high humidity, temperatures between 15°C and 38°C, abundant vegetation, and subsoil water.[10] *L donovani* transmission also occurs at altitudes over 1000 m in the hilly regions of Nepal[29] and Bhutan.[30] The disease is most common in poor farming villages where houses typically have mud walls and earthen floors, and livestock is kept under the same roof or at close distance, creating a favourable ecological niche for *Phlebotomus argentipes* sandflies. In east Africa, *L donovani* transmission is closely linked to the sandfly habitat: *Acacia* or *Balanites* forests and black cotton soil for *Phlebotomus orientalis*, and in and around termite mounds for *Phlebotomus martini*. Further details on transmission and infectivity of *L donovani* can be found in the appendix (p 10).

The domestic dog is the primary reservoir of *L infantum*, although other mammalian reservoirs exist, particularly in central Asia.[31] Surveys in southwestern Europe show a median 10% *L infantum* seroprevalence in dogs, ranging from 0% to 18%.[32] A cohort study in Italy showed that all infected dogs developed symptomatic disease over a 2-year timespan.[33] Other PCR-based studies have shown asymptomatic infection in up to 80% of dogs from endemic areas, of which substantial proportions were infectious.[34] In the Mediterranean Basin, visceral leishmaniasis typically occurs in rural regions, but a recent outbreak in Spain occurred in an urban area close to Madrid, and was linked to a wild hare reservoir.[35] Risk factors for visceral leishmaniasis in the Latin–American region are similarly linked with dog reservoirs. Sporadic non-vector transmission routes have been described, including congenital,[36] transfusion,[37] organ transplant,[38,39] or laboratory accidents.[40] In Spain, direct transmission of *L infantum* has been observed in drug users co-infected with HIV through sharing needles.[41]

	Subgenus	Clinical form	Main clinical features	Natural progression	Risk groups	Main reservoir	High-burden countries or regions	Estimated annual worldwide incidence
*Leishmania donovani**	*Leishmania*	VL and PKDL	Persistent fever, splenomegaly, weight loss, and anaemia in VL; multiple painless macular, papular, or nodular lesions in PKDL	VL is fatal within 2 years; PKDL lesions self-heal in up to 85% of cases in Africa but rarely in Asia	Predominantly adolescents and young adults for VL; young children in Sudan and no clearly established risk factors for PKDL	Humans	India, Bangladesh, Ethiopia, Sudan, and South Sudan	50 000–90 000 VL cases; unknown number of PKDL cases
*Leishmania tropica**	*Leishmania*	CL, LR, and rarely VL	Ulcerating dry lesions, painless, and frequently multiple	CL lesions often self-heal within 1 year	No well defined risk groups	Humans but zoonotic foci exist	Eastern Mediterranean, the Middle East, and northeastern and southern Africa	200 000–400 000 CL
*Leishmania aethiopica**	*Leishmania*	CL, DCL, DsCL, and oronasal CL	Localised cutaneous nodular lesions; occasionally oronasal; rarely ulcerates	Self-healing, except for DCL, within 2–5 years	Limited evidence; adolescents	Hyraxes	Ethiopia and Kenya	20 000–40 000 CL
*Leishmania major**	*Leishmania*	CL	Rapid necrosis, multiple wet sores, and severe inflammation	Self-healing in >50% of cases within 2–8 months; multiple lesions slow to heal, and severe scarring	No well defined risk groups	Rodents	Iran, Saudi Arabia, north Africa, the Middle East, central Asia, and west Africa	230 000–430 000 CL
*Leishmania infantum**	*Leishmania*	VL and CL	Persistent fever and splenomegaly in VL; typically single nodules and minimal inflammation in CL	VL is fatal within 2 years; CL lesions self-heal within 1 year and confers individual immunity	Children under 5 years and immunocompromised adults for VL; older children and young adults for CL	Dogs, hares, and humans	China, southern Europe, Brazil, and South America for VL and CL; Central America for CL	6200–12 000 cases of Old World VL and 4500–6800 cases of New World VL; unknown number of CL cases
Leishmania mexicana†	*Leishmania*	CL, DCL, and DsCL	Ulcerating lesions, single or multiple	Often self-healing within 3–4 months	No well defined risk groups	Rodents and marsupials	South America	Limited number of cases, included in the 187 200–300 000 total cases of New World CL‡
Leishmania amazonensis†	*Leishmania*	CL, DCL, and DsCL	Ulcerating lesions, single or multiple	Not well described	No well defined risk groups	Possums and rodents	South America	Limited number of cases, included in the 187 200–300 000 total cases of New World CL‡
Leishmania braziliensis†	*Viannia*	CL, MCL, DCL, and LR	Ulcerating lesions can progress to mucocutaneous form; local lymph nodes are palpable before and early on in the onset of the lesions	Might self-heal within 6 months; 2·5% of cases progress to MCL	No well defined risk groups	Dogs, humans, rodents, and horses	South America	Majority of the 187 200–300 000 total cases of New World CL‡
Leishmania guyanensis†	*Viannia*	CL, DsCL, and MCL	Ulcerating lesions, single or multiple that can progress to mucocutaneous form; palpable lymph nodes.	Might self-heal within 6 months	No well defined risk groups	Possums, sloths, and anteaters	South America	Limited number of cases, included in the 187 200–300 000 total cases of New World CL‡

VL=visceral leishmaniasis. PKDL=post-kala-azar dermal leishmaniasis. CL=cutaneous leishmaniasis. LR=leishmaniasis recidivans. DCL=diffuse cutaneous leishmaniasis. DsCL=disseminated cutaneous leishmaniasis. MCL=mucocutaneous leishmaniasis. *Old World leishmaniasis. †=New World leishmaniasis. ‡Estimates are of all New World leishmaniases, with *Leishmania braziliensis* comprising the vast majority of these cases.

Table 1: **Clinical and epidemiological characteristics of the main *Leishmania* species**

In immunocompromised patients, *Leishmania* parasites can persist for decades after treatment, since there appears to be no sterile immunity.[42] Fulminant reactivation of the infection is possible when immunity is compromised—eg, due to post-transplant immunosuppressive therapy, use of immunomodulators, advanced age, or HIV infection.

Post-kala-azar dermal leishmaniasis

This type of leishmaniasis is a skin condition that occurs after treatment of visceral leishmaniasis due to *L donovani*. The pathophysiology of post-kala-azar dermal leishmaniasis is linked to an interferon-γ-driven host immune response against residual dermal parasites. Incomplete treatment and exposure to ultraviolet light are risk factors,[43] while certain treatments lead to a higher incidence of post-kala-azar dermal leishmaniasis.[44,45] However, up to 5% of Indian patients with post-kala-azar dermal leishmaniasis never reported a previous episode of visceral leishmaniasis.[43] Post-kala-azar dermal leishmaniasis occurs in 5–10% of cases of visceral leishmaniasis in Asia developing 2–3 years after treatment, whereas it is seen in up to 50% of cases in east Africa usually within 1 year of treatment. In east Africa, more than 85% of post-kala-azar dermal leishmaniasis lesions are self-healing within 12 months.[43] These lesions typically pose solely as aesthetic problems to patients, although it can affect quality of life, particularly in younger adults.[46] A small number of patients will develop severely debilitating forms (figure 4). Importantly, the lesions are infectious to sandflies[47] and, if untreated, might remain infectious for

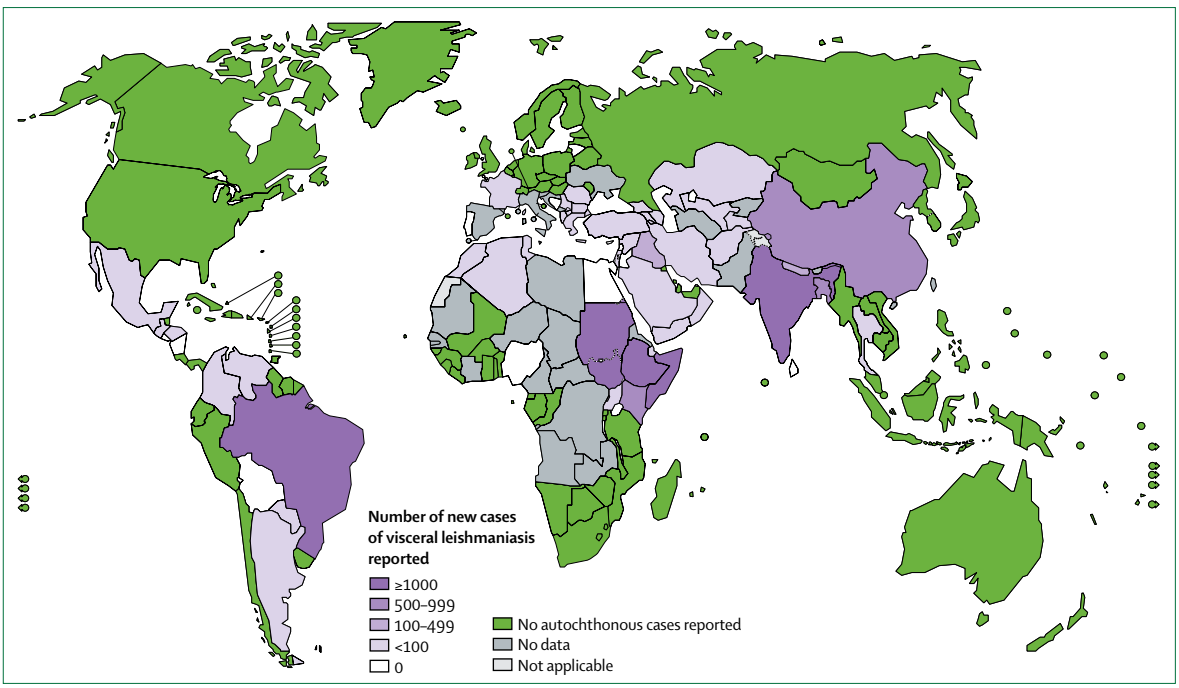

Figure 2: **Status of endemicity of visceral leishmaniasis worldwide in 2016**
Reproduced from WHO,[6] by permission of the World Health Organization.

