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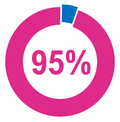
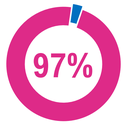
Epidemiology & transmission

Zoonotic visceral leishmaniasis (ZVL) is a widespread, highly fatal disease caused by the protozoan parasite *Leishmania infantum*. The disease was first reported in 1913, it was likely introduced to Brazil following colonization from the Spanish and Portuguese. VL was originally focused in rural areas but has since been spread to cities due to migration of humans, animal hosts and vectors; its prevalence and impact is intrinsically tied to poor nutrition and socioeconomic instability. The main vector of the disease in Brazil is the female phlebotomine sandfly *Lutzomyia longipalpis*. Transmission involves a series of successive bloodmeals by *L. longipalpis,* injecting canine and human hosts with the promastigote form of the parasite and subsequently ingesting the amastigote form. As the parasite is transmitted via movement of infected blood, disease can also occur following intravenous drug use, blood transfusions, organ transplantations and other medical procedures (van Griensven and Diro, *2019*).



of cases of visceral leishmaniasis are fatal if left untreated (WHO, *2022*).



of cases in Latin America were reported in Brazil as of 2019, illustrated in Figure 1 (Soares Santana et al., (2021)

Disease

Visceral leishmaniasis itself is brought on by the targeting of the reticulo-endothelial system in various tissues (van Griensven and Diro, *2019*). Infection is found throughout the entire mononuclear phagocytic system, but the liver, spleen and bone marrow are the most severely affected. The incubation period can last from 2-6 months before clinical signs of disease are displayed, though individuals can also be asymptomatic. The symptoms of VL can vary depending on location, but often include weight loss, high fever, cutaneous lesions, enlargement of the liver, spleen or lymph nodes (Tiago et al., *2020*). The disease is highly fatal without treatment, with L. infantum having been described as the "deadliest parasitic killer after malaria" (Makoni, *2021*). Several stages of progression are associated with zoonotic visceral leishmaniasis, ranging from acute to chronic. There is also distinct possibility of relapse even following successful treatment due to latent amastigotes inhabiting macrophages (Kumar et al., *2020*). The disease is especially prevalent in children under 10 years and immunocompromised adults.

It's been described as the **"deadliest parasitic killer** after malaria".

Introducing *Leishmania infantum*

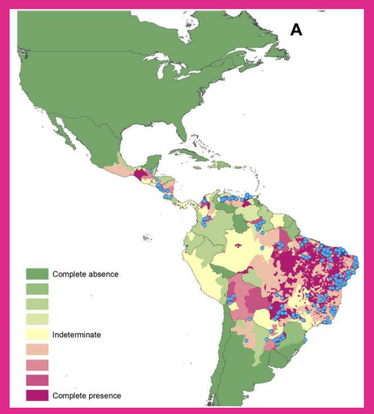


Figure 1. Reported presence of visceral leishmaniasis in the Americas. Blue dots represent centers of occurrences, with the majority being focused on the east coast of Brazil (Pigott et al., *2014*)

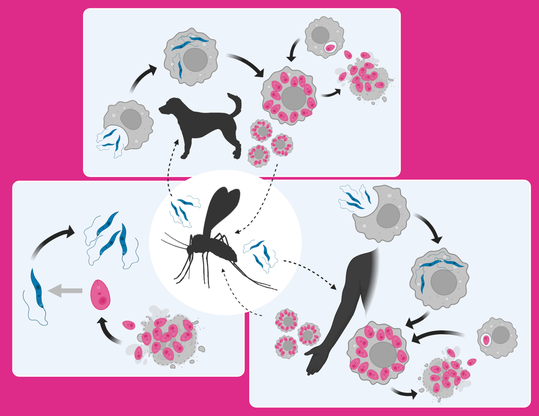


Figure 2. Life cycle of Leishmania infantum. Illustrates the rotation of inhabiting canine hosts, humans hosts and the sandfly vector. Made by author using BioRender.

Life cycle

The life cycle of *L. infantum* revolves around the transition between two forms: the promastigote (represented by narrow blue cells) and the amastigote (the circular pink cells) . During a bloodmeal, a female sandfly releases promastigotes into the dog or human host, along with salivary proteins and gut microbiota. Macrophages engulf and phagocytose the parasite cells, where they replicate by simple division and transform into infectious amastigotes. The infected macrophages burst, allowing the amastigotes to invade and infect other macrophage cells, as shown in Figure 2 above. Compromised macrophages are then taken up during another bloodmeal before lysing in the gut, the liberated amastigotes are able to transition back into promastigotes and multiply once again. The sandfly can now transmit the disease further to other mammalian hosts, completing the cycle.

Diagnosis

Diagnosing zoonotic visceral leishmaniasis proves difficult for several reasons: asymptomatic cases; a multiple month incubation period; confusion or coinfection with similarly presenting diseases like typhoid, tuberculosis and malaria. Testing methods can be targeted towards the clinical, immunological, microbiological or molecular aspects of VL, with the most common being antigen-based rapid diagnostic tests (RDT), direct agglutination tests (DAT) and microscopy. The RDT tests for presence of recombinant protein K39 antibodies via immunochromatographic strip (ICT) (Kumar et al., *2020*). In order to further attempts to eradicate visceral leishmaniasis, diagnosis needs to meet the criteria of ease of use, sensitivity, low cost, fast results and accessibility. This illustrates how necessary and significant the introduction of a rapid diagnostic test is, due to the global prevalence of the disease.

Treatment

As there's no human vaccine, current VL treatment consists of drug therapies with varying degrees of side effect severity and toxicity. The specific drug compound depends on location, though liposomal amphotericin B is the primary choice in endemic areas as it's effective and generally safe. Unfortunately, because the drug has also proved effective against mucormycosis, demand for it increased during the pandemic, resulting in a global shortage for VL treatment (Makoni, *2021*). Following liposomal amphotericin B, antimonials have proved the most effective but it is highly toxic, and resistance has since developed. Due to these shortfalls, combination therapies are being investigated, along with adapted strategies required for immunocompromised individuals.

Prevention and control

The lack of a human vaccine and prevalence of both vector and reservoir hosts renders prevention of visceral leishmaniasis extremely difficult. Hence, the focus has been directed towards implementing control strategies, which come with their own concerns. Control of vectors, reduction of animal hosts and early detection in humans have been identified at the main targets of control initiatives. The most impactful avenue is to disrupt the transmission cycle, which would be to treat and prevent VL in dogs. This would require long term commitment to expensive treatment in addition to issues administering the treatment across Brazil (Bi et al., *2018*).

What's next?

In the case of zoonotic visceral leishmaniasis, the pathology and mechanisms are relatively well understood. The future work lies in developing practical, realistic approaches to widespread treatment and prevention as a neglected tropical disease (NTD). Current research involves using mathematical models for transmission and disease progression, but the distinct lack of real-world data invites the problem of application to large scale human populations. This is further limited by the lack of diversity in available computer models. An example of successful elimination progress can be seen in across south Asia due to large donor funding and political backing allowing access to diagnosis, treatment and control tools (Makoni, *2021*). The replication of these circumstances in Brazil would lead to significant steps in the right direction towards elimination and eradication.

References

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