InfoLEISH

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EDITORIAL

Time is inexorable and 2030 is getting closer. The WHO road map for neglected tropical diseases 2021-2030 set specific and cross-cutting targets and strategies for the control of cutaneous leishmaniasis (CL) worldwide, aiming to detect and report 85% of all CL cases and treat 95% of all those detected and reported cases in all CL-endemic countries. Three critical actions were identified: 1) developing an oral or topical treatment to be used at health centre level; 2) availability of rapid diagnostic tests (RDTs) for case detection and treatment; and 3) improving surveillance and monitoring of the impact of control interventions.

As time passes, while some progress has been made, we see with concern that the target for CL control might not be achieved by 2030 as planned.

DNDi, in collaboration with its partners, continues advancing in the development of an oral drug and is now planning a proof-of-concept study, expected to be initiated in 2024, to test a new oral chemical entity. We also expect to complete in 2024 the multiple ascending dose study of the CpG D35 immunomodulator which is now being conducted in Colombia.

Several groups, at different clinical stages, are working with different topical formulations and one more oral compound. However, considering the attrition rate of all compounds during clinical development, the time needed to conduct phase II and III studies, the funding needs, and all Chemistry, Manufacturing and Controls studies required by stringent regulatory authorities to register a new treatment, we don't think that any of the above-mentioned treatment options will be available by 2030.

A similar phenomenon is observed in the field of diagnostic: there is lack of affordable and sensitive RDTs for the detection of CL cases at the primary healthcare level. Looking at the international scenario, it seems that a RDT for CL detection will not be available by 2030 either.

A critical and major bottleneck hindering research and development efforts of CL diagnostics and treatments remains the lack of funding. Astonishingly, despite all the evidence regarding the burden of CL on patients' quality of life, disability, social segregation and mental health, most donors, funding agencies and other stakeholders continue to disregard CL as an important NTD. Radical changes are needed to shift this understanding and bring more funds for CL R&D. Therefore, all of us must urgently undertake every effort to raise CL awareness on every opportunity.

BYRON ARANA, DNDi

Summary

CHALLENGES AND URGENT ACTIONS FOR THE DIAGNOSIS OF CUTANEOUS LEISHMANIASIS: A MANIFESTO BY REDELEISH RESEARCHERS

MARINA CERTO, JOELLE RODE, and DIOGO GALVÃO, DNDi



The innovation and access gap in relation to diagnosis continues to represent one of the major challenges for the control of cutaneous leishmaniasis (CL) as a public health issue. The development of rapid, high-performance, diagnostic tests that are easy to use at the primary health care level is critical to reach the targets set for CL in the World Health Organization (WHO) Roadmap for Neglected Tropical Diseases 2021-2030. Currently, the lack of adequate tools leads to diagnosis and treatment delays, increasing the suffering and the risk of morbidity for the affected people.

To guide this need for innovation, the Foundation for Innovative New Diagnostics (FIND), together with experts from endemic regions, has proposed a target product profile (TPP). This TPP was approved by the WHO Diagnostic Technical Advisory Group (WHO DTAG) for Neglected Tropical Diseases, which establishes the requirements for the development of rapid diagnostic tools for dermal leishmaniasis.

Recognizing this R&D priority, in August 2022, during their seventh meeting held at the WorldLeish 7 international congress, redeLEISH researchers launched a Manifesto aimed at the scientific community, health authorities and funders. The document draws attention to the urgent need for the technological development of user-friendly diagnostic tests for CL, guided by the criteria set forth in the TPP. Given the scarcity of resources, the Manifesto also highlights the urgent need of increasing incentives and

funding for all stages of the process. According to the latest G-Finder report[1], in 2021 only US$200,000 were invested in research and development (R&D) for leishmaniasis diagnosis, accounting for 0.5% of the total funding for the disease (US$40 million).

Stakeholders need to jointly commit to boost the development, validation, production and implementation of new and suitable diagnostic tools for this disease. In addition, it is important to encourage initiatives that allow patients affected by CL to access early diagnosis and treatment.

To contribute to the priority actions listed in the Manifesto and as recommended at the redeLEISH meeting, a working group was created, with the participation of several of the network's collaborators.

Since its release, the Manifesto has been shared in various digital media and in conferences, such as the Congress of the Brazilian Society of Tropical Medicine (MEDTROP 2022) and the XVIII Colombian Congress of Parasitology and Tropical Medicine. •

redeLEISH would like to acknowledge the widespread support received and the more than 700 signatures collected up to May 2023. The Manifesto is still available to sign. Please support and spread the word about this initiative through the online petition here:

Reference

[1] https://www.policycuresresearch.org/analysis/#45419007f46cdb352

EVALUATION OF AN IMMUNOCHROMATOGRAPHIC ANTIGEN DETECTION KIT FOR DIAGNOSIS OF ULCERATED CUTANEOUS LEISHMANIASIS: A MULTICENTER STUDY IN BRAZIL

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Tegumentary leishmaniasis affected an average of 16,471 people per year in Brazil between 2017 and 2021. In about 95% of cases, it was the cutaneous form (CL)[1]. Differential diagnosis includes mainly pyoderma, subcutaneous and systemic mycoses, vasculopathies and skin cancer. Correct diagnosis is necessary for the timely start of a specific treatment, which is carried out with toxic medications and should preferably begin upon laboratory confirmation. Treating a different condition as CL may worsen the patient's prognosis.

