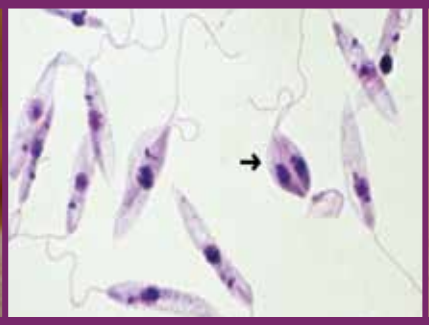
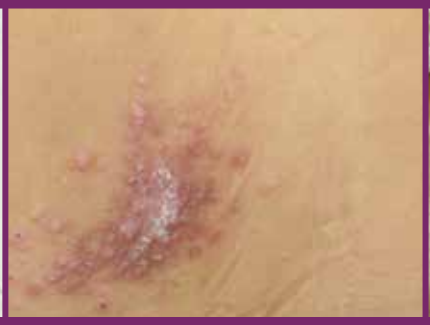
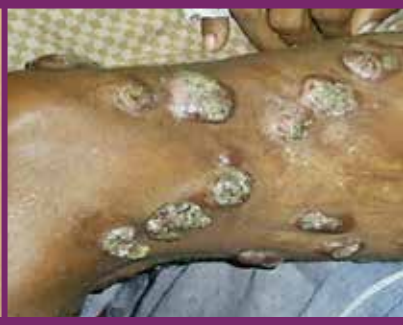
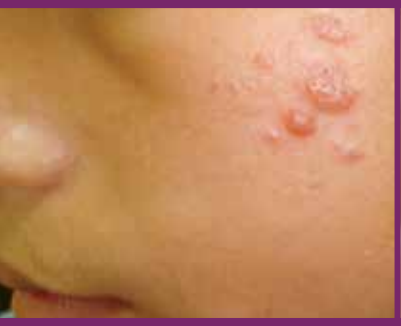
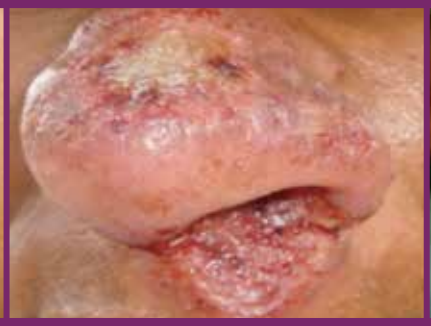
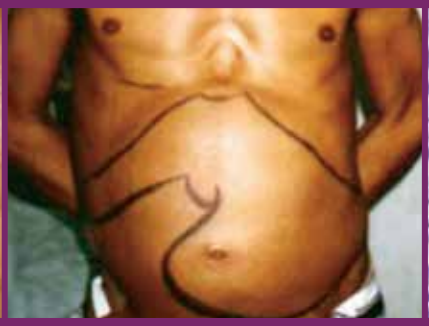
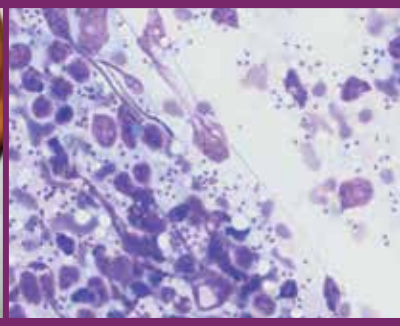
LEISHMANIASIS IN THE AMERICAS

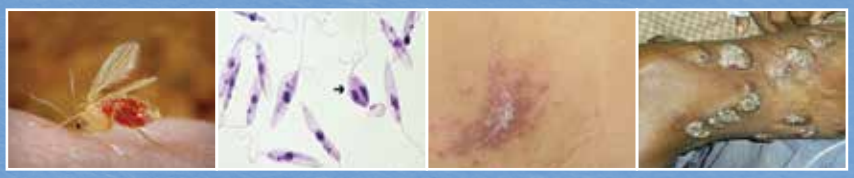
TREATMENT RECOMMENDATIONS

Pan American Health Organization

World Health Organization
REGIONAL OFFICE FOR THE Americas

COVER PHOTOS:

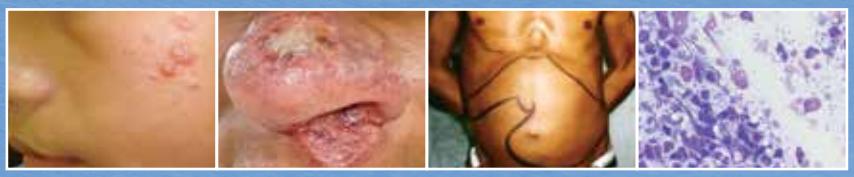


Lutzomyia–engorged female (enlarged photo) Vilela, MIOC–Fiocruz, Brazil

Leishmania–Promastigote Costa, JML CPq GM–Fiocruz, Brazil

Cutaneous leishmaniasis Zerpa, OR, Instituto de Biomedicina. Universidad Central de Venezuela

Diffuse cutaneous leishmaniasis Costa, JML CPq GM–Fiocruz, Brazil



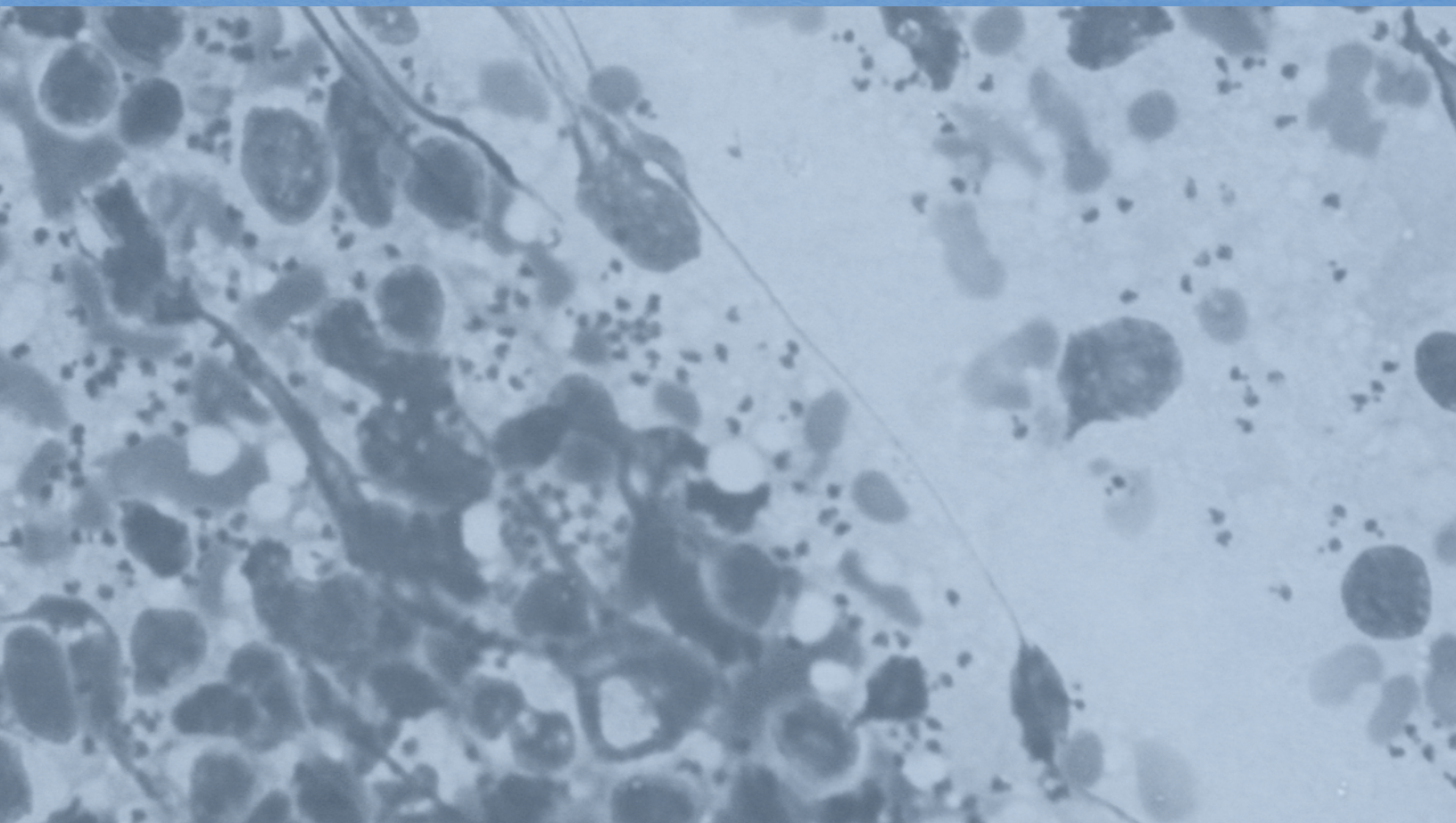
Atypical cutaneous leishmaniasis Ministry of Health of Honduras, National Leishmaniasis Program of Honduras

Mucocutaneous leishmaniasis Maia-Elkhoury, ANS, PAHO/WHO, Brazil; Soler, RC, Emílio Ribas Institute, Brazil

Visceral leishmaniasis. Costa, JML CPq GM–Fiocruz, Brazil

Leishmania Courtesy of Laboratório de Soroepidemiología and Imunobiología, Institute of Tropical Medicine of São Paulo, USP, Brazil

Graphic design: Miki Fernández/ULTRAdesigns



LEISHMANIASIS IN THE AMERICAS TREATMENT RECOMMENDATIONS

Pan American Health Organization

World Health Organization
REGIONAL OFFICE FOR THE Americas

Communicable Diseases and Health Analysis

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ANNEXES

ACKNOWLEDGMENTS

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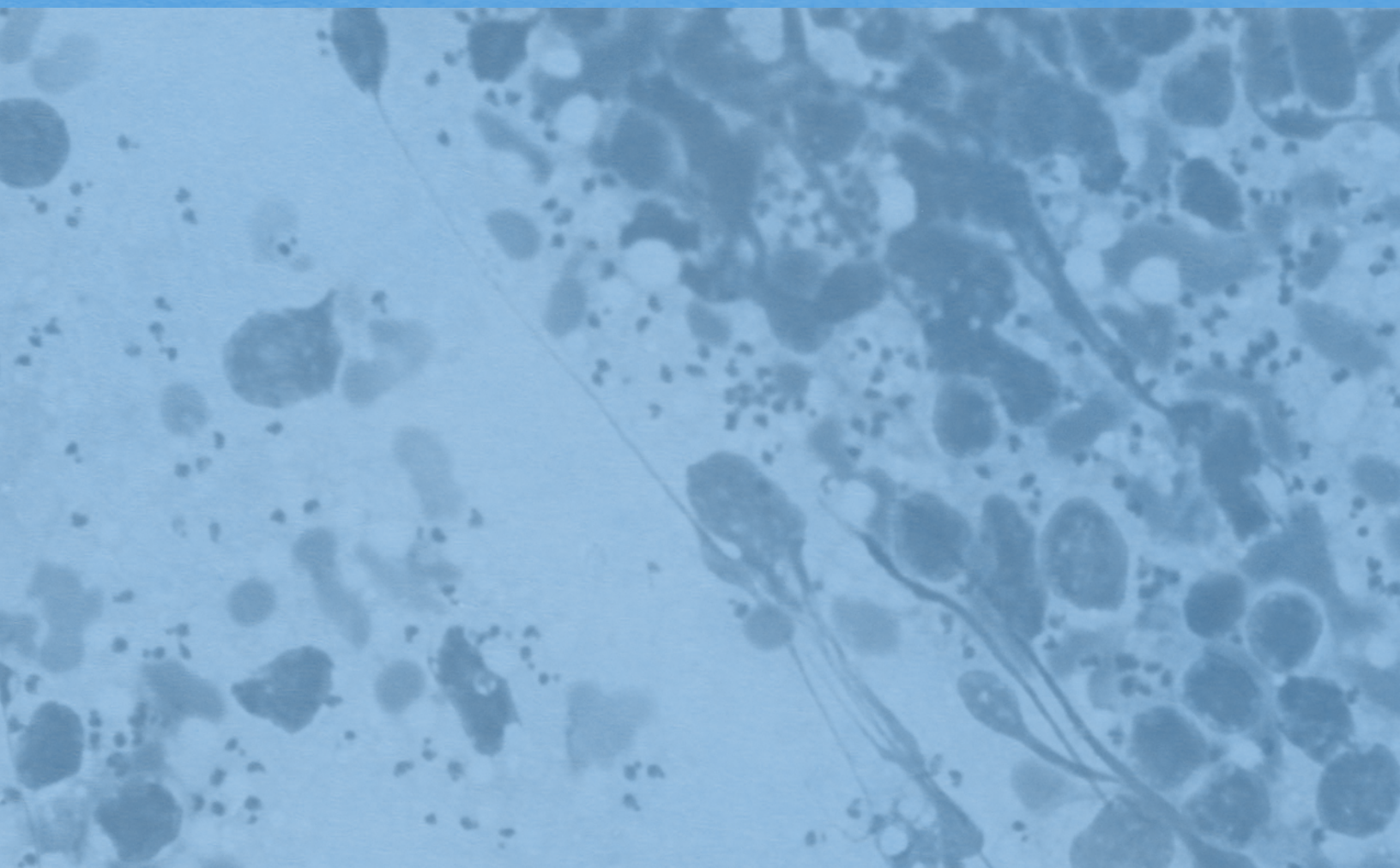


ABSTRACT

The different forms of leishmaniasis are an important public health problem in the Americas due to their widespread distribution and high prevalence. Their complex cycle of transmission includes different species of parasites, reservoir hosts, and vectors. In addition, the risk factors of transmission are linked to socioeconomic and environmental patterns that make it even more difficult to control the disease. *Leishmania* infection causes a number of clinical symptoms in humans involving the skin, mucosa of the upper respiratory tract, and visceral organs.

In 2010, the World Health Organization (WHO) Expert Committee on the Control of Leishmaniases updated and revised recommendations for leishmaniasis at the global level. The new guidelines, *Control of the leishmaniases*, were published as part of the WHO Technical Report Series 949 (WHO TRS-949). The report highlighted the importance of early and appropriate treatment of affected persons to address the fact that public health treatment options available in the Region are often limited and characterized by highly toxic drugs. Futhermore, major differences were observed in treatment responses across different countries, regions, and continents and by parasite species.

Based on the available evidence, the WHO Expert Committee cited the need for alternative, local treatments to avoid toxicity from systemic treatment. The Committee also underscored the need to consider the disproportion between the relatively benign course of cutaneous leishmaniasis (CL) and the frequency and severity of adverse effects associated with the drugs available for systemic treatment.

The new guidelines adapt and update previous WHO recommendations for the Region, based on WHO standards for guideline development, and take into account the specific characteristics of the leishmaniases in the Americas, differences in the organization of health services in the Region, evidence from recent studies on treatment, and the need to provide recommendations for specific questions not previously addressed.

This publication aims to disseminate knowledge and serve as a tool for health professionals who work directly with these diseases, assisting national leishmaniasis control programs in strengthening therapeutic alternatives by improving the standardization, organization, and accessibility of health services for those affected by leishmaniases in the Americas.

In addition, these guidelines underscore the need to include all scientific evidence on leishmanias available in each country in the national control programs, taking into consideration the idiosyncrasies of the circulating parasite species and clinical features of the disease as well as the ways in which those affected by it access health services. They also highlight the need to conduct controlled clinical trials to assess newly available treatment alternatives—particularly local treatments—to generate further evidence on their efficacy and safety in the Latin American context.

The treatment option for any given patient must be selected on the basis of clinical presentation, number and location of lesions, parasite species, drug availability, and level of care, among other considerations, and the treating clinician should be able to choose between local or systemic treatment.

Key recommendations

Key recommendations for the treatment of leishmaniasis in the Americas, based on the available evidence, are described below by clinical form of the disease.

Cutaneous leishmaniasis

- Use of pentavalent antimonials (**high-quality evidence, strong recommendation**).
- Use of miltefosine for infections caused by *L. panamensis* and *L. guyanensis* (**high-quality evidence, strong recommendation**).
- Use of ketoconazole for infections caused by *L. mexicana* and *L. panamensis* (**low-quality evidence, weak recommendation**).
- Use of pentamidine isethionate (**low-quality evidence**); ketoconazole (**low-quality evidence**); or miltefosine (**moderate-quality evidence**); or liposomal amphotericin B (**very low–quality evidence**); or amphotericin B deoxycholate (**very low–quality evidence**), in cases of therapeutic failure or in special situations (**weak recommendation**).
- Use of thermotherapy (**moderate-quality evidence**) or intralesional antimonials (**very low–quality evidence**), when systemic treatment is not indicated and/or local treatment is required, according to established criteria (**weak recommendation**).

Mucosal or mucocutaneous leishmaniasis

- Use of pentavalent antimonials to treat mucosal or mucocutaneous leishmaniasis (**low-quality evidence, strong recommendation**).
- Use of pentavalent antimonials plus oral pentoxifylline (**low-quality evidence**) or liposomal amphotericin B (**low-quality evidence**), or amphotericin B deoxycholate (**very low–quality evidence**), or pentamidine isethionate (**low-quality evidence**), or miltefosine (**very low–quality evidence**) in cases of therapeutic failure with other drug options or in special situations (**weak recommendation**).

Visceral leishmaniasis

- Use of liposomal amphotericin B, pentavalent antimonials, or amphotericin B deoxycholate (**very low–quality evidence, strong recommendation**).
- Use of liposomal amphotericin B, pentavalent antimonials, or amphotericin B deoxycholate in cases of coninfection with HIV/AIDS (**very low–quality evidence, strong recommendation**).
- Use of liposomal amphotericin B, pentavalent antimonials, and amphotericin B deoxycholate for secondary prophylaxis after first episode (**very low–quality evidence, strong recommendation**).
- Use of liposomal amphotericin B to treat special cases (**very low–quality evidence, strong recommendation**).

RESUMEN

Las leishmaniasis son un importante problema de salud pública en las Américas debido a su amplia distribución y elevada prevalencia. Su complejo ciclo de transmisión comprende diferentes especies de parásitos, reservorios y vectores. Además, los principales factores de riesgo, resultantes de los procesos sociales, económicos y ambientales, favorecen su transmisión y dificultan su control. La infección por *Leishmania* puede causar en el humano un conjunto de síndromes clínicos que pueden comprometer la piel, las mucosas de las vías aéreas superiores y las vísceras.

En 2010, el Comité de Expertos en Leishmaniasis de la Organización Mundial de la Salud (OMS) actualizó y modificó las recomendaciones para las leishmaniasis a nivel global, que fueron publicadas el mismo año en el "WHO Technical Report Series, 949 - *Control of the Leishmaniasis*" (WHO-TRS, 949). Entre las acciones de control, el informe resaltó la importancia del diagnóstico temprano y tratamiento adecuado de las personas afectadas, particularmente por el hecho que en las últimas décadas el tratamiento utilizado en salud pública se caracterizó por la escasez de opciones terapéuticas con medicamentos que causan gran toxicidad. Asimismo, se observó gran heterogeneidad de las respuestas al tratamiento entre los diferentes países, regiones y continentes y entre las diferentes especies del parásito.

Basados en la evidencia disponible, las recomendaciones del Comité de Expertos en Leishmaniasis de la OMS apuntaron hacia la necesidad del uso de alternativas de tratamiento directamente aplicadas sobre las lesiones cutáneas evitando la toxicidad de las drogas parenterales. Igualmente, llamaron la atención sobre la necesidad de considerar el escenario que se caracteriza por la desproporción entre el curso relativamente benigno de la leishmaniasis cutánea (LC) y la frecuencia y magnitud de los eventos adversos asociados con los medicamentos disponibles para su tratamiento sistémico.

Se actualizaron y adaptaron las recomendaciones de la OMS al contexto regional, particularmente debido a la necesidad de tomar en cuenta las características específicas de las leishmaniasis en las Américas, a las diferencias en la organización de los servicios de salud de la región, a la necesidad de incorporar la evidencia proveniente de estudios recientes para el tratamiento de esta enfermedad y proporcionar recomendaciones para preguntas especificas no contempladas previamente, en base los estándares para la elaboración de guías de la OMS.

Esta publicación busca difundir el conocimiento y ser una herramienta para los profesionales de salud que trabajan directamente con estas enfermedades, apoyando los programas nacionales de control de leishmaniasis para que fortalezcan las alternativas terapéuticas, por medio de la estandarización, estructuración y mejora del acceso de las personas afectadas a los servicios de salud en las Américas.

Además, esta publicación llama la atención sobre la necesidad de incorporar en los programas nacionales de control, la evidencia científica disponible en cada país, considerando sus peculiaridades relativas a las especies de parásitos circulantes, características clínicas y formas de acceso a los servicios de salud. A su vez pone de presente la necesidad de llevar a cabo ensayos clínicos controlados que evalúen nuevas alternativas terapéuticas disponibles, particularmente con el empleo de esquemas terapéuticos locales, a fin de disponer de mayores evidencias sobre su eficacia y seguridad en el contexto latinoamericano.

La selección de la opción terapéutica que debe recibir el paciente debe ser tomada de acuerdo a las presentaciones clínicas, número y localización de las lesiones, especie del parásito, disponibilidad de medicamentos, nivel de atención, etc., pudiendo el profesional de la salud tratante, optar por tratamiento local o sistémico.

Recomendaciones clave

La evidencia disponible permite presentar las siguientes recomendaciones para el tratamiento de las leishmaniasis en las Américas:

Leishmaniasis cutánea

- Se recomienda el uso de los antimoniales pentavalentes para tratar la leishmaniasis cutánea (**calidad alta y recomendación fuerte**).
- Para la leishmaniasis cutánea producida por *L. guyanensis* y *L. panamensis* se recomienda el uso de miltefosina (**calidad alta y recomendación fuerte**).
- Para la leishmaniasis cutánea producida por *L. mexicana* y *L. panamensis* se recomienda el uso de ketoconazol (**calidad baja y recomendación débil**).
- Se recomienda el uso de isetionato de pentamidina (**calidad baja**), ketoconazol (**calidad baja**), o del miltefosine (**calidad moderada**) o anfotericina B liposomal (**calidad muy baja**), o de la anfotericina B desoxicolato (**calidad muy baja**), en caso de falla terapéutica o situaciones especiales (**recomendación débil**).
- Se recomienda el uso de termoterapia (**calidad moderada**) o antimoniales intralesionales (**calidad muy baja**), cuando no esté indicado realizar tratamientos sistémicos o se requiera efectuar tratamientos locales de la leishmaniasis cutánea, acorde los criterios establecidos (**recomendación débil**).

Leishmaniasis mucosa o mucocutánea

- Se recomienda el uso de los antimoniales pentavalentes para tratar la leishmaniasis mucosa o mucocutánea (**calidad baja y recomendación fuerte**).
- Se recomienda el uso de los antimoniales pentavalentes **+** pentoxifilina oral (**calidad baja**), o de la anfotericina B liposomal (**calidad muy baja**), o de la anfotericina B desoxicolato (**calidad muy baja**) o del isetionato de pentamidina (**calidad muy baja**) o del Miltefosine (**calidad muy baja**) en caso de falla terapéutica de las otras opciones de medicamentos o en situaciones especiales (**recomendación débil**).

Leishmaniasis visceral

- Se recomienda el uso de la anfotericina B liposomal, los antimoniales pentavalentes o la anfotericina B desoxicolato para tratar la leishmaniasis visceral (**calidad muy baja y recomendación fuerte**).
- Se recomienda el uso de la anfotericina B liposomal, los antimoniales pentavalentes o la anfotericina B desoxicolato para el tratamiento de leishmaniasis visceral y coinfección VIH-sida (**calidad muy baja y recomendación fuerte**).
- Se recomienda el uso de la anfotericina B liposomal, los antimoniales pentavalentes y la anfotericina B desoxicolato en la profilaxis secundaria después del primer episodio de LV (**calidad muy baja y recomendación fuerte**).
- Se recomienda el uso de la anfotericina B liposomal para tratar casos especiales de leishmaniasis visceral (**calidad muy baja y recomendación fuerte**).

SCOPE AND PURPOSE

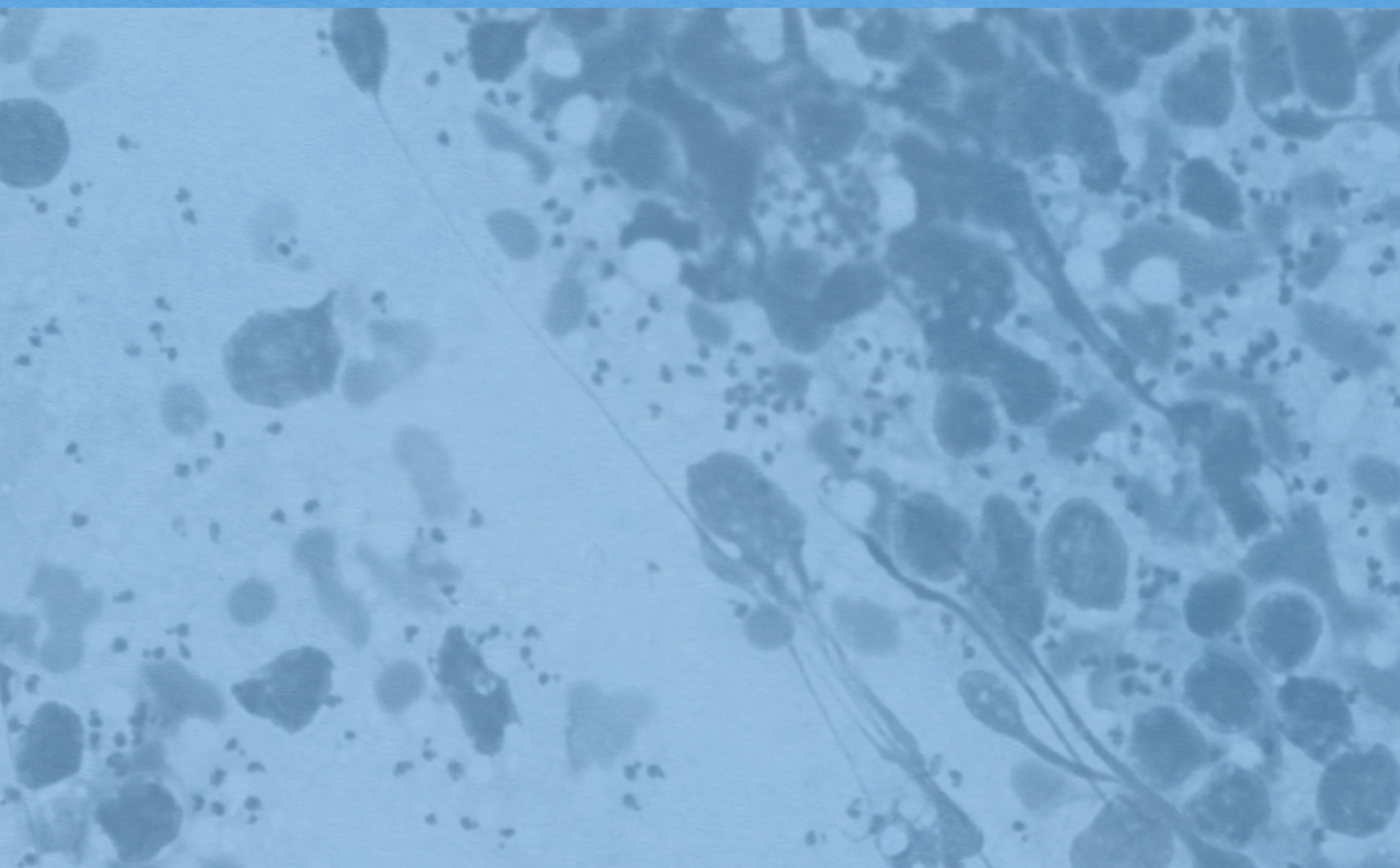
The purpose of this publication is to update and adapt WHO recommendations on therapeutic interventions for leishmaniasis to the Region, fostering updated scientific evidence on the management of the disease region-wide. The recommendations may also help foster technical and scientific interrelationship across countries.

This guide provides Member States and their partners with the best available evidence for determining the most effective ways to reduce the case-fatality rate for visceral leishmaniasis and severe forms of mucosal leishmaniases and thus help reduce the burden of these neglected diseases as a public health problem.

The guidelines include recommendations for treating cutaneous, mucosal, and visceral leishmaniasis, including criteria for local treatments and the level of care in which the recommendations should be available. A summary of the evidence used to formulate the recommendations is also included.

Target audience

These recommendations are designed for health professionals in the Americas region, including: 1) ministry of health managers and technical personnel; 2) those in charge of developing guidelines for national leishmaniasis control programs; 3) those in charge of planning and procuring the supplies required for ensuring people with leishmaniasis have timely and appropriate access to treatment; and 4) those responsible for patient care across all levels of the health care system.



INTRODUCTION

The leishmaniases are diseases that mainly affect those who are the poorest and who have the most difficulty obtaining health care. In the Americas, leishmaniasis constitutes a public health problem due to its high incidence and morbidity, broad geographic distribution, and variety of parasite species and clinical forms combined with the limited therapeutic regimens available and adequate prevention measures (*1–5*).

The Pan American Health Organization (PAHO), Regional Office of the World Health Organization in the Americas (WHO), works to support the organization and strengthening of leishmaniasis control programs in endemic countries to reduce morbidity and mortality from this disease across the Region, in accordance with its mandate and within the framework of World Health Assembly (WHA) resolutions 60.13 of 2007 (*6*) and PAHO/WHO Directing Council (DC) resolution 49.R19 of 2009 (*7*).

In March 2010, WHO held a meeting of the Expert Committee on the Control of Leishmaniases to review and update its recommendations for control of the disease, which were published in 1990. The publication documenting the results of that meeting, *Control of the leishmaniases* (2010) (WHO Technical Report Series 949), included new knowledge on the epidemiology, clinical aspects, diagnosis, and treatment of the disease. Based on that evidence, new recommendations for leishmaniases were presented (*8*).

In recent years, there have been major scientific advances with regard to leishmaniasis, mainly in diagnosis and treatment. One of the main points highlighted in Control of the leishmaniases is the recommended use of local therapeutic alternatives for the cutaneous form of the disease (*6*), as opposed to the standard protocol in the Americas, where the most common treatments are systemic and the available drugs cause toxicity (*8–14*). Most of these drugs are pentavalent antimonials—derivatives of antimony (sodium stibogluconate and meglumine antimoniate) that have been used for decades worldwide as first-line leishmaniasis therapeutic agents—but other drugs such as pentamidine isethionate, different formulations of amphotericin B, pentoxifylline, miltefosine, and ketoconazole, are also available in the Region for treating the various clinical forms of the disease.

The use of local treatments for cutaneous leishmaniasis remains limited in the Region and is restricted to specific areas. However, WHO recommends these treatments nonetheless because 1) it is recognized that no single treatment method eradicates leishmaniasis infection and 2) local treatments are usually less toxic than standard systemic drug treatments, and better accepted by patients. Systemic drugs recommended for leishmaniasis usually cause adverse effects—unfavorable events associated with the use of a drug that can be mild, moderate, or serious and require special attention, including investigation of the clinical history and current condition of the patient and appropriate monitoring during and after treatment (*8–15*). The principal adverse events for the drugs used to treat leishmaniasis are described in Annex 1.

Responses to leishmaniasis treatments are heterogeneous and depend on the parasite species, geographic location, immunogenetic profile of the affected individual, and general relationship of the parasite to its vectors, reservoirs, and hosts (*8–15*). Due to the clinical and epidemiological complexity of the disease, and the range in therapeutic responses, new clinical trials for leishmaniasis have recently been conducted in the Americas. To address the challenges posed by these disease characteristics, WHO recommendations for treatment of cutaneous, mucosal, and visceral leishmaniases in the Americas, including the criteria for the indication of local treatment for cutaneous leishmaniasis, were updated and adapted for the Region in accordance with WHO standards for guideline development.

FORMULATING THE QUESTIONS: PICO[1]

Leishmaniases in the Americas are caused by a wide range of parasite species with different geographic distributions, leading to multiple clinical forms of the disease with varied therapeutic responses to treatment.

To address the need for updated WHO recommendations for leishmaniasis treatment relevant to the Region, a group of experts on leishmaniasis was assembled to formulate, present, and discuss specific questions on leishmaniasis treatment in the Americas. At the first group meeting in September 2011, the questions listed below were formulated over the course of the discussions to inform the review, analysis, and evaluation of evidence on therapeutic interventions. For each question, the experts took into consideration interventions and studies carried out on the topic, and the expected primary effects, as well as the species of *Leishmania* involved, criteria for cure, adverse events, and length of follow-up.

For the studies, the primary result evaluated was clinical cure of lesions after six months of treatment. The criteria used to define "clinical cure" for the different clinical forms of the disease were as follows:

- Cutaneous leishmaniasis: scarring with complete re-epithelialization and flattening of lesion margins; disappearance of induration at the base; disappearance of any lymphangitis or adenitis; absence of new lesions.
- Mucosal leishmaniasis: regression of all clinical signs of lesions, evaluated by nose, and mouth examination.
- Visceral leishmaniasis: disappearance of fever, and reduction or complete absence of hepatosplenomegaly.

Question 1: Taking into account the epidemiological, biological, and clinical aspects of the leishmaniases in the Americas (cutaneous, mucocutaneous, mucosal, and visceral), what interventions are indicated for management of affected persons?

- What is the efficacy and safety of the various systemic treatments for cutaneous leishmaniasis in the Americas compared to pentavalent antimonials?
- What is the efficacy and safety of the various systemic treatments for persons with cutaneous, mucosal, or visceral leishmaniasis in the Americas compared to pentavalent antimonials, liposomal amphotericin B, or amphotericin B deoxycholate, and other standard treatments?

Question 2: What is the efficacy and safety of alternative systemic treatments for persons in the Americas with leishmaniases who 1) are infected by different *Leishmania* species and 2) have different clinical forms of cutaneous leishmaniases?

- What is the efficacy and safety of alternative systemic treatments (miltefosine, ketoconazole, allopurinol, etc.) for persons with cutaneous leishmaniasis in the Americas compared to meglumine antimoniate?

Question 3: Taking into account the epidemiological, biological, and clinical aspects of cutaneous leishmaniases in the Americas, what is the scientific evidence and what are the criteria for local treatment?

- What is the efficacy and safety of local treatments (intralesional, thermotherapy, etc.) for persons with cutaneous leishmaniasis in the Americas?

[1] "PICO" refers to four elements that should be specified in a research question governing a systematic search of scientific evidence: population, intervention, comparator, and outcome(s).

Question 4: What is the scientific evidence for the use of secondary prophylaxis with systemic drugs in patients coinfected with visceral leishmaniasis and HIV/AIDS?

- What is the efficacy and safety of secondary prophylaxis with systemic treatments for people coinfected with visceral leishmaniasis and HIV/AIDS to reduce relapses of the visceral leishmaniasis?

In the group meeting discussions used to formulate the final treatment recommendations provided later in this guide, questions 1 and 2 covered systemic interventions indicated for treatment of persons affected by the different clinical forms of leishmaniasis as well as different *Leishmania* species, whereas questions 3 and 4 covered specific issues involved in local treatment of cutaneous leishmaniasis and secondary prophylaxis in coinfection with visceral leishmaniasis and HIV/AIDS, as well as the reduction of relapses of visceral leishmaniasis.

The scope and purpose of the four PICO questions described above led to a comprehensive review of the evidence and helped generate the results described in the sections below.

SUMMARY OF THE EVIDENCE

The search for systematic reviews evaluating the effectiveness and safety of different interventions in the treatment of leishmaniases in the Americas identified six studies (*8–10, 12–14*), which were evaluated individually. The systematic review published in 2009 by the Cochrane Collaboration (*8*) (which received an AMSTAR[2] rating of 11 out of 11 for quality) identified 38 randomized clinical trials that evaluated different interventions for the treatment of cutaneous and mucocutaneous leishmaniasis (40 different comparisons) among 2 728 participants from 10 countries of Latin America and the Caribbean (Bolivia, Brazil, Colombia, Ecuador, El Salvador, Guatemala, Honduras, Panama, Peru, and Venezuela). The principal outcome was the percentage of patients cured at three months of treatment. Due to deficiencies in the design and reporting of several of the clinical trials, there are considerable limitations in the available evidence for the development of treatment recommendations for American cutaneous and mucocutaneous leishmaniasis. For treatment of *L. braziliensis* and *L. panamensis* infections, intramuscular (IM) meglumine antimoniate (MA) was better than oral allopurinol for 28 days. Intravenous (IV) MA for 20 days was better than 7-day and 3-day IV MA plus paromomycin plus 12% methylbenzethonium chloride. Oral allopurinol plus IV antimonials was better than IV antimonials alone (*8*). For *L. braziliensis* infections, oral pentoxifylline plus IV sodium stibogluconate (SSG) was better than IV SSG alone; and IV MA had better cure rates than IM aminosidine sulfate and IV pentamidine isethionate. For L. panamensis infections, oral ketoconazole, oral miltefosine, and topical paromomycin plus methylbenzethonium chloride were all better than placebo.

The systematic review conducted in 2008 (*14*) and published in the Cochrane review concluded that even though pentavalent antimonials were considered the first-line therapeutic regimen for cutaneous leishmaniases, aspects such as cost, adverse events, local experience, and availability of interventions should always be taken into account in selecting the proper treatment. Similar results were reported in a systematic review of studies that evaluated mucosal leishmaniasis in Latin America (*12*) in which it was found that pentamidine and amphotericin were as effective as MA, the drug recommended by the authors for treatment of mucosal leishmaniasis. An additional review (*10*) was excluded due to its narrative format, which resulted in a low score on the AMSTAR scale (*57*). Evidence from three of the reviews mentioned above (*10, 12, 14*) was not taken into account in the Cochrane review (*8*) but was included in the systematic review update described below (*16*).

The systematic review update (*16*) conducted during the development of this guide identified 10 new randomized clinical trials for treatment of cutaneous leishmaniasis. No additional studies were found that included subjects with mucocutaneous, mucosal, or visceral leishmaniasis. For *L. panamensis* and *L. guyanensis* infections, miltefosine was better than MA; this difference was not corroborated for L. braziliensis infections. MA was better than pentamidine isethionate for treatment of L. braziliensis infection but not for treatment of L. guyanensis. Imiquimod was better than placebo at three months of treatment. A single session of thermotherapy and nitric oxide were not superior to MA. When possible, the systematic review update (*16*) integrated the results from the Cochrane review (*8*) with the results of the individual studies cited within the review and reported the results of the meta-analyses that were conducted. The systematic review update also includes a summary of the main findings of the Cochrane review (*8*) plus new evidence. The GRADE[3] Summary of Findings Tables (Annex 2) include information on studies from both the systematic review update and the Cochrane review.

A systematic review published in 2010 (AMSTAR rating 6 out of 11) evaluated control of visceral leishmaniasis in humans and dogs. The authors (*13*) identified four studies (none randomized) that evaluated amphotericin B

[2] Assessment of multiple systematic reviews (measurement tool assessing methodological quality of systematic reviews).

[3] Grading of Recommendations Assessment, Development and Evaluation (systematic approach for rating the quality of evidence and the strength of recommendations).

cholesterol dispersion, liposomal amphotericin B, and sitamaquine in a limited number of subjects. Amphotericin B cholesterol dispersion for 7 and 10 days was effective in one study. Liposomal amphotericin B at a 20-mg/kg total dose was better than at a smaller dose. One study found that sitamaquine was not effective in treatment of visceral leishmaniasis and serious adverse events were reported.

Oliveira et al. conducted a systematic review of adverse events from interventions used in the treatment of cutaneous leishmaniasis (*9*). The most frequent adverse events following administration of pentavalent antimonials were musculoskeletal pains, gastrointestinal disturbances, headache, electrocardiographic changes, and increases in liver and pancreatic enzymes. Patients treated with liposomal amphotericin presented mild dyspnea and erythema; those treated with miltefosine frequently presented vomiting, nausea, headache, diarrhea, and increased creatinineand aminotransferases. A systematic review published in 2011 evaluated studies that described factors predictive of visceral leishmaniasis relapse in patients coinfected with HIV, 11 of which reported on secondary prophylaxis. The meta-analysis of these studies suggests that secondary prophylaxis decreases relapses of visceral leishmaniasis (*50*). Some observational studies conducted in the Americas have evaluated various mortality risk factors in patients with visceral leishmaniasis (*51–53*). The study by Madalosso et al. (2012) found that severe anemia, hemorrhages, heart failure, jaundice, diarrhea, fever > 60 days, age > 50 years, and antibiotic use were significantly associated with death from visceral leishmaniasis (*51*). Another study conducted specifically in patients aged < 15 years with visceral leishmaniasis found that risk of dying from visceral leishmaniasis was associated with the hemorrhages of the mucous membranes, jaundice, dyspnea, suspected or confirmed bacterial infections, neutrophil count of 500/mm^3, and platelet count of 50 000/mm^3 (*52*). The study by Costa et al. (2010) reported that bacterial infection and bleeding are mutually exclusive events that lead to death, and identified specific risk factors for death from bacterial infection (age < 1 year, age ≥ 40 years, vomiting, dyspnea, edema, HIV/AIDS, etc.) and bleeding (jaundice, severe thrombocytopenia, liver injury, kidney failure, etc.) (*53*).

RECOMMENDATIONS

The selection of treatment options for leishmaniases in the Americas should be based on clinical manifestations, number and location of lesions, Leishmania species, overall condition of the patient, and drug availability, according to the criteria listed in the tables below.

It should be noted that in the Americas cutaneous leishmaniasis tends to be more severe and follow a longer course compared to other geographic areas. Some patients infected by *L. amazonensis* and *L. Mexicana* might develop the diffuse cutaneous form of the disease, which is difficult to cure with currently available treatments. In addition, the species *L. braziliensis*, *L. panamensis*, and *L. guyanensis* can progress to the point where the mucous membranes become compromised, due to metastasis, even in patients that have received or are receiving systemic or local treatment. There is little evidence from the Region to support the broad use of local therapies but these treatments are recommended in special situations and when the attending health professional feels their benefits outweighs the risks to the patient.

Before adding new therapeutic regimens to control programs for wide use in public health, policymakers should consider the following: 1) the quality of the evidence obtained from available local studies; 2) the weight of potential patients benefits compared to the potential harms and burdens; 3) the cost of providing the treatments; 4) whether or not it is a good use of resources; and 5) whether or not the structure/organization of the health system allows for patient monitoring for detection of long-term complications.

Due to the biological, epidemiological, and clinical aspects inherent in this disease in the Americas, findings from local and regional studies and the availability of and access to products in the Region should also be included in the evaluation.

The updated/adapted WHO recommendations for treatment of leishmaniases in the Americas are listed below, rated according to the quality of the evidence (very low, low, moderate, or high) and the strength of the recommendation (weak versus strong). The clinical condition of the patient should always be taken into consideration when selecting therapeutic options.

Cutaneous leishmaniasis

- Use of pentavalent antimonials (**high-quality evidence, strong recommendation**), GRADE Tables 1–7, Annex 2 (*17–22, 26–29, 31, 32*).
- Use of miltefosine for infections caused by L. guyanensis and L. panamensis, (**high-quality evidence, strong recommendation**), GRADE Table 2, Annex 2 (*17, 26*).
- Use of ketoconazole for infections caused by L. mexicana and L. panamensis, (**low-quality evidence, weak recommendation**), GRADE Table 7, Annex 2 (*8, 31, 32*).
- Use of pentamidine isethionate (**low-quality evidence**), ketoconazole (low-quality evidence), or miltefosine (**moderate-quality evidence**) or liposomal amphotericin B (**very low–quality evidence**), or amphotericin B deoxycholate (**very low–quality evidence**) in cases of therapeutic failure with other drug options or in special situations (weak recommendation), GRADE Tables 2 and 4 (*8*).
- Use of thermotherapy (**moderate-quality evidence**) or intralesional antimonials (**very low–quality evidence**) when systemic treatments are not indicated and/or local treatment is required, according to established criteria (**weak recommendation**), GRADE Table 4, Annex 2, Table 4 (*8, 18*).

Suggested therapy regimens and options are shown in Tables 1, 2, and 4.

TABLE 1: Local treatments for cutaneous leishmaniasis by quality of the evidence and strength of the recommendation[a,b]

Intervention (by quality of the evidence)[c,d]	Form of administration	Regimen	Quality of the evidence	Strength of the recommendation[e]	References
Thermotherapy	Application of localized heat with electromagnetic device generating high-frequency waves	After local anesthesia, electrode is applied at 50°C for 30-second periods, until the entire area of the lesion is covered, for 1–3 sessions, at 1-week intervals[c]	**Moderate**[d]	**Weak** Restricted for constant indications described in "Therapeutic Options" table. Randomized trials are needed in different geographic areas and with different species, increasing the number of applications and follow-up time when lesions are produced by *L. braziliensis*	**GRADE Table 4, Annex 2** (*18, 21, 22, 25*) Brazil (Lobo et al., 2006), Colombia (López et al., 2012), and Guatemala (Navin et al., 1990)
Intralesional antimonials	Intradermal injection	1–5 infiltrations of 1–5 ml per session, depending on lesion size (i.e., the quantity used is whatever is necessary to cover the lesion) every 3–7 days[c]	**Very low**	**Weak** Use restricted to groups with contraindications for systemic treatments (see "Therapeutic Options" table) Randomized trials are needed in different geographic areas and with different species, increasing the number of applications and follow-up time when lesions are produced by L. braziliensis (Blum et al., 2012)	Gadelha et al., 1990; Oliveira-Neto et al., 1997; Blum et al., 2012 (*23–25*)

[a] The clinical and therapeutic response of the disease caused by different Leishmania populations of the same or different species varies by geographic area.

[b] Therapeutic indications for special treatments for cutaneous and mucosal leishmaniasis are described in the Recommendations section.

[c] Indications and/or restrictions for use are described in the "Therapeutic Options" table.

[d] Evidence is based on randomized trials and rated according to the GRADE method (Annex 2).

[e] Criteria for rating "strength of the recommendation" are defined in "Process for Development of This Guide."

TABLE 2: Systemic treatments for cutaneous leishmaniasis by quality of the evidence and strength of the recommendation[a,b]

Intervention (by quality of the evidence)[c,d]	Form of administration	Regimen	Quality of the evidence	Strength of the recommendation[f]	References
Pentavalent antimonials	Intravenous or intramuscular	10–20 mg Sb^{+5}/kg/day of pentavalent antimony in single daily dose for 20 days Indication for doses (10, 15, or 20 mg Sb^{+5}) should be based on local evidence Maximum dose of 3 ampoules/day to reduce adverse effects	**High**[e]	**Strong**	**GRADE Tables 1–7, Annex 2** (*8, 17–22*) Evidence available for different Leishmania species (Vélez, 1997; Chrusciak-Talhari et al., 2011; Vélez et al., 2010)
Miltefosine	Oral	1.5–2.5 mg/kg/day, with maximum dose of 150 mg/day, for 28 days It is suggested that divided doses be taken after meals to reduce adverse gastrointestinal effects	**High**[e] for localized skin lesions **Moderate**[e] for localized skin lesions	**Strong** Indicated for *L. guyanensis* and *L. panamensis* (Table 2, Annex 1) **Weak** For all other *Leishmania* species Trials recommended with different species in different areas	**GRADE Tables 1–2, Annex 2** (*17, 19, 20, 26, 28, 29*) Evidence for localized cutaneous leishmaniasis available in Bolivia, Brazil, and Colombia (Chrusciak-Talhari et al., 2011; Machado et al., 2010; Vélez et al., 2010; Rubiano et al., 2012; Soto et al., 2008) Evidence for diffuse cutaneous leishmaniasis in Venezuela, but with therapeutic combination (Zerpa & Convit, 2009)
Pentamidine isethionate	Intramuscular	3–4 mg/kg/day in 3–4 doses on alternate days	**Low**[e]	**Weak** Better results with *L. guyanensis* Randomized trials recommended in different areas and with different species	**GRADE Table 3, Annex 2** (*8, 30*) Evidence available in Brazil, Colombia, and Peru (Correia et al.,1996; Paula, 2003; Andersen, 2005; Robledo, 2006; Neves et al., 2010)
Ketoconazole	Oral	600 mg/day for 28 days	**Low**[e]	**Weak** Indicated for *L. panamensis* and *L. mexicana* Randomized studies recommended in different areas and with different species	**GRADE Table 7, Annex 2** (*8, 31, 32*) Evidence available in Guatemala and Panama with *L. mexicana* and *L. panamensis* (Saenz & Paz, 1990; Navin et al., 1992)

TABLE 2: Systemic treatments for cutaneous leishmaniasis by quality of the evidence and strength of the recommendation[a,b] (cont.)

Intervention (by quality of the evidence)[c,d]	Form of administration	Regimen	Quality of the evidence	Strength of the recommendation[f]	References
Liposomal amphotericin B	Intravenous	2–3 mg/kg/day up to 20–40 mg/kg total dose	**Very low**	**Weak** Alternative in cases with contraindications for amphotericin B deoxycholate, therapeutic failure with other drug options, or special situations	Available evidence (*33–35*) (Motta & Sampaio, 2012; Saldanha et al., 2009; Wortmann et al., 2010)
Amphotericin B deoxycholate	Intravenous	0.7 to 1 mg/kg/day up to 25–30 total doses	**Very low**	**Weak** Alternative in cases of treatment failure or special situations Requires careful management due to adverse effects	Evidence (*29, 36*) (Zerpa & Convit, 2009; Morrison et al., 2010)

[a] The clinical and therapeutic response of the disease caused by different Leishmania populations of the same or different species varies by geographic area.

[b] Therapeutic indications for special treatments for cutaneous and mucosal leishmaniasis are described in the Recommendations section.

[c] Indications and/or restrictions for use are described in the "Therapeutic Options" table.

[d] Prior considerations should be taken into account at the beginning of treatment and monitoring.

[e] Evidence is based on randomized trials and rated according to the GRADE method (Annex 2).

[f] Criteria for rating "strength of the recommendation" are defined in "Process for Development of This Guide."

Mucosal or mucocutaneous leishmaniasis

- Use of pentavalent antimonials (**low-quality evidence, strong recommendation**), GRADE Tables 8 and 9 (Annex 2) and Tables 3 and 4 (*38–40*).
- Use of pentavalent antimonials plus oral pentoxifylline (low-quality evidence), or liposomal amphotericin B (**very low–quality evidence**), or amphotericin B deoxycholate or pentamidine isethionate (**very low–quality evidence**), or miltefosine (**very low–quality evidence**) in cases of therapeutic failure with other drug options or in special situations (**weak recommendation**), GRADE Tables 9 and 10 (Annex 2) and Tables 3 and 4 (*40–45*)

Suggested therapy regimens and options are shown in Tables 3 and 4.

TABLE 3: Treatments for mucosal or mucocutaneous leishmaniasis by quality of evidence and strength of the recommendation[a,b]

Intervention (by quality of the evidence)[c,d]	Form of administration	Regimen	Quality of the evidence[e]	Strength of the recommendation[f]	References
Pentavalent antimonials	Intravenous or intramuscular	20 mG Sb^{+5}/kg/day of pentavalent antimony in a single daily dose for 30 continuous days	**Low** and **Very low**	**Strong**	**GRADE Table 8–10, Annex 2** (*37– 39*) (Figueiredo et al., 1991; Franke et al., 1994; Machado et al., 2007)
Pentavalent antimonials + oral pentoxifylline	Intramuscular or intravenous Sb^{+5} oral pentoxifylline	20 mg Sb^{+5}/kg/day for 30 days plus 400 mg pentoxifylline every 8 hours for 30 days	**Low**	**Weak** Evidence from one randomized trial with limited number of participants More studies needed	**GRADE Table 10, Annex 2** (*39*) (Machado et al., 2007)
Liposomal amphotericin B	Intravenous	2–3 mg/kg/day up to a cumulative dose of 3.5 g	**Very low**	**Weak** Alternative in cases of treatment failure or treatment of special cases	(40, 41) (Sampaio & Marsden, 1997; Lambertucci & Silva, 2008)
Amphotericin B deoxycholate	Intravenous	0.7–1 mg/kg/day up to 25–45 total doses	**Very low**	**Weak** Alternative in cases of treatment failure or special cases Requires careful management due to adverse effects	(*42, 43*) (Rodriguez et al., 1995; Dedet et al., 1995)
Pentamidine isethionate	Intramuscular	3–4 mg/kg/day in 7–10 doses on alternate days	**Very low**	**Weak**	(*44*) (Amato et al., 1998)
Miltefosine	Oral	1.5–2.5 mg/kg/day for 28 days with maximum daily dose of 150 mg	**Very low**	**Weak**	(*45*) Evidence available only in Bolivia (Soto et al., 2009)

[a] The clinical and therapeutic response of the disease caused by different Leishmania populations of the same or different species varies by geographic area.

[b] Therapeutic indications for special treatments for cutaneous and mucosal leishmaniasis are described in the Recommendations section.

[c] Indications and/or restrictions for use are described in the "Therapeutic Options" table.

[d] Prior considerations should be taken into account at the beginning of treatment and monitoring.

[e] Evidence is based on randomized trials and rated according to the GRADE method (Annex 2).

[f] Criteria for rating "strength of the recommendation" are defined in "Process for Development of This Guide."

TABLE 4: Treatment options for cutaneous and mucosal leishmaniases in the Americas by clinical presentation, therapeutic indication, and level of care[a,b]

Clinical presentation	Therapeutic indication (by quality of evidence)	Level of care
Localized cutaneous leishmaniasis ■ Single lesion up to 900 mm^2 (3-cm diameter) in any location except head and periarticular regions, absence of immunosuppression, and possibility of monitoring	**Local**[c] ■ Thermotherapy (for restrictions on use see the "Therapeutic Options" table) ■ Intralesional pentavalent antimonials	Referral center
	Systemic ***First-line*** ■ Pentavalent antimonials ■ Miltefosine ■ Pentamidine isethionate *(L. guyanensis* and *L. panamensis*) ■ Ketoconazole (*L. mexicana* and *L. panamensis*)	First or second level
	Second-line ■ Amphotericin B	Second level or referral center
Localized cutaneous leishmaniasis ■ Single lesion larger than 900 mm^2 in any location or ■ Single lesion of any size, on head or periarticular regions or ■ Multiple lesions ■ Single lesions previously treated locally that did not respond or relapsed	**Systemic** ***First-line*** ■ Pentavalent antimonials ■ Miltefosine ■ Pentamidine isethionate *(L. guyanensis* and *L. panamensis*) ■ Ketoconazole (*L. mexicana* and *L. panamensis*)	First or second level
	Second-line ■ Pentamidine isethionate ■ Amphotericin B ■ Liposomal amphotericin B	Second level or referral center
Disseminated cutaneous leishmaniasis	**Systemic** ***First-line*** ■ Pentavalent antimonials ***Second-line*** ■ Liposomal amphotericin B ■ Amphotericin B	Second level or referral center
Diffuse cutaneous leishmaniasis	**Systemic** ■ Pentavalent antimonials ■ Liposomal amphotericin B ■ Pentamidine isethionate ■ Amphotericin B deoxycholate	Referral center
Mucosal leishmaniasis	**Systemic** ■ Pentavalent antimonials + pentoxifylline ■ Pentavalent antimonials ■ Liposomal amphotericin B ■ Pentamidine isethionate ■ Amphotericin B deoxycholate	Referral center

[a] The clinical and therapeutic response of the disease caused by different *Leishmania* populations of the same or different species varies by geographic area.

[b] Therapeutic indications for special treatments for cutaneous and mucosal leishmaniasis are described in the Recommendation section.

[c] Decisions on whether to add local treatments as a therapeutic option for cutaneous leishmaniasis should be based on the available evidence for each country.

Treatment of special cases of cutaneous and mucosal leishmaniasis

To formulate treatment recommendations for special cases of cutaneous and mucosal leishmaniasis (cases for which no clinical trials or observational studies were found), the Committee of Experts considered existing clinical experience, case reports, and the risk/benefit of interventions for each of the following situations:

- Pregnant women: Thermotherapy is recommended, and cases requiring systemic treatment should be referred to a referral center. The indicated drug is liposomal amphotericin B or amphotericin B (**weak recommendation**), GRADE Table 4, Tables 1, 2, and 4. Antimony salts, miltefosine, and pentamidine are contraindicated.
- Breastfeeding women: Intralesional antimonials, or thermotherapy, or amphotericin B, or miltefosine is recommended, ensuring contraception (**weak recommendation**), GRADE Table 4, Tables 1, 2, and 4. Contraindication is relative for systemic antimonials.
- Patients with electrocardiogram (ECG) changes: Local or systemic treatment with miltefosine is recommended (**weak recommendation**), GRADE Table 4, Tables 1, 2, and 4. Antimony salts and pentamidine are contraindicated.
- Patients with nephropathy, hepatopathy, heart disease: Local treatments are recommended for cutaneous leishmaniasis (**weak recommendatio**n), GRADE Table 4, Tables 1 and 4. Liposomal amphotericin B is also suggested (weak recommendation), Table 3.
- Comorbidity with tuberculosis: Special care is recommended in monitoring adverse events due to drug interactions, primarily when two treatments are used concomitantly.
- Patients with HIV and other causes of immunosuppression: Liposomal amphotericin B or amphotericin B deoxycholate is recommended (**weak recommendation**).
- Patients > 50 years: Careful clinical assessment is needed. Consideration of alternatives to systemic antimonials is recommended, given the risk of serious adverse effects.
- Patients with treatment failure: With local treatment failure, repeating the treatment or changing to systemic treatment is recommended. In the case of failure of systemic treatment, after two treatments with the original drug/regimen, the use of a different drug or regimen is recommended.

Visceral leishmaniasis

Ideally, treatment of visceral leishmaniasis should cure the patient, reduce the risk of relapse, and reduce the possibility of drug-resistant parasite strains. To ensure full completion of treatment and the detection of any adverse effects, treatment regimens should be fully supervised by the health team. Etiological treatment options are described below. It is important to ensure comprehensive treatment, including adequate hydration and feeding. If necessary, severe anemia should be corrected with blood transfusions and concomitant infections should be treated with the corresponding anti-infectives, based on the opinion of the treating health professionals. A successful therapy is one that improves the general condition, resolves fever, enables resolution of hepatosplenomegaly, and enables blood values to return to normal.

An initial cure is defined as the absence of fever and clinical improvement at the end of treatment. Complete regression of hepatomegaly or splenomegaly can take several months. A good indicator of a definitive cure is the absence of clinical relapse six months after treatment.

- Liposomal amphotericin B, pentavalent antimonials, or amphotericin B deoxycholate recommended to treat visceral leishmaniasis (**very low–quality evidence, strong recommendation**), GRADE Table 11, Annex 2, and Table 5.
- Liposomal amphotericin B, or pentavalent antimonials, or amphotericin B deoxycholate recommended for treatment of coinfection with visceral leishmaniasis and HIV/AIDS (**very low–quality evidence, strong recommendation**), GRADE Table 11, Annex 2, and Table 6.

The effectiveness of secondary prophylaxis after a first episode of successfully treated visceral leishmaniasis has not been established. A meta-analysis of studies (not conducted in Latin America) found that secondary prophylaxis in patients coinfected with visceral leishmaniasis and HIV/AIDS significantly reduces visceral leishmaniasis relapse rates (*50*).

To date, there have not been any controlled clinical trials that demonstrate the superiority of any therapeutic schemes; therefore, selection of the regimen should be based on the toxicity profile and interactions with other drugs used by the patient.

Secondary prophylaxis is recommended in all patients with a CD4 T-lymphocyte count < 350/ mm^3.

- Liposomal amphotericin B, pentavalent antimonials, or amphotericin B deoxycholate recommended in secondary prophylaxis after the first episode of visceral leishmaniasis (**very low–quality evidence, strong recommendation**), Table 7.

The clinical course of visceral leishmaniasis is complex and requires care and monitoring during treatment. The following treatment is thus recommended for special cases:

- Liposomal amphotericin B (**very low–quality evidence, strong recommendation**), Table 11, Annex 2 (*51–53*).

Regimens for the suggested drugs are shown in Tables 5, 6, and 7.

TABLE 5: Treatments for visceral leishmaniasis by quality of the evidence and strength of the recommendation

Intervention[a,b]	Form of administration	Regimen	Quality of the evidence	Strength of the recommendation[c]	Level of care	References
Liposomal amphotericin B	Intravenous	3–5 mg/kg/day for 3–6 days up to 20 mg/kg total dose	**Very low**	**Strong**	Second level or referral center	(*13, 46*) (Berman et al., 1998)
Pentavalent antimonials	Intravenous or intramuscular	20 mg/Sb^{+5}/kg/day for 28 days	**Very low**	**Strong**	First and second level and referral center	(*13*) Low-quality evidence in the Americas (Romero et al., 2010)
Amphotericin B deoxycholate	Intravenous	1 mg/kg/day for 14 days up to a total dose of 800 mg	**Very low**	**Strong**	Second level or referral center	(*13, 47, 48*)(Dietze et al., 1993, 1995)

[a] Criteria for rating "quality of the evidence" are defined in Annex 2.

[b] Prior clinical considerations should be taken into account at the beginning of treatment and monitoring.

[c] Criteria for rating "strength of the recommendation" are defined in "Process for Development of This Guide."

TABLE 6: Treatments for visceral leishmaniasis and HIV/AIDS coinfection[a]

Intervention	Form of administration	Regimen	Level of care	Reference
Liposomal amphotericin B	Intravenous	3–5 mg/kg/day up to 20–40 mg/kg total dose	Referral center	(*49*) (Bern et al., 2006)
Pentavalent antimonials	Intravenous or intramuscular	20 mg/Sb^{+5}/kg/day for 28 days	Referral center	
Amphotericin B deoxycholate	Intravenous	1 mg/kg/day for 14 days up to a total dose of 800 mg	Referral center	

[a] Listed in order of priority depending on drug availability in each country.

TABLE 7: Recommended secondary prophylaxis regimens for patients coinfected with visceral leishmaniasis and HIV/AIDS

Intervention (in order of priority depending on drug availability in each country)[a,b]	Form of administration	Regimen	Quality of the evidence	Strength of the recommendation[c]	Level of care	References
Liposomal amphotericin B[d]	Intravenous	3–5 mg/kg/dose every 3 weeks	**Very low**	**Strong**	Referral center	*(50)* (Cota, 2011),
Pentavalent antimonials	Intravenous or intramuscular	20 mg/Sb^{+5} every 2 weeks	**Very low**	**Strong**	Referral center	
Amphotericin B deoxycholate	Intravenous	1 mg/kg/dose every 2 weeks	**Very low**	**Strong**	Referral center	

[a] Criteria for rating "quality of the evidence" are defined in Annex 2.

[b] Prior clinical considerations should be taken into account at the beginning of treatment and monitoring.

[c] Criteria for rating "strength of the recommendation" are defined in "Process for Development of This Guide."

[d] Treatment of special cases should give priority to liposomal amphotericin B.

Treatment of special cases of visceral leishmaniasis

The selection of treatment for special cases of visceral leishmaniasis should take into account the drug toxicity profile and the risk of death associated with the disease (*51–53*). Liposomal amphotericin B[4] is indicated in patients that meet at least one of the following criteria:

- Age > 50 years
- Age < 1 year
- Kidney failure
- Liver failure
- Heart failure
- Corrected QT interval greater than 450 msec
- Concomitant use of drugs that alter QT interval
- Hypersensitivity to pentavalent antimonials or to other drugs used for treatment of visceral leishmaniasis
- HIV infection
- Comorbidities that compromise immunity
- Use of immunosuppressive medication
- Treatment failure with pentavalent antimonials or other drugs used to treat visceral leishmaniasis
- Pregnant women.

[4] When it is impossible to use liposomal amphotericin B for the above-described situations, amphotericin B deoxycholate is the therapeutic alternative.

DISSEMINATION, ADAPTATION, IMPLEMENTATION, AND UPDATE

This guide is a translation of the Spanish original version, the official language of most of the countries in the Americas with endemic leishmaniasis. Evaluation of the quality of these recommendations is best achieved by integrating and testing them in the national leishmaniasis control programs and scientific communities in the Region, and in health professional curricula at Latin American universities and public health services.

Dissemination

The Spanish-language version (Leishmaniasis en las Américas: recomendaciones para el tratamiento) was first disseminated electronically but later printed and distributed in the endemic countries. Designed to strengthen surveillance and control of leishmaniasis in the Americas, where proper diagnosis and treatment of the disease is the principal strategy, the guide was distributed through the PAHO/WHO regional partner network, including the PAHO/WHO Representative Office in each country, the ministries of health of the Member States, the WHO Collaborating Centres, universities, and other United Nations agencies and nongovernmental organizations. The guide is also being disseminated through on-site or distance education and training as a virtual course. The PAHO Disease Control Area, with the support of the Latin American and Caribbean Center on Health Sciences Information (BIREME, a PAHO/WHO specialized center) and PAHO's Virtual Campus of Public Health (a technical cooperation strategy to strengthen institutional capacities and public health practices in the Americas), has developed the virtual course.

In addition, the systematic review update conducted during the development of this guide has been published in an open-access journal to disseminate the findings (*16*).

Adaptation and implementation

Using this guide, ministries of health in the Americas will be able to implement WHO's updated/adapted recommendations for leishmaniasis treatment in the Americas, through the national control programs and with the support of local experts, taking into account the local context, access to treatments, the operating capacity of the health services, and the risks and benefits of the interventions.

To facilitate the implementation of the recommendations at the regional, national, and local level, PAHO's internal production team has been working with the national teams through the Evidence Informed Policy Network (EVIPNet). EVIPNet promotes national mechanisms to facilitate the daily use of evidence, obtained through research, to support decision-making among health care professionals.

PAHO has also been working to promote access to strategic public health supplies in the Americas through its Strategic Fund, which links the procurement of drugs and essential public health products across the Region. In 2012, with the support of the respective PAHO technical areas, the Strategic Fund added the drugs recommended for leishmaniasis treatment to the supply of public health products available in the Americas, prequalifying the supply laboratories that met the quality standards for WHO-approved drugs. The process used to procure the drugs, which includes prior annual planning, product supply, PAHO Member State status, and subsequent programming of the quantities necessary to meet national demands, results in reduced costs to Member Countries and improved availability of the drugs required to treat leishmaniasis in the Region.

Monitoring and evaluation of the implementation and update of this guide

The impact of the recommendations provided in this guide can be evaluated across the countries of the Americas through monitoring and evaluation of national control programs and with the support of local experts.

Use of the recommendations in the Region should be evaluated annually for three years based on the following indicators:

- The proportion of leishmaniasis-endemic countries in the Americas that used or adopted all or part of this guide to establish and define national leishmaniasis treatment guidelines.
- The proportion of leishmaniasis-endemic countries in the Americas that include one or more of the drug treatment options for leishmaniasis in their public health programs.
- The proportion of health professionals in leishmaniasis-endemic countries in the Americas who completed leishmaniasis training through PAHO's virtual course (online or on site), which includes these recommendations.

Implications for research

This publication calls attention to 1) the need to increase investment in the development of new tools for leishmaniasis treatment, and 2) the urgency of conducting new, well-designed clinical trials to evaluate drug treatment efficacy and safety in the Region. Clinical trials should be conducted according to international standards for good clinical practices, and health authorities should integrate the results-based evidence from the trials to update local guidelines for managing the disease.

PROCESS FOR DEVELOPMENT OF THIS GUIDE

The method used to develop this publication was based on the WHO Handbook for Guideline Development, which was published in 2010 (*54*) and updated in 2012 (*55*).

Advisory groups

Through its advisors and consultants, PAHO/WHO provides technical cooperation to Member Countries in the Americas to improve the health status of the Region's population and support the development and strengthening of the national leishmaniasis control programs. To help address the need for updated and adapted recommendations for leishmaniasis treatment in the Americas, an internal (PAHO/WHO) production team was formed (Annex 3) to organize and coordinate the formulation of the new recommendations. A WHO representative was also involved and assisted in the review of the guide's contents.

For the external production team, PAHO invited a group of leishmaniasis experts and ministry of health representatives from some of the Member States (Annex 4), relying on technical criteria, to update leishmaniasis treatment recommendations in the Americas. The group was identified through an open selection process designed to achieve balance in terms of both gender and countries, and included experts in various health disciplines related to leishmaniasis (specialists in infectious disease, dermatology, tropical medicine, epidemiology, and public health; policymakers; researchers; health care providers; etc.). It also included members of the WHO Expert Committee on the Control of Leishmaniases (*5*), to provide expertise on leishmaniasis treatment options, and other specialists who represented the Region at the March 2010 planning meeting in Geneva. This panel of experts and decision-makers helped establish the scope and purpose of the guide, define the questions and outcomes of interest, review the evidence, reach consensus on the recommendations, and review the final version of the guide. The final draft of the guide was submitted to five technical reviewers, for their analysis and technical contributions, and two methodological reviewers, who evaluated the quality of the guide using the AGREE II instrument (Annex 5).

Scope of guide, evaluation of evidence, and decision-making process

In 2011, a meeting was held in Medellín, Colombia, with the following participants: 16 members of the PAHO internal production team, 10 of whom were recognized experts on leishmaniasis representing six countries; three staff members from PAHO, and three representatives from the Colombia and Brazilian ministries of health. At the meeting, based on the questions and recommendations presented in the WHO technical document Control of the Leishmaniases (*5*), and on the Cochrane review (*8*), PAHO's internal production team formulated, discussed, and reviewed specific questions about leishmaniasis, taking into account the different clinical forms and parasite species of the disease, interventions and comparators, and therapeutic responses. They also considered recommendations on the importance of the outcomes that will be obtained from clinical studies on the leishmaniases (*56*).

PAHO's internal production team, together with a PAHO/WHO methodologist, conducted a systematic review of systematic reviews of studies that evaluated leishmaniasis interventions carried out in Latin America and the Caribbean from 2008 onward. To identify the reviews, a literature search was conducted (to July 2012, later updated to November 2012) in the following databases as of July 2: Cochrane Library, EMBASE, LILACS (Latin American and Caribbean online health sciences library), and PubMed. The search terms for the systematic review update (*16*) were similar to the ones used to gather information for the leishmaniasis search, with the addition of search terms to identify reviews ("review" "meta-analysis") and specific geographic areas (Annex 7).

The systematic reviews that were included evaluated the efficacy and safety of leishmaniasis treatments in the Americas during the period 2007–2012; there was no restriction on the language of the publications. Evaluation of the quality of the studies selected—using the AMSTAR quality evaluation instrument (*57*)—and extraction of information was carried out by two methodological reviewers. Six studies that met the inclusion criteria (*8–10, 12–14*) were identified. The systematic review update (*16*) was conducted in order to integrate several additional leishmaniasis studies identified after the Cochrane systematic review was published in 2009 (*8*).

The systematic review update identified randomized clinical trials that evaluated interventions for the treatment of cutaneous, mucocutaneous, cutaneous, and visceral leishmaniasis in the New World. The review used the methodology suggested by the Cochrane Collaboration handbook for the selection of studies, assessment of risk of bias, and data extraction and synthesis of the evidence (*58*). The search (to July 2012) was done in the following databases: PubMed, Cochrane Library, EMBASE, and LILACS. The search strategy was similar to the one used previously (*8*). In addition, the references of the selected studies were reviewed to identify other studies. Other sources were also searched, including WHO's International Clinical Trials Registry Platform (ICTRP) (using the key word "* leishmaniasis"), and authors who were experts on the subject were contacted. There was no restriction on the language of publication. The selection of studies, assessment of risk of bias, and data extraction were carried out independently by two methodological reviewers. Details concerning the methodology of the review are described in the systematic review update (*16*). The systematic review update identified 10 new randomized clinical trials (*16*) in addition to the 38 studies previously identified by the Cochrane review (*8*). GRADE tables were prepared to supplement the recommendations, which were presented, reviewed, and discussed by the group of experts.

The GRADE approach categorizes the quality of evidence as "high," "moderate," "low," or "very low." In this guide, these classifications of quality were applied to the body of evidence evaluated for each specific question and not to the individual studies. The GRADE profiler software program[5] (version 3.6) (Cochrane Collaboration, Oxford, UK) was used to generate the GRADE tables (Annex 1), which rate the quality of the evidence as follows:

- HIGH quality: The guideline development group is very confident that the true effect lies close to the estimate of the effect.
- MODERATE quality: The guideline development group is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- LOW quality: Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- VERY LOW quality: The guideline development group has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Five factors can decrease the quality of the evidence: 1) study limitations; 2) consistency (the similarity of results across studies); 3) directness (synonymous with "generality," "external validity of study results," and "applicability"); 4) imprecision (results are considered imprecise when studies include relatively few patients and few events and thus have wide confidence intervals for the effect estimate); and 5) reporting bias (also called publication bias), which is an under- or over-estimate of the underlying beneficial or detrimental effect due to the selective publication of studies or of end results. For clinical situations for which no controlled studies were available (special cases), studies identified by the search strategies were taken into account.

[5] http://tech.cochrane.org/revman/gradepro

Recommendations were classified for each available treatment, according to the following criteria:

- Weak (conditional): The guideline development group considers the potential benefits of the intervention to most likely be greater than the potential risks, but the evidence is local and limited and its use in public health is restrictive or no longer used in the region.
- Strong (solid): The guideline development group considers the potential benefits of the intervention greater than the potential risks, and regardless of whether the evidence is limited or not it is widely used in public health.

To produce the recommendations, the following information was taken into account: the previously identified systematic reviews (*8–10, 12–14*), the WHO advisory group document (*5*), the findings of the systematic review update (*16*), and the GRADE tables. A second meeting, held during the International Congress for Tropical Medicine in Rio de Janeiro in September 2012, was attended by most of the experts who attended the first meeting (those who did not attend in person submitted their opinion electronically). Each recommendation was formulated by consensus among the PAHO internal production team, which was responsible for leading the discussion whenever there was no initial consensus. The basis for consensus was the available evidence. Development of the recommendations was supported by 1) the quality of the evidence; 2) the balance of potential benefits to the patient compared to potential harms and burdens; 3) values and preferences; and 4) use of resources. All members of the guideline development group declared their potential conflicts of interest according to WHO standards. No important differences of opinion or conflicts arose during the process.

MANAGEMENT OF CONFLICTS OF INTEREST

A Conflict of Interest statement and form was sent to all potential participants in the production of this guide asking them to declare any conflicts of interest. In accordance with the procedures established by WHO, the forms submitted by the participants were reviewed by PAHO's internal production team. Details of this process are provided in Annex 6.

Guide updates

Given the new evidence and the increase in therapeutic clinical trial reports from research groups, the internal and external production teams that produced this guide have deemed it necessary to periodically update the recommendations for leishmaniasis diagnosis and treatment in the Americas. Based on information from WHO ICTRP, several clinical trials evaluating various interventions in the Americas were identified, 22 of which are evaluating various treatments for the different clinical forms of leishmaniasis in the Region. The selected studies were limited to those that have been recently completed, are in the recruitment phase, or have yet to recruit. It is therefore recommended that this guide be reviewed and updated in three to five years.

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ANNEXES

ANNEX 1

Drugs used in the systemic treatment of leishmaniasis in the Americas: characteristics and principal adverse events

Systemic (drug) treatments are the most common way of treating the different clinical forms of leishmaniasis in the Americas. However, the toxicity from the drugs that are used causes mild, moderate, and severe adverse events. Table 12 (Annex 2) presents the general frequency of clinical, laboratory, and electrocardiographic adverse events among patients treated with pentavalent antimonials and pentamidine isethionate, identified by a systematic review of adverse effects from treatment of cutaneous leishmaniasis in the New World *(9)*.

The drugs that are currently available in the Region for systemic treatment include pentavalent antimonials, pentamidine isethionate, various formulations of amphotericin B, pentoxifylline, miltefosine, and ketoconazole. These drugs and their main adverse effects are described in brief below (*5, 8, 9*).

Pentavalent antimonials (Sb^{+5})

The pentavalent antimonials currently available on the market are sodium stibogluconate (Pentostam® or generic) and meglumine antimoniate (Glucantime® or generic). They are chemically similar, and their toxicity and efficacy are related to their pentavalent antimony content (Sb^{+5}): meglumine antimoniate solution contains 81 mg/ml of Sb^{+5}, whereas sodium stibogluconate solution contains 100 mg/ml of Sb^{+5}. The injection may be given intramuscularly or intravenously either by infusion (5–10 minutes) or by slow injection through a fine needle (23–25 gauge, 0.6–0.5 mm) to avoid any risk of subsequent thrombosis.

Antimonials are distributed in high concentrations in plasma, liver, and spleen; they have a half-life of 8 hours in adults and 5 hours in children, with a fast rate of absorption. Excretion is through urine (80% in 6 hours) and is complete 24–76 hours after administration; elimination is faster in children.

Response to antimonial treatment varies considerably depending on parasite species and strain, immunological status of the patient, and the clinical form of the disease.

Adverse effects related to the musculoskeletal system (e.g., myalgia and arthralgias) were most common and often caused interruption of treatment. These types of adverse effects can be serious, especially in older patients, but usually respond to nonsteroidal anti-inflammatory drugs. Headache, anorexia, nausea, and fever are also frequently reported during use of drugs available for systemic treatment.

Serum alanine aminotransferase, alkaline aminotransferase, aspartate aminotransferase, and lipase may also increase, although not by much. Hyperamylasemia with or without acute pancreatitis is another frequent adverse effect, and may be the cause of frequently reported nausea and abdominal pain. There have been occasional reports of a drop in hemoglobin and leukocytes or an increase in serum concentrations of urea nitrogen and creatinine. Dose- and time-dependent effects can be seen in an electrocardiogram (ECG), including reversible changes such as an increase in P-wave amplitude, T-wave inversion (or reduction in its height), S-T segment elevation, or QT interval prolongation, the most serious adverse effect and the one usually associated with death.

Pentavalent antimonials are contraindicated during pregnancy. Studies have not been conducted in humans or animals, which means that its use is not recommended during breastfeeding. Special care should be taken with its

administration in patients with heart disease, especially conduction defects, as it can cause arrhythmia. It can also lead to changes in liver function, pancreatitis, or renal tubular dysfunction. Deaths of patients associated with use of this drug have been reported.

Resistance to antimonials is a growing problem, mainly with the anthroponotic *Leishmania* species, and is associated with the use of incomplete treatments.

Amphotericin B

To date there are four formulations of amphotericin B:

Amphotericin B deoxycholate: This drug acts by altering the permeability of the cellular membrane. It is administered intravenously in 5% dextrose for 2 hours, at a dose of 0.7–1.0 mg/kg/day or on alternate days, until a total cumulative dose of 25 mg/kg is reached (approximately 42 doses). This is a very effective drug, with cure rates up to 98%, but its use is limited due to frequent adverse effects (IV infusions). This treatment should be administered in the hospital to enable continuous patient monitoring. The most common reactions are high fever, chills, and thrombophlebitis of the injected vein. Both tubular and glomerular nephrotoxicity are common, leading to frequent interruption of treatment in some patients, either from increase in urea and creatinine or development of severe hypokalemia. Other uncommon but serious toxic effects are myocarditis and severe hepatitis. Proper hydration and other prevention strategies are very important to prevent or reduce renal, liver, and cardiac toxicity.

Amphotericin B lipid formulations: Formulations of amphotericin B used for leishmaniasis treatment include liposomal amphotericin B, amphotericin B colloidal dispersion, and amphotericin B lipid complex. These treatments are similar to amphotericin B deoxycholate in their efficacy but are significantly less toxic. Most clinical trials in leishmaniasis have been conducted with the liposomal amphotericin B formulation; for this reason, it is important to do studies with other lipid formulations.

a) Liposomal amphotericin B is a lipid formulation of amphotericin B and hydrogenated soy phosphatidylcholine, distearoylphosphatidylglycerol, and cholesterol, which is administered intravenously at a dose of 3–5 mg/kg of weight/day for 3–5 days for treatment of visceral leishmaniasis, with efficacy > 98%. The small vesicles of lipids that contain the drug are phagocytized by the macrophages, fusing with the membrane of the phagosome to liberate the drug directly on the parasite.

b) Amphotericin B colloidal dispersion is a lipid formulation of amphotericin B and cholesterol sulfate.

c) Amphotericin B lipid complex is a lipid formulation of amphotericin B and dimyristoyl phosphatidylcholine and dimyristoyl phosphatidylglycerol.

Similarly, therapeutic responses differ depending on the clinical form of the disease and the species of *Leishmania*.

Pentamidine isethionate

Pentamidine isethionate is an aromatic diamidine derivative that interacts with kinetoplast DNA, inhibits topoisomerase II, and interferes with glycolysis. It is administered intramuscularly at a dose of 3–4 mg/kg on alternate days for 3–4 doses. The cure rate ranges from 84% to 96%.

It is used for treatment of cases that do not respond to other drugs and in situations where local therapeutic response is known, based on the circulating Leishmania species. There are contraindications to its use in patients with liver, pancreatic, or renal impairment.

The most frequent secondary adverse events from pentamidine isethionate may be mild or moderate, such as pain and edema at the application site, abscesses, dizziness, fever, headache, adynamia, nausea, and joint pain. Rhabdomyolysis has also been reported, especially when the drug is used in high doses.

Serious adverse events such as acute hypotension or hypoglycemia are frequent, especially when the drug is applied very quickly or when the patient gets up too soon after the injection. Therefore, keeping the patient in a reclining position for 15 minutes after administration is recommended. Adverse cardiovascular events similar to those for pentavalent antimonials have also been observed, with QT-interval prolongation the most frequent.

Miltefosine

Miltefosine is a derivative of hexadecylphosphocholine that was originally developed originally as an oral cancer drug but has been shown to have antileishmanial activity. Miltefosine was the first oral drug used for leishmaniasis treatment. Dosage is based on the patient's weight.

Miltefosine is also used in Asia as an antiparasitic drug for the treatment of visceral leishmaniasis, but responses were not satisfactory for *L. infantum*, a species circulating in the Americas. For cutaneous leishmaniases, variable efficacy has been shown, depending on species and geographic area.

Miltefosine produces gastrointestinal adverse effects such as nausea, accompanied at times by vomiting, diarrhea, and loss of appetite, which decreases adherence to treatment. Occasionally, the side effects can be severe and require interruption of treatment. These include skin allergy and elevated hepatic transaminase concentrations (below critical levels). There have also been reports of allergic reactions such as Steven-John syndrome.

Miltefosine is potentially teratogenic and has a prolonged half-life in the body. In women of childbearing age, adequate contraception must be ensured during treatment and for three months afterward.

Pentoxifylline

Pentoxifylline has been used in combination with antimony derivatives to treat mucocutaneous leishmaniases caused by *L. braziliensis*, but experience is limited. Frequent side effects include nausea, arthralgia, dizziness, abdominal pain, and diarrhea (*33*).

ANNEX 2. GRADE summary of findings tables

TABLE 1

Authors: Chrusciak-Talhari 2011 (Brazil); Rubiano 2012 (Colombia); Machado 2010 (Brazil); Vélez 2010 (Colombia); Soto 2008 (Bolivia)
Date: 30 Nov. 2012 ***Question:*** Miltefosine versus meglumine antimoniate for cutaneous leishmaniasis?[1] Outcome: Cure, failure, and adverse events
Reference: Interventions for American Cutaneous and Mucocutaneous Leishmaniasis: A Systematic Review Update

EVALUATION OF QUALITY							NUMBER OF PATIENTS		EFFECT			
No. of studies	Design	Risk of bias	Inconsistency	Indirect	Imprecision	Other considerations	Miltefosine	Meglumine antimoniate	Relative (95% CI)	Absolute/ 1000	QUALITY	IMPORTANCE
Complete cure (ITT) (mean follow-up 6 months; evaluated by photography[2]) Chrusciak-Talhari 2011 (Brazil); Vélez 2010 (Colombia); Machado 2010 (Brazil); Rubiano 2012 (Colombia)												
4	Randomized trials	Not serious	Serious[3]	Not serious	Not serious	None	219/323 (67.8%)	175/261 (67%)	RR 1.12 (0.85 to 1.47)	80 (-101 to 315)	MODERATE	Important
								0%		–		
Complete cure in American children (mean follow-up 6 months; evaluated by photography) Chrusciak-Talhari 2011 (Brazil); Machado 2010 (Brazil); Rubiano 2012 (Colombia)												
3	Randomized trials	Not serious	No inconsistency[4]	Not serious	Not serious	None	75/99 (75.8%)	52/77 (67.5%)	RR 1.16 (0.96 a 1.4)	108 (- 27 to 270)	HIGH	Important
								0%		–		
Complete cure Adults Brazil and Colombia: *L. guyanensis* and *L. panamensis* (mean follow-up 6 months; evaluated by photography) Chrusciak-Talhari 2011 (Brazil); Vélez 2010 (Colombia)[5]												
2	Randomized trials	Not serious	Serious[6]	Not serious	Not serious	None	58/75 (77.3%)	19/39 (48.7%)	RR 1.01 (0.62 - 1.65)	5 (-185 to 317)	MODERATE	Important
								0%		–		
Cure - *Leishmania guyanensis* (mean follow-up 6 months; evaluated by photography) Chrusciak-Talhari 2011												
1	Randomized trials	Not serious	Not applicable	Not serious	Not serious	None	14/56 (25%)	12/28 (42.9%)	RR 0.58 (0.31 - 1.09)	180 (- 296 to 39)	MODERATE	Important
								0%		–		
Severe adverse events on follow-up (mean follow-up 6 months; evaluated by photography) Chrusciak-Talhari 2011 (Brazil); Vélez 2010 (Colombia); Machado 2010 (Brazil); Rubiano 2012 (Colombia)[5]												
4	Randomized trials	Not serious	No inconsistency	Not serious	Serious[7]	None	3/322 (0.93%)	1/260 (0.38%)	RR 1.55 (0.23 - 10.56)	2 (- 3 to 37)	MODERATE	Critical
								0%		–		
Treatment failure (ITT) *L. guyanensis* and *L. panamensis* (mean follow-up 6 months; evaluated by clinic) Chrusciak-Talhari 2011 (Brazil) and Rubiano 2012;												
2	Randomized trials	Not serious	No inconsistency[4]	Not serious	Not serious	None	23/69 (33.3%)	14/33 (42.4%)	RR 0.89 (0.32 - 2.49)	47 (288 to 632)	HIGH	Importante
								0%		–		
General treatment failure (mean follow-up 6 months; evaluated by photography) Chrusciak-Talhari 2011 (Brazil); