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Leishmanioses: avanços científicos no controlo, diagnóstico e epidemiologia moleculares no contexto dos Países de Língua Oficial Portuguesa

Leishmaniasis: scientific advances in control, diagnosis and molecular epidemiology in the context of Portuguese speaking countries

Leishmanioses: avancées scientifiques dans le contrôle, le diagnostic et l'épidémiologie moléculaire dans le contexte des pays lusophones

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Resumo

As leishmanioses são doenças tropicais negligenciadas causadas por parasitas protozoários do género *Leishmania*. Embora as estratégias e esforços de controle tenham contribuído para a redução da sua prevalência e impacto, até 1 milhão de casos ainda ocorrem por ano, e a leishmaniose visceral ainda mata até 90 000 pessoas anualmente. Alguns importantes avanços no controle da leishmaniose são apresentados e discutidos nesta revisão, com foco nos países de língua portuguesa. Compara-se a situação epidemiológica da leishmaniose humana em Portugal e no Brasil e analisam-se casos notificados noutros países. Os métodos de diagnóstico são revistos de forma breve e genómica e sistemas de aprendizagem de máquina ("machine learning") são discutidos juntamente com a necessidade de algoritmos validados. O desenvolvimento de medicamentos e vacinas é discutido, incluindo o potencial para vacinas terapêuticas e de RNA. O advento da epidemiologia genómica é analisado, inclusivamente na redefinição da taxonomia de *Leishmania*, assim como o uso de ferramentas moleculares para identificação de potenciais reservatórios. Por fim, aborda-se os primeiros passos no desenvolvimento da medicina de precisão. Em conclusão, embora tenha havido avanços importantes no controle da leishmaniose, ainda permanecem desafios significativos, que podem ser efetivamente superados com o aumento do investimento e um maior compromisso político.

Palavras-chave: Leishmaniose, diagnóstico, vacinas, fármacos, epidemiologia molecular, medicina de precisão

Abstract

Leishmaniases are neglected tropical diseases caused by protozoan parasites of the genus *Leishmania*. Although control strategies and efforts have contributed to a reduction in the overall prevalence and in the burden of disease, up to 1 million cases still occur every year, and visceral leishmaniasis still kills up to 90 000 people annually. Selected advances in the control of Leishmaniasis are presented and discussed in this review, with a focus on Portuguese speaking countries. The epidemiological situation of human leishmaniasis is compared in Portugal and Brazil, and reports of cases in other countries are analyzed. Diagnostic methods are briefly reviewed, and genomics and machine learning systems are discussed alongside the need for validated algorithms. Drug and vaccine development are discussed, including the potential for therapeutic and RNA vaccines. The advent of genomic epidemiology is analyzed, including in the redefinition of *Leishmania* taxonomy, as well as the use of molecular tools for identification of potential reservoirs. Finally, the prospect of precision medicine is addressed. In conclusion, although important advances are under way for leishmaniasis control, significant challenges still remain, which can be effectively overcome by increased investment and stronger political commitment.

Keywords: Leishmaniasis, diagnosis, vaccines, drugs, molecular epidemiology, precision medicine.

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Résumé

Les leishmanioses sont des maladies tropicales négligées causées par des parasites protozoaires du genre *Leishmania*. Bien que les stratégies et les efforts de lutte aient contribué à réduire la prévalence globale et la charge de morbidité, jusqu'à 1 million de cas surviennent encore chaque année et la leishmaniose viscérale tue encore jusqu'à 90 000 personnes par an. Certaines avancées dans le contrôle de la leishmaniose sont présentées et discutées dans cette revue, en mettant l'accent sur les pays lusophones. La situation épidémiologique de la leishmaniose humaine est comparée au Portugal et au Brésil, et les déclarations de cas dans d'autres pays sont analysées. Les méthodes de diagnostic sont brièvement passées en revue, et les systèmes de génomique et d'apprentissage automatique sont discutés parallèlement au besoin d'algorithmes validés. Le développement de médicaments et de vaccins est discuté, y compris le potentiel de vaccins thérapeutiques et à ARN. L'avènement de l'épidémiologie génomique est analysé, notamment dans la redéfinition de la taxonomie des *Leishmania*, ainsi que l'utilisation d'outils moléculaires pour l'identification de réservoirs potentiels. Enfin, la perspective de la médecine de précision est abordée. En conclusion, bien que des avancées importantes soient en cours dans la lutte contre la leishmaniose, des défis importants subsistent, qui peuvent être efficacement surmontés par des investissements accrus et un engagement politique plus fort.

Mots-clés: Leishmaniose, diagnostic, vaccins, médicaments, épidémiologie moléculaire, médecine de précision.

Introduction

Leishmaniasis is a neglected tropical disease caused by protozoan parasites of the genus *Leishmania*, Order Kinetoplastida. Despite control improvements and efforts, it is estimated that 700 000 to 1 million new cases still occur per year, worldwide [1], a significant percentage of which is unreported. Of the different clinical forms of leishmaniasis, cutaneous leishmaniasis (CL) is the most common, and visceral leishmaniasis (VL), which is almost always fatal if not treated, has an incidence of 50 to 90 000 per year.

The life cycle of *Leishmania* includes a vertebrate host and a vector, a phlebotomine sand fly. Most vertebrate hosts are mammals, including humans, as well as rodents, canids, marsupials, hyraxes, and others, although the sub-genus *Leishmania* (*Sauroleishmania)* has adapted to reptiles [2]. In the mammal, the amastigote form is an intracellular parasite of macrophages, and in the vector is transforms into the promastigote form, characterized by the presence of a long anterior flagellum. The parasite migrates to the sand fly stomodeal valve and is injected in the vertebrate's skin. Exposure to the parasite may not implicate development of clinical symptoms.

In the cutaneous form, the parasites remain at the site of injection and produce an ulcerated lesion, that does not heal with antibiotics. In the visceral form, the parasites reach internal organs, such as the liver, the spleen, the bone marrow, and lymph nodes, leading to immunosuppression. Visceral leishmaniasis has a high mortality rate without treatment. The mucocutaneous form also results from the parasites leaving the site of injection, causing lesions in the mucosa and cartilage, particularly in the head, such as in the nasal and oral cavities and ears. The parasites responsible for the mucocutaneous form, or mucocutaneous leishmaniasis (MCL), can also cause skin lesions away from the site of injection. Other forms include post-kala-azar dermal leishmaniasis caused by some of the same parasites that are agents of visceral leishmaniasis in East Africa and the Indian sub-continent. Visceral leishmaniasis is distributed throughout Southern Europe, Asia, Central America, North and East Africa, but reaches the highest prevalence in South America and the Indian sub-continent. Cutaneous leishmaniasis is found in America, Europe, Africa, and Asia, while mucocutaneous leishmaniasis is restricted to South and Central America.

The taxonomy of the genus *Leishmania* is complex and dynamic. The most recent taxonomic review (2018) proposed to keep the sub-genera *Leishmania (Leishmania)*, *Leishmania (Viannia)*, *Leishmania (Sauroleishmania)* and created a new sub-genus - *Leishmania (Mundinia)* -, created the new genus *Porcisia*, for parasites of guinea pigs, and reclassified some species previously included in the genus *Leishmania* into the genus *Endotrypanum* (2). At species level, the number of species is still debated, particularly regarding closely related species such as *L. infantum* and *L. donovani*, or *L. braziliensis* and *L. peruviana* [3].

In this brief review, I will address the status of human leishmaniasis in Portuguese-speaking countries and selected important scientific advances in the control, including diagnostics, treatment and vaccines, and the molecular epidemiology of leishmaniasis.

Leishmaniasis in endemic Portuguese speaking countries

Among the Portuguese speaking countries leishmaniasis is endemic and has historically been present in Portugal and Brazil, although the epidemiological setting is markedly different.

Leishmania infantum is endemic both in Portugal and Brazil, having been transported to Latin America by European settlers within the last 500 years, where it became referred to as the synonymous species *L. chagasi* [4,5]. This species is the agent responsible for VL in both countries, and it can also cause cutaneous leishmaniasis [6,7]. Whereas it is transmitted by species of the genus Phlebotomus in Portugal, as in Europe, it encountered a different but permissible vector in Brazil: *Lutzomyia longipalpis* [8].

VL by *L. infantum* had been associated with higher incidences in children, but the association with the HIV/AIDS epidemic has increased the incidence, particularly among adults. In Portugal, this increase took place mainly in the 1990s but, thanks to HAART implementation, the median incidence has decreased from 0.50 in 2010–2012 to 0.37 /100 000 inhabitants in 2013–2018 [9], but with a reported incidence of 0.1/100 000 inhabitants/year from 2015-17, with only 6 cases reported in 2018 [10], in children and adults. In contrast, in Brazil, and despite control measures, the proportion of *HIV-Leishmania* co-infections has increased steadily since 2018 along with the case fatality rate (above 10%), even though the number of cases and the number of deaths has decreased [11]. Brazil still reported the highest number of cases (97%) as well as the highest incidence among South American countries in 2021.