In the Brazilian public health network, the most accessible diagnostic method is directly examining the lesion scraping[2,3]. The level of complexity, which requires laboratory structure and specialized professionals, along with the high cost of histopathology, culture and molecular tests[3], restricts them to reference centers. Trained healthcare professionals collect samples for direct examination by ulcer scraping when physicians are unavailable. Such procedures do not require anesthesia, especially in conditions of scarcity of other laboratory resources[3]. Sensitivity of direct examination with staining for *Leishmania* varies depending on where in the lesion the material was collected from, and the expertise of the individual reading the slide[3].

The National Health Surveillance Agency (ANVISA) has recently approved a diagnostic kit, the *LSH Cutânea ECO Teste*[4], for qualitative detection by immunochromatography with specific anti-peroxidoxin antibody of antigens of *Leishmania* species causing cutaneous leishmaniasis, including *L. (V.) braziliensis* and *L. (L.) amazonensis*. The result is available within 20 to 30 minutes, and the kit can be stored at room temperature (2 to 30°C)[4], which is an additional advantage. A similar rapid immunochromatographic test for *Leishmania* antigen detection was assessed in Suriname in an endemic area of *L. (V.) guyanensis*[5], and in Peru in an endemic area mainly of *L. (V.) braziliensis*[6]. The test showed good specificity, but lower sensitivity as compared to PCR. In Afghanistan, the same test resulted in greater sensitivity[7], which can be explained by different parasite loads of *Leishmania* species from Asia, Europe and Africa when compared to the Americas, or antigenic differences among species[6].

References

[1] BRASIL. Ministério da Saúde. DATASUS. Leishmaniose tegumentar americana – Casos confirmados notificados no Sistema de Informação de Agravos de Notificação – Brasil. Available on: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sinannet/cnv/ltabr.def Accessed on 28/04/23.

[2] Goto H, Lindoso JAL. Current diagnosis and treatment of cutaneous and mucocutaneous leishmaniasis. Expert Rev Anti Infect. Ther. 2010; 8(4):419-33.

[3] Mello CX, Madeira MF. Skin scraping is the most accessible technique for the parasitological diagnosis of American tegumentary l.eishmaniasis. Am J Trop Med Hyg. 2015; 92(5): 1082.

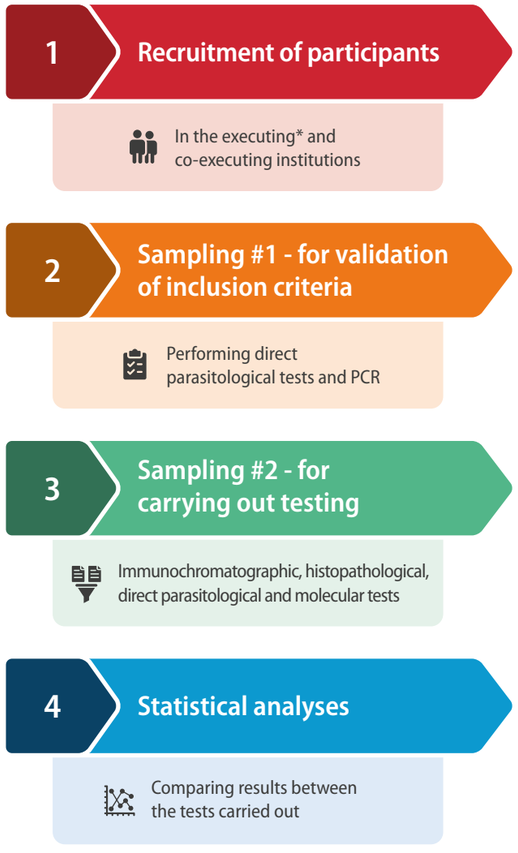
[4] Agência Nacional de Vigilância Sanitária. Consultas. Produto LSH Cutânea ECO Teste. Available on: https://consultas.anvisa.gov.br/#/saude/25351534657201773/ Accessed on 20/01/22.

[5] Schallig HDFH, Hu RVP, Kent AD et al. Evaluation of point of care tests for the diagnosis of cutaneous leishmaniasis in Suriname. BMC Inf Dis. 2019; 19:25.

[6] Grogl M, Joya CA, Saenz M, et al. Evaluation of a diagnostic device, CL Detect rapid test for the diagnosis of New World cutaneous leishmaniasis in Peru. PLoS Negl Trop Dis. 2023; 17(3): e0011054;

[7] Vink MMT, Nahlzat SM, Rahimi H et al. Evaluation of point-of-care tests for cutaneous leishmaniasis diagnosis in Kabul, Afghanistan. EBioMedicine. 2018; 37: 453-60.

It is important to point out that in the *Leishmania* species common in Brazil, especially in *L. braziliensis*, genotypic differences are known to be expressed in different phenotypes[8]. Therefore, a multicenter study will be carried out in several reference units for CL in different geographic and epidemiological contexts (Rio de Janeiro, Minas Gerais, São Paulo, Mato Grosso do Sul and Rondônia). The performance (sensitivity, specificity, positive and negative predictive values) of the *LSH Cutânea ECO Test* in the diagnosis of CL will be evaluated in clinical samples obtained from patients with ulcerated skin lesions and who have not yet undergone specific treatment for CL. The result will be compared with the direct parasitological examination and qPCR. Test results will be analyzed according to different collection instruments, infecting species, and parasite loads. This study will allow to evaluate a rapid diagnostic method that is simple to carry out and interpret, with potential to be used at the point of care for patients with suspected CL. This would represent a great improvement in health care. •



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Reference

[8] Silva CS, Guimarães LH, Silva JA, Magalhães V, Medina L, Queiroz A, Paulo Machado PRL, Schriefer A. Molecular epidemiology and in vitro evidence suggest that *Leishmania braziliensis* strain helps determine antimony response among American tegumentary leishmaniasis patients. Acta Tropica. 2018; 178:34-39.

DEVELOPMENT OF A SECOND-GENERATION MONTENEGRO INTRADERMAL REACTION TEST IN BRAZIL

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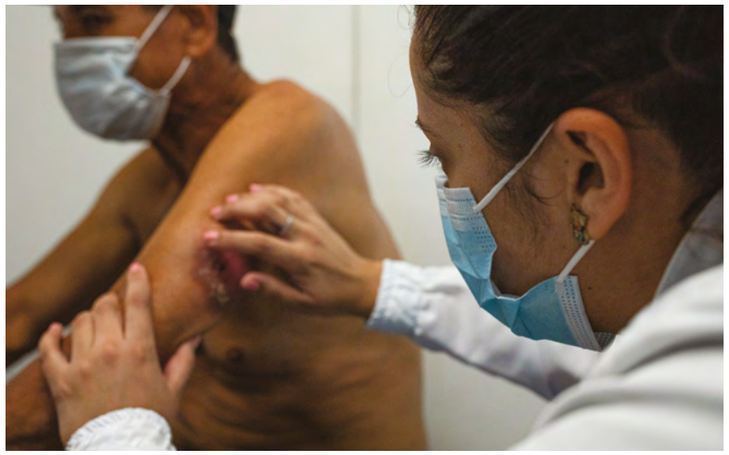
Leishmaniasis is caused by protozoa of the genus *Leishmania*, transmitted by sandflies (Phlebotominae) in various regions of Latin America. Currently, more than a billion people are at risk of infection in endemic areas, with more than a million new cases annually. Cutaneous leishmaniasis (CL) is characterized by nodules and ulcers, which self-limit within 3 to 18 months and may leave scars; the mucosal form is more debilitating, with lesions in the mucous membranes of the nose, mouth and throat that can lead to disfigurement and sometimes death. In humans, immune response primarily mediated by TH1 cells has been associated with cases of CL and American Tegumentary Leishmaniasis (ATL), which is reflected in the development of diagnostic methods.



In Brazil, the Center for Immunobiological Production and Research (CPPI, as per abbreviation in Portuguese), under the Health Department of the State of Paraná, produced and distributed the Montenegro antigen, preserved with 0.4% phenol, for the Montenegro intradermal reaction test (IDRM) for the Public Health Network. However, its production, despite being the only one in the world, was halted in 2013 by the National Health Surveillance Agency (ANVISA) as it considered this antigen's production plant inadequate with regards to its classification. It is worth mentioning that the antigenic agents responsible for the delayed hypersensitivity reaction shown by the test are still unknown and that, as it is an allergic test and is used *in vivo*, it requires carefully standardized and controlled production. Therefore, it is urgent to develop an IDRM test that continues to be easy to perform, with high sensitivity and low cost. It must also be more modern and safer, using purified or semi-purified antigen, just like the purified protein antigen used to diagnose tuberculosis.

The lack of IDRM tests directly impacted tegumentary and mucosal leishmaniasis diagnosis, particularly for health units. Many cases occur in remote areas which have few available options of diagnostic tests, such as parasitological culture, PCR, and histopathology. In such places, diagnosis performed by health professionals trained in IDRM testing circumvented the lack of doctors for biopsy sample collection and laboratories with infrastructure for other diagnostic techniques, enabling a quick diagnosis and better chances of successful treatment. In addition, mucosal lesions may be in an anatomical site difficult to collect from, making diagnosis difficult.

IDRM test is key in a country like Brazil, where there are many cases scattered throughout the country. The lack of human resources for healthcare in some areas and financial resources to carry out more complex diagnostic techniques worsen the disease's chronicity, making it more difficult to treat. The challenge ahead is to develop a standardized IDRM test following ANVISA's regulations to strengthen tegumentary and mucosal leishmaniasis control. •

WHO APP FOR CAPACITY BUILDING ON SKIN NEGLECTED TROPICAL DISEASES

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World Health Organization (WHO)

The Global Neglected Tropical Diseases (NTD) Programme of the World Health Organization (WHO) has included the integrated control and management of skin NTDs as a key strategy in its roadmap 2021-2030, *"Ending the neglect to attain the Sustainable Development Goals"*.

Capacity building of non-specialized front-line health workers is paramount to properly identify and manage common skin conditions because, overall, skin NTDs represent less than 5% to 10% of the skin conditions usually seen by clinicians at the primary health care level.

In 2020, WHO launched a mobile application to facilitate diagnosis of skin NTDs for training purposes[1]. The current version published in Android and iOS, available free of charge, works offline and has an algorithm that allows filtering by country to know which skin NTDs are endemic in each location. The app provides brief information on how to diagnose and treat each condition. It is available in English, French, Spanish and Portuguese.

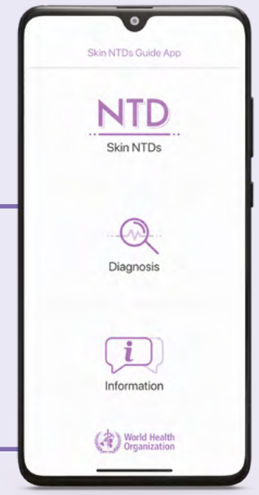
In 2022, WHO developed a beta version of the app by adding common skin conditions in collaboration with until No Leprosy Remains (NLR) and Universal Doctor. The current beta version has two additional algorithms. The first one works offline to assist in the identification of 24 common skin conditions and eight skin NTDs. WHO and the Open University of Catalonia tested this version in Ghana and Kenya, where 44 users gave an app quality mean score of 4/5, a subjective quality score of 3.83/5 and a perceived impact of 4.5/5. The second algorithm is artificial intelligence (AI)-based that classifies images uploaded through the Web for five skin NTDs (Buruli ulcer, cutaneous leishmaniasis, leprosy, post-kala-azar dermal leishmaniasis, and yaws).

WHO is now working on adding all skin NTDs to the AI algorithm and then plans to field test it in real clinical settings. Discussions are also ongoing with app developers to add AI for 24 common skin conditions.

It is important to emphasize that the WHO app is intended for educational purposes only and by no means should be considered a diagnostic medical device. The app provides information and classifies images for a very limited number of diseases so it is always possible that a condition not included in the app is causing the lesions observed by the clinician. The target audience of the app is primarily non-specialized health workers, and it does not replace the input of a dermatologist when deemed necessary, by either referring the patient or through teledermatology consultations.

DNDi is collaborating with WHO and sharing anonymized photographs to train the AI algorithm of the app. •

The link to download the beta version is available upon request for those willing to test it in the field. Contact us at postigoj@who.int.



Reference

[1] https://www.who.int/news/item/16-07-2020-neglected-tropical-diseases-of-the-skin-who-launches-mobile-application-to-facilitate-diagnosis

AMPHODEPOT®, A NEW SINGLE-DOSE THERAPY FOR CUTANEOUS LEISHMANIASIS

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ARIANE SOUSA-BATISTA, COPPE-UFRJ

Cutaneous leishmaniasis (CL) is the most common form of leishmaniasis, accounting for about 90% of the estimated 600,000 to one million cases worldwide per year (WHO, 2023). In general, skin lesions are circumscribed to the site of the bite and persist for months or years, leaving permanent scars when they heal. In the New World, lesions rarely heal on their own and can progress to the more severe mucosal and diffuse forms. The deformations that result from the disease generate social stigma, psychological issues and loss of economic status, especially in poor communities (Bennis et al. 2018). This is why CL should be treated in a timely and definitive manner.

In many countries, the treatment of CL is still based on a series of intramuscular (IM) or intravenous (EV) injections of pentavalent antimonials (Sb^V), pentamidine or amphotericin B (AmB), which are painful, require frequent hospital visits and cause systemic toxicity. Parenteral injections of liposomal AmB do not have the same efficacy for CL as for visceral leishmaniasis (VL), since only 0.1% of injected AmB reaches the skin (Wijnant et al. 2018). To reduce toxicity and increase treatment acceptance by patients with CL, DNDi recommends searching for new therapeutic alternatives for oral or topical use that are safe and fast-acting (DNDi 2023).

Oral miltefosine, which was previously restricted to VL, was recently approved in Brazil for the treatment of CL, but with restrictions due to its teratogenic effect and variable efficacy. As for topical formulations developed with paromomycin or AmB, they have either shown variable efficacy depending on the species (Moradzadeh et al. 2019) or are innocuous (Lopez et al. 2018). Drug-related factors, such as large molecular size (AmB) and low lipophilicity (paromomycin), may contribute to low permeation through the lipid matrix of the stratum corneum, as well as hypertrophy of the epidermis at the borders of the ulcers, where infected macrophages are concentrated (Nylén and Eidsmo 2012).

Due to the lack of adequate topical treatments, local intralesional (IL) treatment with Sb^V has started to be the first therapeutic choice for uncomplicated localized cutaneous leishmaniasis (LCL), with a maximum of three lesions up to 3 cm (PAHO, 2022). Intradermal (ID) or subcutaneous (SC) injections ensure that the drug reaches the site of infection, maximizing its concentration in the target tissue and minimizing systemic exposure. However, due to high hydrophilicity and rapid absorption into the bloodstream, volumes of no more than 5 mL of Sb^V should be infiltrated per lesion, with new doses applied once or twice per week for three to five weeks (PAHO, 2022). In addition to being painful, this can cause undesirable systemic effects (Esfandiarpour et al. 2012), making its application unfeasible for pediatric or pregnant patients. Moreover, the need for frequent visits to health units represents an access barrier to patients from remote regions and of limited financial means.

To circumvent the difficulties with topical absorption and the undesirable systemic absorption, we envisioned the encapsulation of biodegradable polymeric matrices in microspheres as a viable solution for retaining the drug in the dermis. In addition to the depot effect, phagocytosis of the particles by macrophages may favor the targeting of the parasite. We chose a biocompatible and versatile copolymer, PLGA [poly (lactic-co-glycolic acid)]. It is approved by the FDA and EMA for extended-release microspheres of drugs against chronic diseases such as prostate cancer, schizophrenia, and acromegaly (Wang et al. 2016), with a release time ranging from one to six months, depending on the type of PLGA employed. When PLGA degrades, it releases lactic acid and glycolic acid, which are physiological. In our hands, neither Sb^V (meglumine antimoniate) nor Sb^{III} (trivalent) showed good compatibility with the polymer (unpublished data). We then used a synthetic chalcone (CH8) which is very active against *Leishmania*, with hydrophobic and crystalline properties more suitable for encapsulation. We produced particles of 6 µm in diameter with 8% of CH8 in the polymer matrix (Sousa-Batista et al. 2018a). This development was supported by GSK, and it demonstrated in infected rodents the feasibility of proposing a local, single-dose treatment. Subsequent changes in the method allowed increasing the CH8 content from 8% to 18% (Sousa-Batista et al. 2018b), with significant benefits. Even though the preclinical safety of the CH8/PLGA formulation was widely evaluated (Sousa-Batista et al. 2022), using a new drug would imply facing regulatory approval obstacles for a new therapy for leishmaniasis. With this in mind, it was decided to invest first in an already approved drug.

In addition to already being widely used in clinical settings, AmB was chosen because of other advantages: 1) it is the most effective anti-leishmanial drug available; 2) it has low probability of resistance induction; and 3) it is broad spectrum, therefore useful in regions where several *Leishmania* species coexist or when accurate identification of the species is not possible. The biggest technical challenge was its amphoteric nature, which required the development of a new encapsulation process. AmB/PLGA particles, which we registered as AmphoDepot®, of different sizes (0.5 µm to 20 µm), were produced for double depot and intracellular effect. After IL application of a single 5 µg dose of AmB in recent or established lesions in mice infected with *L. amazonensis*, AmphoDepot® was shown to be more effective in controlling the parasite load (97%) compared to free or liposomal AmB (Ambisome®). Pharmacokinetic studies have shown that, after a single IL dose, AmB is retained in the lesion for at least 15 days without being detected in the bloodstream during this period, unlike free AmB, which reaches plasma peak in 12h and remains circulating for 24h (Sousa-Batista et al. 2019). The efficacy of AmphoDepot® has been confirmed in hamsters infected with *L. braziliensis* (in preparation).

AmphoDepot® was re-synthesized following GMP in a certified FUNED laboratory in Brazil, and sterilized with ionizing radiation, maintaining its physical and chemical properties, to be used in a clinical trial with patients with LCL in the state of Minas Gerais, Brazil (protocol being adjusted). Initially, the patient will receive a single dose of AmphoDepot® containing 0.8 mg of AmB in 0.8 mL divided into four perilesional sites in the test cohort. In case of non-remission after one month of follow-up, the patient should receive a second dose, with the final end point at three months after dose one. The control cohort will receive IL Sb^V.

It is worth noting that the total volume of AmphoDepot, of 0.8 mL/lesion, will be six times smaller than the 5 mL of Sb^V infiltration, which is expected to increase patient adherence. The maximum anticipated dose of SC AmphoDepot for four lesions will be only 45 µg/Kg (70 Kg), which is considerably lower than the daily dose of IV AmB deoxycholate (70,000 µg/Kg) or IV liposomal AmB (210,000 µg/Kg). It is also worth mentioning that AmphoDepot's lyophilic powder is very stable at room temperature, which is an advantage for transport, storage and use in tropical regions with limited resources. Finally, since the TG of PLGA is 42°C, it is expected that, in case of low therapeutic response, the combination of AmphoDepot with thermotherapy at a more tolerable temperature (e.g., 45°C), instead of the conventional 50°C/30", may accelerate the local release of AmB, promoting faster and safer healing. The AmphoDepot-thermotherapy therapeutic combination is underway in preclinical studies.

The hope is that this new therapy for LCL can bring more comfort and safety to patients and reduce hospital treatment costs. •

References

Bennis, I., De Brouwere, V., Belrhiti, Z. et al. Psychosocial Burden of Localised Cutaneous Leishmaniasis: A Scoping Review. BMC Public Health 18, 358 (2018). https://doi.org/10.1186/s12889-018-5260-9

DNDi 2023, https://dndi.org/diseases/cutaneous-leishmaniasis/facts/ accessed June 2023.

Esfandiarpour, I., Farajzadeh, S., Rahnama, Z., Fathabadi, E.A., Heshmatkhah, A., Adverse Effects of Intralesional Meglumine Antimoniate and its Influence on Clinical Laboratory Parameters in the Treatment of Cutaneous Leishmaniasis. Int. J. Dermatol. 51:1221–1225 (2012).

López L, Vélez I, Asela C, Cruz C, Alves F, Robledo S, Arana, B. A Phase II Study to Evaluate the Safety and Efficacy of Topical 3% Amphotericin B Cream (Anfoleish) for the Treatment of Uncomplicated Cutaneous Leishmaniasis in Colombia. PLoS Negl Trop Dis 12(7): e0006653. (2018) https://doi.org/10.1371/journal.pntd.0006653

Moradzadeh R, Golmohammadi P, Ashraf H, Nadrian H, Fakoorziba MR. Effectiveness of Paromomycin on Cutaneous Leishmaniasis in Iran: A Systematic Review and Meta-Analysis. Iran J Med Sci. May; 44(3):185-195. (2019).

Nylén S. and Eidsmo L. Tissue Damage and Immunity in Cutaneous Leishmaniasis. Parasite Immunology 34: 551-561 (2012)

PAHO 2022, Pan American Health Organization. Guideline for the Treatment of Leishmaniasis in the Americas. Second Edition. Washington, DC. https://iris.paho.org/handle/10665.2/56120, accessed June 2023.