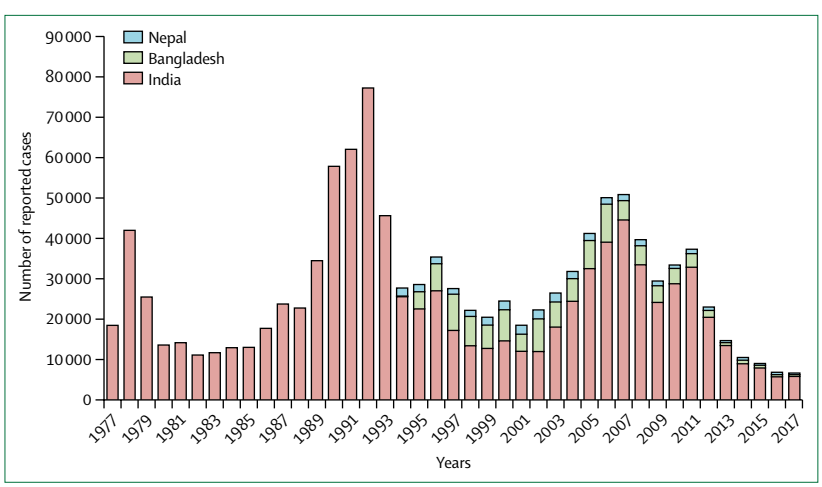

Figure 3: **Cyclical epidemiological patterns of visceral leishmaniasis in south Asia**

decades, potentially constituting reservoirs of infection during interepidemic periods.[48]

Cutaneous and mucocutaneous leishmaniasis

WHO estimates 0·7–1 million annual cases of cutaneous leishmaniasis worldwide. Currently, 90% of these cases occur in Afghanistan, Pakistan, Syria, Saudi Arabia, Algeria, Iran, Brazil, and Peru.[49] Because of forced migration, the number of cutaneous leishmaniasis cases has substantially increased, with imported cases relatively common in non-endemic countries.[50,51]

The *Leishmania* parasites causing cutaneous leishmaniasis are commonly divided into Old World species, such as *Leishmania major, L tropica,* and *Leishmania aethiopica*, that are prevalent around the Mediterranean Basin, the Middle East, the Horn of Africa, or the Indian subcontinent; and New World species, such as *Leishmania amazonensis, Leishmania mexicana, Leishmania braziliensis,* and *Leishmania guyanensis*, that are endemic in Central and South America.[52] These parasites belong to one of two subgenera: *Leishmania* or *Viannia*, a taxonomic difference based on the site of development and attachment of promastigotes in the sandfly gut (table 1).[53]

The epidemiology of cutaneous leishmaniasis in the Americas is complex, with multiple circulating *Leishmania* species in the same geographical area, several reservoir hosts and sandfly vectors, and variable clinical manifestations and therapy response. The pathogenic species in the New World belong to the *L mexicana* (subgenus *Leishmania*) or the *L braziliensis* (subgenus *Viannia*) species complex. Although cutaneous leishmaniasis is considered the mildest manifestation, 1–10% of patients infected with a strain from the *Viannia* subgenus subsequently develop mucocutaneous leishmaniasis (table 1). Mucocutaneous leishmaniasis is a potentially life-threatening and highly disfiguring condition due to the late stage destruction of the oronasopharyngeal mucosa and cartilage, occasionally affecting the larynx leading to aspiration pneumonia.

Cutaneous leishmaniasis is either anthroponotic (*L tropica*) or zoonotic (*L major, L aethiopica,* and all the New World species). Sandflies belonging to the genus *Phlebotomus* (Old World) or *Lutzomyia* (New World)

transmit the parasite. Transmission by other routes is rare. Importantly, mere skin contact with the active lesion is innocuous, as infection requires inoculation of material from active sores. Poor quality housing, male sex, being younger than 15 years, and presence of peridomestic animals are associated with cutaneous leishmaniasis.[54–57] In the New World, proximity to forested areas, sleeping in temporary shelters in crop areas, and dog ownership are strong risk factors.[58–60]

A recrudescence of Old World cutaneous leishmaniasis (figure 5) has been seen in conflict areas of the Middle East,[62] most recently in Syria due to the collapse of the public health system and exposure of non-immune populations.[61] Between 2000 and 2012, Lebanon reported six cases of cutaneous leishmaniasis, compared with 1033 cases in 2013, 97% of which were reported in Syrian refugees.[63] Similar patterns have been observed in Turkey,[64] and a general increase in cutaneous leishmaniasis cases in the Mediterranean region is expected where the vector *Phlebotomus sergenti* is widespread.[65]

Clinical features

Visceral leishmaniasis

Persistent irregular fever and splenomegaly characterise visceral leishmaniasis. Pancytopenia, hepatomegaly, hypergammaglobulinaemia, and weight loss are common, particularly in patients presenting late. The hypergammaglobulinaemia includes (non-protective) antileishmanial antibodies but also autoimmune antibodies that might confuse clinical presentation, particularly in travellers or migrants. Acute malnutrition or wasting is associated with a high parasite burden, particularly in young children,[66] although it is not clear whether this effect is a cause or consequence of poor nutritional status.[67,68] In the Indian subcontinent, hyperpigmentation of the skin is probably a result of cytokine-induced increased production of adrenocorticotropic hormone,[69] leading to the Hindi name *kala-azar*, which loosely translates to black fever.

The onset of visceral leishmaniasis can be acute or insidious, and the incubation period is between 2 weeks and 8 months. Without treatment, the disease is typically fatal within 2 years as a result of secondary bacterial infection or severe anaemia. However, people who are infected might only develop symptoms years later when they become immunosuppressed.[70]

Visceral leishmaniasis–HIV co-infection

Co-infection with HIV is one of the major challenges for visceral leishmaniasis control. HIV was responsible for the re-emergence of visceral leishmaniasis in southern Europe in the late 1990s. In Brazil and India, co-infection of up to 6% are now reported,[71,72] while in Ethiopia up to 18% of patients presenting with visceral leishmaniasis in endemic areas are co-infected.[73]

HIV and *Leishmania* share a common immune-pathological mechanism involving macrophages and dendritic cells, resulting in accelerated progression of both diseases because of increased pathogen replication.[74] Any form of visceral leishmaniasis in an HIV-infected person should be considered a stage 4 AIDS-defining illness,[5] although current WHO guidelines for HIV staging only mention atypical disseminated leishmaniasis.[75] HIV testing should be mandatory in all patients presenting with visceral leishmaniasis, although screening for visceral leishmaniasis in patients with HIV living in endemic areas is recommended. These patients present with more severe and atypical manifestations of visceral leishmaniasis, requiring different diagnostic and management approaches; for example, in east Africa, rapid diagnostic tests have been shown to be less sensitive in HIV-positive patients than in HIV-negative patients,[76] whereas accuracy for co-infected patients in the Indian subcontinent has yet to be established.[77]

Atypical disseminated leishmaniasis might present with parasites isolated from gastrointestinal mucosa, the respiratory tract, and the liver.[78] In India, half of the patients diagnosed with co-infection were not aware of

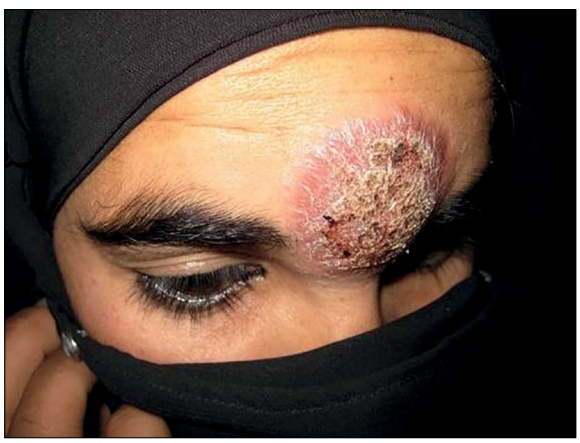

Figure 4: **A patient with a severely debilitating lesion due to post-kala-azar dermal leishmaniasis**
Reproduced from MSF.