Despite the reduction in reported human cases in Portugal, canine *L. infantum* has seemingly spread from a small number of identified endemic regions to the entire country, with an overall prevalence of 12.5 % [12], but with higher prevalence in regions near the border, and the south (Algarve). Conversely, in Brazil, *L. infantum* has become more urbanized [13].

In addition to *L. infantum*, Brazil is endemic for New World species that cause CL and MCL. In 2021, the prevalence was estimated at 13.5 cases /100 000 inhabitants [11], with the highest prevalence in forested areas, particularly the Amazon.

Leishmaniasis in other Portuguese speaking countries

While other Portuguese speaking countries are not considered endemic for leishmaniasis, cases have been reported in Angola, Guinea-Bissau, and East-Timor.

In the 1990s, it was reported a case of seemingly autochthonous VL, caused by *L. infantum*, in a 26 year-old man from Angola, but presenting in Spain, [14]. Since then, only recently, another autochthonous infection was found in a dog in Luanda [15], which tested positive for *Leishmania* through the DAT (direct agglutination test) and PCR. This study included 103 dogs from a veterinary clinic, among which another dog was also found positive but had been imported from Portugal. More recently, in Huambo, two suspected human cases of CL, in two adult males, based on clinical presentation and microscopy [16] and confirmed through nested-PCR [17] following from 38 suspected cases reported in 2017 in one village (Tchissenque) [18], but it was not possible to identify the agent to the species level. It remains uncertain whether leishmaniasis is an emerging disease in Angola or if it had simply gone undetected so far. Considering that Namibia, which borders Angola to the south, is endemic for CL caused by *L. tropica*, it is possible that unreported CL is present in southern Angola, a neglected region of the country. Further research and monitoring are crucial to gain a comprehensive understanding of the situation and prevent outbreaks.

The first report of leishmaniasis in Guinea-Bissau was in an HIV-2 infected 10-year old girl, presenting with "atypical leishmaniasis" in 1988 [19]. Only recently, in a survey of cutaneous lesions in the Bijagós Islands, by a researcher of the National Institute of Health, *Leishmania* DNA was detected by PCR (Mauricio, IL, and Cortes, S, Varela, J – manuscript in preparation). No records of leishmaniasis were found for the other Portuguese speaking African countries: Mozambique, Cape Verde or São Tomé and Príncipe. However, 46 CL cases were reported in East-Timor during November 1999 [20], confirmed by microscopy, by a French military medico-surgical group, deployed with INTERFET (International Force for East Timor). The high number of cases suggested that CL was indeed endemic in East-Timor but had remained undetected.

No other official reports have been published, and a more recent cross-sectional survey of skin infections in the country did not identify skin lesions compatible with CL [21], although a suspected CL case in an adult woman from Dili is mentioned in an epidemiological bulletin [22], which referred that potential vector sandflies were detected in urban Dili by NL Kalra, a WHO medical entomologist. Unfortunately, identification of the *Leishmania* species has not been published so far, and no records of treatment outcome were found.

The WHO Status of Endemicity site lists East-Timor and Guinea-Bissau as "No autochthonous cases" reported as of 2021, and Angola as "Previously reported cases" (https://apps.who.int/gho/data/view.main.NTDLEISHVENDv).

In summary, detection of leishmaniasis cases in African Portuguese speaking countries and East-Timor, has largely been spurious or in small surveys. However, some evidence suggest that it may be under-reported, possibly due to lack of awareness by health professionals, but also lack of knowledge and means for diagnosis.

Diagnosis

Leishmaniasis diagnosis can be accomplished through different methods, which can be grouped in parasitological, immunological, and molecular methods [23, 24], for example. Parasitological methods detect the parasites in biological samples. Immunological methods are used to detect components of the immune response following exposure to the parasites or to detect parasite components (antigens) in circulation. Molecular methods are used to detect nucleic acids of the parasites, usually DNA.

Most diagnostic methods, but particularly parasitological methods, require biological samples, such as skin for CL, which are invasive, although non-invasive methods have been developed for skin forms [25]. Parasites have been isolated from blood in CL cases [26], which may be a less invasive option. The highest sensibility for VL diagnosis is, reportedly, spleen aspirate, which is high risk for the patient, but samples can also be obtained from bone marrow, lymph nodes, and even the buffy coat from blood [23,27] and parasites have also been isolated from blood from other animals [28,29]. Isolation of parasites from MCL cases is difficult, although in studies it was possible to isolate *Leishmania* from blood, even if not from skin lesions [30].

Parasitological methods include microscopy, usually with Giemsa staining, *in vitro* culture, and inoculation in experimental animals [23,24]. Although these methods can be done at a relatively low cost, they require specialized or trained personnel, and can take hours (for microscopy), days (for culture) or weeks (animal model inoculation). Particularly in the case of VL agents, laboratories where infective forms are grown and maintained should also meet safety standards to protect workers from infection.

Several serological methods are available for diagnosis [23,24]. The Montenegro Skin Test detects cellular immunity, maintained by live parasites in the organism. Healthy infected people can be positive. Many serological methods can be cumbersome to prepare, such as those that require whole antigen preparations (such as DAT – direct agglutination test) or even intact parasites (such as IFAT – immunofluorescence antibody test), and skin injection and blood collection are invasive. Improved methods have been developed to reduce the time to diagnosis, such as immunochromatography (ICT) and KATEX for antigen detection in urine, which is also more convenient and less invasive, but sensitivity can be as low as 47%, compared with the sensitivity of most immunological methods (75-100%) [23].

A variety of molecular methods has also been developed for detection of *Leishmania* DNA, or RNA, most based on PCR, including nested and semi-nested-PCR, multiplex PCR, real time PCR, etc., sometimes coupled with restriction enzyme applications (such as PCR-RFLP and AFLP) for species identification [24]. PCR based methods require thermocyclers, which may not be widely available, and isothermal methods, such as NASBA (Nucleic acid sequence-based amplification) and LAMP (loop mediated isothermal amplification), have also been developed. NASBA amplifies RNA, although it can be adapted to amplify DNA. LAMP amplifies DNA by using an enzyme with strong DNA displacement activity (*Bst* DNA polymerase). These methods have been applied to samples such as blood, serum, buffy coat, buccal swabs, urine, and can produce a result from minutes to hours. The sensitivity of these methods tends to be over 80%, although NASBA has reported values as

low as 60%. Specificity can vary with the target and the primers used, with some PCR methods reporting values as low as 60%, while most methods report specificity above 83%, and NASBA above 70% [23]. An advantage of NASBA in relation to DNA detection methods is that it detects live parasites because RNA has a shorter life than DNA, and it is possible that parasite DNA persists in some samples after cell death, although available evidence suggests that it is not the case in the host [31,32]. Many of these methods can be used or adapted to identify *Leishmania* species, such as multiplex PCR, and even for intra-specific genetic diversity studies, particularly when coupled with restriction analysis (PCR-RFLP), for example, but mostly with DNA sequencing of the amplification products. Next-generation sequencing has allowed detection of co-infection with different *Leishmania* species [33] and could permit detection of intra-specific variants, and even the emergence of mutations responsible for drug resistance during treatment [34].

Given the choice and diversity of diagnostic methods, and the relative advantages and disadvantages, which depend on the clinical form of the disease, optimized evidence-based validated algorithms should be developed and published for humans [35] as well as for other animals, such as cats [36], and applied in diagnostics laboratories.

Increasingly, machine learning systems are being developed to facilitate diagnosis, such as to detect amastigotes in slide images [37], thus reducing personnel costs, or applied to novel methods, that yield complex data, such as UV spectroscopy to detect antigen-antibody complexes directly in blood sera from dogs [38].

Treatment

Currently, only five drugs are available for leishmaniasis treatment [39]. Availability is a problem, they can be expensive, often have associated serious side effects, and almost all should be injected, during lengthy treatment courses. Pentavalent antimonials were the first known drugs to be effective and cause DNA damage, while pentamidine affects kinetoplast DNA replication and transcription. Amphotericin B leads to membrane disruption, paromomycin acts on protein synthesis and miltefosine disrupts mitochondrial function. Miltefosine is the only drug so far to become available in oral form and it is effective for Indian VL [40] as well as CL [41], although with less than optimal efficacy. Intralesional antimonials are strongly recommended for CL in Brazil [42], but a recent Cochrane review found that oral miltefosine and intra-muscular meglumine antimoniate (an antimonial) probably increase CL cure rates, but some forms of treatment used are not better than placebo, although data quality should be improved for a more robust evaluation [43].