Sousa-Batista AJ, Pacienza-Lima W, Arruda-Costa N, Falcão CAB, Ré MI, Rossi-Bergmann, B. Depot Subcutaneous Injection with Chalcone CH8-Loaded PLGA Microspheres Aiming at a Single-dose Treatment of Cutaneous Leishmaniasis. Antimicrobial Agents and Chemotherapy 62(3) eD1822-17 (2018a), DOI:10.1128/AAC.01822-17

Sousa-Batista, A.J.; Arruda-Costa N., Rossi-Bergmann B.and Ré M.I. Improved Drug Loading via Spray Drying of a Chalcone Implant for Local Treatment of Cutaneous Leishmaniasis, Drug Development and Industrial Pharmacy 44 (9) (2018b). DOI: 10.1080/03639045.2018.1461903

Sousa-Batista,A.J.; Pacienza-Lima,W., Ré,M.I. and Rossi-Bergmann B. Novel and Safe Single-dose Treatment of Cutaneous Leishmaniasis with Implantable Amphotericin B-loaded Microspheres. International Journal for Parasitology: Drugs and Drug Resistance 11:248-155 (2019). https://doi.org/10.1016/j.ijpddr.2019.06.001

Sousa-Batista, A.d.J.; Arruda-Costa, N.; Pacienza-Lima, W.; Carvalho-Gondim, F.; Santos, R.F.; Da-Silva, S.A.G.; Ré, M.I.; Rossi-Bergmann, B. In Vivo Safety and Efficacy of Chalcone-loaded Microparticles with Modified Polymeric Matrix Against Cutaneous Leishmaniasis. Pharmaceutics, 15, 51 (2023). https://doi.org/10.3390/pharmaceutics15010051

Wang Y, Qu W, Choi SH. FDA's Regulatory Science Program for Generic PLA/PLGA-based Drug Products. Am Pharm Rev 19:5–9 (2016).

WHO 2023, https://www.who.int/news-room/fact-sheets/detail/leishmaniasis accessed June 2023.

Wijnant, G., Bocxlaer, K. Van, Yardley, V., Harris, A., Murdan, S., Croft, S.L., AmBisome® Treatment of Murine Cutaneous Leishmaniasis: Relation Between Skin Pharmacokinetics and Efficacy. Antimicrob. Agents Chemother. 62, e02009-17 (2018). https://doi.org/10.1128/AAC.02009-17. Antimicrob. Agents Chemother. 62, e02009-17 (2018). https://doi.org/10.1128/AAC.02009-17

MSF'S RANDOMISED CLINICAL TRIAL FOR NEW TREATMENT MODALITIES FOR CUTANEOUS LEISHMANIASIS CAUSED BY *LEISHMANIA TROPICA* IN PAKISTAN

KOERT RIJTMEYER,
Médecins Sans Frontières (MSF)

Cutaneous leishmaniasis (CL) is highly endemic in Pakistan and causes a large public health burden, with an estimated 50-100,000 new cases annually. The most affected provinces are Balochistan and Khyber Pakhtunkhwa, in western and north-western Pakistan, where *Leishmania tropica* is the predominant species. Since 2008, Médecins Sans Frontières (MSF) has supported the Ministry of Health with specialised CL clinics providing free diagnosis and treatment services in Quetta (Balochistan), and Peshawar (Khyber Pakhtunkhwa), where MSF has treated a total of 40,000 CL patients to date.

For decades, the mainstay treatment for CL is with antimonial injections (meglumine antimoniate or sodium stibogluconate). The treatment consists of a 3-4-week course of painful intralesional or systemic intramuscular injections, the latter potentially resulting in serious toxicity. However, treatment is rarely available in public hospitals in Pakistan. Because CL is a non-fatal dermal disease, it is not perceived as a public health priority, despite the high incidence of the disease and the large psychosocial impact it has on CL patients and their families.

Until now, there is no established evidence-based option to treat CL caused by the *L. tropica*, besides antimonial injections. Alternative treatment options are not available in Pakistan. Evidence for the effectiveness of thermotherapy (ThermoMed®) in *L. tropica* is scarce and highly variable, but it could be an attractive option because only one treatment session is required. Another promising treatment option is oral miltefosine. There is considerable evidence in the literature of the efficacy of miltefosine in the treatment of CL caused by *L. major*, but no studies have been conducted to evaluate its efficacy in *L. tropica* infections. This oral treatment could benefit CL patients as it can be provided in peripheral health facilities and to patients who have contraindications to systemic antimony treatment (elderly people, and patients with cardiac or renal disease, or diabetes). A combination of thermotherapy and miltefosine may have the advantage of increased efficacy by two therapies with different modes of action, as well as a reduced length of treatment with miltefosine.

For these reasons, in a randomised clinical trial we aim to evaluate whether miltefosine monotherapy (28 days), thermotherapy (single session), and the combination of miltefosine (21 days) and thermotherapy are effective, safe and tolerable alternative treatment options for cutaneous leishmaniasis, and non-inferior to the standard of care treatment with intralesional meglumine antimoniate injections. The aim is to achieve a sample size of 208 patients per arm (832 total).

In October of 2022, patient recruitment started in two MSF clinics in Quetta, and in early 2023 a third study site is planned to start in the MSF clinic in Peshawar. A futility analysis per arm is planned once at least 120 patients (30 per study arm) complete their nominal D91 follow-up visit.

After the study we hope to have an effective and safe alternative first-line treatment for patients with cutaneous leishmaniasis caused by *L. tropica* which can be provided at primary health care level. •

PAHO'S STRATEGIC FUND: IMPROVING ACCESS TO AND AVAILABILITY OF LEISHMANIASIS MEDICATIONS

CHRISTOPHER LIM, NORA GIRON AGUILAR, and KEMEL HALLAR,
PAHO/WHO Strategic Fund



The Pan American Health Organization (PAHO) continues to support countries where leishmaniases are endemic by strengthening actions to achieve the goals of control and elimination of leishmaniasis as a public health issue, in accordance with the mandate given by the PAHO initiative for the elimination of diseases and the World Health Organization (WHO) roadmap for neglected tropical diseases (2021-2035).[1]

To achieve the objective of controlling cutaneous leishmaniasis and eliminating visceral leishmaniasis as a public health issue, actions such as access to early diagnosis, adequate treatment of cases and reducing contact between people and vectors have been promoted to reduce the morbidity and mortality of leishmaniases. In line with the integrated sustainable framework of PAHO's Disease Elimination Initiative, PAHO's Strategic Fund is mandated to support countries in improving access to and availability of safe, effective, high-quality, and affordable antileishmanial drugs.

Since 2004, the Strategic Fund has included on its Medicine List antileishmanial drugs such as meglumine antimoniate 300 mg/ml, liposomal amphotericin B 50 mg, miltefosine 10 mg and 50 mg, and pentamidine isethionate 300 mg. These drugs make up the recommended therapeutic arsenal for systemic treatments of the leishmaniases. They are difficult to acquire for most countries in the region because they are not available in regional pharmaceutical markets and do not have registration, so the Strategic Fund is one of the ways to make them available through established agreements and exceptions issued by member countries to import these products of high value for health care.

In the last five years, the Strategic Fund has procured antileishmanial drugs at affordable prices for 15 countries in the Region of the Americas, especially those that have been negotiated within the framework of the WHO Advisory Committee on Procurement (see Fig.1).

Figure 1: Antileishmanial drugs acquired in the last five years by the Strategic Fund.

Reference

[1] Pan American Health Organization. An Integrated, Sustainable Framework to Elimination of Communicable Diseases in the Americas. Concept Note. Washington, D.C. WHO, 2019.

For antimonial drugs, a price of USD 1.53 per vial has been provided, and for liposomal amphotericin B, USD 16.25 per vial, representing an approximate cost per treatment of USD 92 and USD 1,000, respectively. In this five-year period (2018-2022) the SF has acquired more than 75,000 treatments (see Table 1) among six different products (see Table 2).

TABLE 1 - Number of treatments (see footnote) acquired through the SF by country and medication

Country	Liposomal amphotericin B 50 mg[1]	Meglumine antimoniate 300 mg/ml[2]	Miltefosine 10 mg[3]	Miltefosine 50 mg[3]	Pentamidine isotheniate 300 mg[4]	Total
Colombia	44	34,313	969	298	795	36,419
Brazil	5,663	-	-	3,356	2,225	11,244
Bolivia	167	9,332	190	77	-	9,766
Honduras	51	7,725	26	25	-	7,826
Guatemala	-	4,139	-	-	-	4,139
Ecuador	-	3,784	-	233	-	4,017
Argentina	-	1,333	-	-	-	1,333
Panama	-	-	286	191	-	477
Mexico	-	358	-	21	-	379
Peru	-	-	-	313	-	313
Belize	-	83	-	-	-	83
El Salvador	81	-	-	-	-	81
Costa Rica	-	-	-	71	-	71
Paraguay	48	-	-	-	-	48
Nicaragua	10	-	-	-	-	10
Total	**6,079**	**61,067**	**1,471**	**4,585**	**3,020**	**76,206**

[1] Standard liposomal amphotericin B treatment: 63 vials

[2] Standard meglumine antimoniate treatment: 60 ampoules

[3] Standard miltefosine treatment: 84 tablets

[4] Standard pentamidine treatment: 10 vials

TABLE 2 - Reference prices for antileishmanial drugs through the PAHO Strategic Fund[2]

Drug description	Unit of measurement	FOB/FCA Price (USD)	Treatment cost
Meglumine antimoniate 300 mg/ml	Ampoule	1.53 USD	92 USD
Liposomal amphotericin B 50 mg	Vial	16.25 USD	1000 USD
Amphotericin B deoxycholate 50 mg	Vial	4.82 USD	200 USD
Miltefosine 50 mg	Box of 56 tablets	110 USD	165 USD
Miltefosine 10 mg	Box of 56 tablets	150 USD	224 USD
Pentamidine isotheniate 300 mg	Vial	13.8 USD	138 USD

One of the most significant challenges in acquiring these products is that some continue to be manufactured solely by innovative laboratories. The lack of multi-source generic drugs is a major access barrier, as it severely hinders negotiation for lower prices. Along these lines, the Strategic Fund has worked with endemic countries to consolidate the demand, promoting joint purchases in order to reach affordable prices through economies of scale. In the last year, 10 countries in the region submitted their estimates to consolidate demand and help the manufacturing laboratories plan their production and distribution. A more visible demand in turn helps to mitigate the risks due to production problems, guaranteeing supply and ensuring the production and transport capacity.

The Strategic Fund has provided technical cooperation to plan and consolidate demand to meet needs, develop drug procurement management, and build strategic alliances with other partners and procurement agencies to enable global demand and avoid shortages. This helped to improve access to these medicines, promote quality and efficient procurement, and increase coverage of the affected population. Likewise, the thermotherapy equipment recommended for local treatment of localized cutaneous leishmaniasis has been included in the Strategic Fund List according to predefined criteria.

In 2022, the Regional Leishmaniasis Unit and the PAHO Strategic Fund invited the Ministries of Health of five endemic countries for leishmaniasis in the Region of the Americas (Bolivia, Brazil, Colombia, Guatemala and Nicaragua) to a forum to share methodologies and scenarios used for demand planning for antileishmanial drugs and diagnostics. These countries are part of different sub-regions and account for 94% of the cases of visceral leishmaniasis and 65% of the cases of cutaneous and mucosal leishmaniasis. As conclusions of this meeting, challenges and opportunities in the estimation of needs and procurement have been identified, and the development of a common, validated and precise methodology, applicable to the entire region, has been considered.

Additionally, PAHO has supported the region with donations of medications from the CDE regional warehouse in Panama to meet the supply of small volumes. In the last two years, 18 shipments of medications have been distributed from the warehouse to seven leishmaniasis-endemic countries, representing around 230 standard treatments. This is an interprogrammatic effort to address emergencies in the region by maintaining a strategic stock to avoid shortages.

The Strategic Fund will continue to help strengthen actions to achieve the goals of controlling and subsequently eliminating leishmaniasis, working with the countries in the region to improve access to drugs and diagnostic supplies, negotiating better prices, searching for generic alternatives, strengthening capacities for the quantification of needs and joint purchasing, and improving supply chain management to ensure the timely availability of medications in health care services. •

Reference

[2]https://www.paho.org/en/paho-strategic-fund

PERSPECTIVES OF SOCIAL MOBILIZATION FOR PEOPLE AFFECTED BY LEISHMANIASIS

DIOGO GALVÃO (DNDi) and FELIPE ROCHA (ECLIPSE)

This article aims to highlight how important it is to resume the legacy left by Moacir Antônio Zini, president of the Brazilian Association for Leishmaniasis Pacients (ABRAPleish) – who left us in December 2020 – by reactivating the social mobilization of people affected by leishmaniasis.

Patients affected by Neglected Tropical Diseases (NTDs), who already endure baseline vulnerability, correspond to millions of people unseen and forgotten by control and prevention programs or pharmaceutical innovation. Thus, creating associations of affected people ends up being even more strategic for them. Besides several studies already made available, history itself shows us how much potential social movements in health have and their importance (see for instance the creation of the Brazilian Unified Health System), especially regarding community engagement and definition of health policies and strategies.

"After Moacir passed away, the Association lost strength. And that's sad because I know how much Moacir fought to get ABRAPleish up. Now I see it falling apart little by little as I struggle by myself to keep it alive, with no other members and with major financial difficulties. Not having the Association will be a great loss for me and many other patients who tirelessly seek visibility and need to be heard. Last year, when I managed to attend the Forum's meeting, my hopes were renewed. I have many ideas to put into practice, but I need help," states Talita Zini, Moacir's widow and current president of ABRAPleish.

Therefore, having an active association of people affected by leishmaniasis is paramount and urgent. It is yet another opportunity to expand social control over public management, to participate in developing health policies, to influence strategies and decision-making, to pressure politicians for more investment in research and development on leishmaniasis or NTDs in general, and to demand attention in health and caregiving by strengthening primary care.

In that sense, ECLIPSE (Empowering people with cutaneous leishmaniasis: intervention program to improve the patient's journey and reduce stigma through community education) offers a unique opportunity. It is a multicenter program and a global study investigating the sociocultural impact of cutaneous leishmaniasis. In Brazil, it is being implemented in the Southern Bahia Lowlands. Groups are formed in each community, bringing together local leaders and other key players, which enabled the project to be a participatory and integrated network to discuss, think about and/or elaborate group actions and practices regarding their needs and problems related to health, territory, and commitment.

ECLIPSE and FSBEDIN (Brazilian Social Forum for Fighting Infectious and Neglected Diseases) play a key role in finally achieving active social mobilization of patients affected by leishmaniasis. Both ECLIPSE's and ABRAPleish's delegations were present at the Forum's latest meeting, held last November, during the MEDTROP Conference, opening room for various talks and ideas. We hope to soon have news about resuming our Association, or creating a new one, with a clear and concrete agenda, to finally guarantee its sustainable autonomy. •

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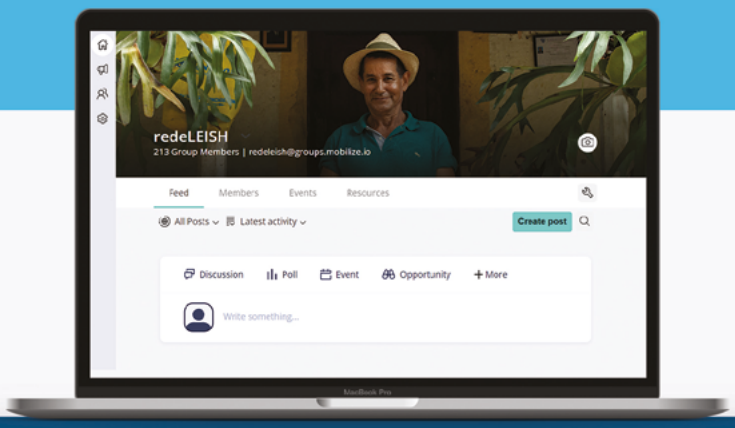

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