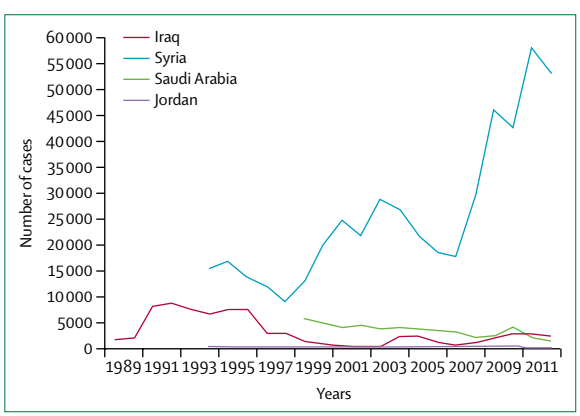

Figure 5: **Recrudescence of Old World cutaneous leishmaniasis in conflict areas of the Middle East**
Reproduced from Salam et al.[61]

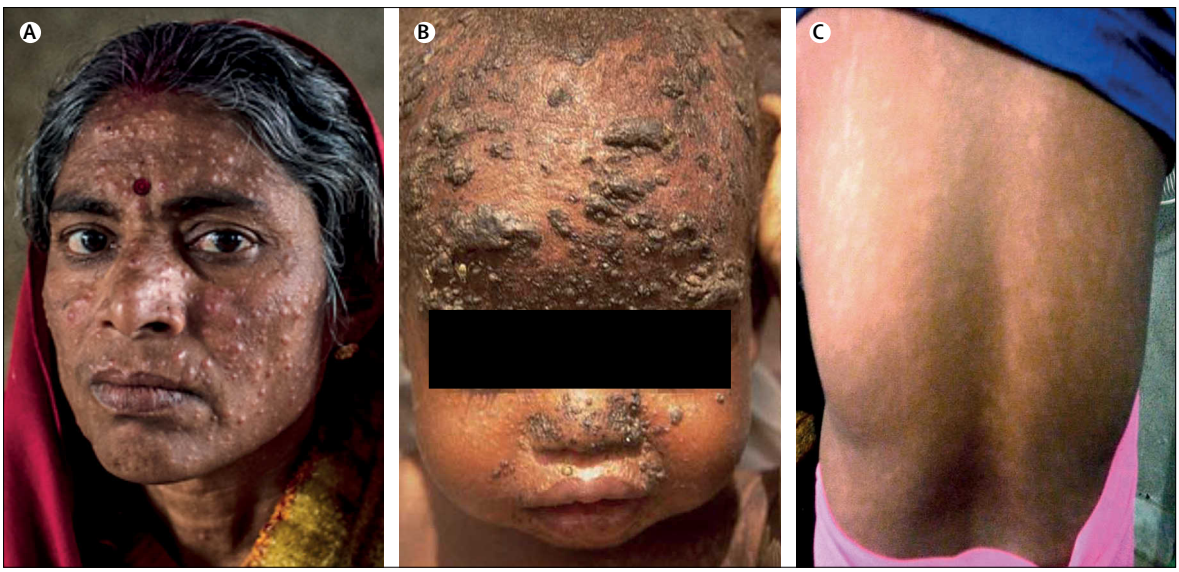

Figure 6: **A female patient (A) and child (B) with erythematous maculopapular rash and a patient with hypopigmented macula (C) due to post-kala-azar dermal leishmaniasis**
(A) and (C) are reproduced from MSF. (B) is reproduced from WHO,[82] by permission of the World Health Organization.

Panel 1: **Grading system for post-kala-azar dermal leishmaniasis in east Africa**[83,84]

Grade 1
Scattered maculopapular or nodular rash on the face, with or without lesions on the upper chest or arms

Grade 2
Dense maculopapular or nodular rash covering most of the face and extending to the chest, back, and upper arms and upper legs, with only scattered lesions on the forearms and legs

Grade 3
Dense maculopapular or nodular rash covering most of the body, including the hands and feet; the mucosa of the lips and palate might be involved

their HIV status[72] while leishmaniasis can be easily mistaken for the myriad of HIV-related opportunistic infections.[79] Co-infection leads also to atypical presentations in cutaneous leishmaniasis, as was observed in an *L major*-related outbreak in Burkina Faso.[80]

Post-kala-azar dermal leishmaniasis

Post-kala-azar dermal leishmaniasis is a late complication of visceral leishmaniasis due to *L donovani*. It is rarely observed in people infected with *L infantum*, but when seen it is typical in those who are immunocompromised.[81] In post-kala-azar dermal leishmaniasis, parasites seem to persist in the skin after treatment, and, whereas systemically the T-helper-1 response dominates, locally in the skin a T-helper-2 profile with high interleukin 10 leads. Patients present with a hypopigmented macular or an erythematous maculopapular rash around the mouth and the trunk, which can gradually extend to the entire body (figure 6). In Asia 90% of cases have the macular type whereas in Africa the papular rash predominates. The preservation of sensation distinguishes these lesions from leprosy. For post-kala-azar dermal leishmaniasis in Africa, a grading system has been developed (panel 1);[83,84] but this grading system does not exist in Asia. Table 2 shows the clinical features of post-kala-azar dermal leishmaniasis in immunocompetent and immunosuppressed groups.[84]

Cutaneous and mucocutaneous leishmaniasis

Cutaneous leishmaniasis is not life-threatening but can lead to substantial cosmetic morbidity, social stigmatisation,[85] and psychological effects.[86] Lesions develop as a papule over weeks to months at the sandfly's biting site. Multiple lesions usually correspond to different bites, although lymphatic spread is possible.[87] The papula then enlarges to a nodule that ulcerates slowly over the following few months. In general, patients are systemically well, and the lesions, although sometimes itchy, do not generate the pain that might be expected from their appearance. In Old World cutaneous leishmaniasis, lesions can develop into hyperkeratotic or wart-like plaques (figure 4). Lesions caused by *L tropica* and *L major* are self-healing within a year but tend to leave permanent scars. Lesions by *L aethiopica*[88] take years to heal and can develop into severe oronasal mucocutaneous leishmaniasis (figure 7) and diffuse forms of cutaneous leishmaniasis. In New World cutaneous leishmaniasis, lesions caused by *L mexicana* tend to be less severe and heal more quickly, whereas the *Viannia* species are associated with more severe

ulcerating lesions and mucocutaneous leishmaniasis (figure 8).

Lesions of cutaneous leishmaniasis are often mistaken for furuncles. Depending on context, clinicians should also consider paracoccidioidomycosis, cutaneous histoplasmosis, sporotrichosis, *Balamuthia mandrillaris* infection, mycobacterial infections, chromoblastomycosis, yaws, cutaneous neoplasms, and partially healed bacterial skin infections as a differential diagnosis.[90]

The rarer variants of cutaneous leishmaniasis—diffuse cutaneous leishmaniasis, disseminated cutaneous leishmaniasis, and leishmania recidivans—correlate with an underlying spectrum of contrasting immune responses.[91] Diffuse cutaneous leishmaniasis is caused by *L amazonensis*, *L aethiopica*, or *L mexicana*; and develops as multiple widespread non-tender, non-ulcerating papules and nodules resembling lepromatous leprosy in patients showing a negative leishmanin skin test (LST). The condition reflects the absence of a cellular immune response, and the dermis is typically and heavily infiltrated with parasites. Disseminated cutaneous leishmaniasis is seen in Latin America and is defined by ten or more mixed-type lesions located in two or more parts of the body. Mucosal involvement is frequent. Histologically, there are very few parasites in the lesions, and disseminated cutaneous leishmaniasis is associated with a positive LST and antileishmanial antibodies.[92,93] Leishmania recidivans typically follows cutaneous leishmaniasis due to *L tropica* that has healed, and it presents as new lesions encircling the old scar, which might progressively expand. Lesions are heavily infiltrated with lymphocytes. This manifestation could be confused with cutaneous tuberculosis. Immunosuppression is a risk factor for both diffuse and disseminated cutaneous leishmaniases.[94]

Mucocutaneous leishmaniasis is characterised by destructive lesions of the nasal septum, lips, and palate, and is caused by a strong immunopathological response. Lesions typically start at the nostrils or the lips, and a history of worsening nasal congestion, epistaxis, or discharge is common.[95] About 90% of mucocutaneous leishmaniasis cases exhibit a scar from their previous cutaneous leishmaniasis episode,[84,85] which might have occurred decades earlier.[96] Mucocutaneous leishmaniasis is thought to be more frequent in immunocompromised individuals.[84] Other risk factors are a primary lesion above the waistline, multiple or large primary lesions, or delayed healing of the primary lesion.[5] Mucocutaneous leishmaniasis is potentially life-threatening, can lead to permanent disfigurement, and needs to be diagnosed and treated rapidly.

	Immunocompetent	Immunocompromised
Parasite type	Mainly *Leishmania donovani*	Mainly *Leishmania donovani* but also *Leishmania infantum*
Frequency	5–10% of treated VL cases in the ISC, up to 50% in east Africa	More frequent
Onset about VL treatment	East Africa <6 months; ISC >6 months	Unknown, but can be considered as IRIS
Main clinical presentation	Macular of maculopapular	Nodular
Severity	Less severe than in immunocompromised	More severe than in immunocompetent
Self-healing	Not common in ISC; usually <12 months in east Africa	No
Other post-kala-azar manifestations	Yes, uveitis	Yes, uveitis
Post-kala-azar dermal leishmaniasis or para-kala-azar dermal leishmaniasis	Post-kala-azar dermal leishmaniasis more common than para-kala-azar dermal leishmaniasis	Para-kala-azar dermal leishmaniasis more common than post-kala-azar dermal leishmaniasis
Parasite numbers	Scant	Abundant
Parasites found in skin	<60%	90%
Ulcerating	No	No, but genital ulcers described
Face affected	Almost always	Not always
Bony protrusions involved (eg, knuckles)	No	Often; symmetrical
Evolution	Typical	Atypical

Adapted from Zijlstra.[84] VL=visceral leishmaniasis. ISC=Indian subcontinent. IRIS=immune reconstitution inflammatory syndrome.

Table 2: **Clinical features of post-kala-azar dermal leishmaniasis in immunocompetent and immunocompromised individuals**

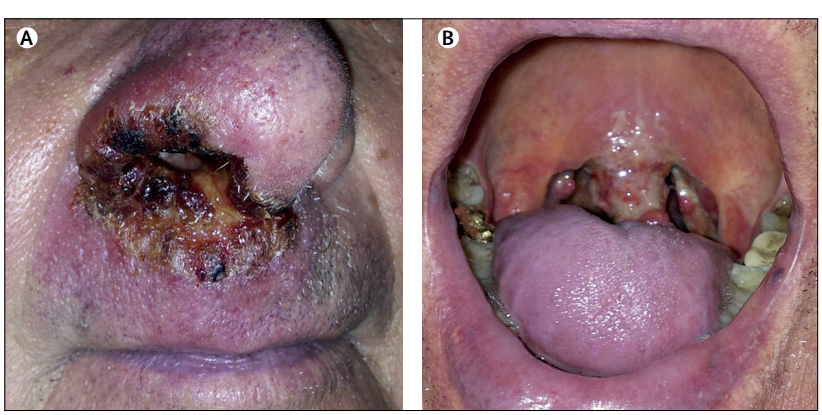

Figure 7: **Severe oronasal mucocutaneous leishmaniasis in a 73-year-old German man with a history of travel to Panama**

(A) A lesion affecting the right nostril, upper lip, and philtrum. (B) Lesions affecting the uvula and the adjacent soft palate. Reproduced from Crovetto-Martínez et al,[89] by permission of Elsevier.

Diagnosis

Visceral leishmaniasis

Febrile splenomegaly is a feature of several infectious diseases; therefore, clinical suspicion of visceral leishmaniasis needs to be confirmed. The classical diagnosis is through microscopic observation of the amastigote parasite stage in tissue specimens or cultures. Amastigotes are round or oval bodies, 1–4 µm in diameter, with a typical rod-shaped kinetoplast and circular nucleus (figure 9).

The sensitivity depends on the tissue: above 90% in the spleen, 50–80% in bone marrow, and even lower in lymph node aspirates.[5] Technique is also of importance because sensitivity increases with longer reading time and more microscope fields examined.[98] Blood samples have low sensitivity, except in HIV-co-infected patients, who have a higher parasitaemia.[99] Splenic aspirates are

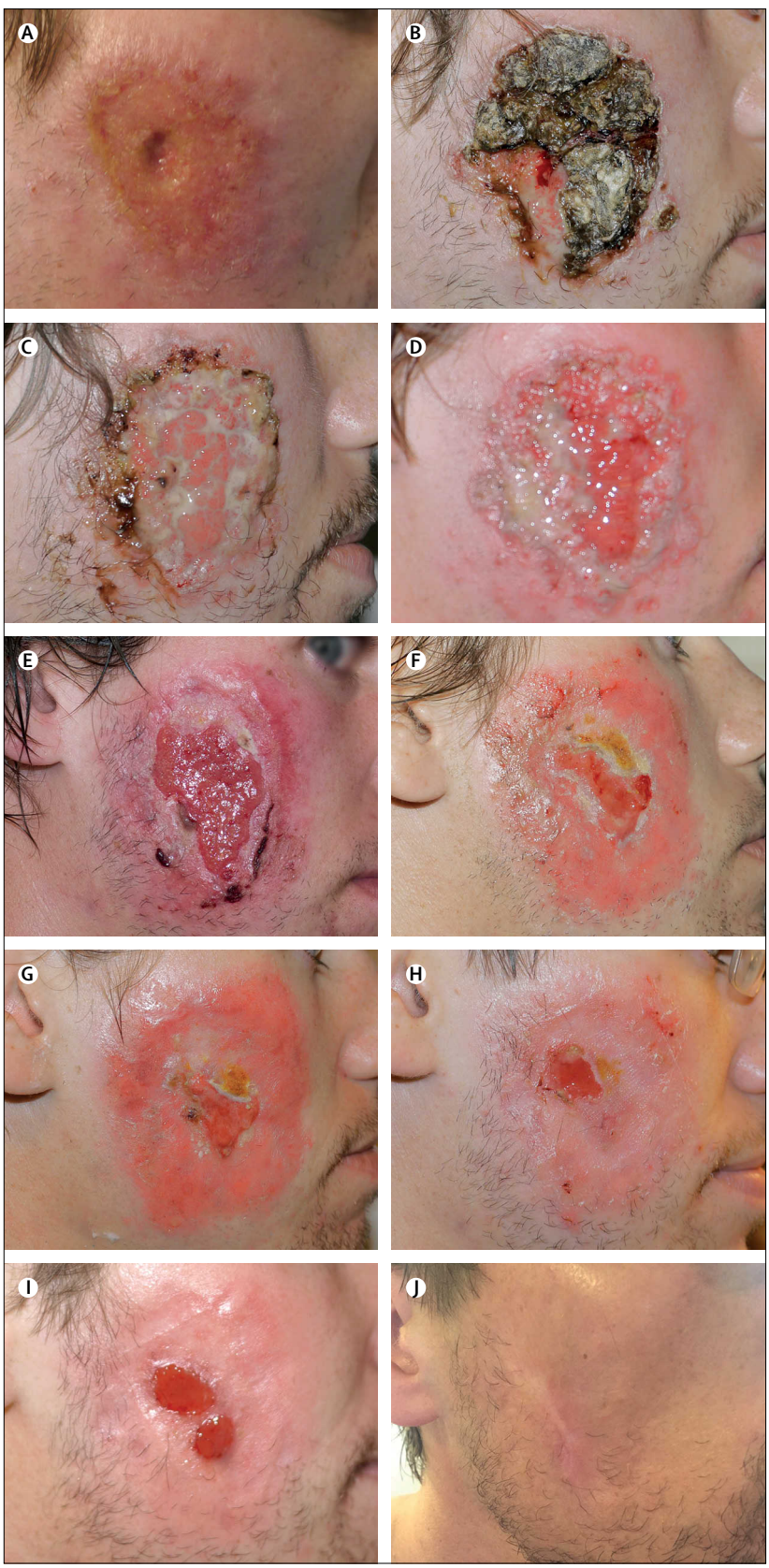

Figure 8: **A male patient with cutaneous leishmaniasis contracted in Bolivia**
Panels (A) to (I) show the healing process of over 12 months. Panel (J) shows the remaining scar after 4 years. Reproduced by permission of Adam Spencer.

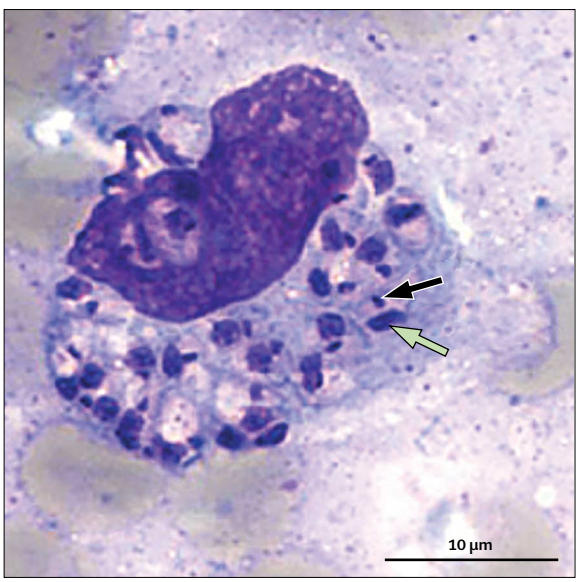

Figure 9: **An infected macrophage with several amastigotes**
The black arrow shows the rod-shaped kinetoplast. The green arrow shows the circular nucleus. Reproduced from CDC,[97] by permission of the US Centers for Disease Control and Prevention.

considered the gold standard, but the procedure has a risk of haemorrhage in one per 1000 procedures.[100]

Several serological assays are available, including direct agglutination test, ELISA, immunofluorescence, and western blot. These antibody detection techniques share a high sensitivity for acute visceral disease but are not strictly specific for this disease stage. Antibodies wane only slowly after cure and are also present in a large number of asymptomatically infected individuals;[101] therefore, serological results should be interpreted in the context of clinical history. Moreover, several of these assays are too complicated for use in endemic areas.

A Cochrane review of rapid diagnostic tests (RDTs) in patients with febrile splenomegaly and no history of visceral leishmaniasis concluded that the sensitivity of the rK39-RDT in the Indian subcontinent was excellent at 97% (95% CI 90–100) but lower in east Africa at 85% (75–93),[77] possibly due to lower antibody concentrations.[102] More recently, an rK28 antigen-based RDT showed better sensitivity in Sudan than the rK39-RDT.[103] Control programmes in Asia and east Africa now recommend treatment for visceral leishmaniasis in suspected cases from endemic areas (ie, those with >2 weeks of fever and splenomegaly) with a positive RDT result. RDTs have the same limitations as other serological tests; therefore, results should be interpreted in a clinical context and cannot be used to diagnose relapses. They have a limited role in immunocompromised individuals

(eg, HIV-positive patients) in whom antibodies might be undetectable or present at low concentrations.[104]

Recent efforts to develop antigen detection tests for visceral leishmaniasis seek specificity for the acute disease stage. A latex agglutination test, KAtex (KALON Biological, UK), detects a heat-stable low molecular weight (5–20 kDa) carbohydrate antigen in urine, showing high specificity of 93% (95% CI 77–99) but moderate sensitivity of 64% (41–86). More recently, promising prototype ELISA kits for antigen detection in urine have been developed,[105] with reported sensitivities above 90% and good correlation with cure.[106] Recent investigations suggest that IgG1 is correlated with acute stage visceral leishmaniasis and might have prognostic value in asymptomatic infection.[107]

In *L infantum*-affected countries and travel clinics, PCR has a role in the diagnostic algorithm. However, in resource-limited settings, molecular techniques are usually not part of routine diagnosis, because they are too complex and expensive. Additionally, their specificity for clinical diagnosis does not seem optimal, probably because they correlate better with infection status than with acute disease.[108] A reverse transcriptase loop-mediated isothermal amplification (LAMP) assay—developed to make the technology more user-friendly[109]—reached a sensitivity of 83%.

The LST, also known as the Montenegro test, is a marker of cellular immune response and measures the delayed-type hypersensitivity reaction. If 48–72 h after the intradermal injection of leishmanin antigen a skin induration of at least 5 mm is observed, the LST is considered positive. The LST is negative in active visceral leishmaniasis because of the anergic state of patients and has little diagnostic value in clinical practice, but it is useful in epidemiological surveys as a marker of previous exposure.

Post-kala-azar dermal leishmaniasis

The differential diagnosis of post-kala-azar dermal leishmaniasis includes leprosy, vitiligo, and fungal infections. It is diagnosed by observation of amastigotes in slit-skin smear or biopsy specimens of lesions. However, the method is not sensitive, ranging from 67–100% in nodular, 36–69% in papular, and 7–33% in macular lesions.[110] Serological evidence in such patients is inconclusive, because antileishmanial antibodies remain positive for several months after visceral leishmaniasis treatment.[111,112] Diagnostic accuracy of molecular methods was part of a recent systematic review, which concluded that sensitivity was high but specificity was low.[113]

In general, an urgent need remains for well designed trials of diagnostic accuracy in post-kala-azar dermal leishmaniasis. In endemic areas, where both slit-skin smears and molecular tests are not feasible, WHO has recommended a clinical algorithm for the diagnosis of post-kala-azar dermal leishmaniasis that takes regional variation and current control strategies into account (figure 10).[115] However, the sensitivity and specificity of this algorithm have yet to be evaluated, and it is possible that there will be substantial numbers of false-positives. This effect is problematic considering that patients are otherwise healthy, with currently no adequately safe treatments available.

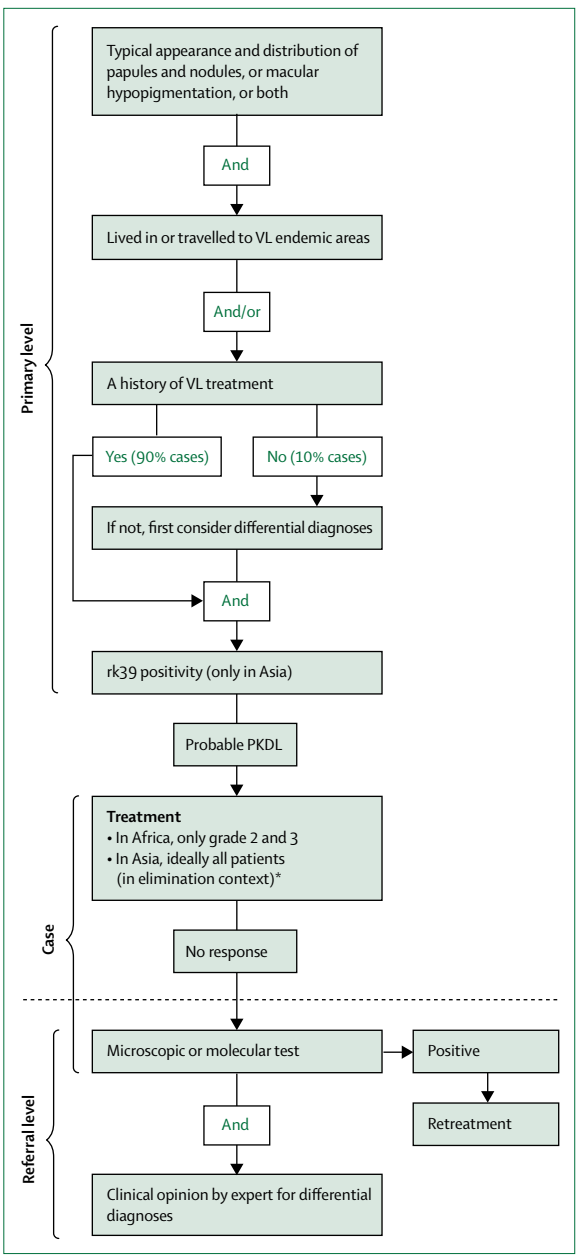

Figure 10: **WHO-recommended clinical algorithm for the diagnosis of PKDL**
PKDL=post-kala-azar dermal leishmaniasis. VL=visceral leishmaniasis. *As soon as an effective and safe regimen is identified. Reproduced from WHO,[114] by permission of the World Health Organization.

Cutaneous and mucocutaneous leishmaniasis

Identification of the species, especially in New World cutaneous leishmaniasis, can be helpful for clinical care. Currently, there is no single reference test for cutaneous

leishmaniasis,[116] but the observation of amastigotes in a clinical specimen establishes the diagnosis,[117] be it from a direct smear of needle aspirate, a skin-slit smear, a biopsy, or cultured material. Given the limited sensitivity of any of these tissue-sampling approaches, a combination is recommended. Recently developed microculture techniques are more sensitive and cost-effective but do not allow for further determination of species.[118]

Molecular methods based on amplification of nuclear or kinetoplast DNA are very sensitive and allow for

	Regimen and dose	Efficacy (cure rate at 6 months)	Main adverse effects	Issues to consider
Leishmania donovani				
East Africa				
Combination treatment	Pentavalent antimonials (20 mg Sb5+* per kg per day of intramuscularly [preferably]) or intravenously plus PM (15 mg [11 mg base] per kg bodyweight per day intramuscularly) for 17 days	91%	Cardiotoxicity, pancreatitis, and hepatotoxicity (SSG); ototoxicity and nephrotoxicity (PM)	Painful to administer, monitoring of renal function, and audiometry where possible
Pentavalent antimonials	20 mg Sb5+* per kg per day intramuscularly or intravenously for 30 days	94%	Cardiotoxicity, pancreatitis, and hepatotoxicity	Painful to administer and prolonged treatment
LAMB	3–5 mg/kg per daily dose by infusion given over 6–10 days up to a total dose of 30 mg/kg	>90%	Shivering, back pain, and nephrotoxicity	End of treatment results only (ie, not 6-month cure rate); results for complicated or severe visceral leishmaniasis in non-HIV patients; observational studies; requires storage <25°C and has a more complex preparation than the previous two treatment options mentioned above; only one WHO prequalified preparation (ie, AmBisome)
Indian subcontinent				
LAMB	10 mg/kg as a single dose, or 3–5 mg/kg per daily dose up to a total dose of 15 mg/kg over 3–5 days	96%	Shivering, back pain, and nephrotoxicity	Requires storage <25°C and has a more complex preparation than the other treatment options in the list—namely, PM (and MF, which is an oral drug); only one WHO prequalified preparation (ie, AmBisome)
Combination treatment	LAMB (5 mg/kg single dose) plus MF (daily for 7 days, as per below)	98%	Shivering, back pain, and nephrotoxicity (LAMB); gastric irritation and hepatotoxicity (MF)	MF is teratogenic; requires contraceptive cover for 3 months; only one WHO prequalified preparation (ie, Impavido)
Combination treatment	LAMB (5 mg/kg single dose) plus PM (daily for 10 days, as per above)	98%	Shivering, back pain, and nephrotoxicity (LAMB); ototoxicity and nephrotoxicity (PM)	Requires ten visits to a health centre; multiple injections (one for intravenous infusion and ten for intramuscular injection)
Combination treatment	MF (as per below) plus PM (as per above), both daily for 10 days,	99%	Gastric irritation and hepatotoxicity (MF); ototoxicity and nephrotoxicity (PM)	MF is teratogenic; requires contraceptive cover for 3 months; requires ten visits to a health centre; multiple injections (ten for intramuscular injection)
Amphotericin B deoxycholate	0·75–1 mg/kg per day by infusion, daily or on alternate days for 15–20 doses	93%	Hypokalaemia, nephrotoxicity, and shivering	Poorly tolerated and prolonged treatment
MF	For children aged 2–11 years, 2·5 mg/kg per day; for ≥12 years and <25 kg bodyweight, 50 mg/day; 25–50 kg bodyweight, 100 mg/day; and >50 kg body weight, 150 mg/day for 28 days	90%	Gastric irritation and hepatotoxicity	Teratogenic; requires contraceptive cover for 3 months; reducing drug susceptibility; linear dosing likely to be suboptimal in children
***L donovani* VL–HIV co-infection**				
East Africa				
LAMB	Infused at a dose of 3–5 mg/kg daily or intermittently for ten doses (days 1–5, 10, 17, 24, 31, and 38) up to a total dose of 40 mg/kg	NA	Hypokalaemia, nephrotoxicity, and shivering	Current WHO-recommended dosage, but based on *L infantum* data; no evidence from this region
LAMB	Intravenous infusion of 5 mg/kg on days 1–5, 10, 17, and 24 up to a total dose of 40 mg/kg	50%	Hypokalaemia, nephrotoxicity, and shivering	Repeating the regimen immediately following failed test of cure increases initial cure rate (day 58) to 67%
Combination treatment	LAMB (30 mg/kg total dose: intravenous infusion 5 mg/kg on days 1, 3, 5, 7, 9, and 11) plus MF (for children aged 2–11 years, 2·5 mg/kg per day; for ≥12 years and <25 kg bodyweight, 50 mg/day; ≥25 kg bodyweight, 100 mg/day for 28 days)	67%	Shivering (LAMB); gastric irritation and hepatotoxicity (MF)	Outcomes from randomised control trial (NCT02011958) soon-to-be published; 5 months contraceptive cover recommended; repeating the regimen immediately following failed test of cure increases initial cure rate (day 58) to 91%
Indian Subcontinent				
LAMB	Infused at a dose of 3–5 mg/kg daily or intermittently for ten doses (days 1–5, 10, 17, 24, 31, and 38) up to a total dose of 40 mg/kg	NA	Hypokalaemia, nephrotoxicity, and shivering	Current WHO recommended dosage, but based on *L infantum* data; no evidence from this region
Combination treatment	LAMB (30 mg/kg total dose) in 6 × 5 mg/kg alternate day infusions plus MF (for children aged 2–11 years, 2·5 mg/kg per day; for ≥12 years and <25 kg bodyweight, 50 mg/day; ≥25 kg bodyweight, 100 mg/day for 14 days)	86%	Shivering (LAMB); gastric irritation and hepatotoxicity (MF)	Observational study results; outcomes from randomised control trial (CTRI/2015/05/005807) soon to be available; 5 months contraceptive cover recommended