There is, thus, scope for improvement of leishmaniasis treatment, and research for alternative drugs is under way, although there are little financial incentives for pharmaceutical companies, as for all neglected tropical diseases. Alternative compounds that have been or are under evaluation are, for example, peptides, as recently reviewed [39], and natural compounds for CL [44].

Vaccine development

Few vaccines have been developed for leishmaniasis, and all that have been commercialized are for canine leishmaniasis (CanLeish) by *L. infantum*, both in Brazil and Europe [45]. Vaccines can be based on whole parasites, either dead or alive-attenuated, or parasite components. The components can be non-specific, such as excreted/secreted proteins, or specific proteins, alone or in combination, such as gp63, LACK, and others. Furthermore, these components can be delivered as proteins or peptides, as DNA, and, thanks to the success of the vaccines against COVID-19, RNA vaccines are also being developed.

There are two vaccines that have been implemented against CanLeish in Brazil: Leishmune (in 2003) and Leish-Tec (in 2013). Leishmune was commercialized by Zoetis and it was based in a fraction of gp63 from *L. donovani*. It was suspended in 2014 [46]. Leish-Tec is based in the recombinant protein A2, which does not interfere with serological diagnosis, and has been commercialized by Hertape Calier Saúde Animal. However, this vaccine, has also been suspended by the Brazilian Ministry of Health as of May 2023, due to issues with antigen concentration [47,48]. A third vaccine has undergone Phase I and II trials, having been considered suitable for Phase III trials [46]. This vaccine is composed of *L. braziliensis* crude antigens with a saponin adjuvant.

In the European Union, including Portugal, CaniLeish was the first vaccine to be approved, in 2011, and commercialized by Virbac, Animal Health (France), with a yearly schedule. CaniLeish was made of excreted/secreted antigens from *L. infantum* promastigotes with a saponin as adjuvant. However, studies showed a lack of efficacy in a one-year study in a natural population [49]. In 2016 was approved a second vaccine, LetiFend, developed by the Laboratorios LETI, Spain, that contains a recombinant protein with five epitopes from four proteins [50]. LetiFend is currently preferred, as it has been shown to cause less severe side effects [51]. Very recently, at the end of 2022, Neoleish by CZ VETERINARIA, S.A., Spain, has been approved by EMA (European Medicines Agency) [52]. This DNA vaccine, coding for the antigen LACK, is applied as nasal spray, which greatly facilitates application. It is well tolerated, but provides immunity for only six months, according to the approval document. None of these vaccines claims to fully prevent disease, but to reduce or block transmission, and to reduce the risk of clinical disease. In addition to the lack of full protection, the other great challenge for *Leishmania* vaccines is long lasting protection, as it has been shown that it requires parasite persistence in the host and some authors advocate using genetically modified live attenuated vaccines [53]. Indeed, CRISPR has been used to generate a second generation attenuated *L. major* vaccine with promising protection results in mice (54) as well as a centrin-deficient *L. mexicana* vaccine with good results against a same species challenge in mice [55] but also against *L. donovani* in hamsters [56].

The development of RNA vaccines for COVID-19 has paved the way for exploring similar strategies against other pathogens, and strategies for developed are being explored [57]. Replicon RNA vaccines have the potential to stimulate not only CD4 T cells but also CD8 T cells, thus generating a much more robust and long-term immune response compared to defined subunits or mRNA. However, the path from vaccine design to widespread vaccine deployment is lengthy and arduous, often hindered by limited and sporadic funding [58]. It is, thus, essential to involve epidemiological and economic modeling for more efficient pathways. These models can provide valuable insights into the optimal deployment of vaccines, considering various factors such as disease transmission dynamics, cost-effectiveness, and population coverage.

Finally, therapeutic vaccines should be considered as a potential support for treatment, considering that the immune status of the host plays a significant role in development and severity of symptomatic disease, as well as in determining treatment outcomes. As a recent example, a combination of allopurinol and immunization with a Leish-F2 antigen formulation has been shown to be essential to achieve long term *L. infantum* clearance in dogs [59].

Molecular epidemiology

Molecular epidemiology studies of leishmaniasis have benefited from new generation DNA sequencing to enter the age of genomic epidemiology thanks to the reduction in costs for whole genome sequencing (WGS) [60]. Such studies elucidate the taxonomy of the parasites and the relationships between the molecular diversity of the parasite and their distribution, clinical presentation, and prognosis. WGS from an increasingly higher number of isolates has allowed higher resolution analyses, such as for *L. donovani* and *L. infantum* [61]. Diagnosis has also benefited from WGS, such as for *L. braziliensis* [62].

Improved molecular tools were fundamental to recently establish subgenus *Leishmania* (*Mundinia*) [2], of which are part the also recently described species *L. macropodum*, *L. martiniquensis* and *L. orientalis*, as well as the yet unnamed *Leishmania* sp. Ghana, as well as *L. enrietti*. This sub-genus, that seems to be an ancestral lineage of *Leishmania*, has emerged as a novel human and animal pathogen throughout the World, in four continents, including Australia [2,63]. One question that emerged regards the vectors of these species, and a potential vector has been identified from experimental evidence as biting midges, genus *Culicoides* (Diptera: Ceratopogonidae) [64]. Molecular tools are essential for detection of *Leishmania* in the vector and confirmation of previously unidentified vectors. However, confirmation of vector capacity must still be undertaken through experimental infection.

The application of molecular tools has been key to investigations into the hosts of Leishmania, to both detect and characterize the parasites. Non-human primates, both sylvatic and in captivity, have been found infected with various species of Leishmania (*L. braziliensis*, *L. shawi*, *L. amazonensis*, *L. infantum*, *L. major*) [65].

Although most infections were asymptomatic, some species have been associated with clinical disease: *Ateles paniscus - L. amazonensis; Callicebus nigrifrons*, *Gorilla gorilla*, *Pongo pygmaeus - L. infantum*. Many other species of non-human vertebrates have also been found infected, with *Leishmania* spp. as analysed in a systematic review in 2021 [66]. For example, *L. infantum* was detected in species of the Orders Carnivora (carnivores), Chiroptera (bats), Cingulata (armadillo), Didelphimorphia (opossum), Eulipotyphla (hedgehog), Lagomorpha (rabbit, hare), Pilosa (anteater) and Rodentia (rodents), and, recently, also in bovines (Order Artiodactyla) in Brazil [29].

Precision medicine

Demonstrably, the clinical outcome of *Leishmania* infection is heavily dependent on the immune status of the human host, and genetic epidemiology studies have also shown that it is also dependent on the genetic make-up of the host [67]. A single factor, HLA-DRB1, has been implicated in susceptibility to *L. donovani* and *L. infantum* infection in, respectively, India and Brazil. Six loci have been implicated in susceptibility to CL by *L. braziliensis* [68] and SNPs implicated in susceptibility to CL are related to immune response and prognosis [69].

Simultaneously, it has been shown that the genome of the parasite explains 83% of the mortality by *L. infantum* in northeastern Brazil, while the patient sex explains 60% [70]. The study found significant associations between 17 copy number variants (CNV) in the parasite and mortality. Such studies lead the way for precision medicine, in which patient and parasite markers allow more precise prognosis and tailored treatment schedules, such as outlined for control of VL by *L. donovani* [71].

Conclusions

Leishmaniasis remains a significant challenge for control in humans and reservoirs, but advancements in control tools offer a significant opportunity to reduce the burden of this neglected disease, particularly in disadvantaged populations. Improvements in diagnostic tools have led to greater speed and accessibility of diagnosis. Furthermore, safer, and more effective drug formulations and combinations have improved treatment choices, but cheaper safer drugs are still needed, particularly in light of increasing drug resistance. Vaccination would be an important control tool, but existing vaccines are limited in scope, provide limited protection, and implementation issues have been encountered, leading to suspension of some. RNA vaccines hold great promise for long-lasting and effective protection. To enhance control strategies, genomic epidemiology studies, along with identification of reservoirs and vectors, can improve models. Better understanding of host and parasite genetic factors, through genome wide association studies, will enable implementation of personalized, precision medicine, which can be tailored for host-parasite combinations, resulting in optimized, effective, and safer treatments. While effective control of these neglected diseases remains a challenging goal, significant strides are being made in combating leishmaniasis and improving the lives of those affected.

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Conflicts of interest

The author declares that she has no conflicts of interest regarding the subject of this work.

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