(Table 3 continues on next page)

	Regimen and dose	Efficacy (cure rate at 6 months)	Main adverse effects	Issues to consider
(Continued from previous page)				
Leishmania infantum				
All regions				
LAMB	3–5 mg/kg per daily dose by infusion given over 3–6 days, up to a total dose of 18–21 mg/kg	90–98%	Hypokalaemia, nephrotoxicity, and shivering	Current WHO recommended dose
Pentavalent antimonials	20 mg Sb5+* per kg per day intramuscularly or intravenously for 28 days	97%	Cardiotoxicity and hepatotoxicity	Retrospective observational study of 111 children in Brazil
LAMB	10 mg/kg per daily dose by infusion given over 2 days, up to a total dose of 20 mg/kg	96%	Hypokalaemia, nephrotoxicity, and shivering	Limited evidence and small sample sizes
Amphotericin B deoxycholate	0·75–1·0 mg/kg per day by infusion, daily or on alternate days for 20–30 doses, for a total dose of 2–3 g	NA	Hypokalaemia, nephrotoxicity, and shivering	No regional evidence; difficult treatment with many side-effects
***L infantum* VL–HIV co-infection**				
All regions				
LAMB	Infused at a dose of 3–5 mg/kg daily or intermittently for ten doses (days 1–5, 10, 17, 24, 31, and 38) up to a total dose of 40 mg/kg	80%	Hypokalaemia, nephrotoxicity, and shivering	..

Sb5+=pentavalent antimonial. PM=paromomycin. SSG=sodium stibogluconate. LAMB=liposomal amphotericin B. MF=miltefosine. NA=not available. *Sb5+ can be either sodium stibogluconate (SSG) or meglumine antimoniate (MA); the respective doses are equivalent.

Table 3: **Recommended treatments for visceral leishmaniasis**

identification of the *Leishmania* species. This assay is particularly useful in travel clinics and regions where several *Leishmania* species coexist. Again, the tissue-sampling approach is important to enhance the sensitivity of the assay. Molecular tests are especially important where simpler techniques fail—eg, in mucosal lesions where parasites are sporadic, and in chronic lesions—and recently developed real-time kDNA PCR assays have shown to be highly accurate for detection and quantification of *Viannia* species in lesion biopsies.[119] The LAMP technique achieved a sensitivity of 98% on 40 patients with cutaneous leishmaniasis in a proof-of-concept study.[109] So far, the combined use of classical parasitological methods with PCR-based detection offers an improved approach to the diagnosis of cutaneous leishmaniasis.

Serological tests and the LST are of little use in the diagnosis of cutaneous leishmaniasis. Newer immunological tests are emerging, such as the use of chemiluminescent ELISA to measure anti-α-galactosyl antibodies, which have been shown to be up to nine-times higher in people with *L tropica* or *L major* infections than in healthy people.[120] The cutaneous leishmaniasis Detect Rapid Test (Inbios International, Seattle, WA, USA) is commercially available, targeting the peroxidoxin antigen of the parasite.[121]

Treatment

Visceral leishmaniasis

For decades, visceral leishmaniasis was treated by pentavalent antimonial monotherapy, available in two formulations: sodium stibogluconate and meglumine antimoniate. Increasing non-response in India led to increased dosage recommendations, currently up to 20 mg/kg per day either by intramuscular injection or intravenous infusion over the course of 28–30 days. Aside from being painful if administered intramuscularly, antimonials are cardiotoxic and can induce arrhythmias.[122] This adverse effect is particularly evident in HIV–visceral leishmaniasis co-infection.[123] In the Indian subcontinent, sodium stibogluconate is no longer recommended because of drug resistance.[5,124]

Recent clinical research has focused on shorter regimens and avoiding resistance.[5,125] The first breakthrough was oral miltefosine, registered in India in 2002, followed by the injectable paromomycin in 2006, several short combination regimens, and single-dose liposomal amphotericin B (LAMB; table 3). Miltefosine was adopted in 2005, as the first-line regimen by the Asian elimination initiative. However, after a decade of use there is evidence of reduced effectiveness in both visceral leishmaniasis and post-kala-azar dermal leishmaniasis, while the existing linear dosing recommendations in children (ie, mg per kg bodyweight) are likely to result in under-dosing and treatment failure.[126]

In east Africa, 20 mg/kg per day of sodium stibogluconate, in combination with intramuscular paromomycin (15 mg/kg) over 17 days is the treatment of choice (table 3).[5,127] In general, evidence in this region is limited to end-of-treatment outcomes (rather than the standard 6 months) because of high follow-up loss from migration. In east African patients with complicated visceral leishmaniasis, or those who are elderly or pregnant, treatment with LAMB is recommended because of its better safety profile. However, routine use of LAMB monotherapy in non-severe patients has not proven to be as effective as in Asia, and is not recommended.[128]

Panel 2: **Current WHO recommendations for treatment of post-kala-azar dermal leishmaniasis with evidence grading**

East Africa

Combination treatment

Pentavalent antimonials (20 mg Sb5+* per kg per day intramuscularly or intravenously) for 17–60 days plus paromomycin (15 mg in 11 mg base per kg per day intramuscularly) for 17 days when indicated; the evidence for this regimen is graded C

Pentavalent antimonial

20 mg Sb5+* per kg per day intramuscularly or intravenously for 30–60 days when indicated; the evidence for this regimen is graded C

Liposomal amphotericin B

2·5 mg/kg per day by infusion for 20 days when indicated; the evidence for this regimen is graded C

Miltefosine

100 mg per day for 28 days might be beneficial in patients co-infected with HIV and post-kala-azar dermal leishmaniasis; the evidence for this regimen is graded C

Bangladesh, India, and Nepal

Miltefosine

100 mg orally per day for 12 weeks for patients weighing >25 kg; 50 mg orally per day for 12 weeks for patients weighing <25 kg; the evidence for this regimen is graded A†

Amphotericin B deoxycholate

1 mg/kg per day by infusion, up to 60–80 doses delivered over 4 months; the evidence for this regimen is graded C

Liposomal amphotericin B

5 mg/kg per day by infusion two times per week for 3 weeks for a total dose of 30 mg/kg; the evidence for this regimen is graded C†

WHO evidence grading system: evidence obtained from at least one properly designed randomised controlled trial was graded A; evidence obtained from well designed trials without randomisation was graded B; and opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees were graded C. Sb5+=pentavalent antimonial. *Sb5+ can be either sodium stibogluconate or meglumine antimoniate; the respective doses are equivalent. †Because the safety of courses of miltefosine lasting longer than 4 weeks has not been evaluated, all patients should be closely monitored for side-effects. †Although additional evidence is needed, potassium supplementation is recommended for this regimen given in a patient's diet (for all patients) or through intravenous infusion (for those with proven severe hypokalaemia). To prevent serious adverse effects caused by hypokalaemia, patients should be monitored for any related signs or symptoms. Hypokalaemia should be suspected in all patients with general weakness, nausea, myalgia, muscle weakness, or cramps occurring during or after treatment.

For all visceral leishmaniasis caused by *L infantum* and for visceral leishmaniasis caused by *L donovani* in Asia, sodium stibogluconate has been superseded by LAMB as first-line treatment (table 3). To date, the only LAMB formulation approved by the US Food and Drug Administration (FDA) and WHO for the treatment of visceral leishmaniasis is AmBisome (Gilead Sciences, Dimas, CA, USA).[128] Other lipid emulsions, lipid suspensions, and alternative LAMB formulations are available.[129] However, comparative studies are required before alternative preparations can be considered for routine use in visceral leishmaniasis. Since 2010, for visceral leishmaniasis caused by *L donovani* in the Indian subcontinent during the attack phase of elimination, WHO recommends 10 mg/kg of LAMB as a single dose by infusion or 3–5 mg/kg per daily dose infusion over 3–5 days up to a total dose of 15 mg.[130] As of 2017, more than 13 000 patients have been treated with this regimen under regular programme conditions across the Indian subcontinent.[131] An alternative to the LAMB regimen is one of several combination regimens listed in table 3, whose use is planned to be adopted once elimination targets have been reached to mitigate the risk of resistance developing to LAMB.

The evidence base for the management of HIV-negative relapse patients remains scarce. Retreatment with 30 mg/kg of LAMB is given in east Africa, whereas treatment with either a higher dose of LAMB (eg, 20 mg/kg in four divided doses over 4 days)[132] or a different combination therapy is appropriate in Asia.

HIV–visceral leishmaniasis co-infection

Co-infected patients require higher doses and longer treatment than immunocompetent patients. They are at increased risk of relapse and death, which appears inversely correlated with CD4 counts. Furthermore, visceral leishmaniasis adversely affects the response to antiretroviral therapy.[133,134] Poor outcomes, increased predisposition to drug toxicity, and more general treatment challenges are well documented in the literature.[42] At the same time, with so few treatment options available, the risk of decreasing drug sensitivity is of concern in this group of patients for whom relapse is the rule rather than the exception.

Visceral leishmaniasis should be treated as an opportunistic infection if diagnosed in a patient with HIV,[135] warranting initiation of lifelong antiretroviral therapy regardless of CD4 count.[5] There is no clear evidence for the best treatment regimen for co-infected patients. Current WHO recommendations are based on experience from southern Europe, where a total dose of 40 mg/kg of LAMB is administered in 8–10 doses over 38 days (table 3).[136] However, a slightly lower total dose of 30 mg/kg in the east African setting showed poor results, with parasitological failure in 32% of patients, despite clinical improvement.[137] Randomised controlled trials are concluding in both Ethiopia and India comparing combinations of LAMB and miltefosine with LAMB monotherapy.[138,139]

Secondary prophylaxis for co-infected patients is not well described outside Europe. International guidelines recommending LAMB prophylaxis[5,140] are based on limited evidence from one small randomised study[106] and a few case series in Europe.[141,142] More recently, an open-label prospective cohort study of co-infected patients in Ethiopia showed monthly infusions of 4 mg/kg of pentamidine isoethionate resulted in 29% failure rates within 1 year,[143] compared with 56% reported in previous observational studies.[144] In the Indian subcontinent, pentamidine isoethionate is not appropriate because of increased risk of inducing diabetes[145] nor is miltefosine considering that it increases treatment failure rates.[146] Prophylaxis with LAMB formulations remain an option, but potential for resistance developing to what is the only remaining front-line drug remains a major concern. One recent retrospective study in India concluded secondary prophylaxis, using a 1 mg/kg

monthly infusion of amphotericin B deoxycholate, was the sole significant predictor against death in co-infected patients over 12 months (hazard ratio 0·09).[147] However, prospective controlled studies are needed before regional policy recommendations are made.

Post-kala-azar dermal leishmaniasis

Evidence for treatment regimens for post-kala-azar dermal leishmaniasis is scarce, and the absence of standardised endpoints makes comparison difficult. Panel 2 shows current WHO recommendations. Generally, post-kala-azar dermal leishmaniasis in east Africa does not require treatment as the majority self-heal except for severe cases. By contrast, post-kala-azar dermal leishmaniasis in the Indian subcontinent is treated. However, considering that patients with post-kala-azar dermal leishmaniasis are typically healthy aside from cosmetic impact, the risk of treatment side-effects should be weighed against the aesthetic and public health benefits.

Cutaneous and mucocutaneous leishmaniasis

Most cutaneous leishmaniasis lesions will self-heal over 2–18 months.[90,91] A recent meta-analysis[148] reviewing clinical trials between placebo and study groups of no treatment for cutaneous leishmaniasis reported low spontaneous cure rates at 9 months (26%, 95% CI 16–38), particularly in *L braziliensis* (6%, 0–20). A conservative approach can be appropriate if there is evidence of spontaneous regression or in case of a well localised lesion caused by *L major* and *L mexicana*, as spontaneous healing usually occurs within 4 months in 70% of *L major* and 88% of *L mexicana* cases in immunocompetent hosts.[149] The decision to treat is driven by the need to accelerate cure, reduce scarring and the risk of dissemination, or later progression to mucocutaneous leishmaniasis, and can be supported by positive diagnosis and speciation. Other criteria for initiating treatment are multiple lesions (>5), large individual lesions (>4 cm), duration of more than 6 months, or location over a sensitive area such as the face or joints.[150,151] A recent comprehensive treatment guideline published by the Infectious Diseases Society of America[140] has suggested a management classification based on simple or complex cutaneous leishmaniasis, with local therapy recommended for non-self-curing simple cutaneous leishmaniasis and systemic therapy for complex cutaneous leishmaniasis (panel 3).

Two Cochrane reviews considered the evidence base for the treatment of cutaneous leishmaniasis as weak, because of the absence of standardisation and poor trial design.[152,153] Recently, efforts have been made to develop unified criteria and to define measurable and comparable endpoints.[154] Traditionally, treatments for cutaneous leishmaniasis have been in the form of intralesional injections (most commonly sodium stibogluconate), cryotherapy, thermotherapy, or topical application of agents such as paromomycin (panel 4). A combination of intralesional antimonials and cryotherapy is the first-line treatment option for Old World cutaneous leishmaniasis according to European guidelines, and can also be considered in New World cutaneous leishmaniasis where there is low risk for mucosal involvement.[150,155] Combining these approaches results in higher cure rates (89–91%) compared with either cryotherapy (57–75%) or intralesional antimonial alone (56–75%).[156–158]

Paromomycin ointment containing methylbenzethonium chloride twice a day for 10–20 days has been shown in a meta-analysis to be comparable to intralesional antimonial injections for *L major* cutaneous leishmaniasis.[159] Another paromomycin ointment containing 0·5% gentamycin showed similar efficacy for the treatment of New World cutaneous leishmaniasis. Recent phase 3 studies of cutaneous leishmaniasis caused by *L major* in Tunisia showed cure rates of 81–82%,[160] and those due to *L braziliensis* and *Leishmania panamensis* in Panama showed cure rates of 80% (NCT01790659). However, these results compare with a placebo cure rate of 58%, and almost no difference between formulations combining paromomycin and gentamicin or paromomycin alone. Thermotherapy has been rediscovered as a treatment; amastigotes are heat sensitive, and application of heat through radiofrequency heat therapy—up to a temperature of 40–42°C in a single session—led to cure

***Panel 3:* Clinical characteristics of New World cutaneous leishmaniasis that might modify management**

Simple cutaneous leishmaniasis

- Caused by a *Leishmania* species unlikely to be associated with mucosal leishmaniasis
- No mucosal involvement noted
- Absence of characteristics of complex cutaneous leishmaniasis
- Only single or a few skin lesions
- Small lesion size (diameter <1 cm)
- Location of lesion feasible for local treatment
- Non-exposed skin (ie, not cosmetically important)
- Immunocompetent host
- Lesions resolving without previous therapy

Complex cutaneous leishmaniasis

- Caused by a *Leishmania* species that can be associated with increased risk for mucocutaneous leishmaniasis, particularly those of the *Viannia* subgenus
- Local subcutaneous nodules
- Large regional lymphadenopathy
- More than four skin lesions of substantial size (eg, >1 cm)
- Large individual skin lesion (diameter >5 cm)
- Local treatment is not feasible because of the size or location of lesion
- Lesion on face including ears, eyelids, or lips; fingers, toes, or other joints; or genitalia
- Immunocompromised host (especially on cell-mediated immunity)
- Clinical failure of local therapy
- Unusual syndromes—eg, leishmaniasis recidivans, diffuse cutaneous leishmaniasis, or disseminated cutaneous leishmaniasis

This panel was adapted from the 2016 Infectious Diseases Society of America and American Society of Tropical Medicine and Hygiene guidelines.[140]

Panel 4: **Selected treatment regimens for cutaneous and mucocutaneous leishmaniasis**

Cutaneous leishmaniasis

Old World Leishmania major

Local treatment regimens:

- 15% paromomycin plus 12% methylbenzethonium ointment for 20 days; the evidence for this regimen is graded A
- Intralesional antimonials plus cryotherapy, both every 3–7 days for up to 5 sessions; the evidence for this regimen is graded A

Systemic treatment regimens:

- Oral fluconazole 200 mg for 6 weeks; the evidence for this regimen is graded A
- Pentavalent antimonials 20 mg/kg per day for 10–20 days; the evidence for this regimen is graded D
- Pentavalent antimonials 20 mg/kg per day plus pentoxifylline, 400 mg three times daily for 1–20 days; the evidence for this regimen is graded A

Old World Leishmania tropica and Leishmania infantum

Local treatment regimens:

- Thermotherapy, 1–2 sessions with localised heat (50°C for 30 s); the evidence for this regimen is graded A
- Pentavalent antimonials 20 mg/kg per day for 10–20 days; the evidence for this regimen is graded D
- Pentavalent antimonials 20 mg/kg per day for 15 days plus oral allopurinol 20 mg/kg for 30 days to treat recidivans caused by *L tropica*; the evidence for this regimen is graded C

New World Leishmania mexicana

Local treatment regimens:

- 15% paromomycin plus 12% methylbenzethonium ointment for 20 days; the evidence for this regimen is graded B

Systemic treatment regimens:

- Ketaconazole 600 mg once daily for 28 days (adult); the evidence for this regimen is graded B
- Oral miltefosine 2·5 mg/day for 28 days; the evidence for this regimen is graded B

New World Leishmania braziliensis

Local treatment regimens:

- Thermotherapy, 1–2 sessions with localised heat (50°C for 30 s); the evidence for this regimen is graded A

Systemic treatment regimens:

- Pentavalent antimonials 20 mg/kg per day for 10–20 days; the evidence for this regimen is graded C
- Liposomal amphotericin B 2–3 mg/kg per day up to 20–40 mg/kg total dose; the evidence for this regimen is graded C

New World Leishmania panamensis and Leishmania guyanensis

Local treatment regimen:

- Intralesional antimonials 1–5 mL per session every 3–7 days for up to 5 sessions; the evidence for this regimen is graded B

Systemic treatment regimens:

- Pentamidine isethionate intramuscularly on alternate days for three doses; the evidence for this regimen is graded C
- Pentavalent antimonials 20 mg/kg per day for 10–20 days; the evidence for this regimen is graded C
- Oral miltefosine 2·5 mg/day for 28 days; the evidence for this regimen is graded B

Mucocutaneous leishmaniasis

Any New World Leishmania species

Systemic treatment regimens:

- Pentamidine isethionate intramuscularly on alternate days for three doses; the evidence for this regimen is graded C
- Pentavalent antimonials 20 mg/kg per day plus pentoxyfylline, 400 mg three times daily for 1–20 days; the evidence for this regimen is graded A
- Liposomal amphotericin B 2–3 mg/kg per day up to 40–60 mg/kg total dose; the evidence for this regimen is graded C

WHO evidence grading system: evidence obtained from at least one properly designed randomised controlled trial was graded A; evidence obtained from well designed trials without randomisation was graded B; opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees were graded C; and expert opinion without consistent or conclusive studies was graded D. This panel was adapted from WHO.[5]

rates as high as 89% in *L major* and 94% in *L tropica*.[155] However, time to cure is variable, and results have not been consistently replicated. A cheap (US$3) and reusable device able to deliver consistent temperatures of 50–54°C for 3 min to each lesion for 7 days showed an overall cure rate of 60% at 6 months for *Leishmania peruviana, L guyanensis*, and *L braziliensis* cutaneous leishmaniasis.[161]

Systemic treatment for cutaneous leishmaniasis is usually reserved for immunosuppressed patients, extensive lesions, refractory disease, and–most importantly–mucocutaneous manifestations (panel 4).[5] Also, all cases of cutaneous leishmaniasis caused by *L braziliensis* and *L infantum* should be considered for systemic treatment.[162] Options include the effective but relatively toxic intravenous sodium stibogluconate regimen at 20 mg/kg for 20 days.[152] An increase in treatment failure with this regimen in *Viannia* species[163] might be associated with the parasites themselves harbouring a double-stranded RNA virus named Leishmania virus 1 (LRV1).[164,165] Alternatively, oral miltefosine for 28 days at the same dose used in the treatment of visceral leishmaniasis has been shown to be as effective as sodium stibogluconate in New World cutaneous leishmaniasis, and might also be used as a treatment for Old World cutaneous leishmaniasis, although evidence is based on case series rather than controlled studies.[166] The use of LAMB has been investigated at the FDA-recommended dose for visceral leishmaniasis (3 mg/kg per day for

Panel 5: Research priorities for leishmaniasis

Visceral leishmaniasis elimination in the Indian subcontinent

- Assess the effect of the elimination efforts
- Develop surveillance methods to timely detect case clusters before full-blown resurgence
- Assess feasibility and desirability of elimination (zero transmission to humans) of *Leishmania donovani*
- Develop a validated proxy marker for infectiousness of humans as alternative for xenodiagnosis
- Develop a practical, affordable marker of cellular immunity (eg, GMP-produced standardised leishmanin antigen or validated IGRA tests)

Vector and reservoir control

- Develop sustainable and targeted vector control strategies
- Reach better understanding of vector bionomics and its interactions with a reservoir, particularly in Africa
- Document vector population characteristics, including insecticide resistance
- Develop new vector and reservoir control technologies, including markers of successful control

Vaccines

- Research on vaccines to prevent leishmania infection, disease progression and with effect on transmission
- Research on vaccines for immunotherapy alone or in combination with other treatments

Diagnostics

- Develop affordable and reliable (species-specific) diagnostic tests for cutaneous leishmaniasis
- Develop a point-of-care biomarker for diagnosis of patients with relapse visceral leishmaniasis
- Develop a point-of-care test for the diagnosis of acute stage visceral leishmaniasis
- Develop more accurate tests for visceral leishmaniasis–HIV co-infection
- Develop markers for assessment of cure in visceral leishmaniasis, post-kala-azar dermal leishmaniasis, and cutaneous leishmaniasis
- Develop markers for asymptomatic infections

Treatment

- Oral, safe, short course (<10 days) drugs for both visceral leishmaniasis and cutaneous leishmaniasis
- Better treatment or prophylaxis for visceral leishmaniasis–HIV co-infection
- Safe and short course treatment for post-kala-azar dermal leishmaniasis and mucocutaneous leishmaniasis
- Modalities to boost parasite clearance (eg, immunomodulators)
- Drugs safe and effective enough to treat patients who are asymptomatic and patient with post-kala-azar dermal leishmaniasis

GMP=Good Manufacturing Practices. IGRA=Interferon γ Release Assay.

7 days given on days 1–5, 14, and 21 for a total dose of 21 mg/kg).[140] Observational studies have suggested pan-species' cure rates of between 80% and 90%,[167,168] but no controlled trials have been undertaken.

Importantly, yearly follow-up is recommended in patients treated for *L braziliensis* for up to a decade to ensure any progression to mucocutaneous leishmaniasis is identified early. Patients should also be counselled to report persistent nasal discharge, epistaxis, or blockage to the responsible clinician. Unlike in visceral leishmaniasis,[169] co-infection with helminths in the clinical course of *L braziliensis* has been recently shown to negatively influence patient outcomes.[170,171] However, early treatment with antihelminth therapy has not shown any effect.[172]

Prevention and control

To date, there is no registered vaccine that prevents human leishmaniasis. Several candidate vaccines that incorporate a range of antigens are in preclinical development,[173] but currently only three are in clinical studies. Most people who recover from leishmaniasis are immune to further infection, providing a good rationale for the research focus on vaccine development, as illustrated through the ancient practice of leishmanisation. Further details on the current status of leishmania vaccines and role of immunotherapy is included in the appendix (pp 11, 12).

Because patients with untreated visceral leishmaniasis, post-kala-azar dermal leishmaniasis, and cutaneous leishmaniasis are reservoirs of parasites, early case detection and management is one of the main control strategies. Many countries still rely on self-presentation of patients for care rather than active case detection, suggesting that many cases will remain within communities for prolonged periods, particularly when awareness of leishmaniasis is low. Recently, the important role of treatment delay in maintaining transmission was highlighted—ie, the duration between onset of symptoms and adequate treatment, as these people are highly infectious.[174] Although mathematical modelling pointed to the potential role of asymptomatic carriers of *L donovani* to maintain transmission, empirical evidence and recent observational studies stress the importance of the transmission from clinical cases and post-kala-azar dermal leishmaniasis.[175] This emphasises the importance of early detection and treatment for public health purposes, beyond the clinical benefit for the individual.

Vector control strategies in Asia are based on indoor residual spraying, long-lasting insecticidal nets, and environmental management. Indoor residual spraying is the main intervention in the elimination initiative of visceral leishmaniasis in the Indian subcontinent.

Recently, emerging resistance to DDT (dichlorodiphenyltrichloroethane) has been described,[176] and India has recently shifted to synthetic pyrethroids as also used in Bangladesh and Nepal. Although a long-lasting insecticidal bednet confers some personal protection against sandfly bites, its effectiveness to reduce the incidence of visceral leishmaniasis at the population level is not established. A cluster randomised trial done in India and Nepal did not show reduced transmission in villages where long-lasting insecticidal bednets were distributed compared with those where they were not distributed.[177] The absence of effect was attributed to transmission taking place outdoors, close to cattle sheds. The paucity of evidence available on environmental management showed no convincing effect of lime plastering of houses.

In east Africa, it is assumed that the vector mainly bites outdoors and there is no evidence for the effectiveness of insecticide spraying. Selective outdoor residual spraying in villages might be effective in reducing vector density, but in vast endemic areas where the population moves through *Acacia* or *Balanites* forests, such as in south Sudan, outdoor residual spraying is not feasible. Data from an observational study showed that mass long-lasting insecticidal bednet distribution in Sudanese villages had a protective effect of 59% (95% CI 25–78) against visceral leishmaniasis 17–20 months after distribution. This finding was observed despite the fact that the use of the long-lasting insecticidal bednets in the hottest months (April to June, which coincides with the biting season for sandflies) was very low (<10%).[178] As *P orientalis* bites between dusk and dawn, bednets might not be fully protective.

Reservoir control might be relevant in zoonotic foci (*L infantum* and *L major*) and was practised in the former USSR, but not in Europe. In Brazil, the effectiveness of the national policy of culling infected dogs is contested.[179] Three dog vaccines have been registered in either Brazil or Europe, with two (Leishmune and CaniLeish) conferring some protection under natural conditions. Deltamethrin-treated dog collars when systematically applied to all dogs were shown to protect against *Leishmania* infection in children in Iran.[180]

Global health policy, control, and elimination

In 2012, WHO published a roadmap on neglected tropical diseases, including the regional elimination of visceral leishmaniasis in the Indian subcontinent by 2020. For cutaneous leishmaniasis, a specific target was set in the eastern Mediterranean region: to detect 70% of all cases and to treat at least 90%. The elimination campaign of visceral leishmaniasis in the south Asian region launched in 2005 seems to have had some effect as reflected in a steady decrease in case numbers (figure 3). However, political and donor interest in visceral leishmaniasis is likely to wane once the target has been reached,[146] while there is no guarantee for long-term impact in a disease with cyclical transmission patterns and changing foci.[181] Therefore, an urgent research question is whether the more ambitious goal of zero transmission of the pathogen to humans is technically feasible and safe, given it might shift the age at infection and lower the herd immunity. Further details on control and elimination can be found in the appendix. Panel 5 lists crucial knowledge gaps for elimination of visceral leishmaniasis in Asia and control of visceral leishmaniasis and cutaneous leishmaniasis in other regions.

Conclusion

The Asian elimination initiative of visceral leishmaniasis and the 2012 London Declaration on neglected tropical diseases[182] have raised global awareness about the leishmaniases and substantially increased funding for control. Despite this increased interest, some of the classical challenges of a neglected tropical disease remain intact: few therapeutic options, suboptimal diagnostics, and poor community awareness—particularly for cutaneous leishmaniasis, which is not included in priority rankings. Moreover, many challenges remain in the elimination initiative of visceral leishmaniasis, primarily that once the target is reached, it is possible that the gains made will be reversed in time when political and donor focus shifts elsewhere, without having achieved a lasting outcome. There remain knowledge gaps that continue to hinder global progress in controlling leishmaniasis; while the optimisation of control tools remains a priority need. The question of whether a case can be built for the elimination of any transmission to humans of *L donovani* needs to be rapidly addressed.

Contributors

SB did the literature search and drafted the manuscript, and MB and SLC revised several versions critically. MB elaborated the section on epidemiology, diagnosis, and control. SLC elaborated the sections on vaccines and drug development. MB and SLC edited and reviewed the final manuscript. All authors approved the final manuscript.

Declaration of interests

We declare no competing interests.

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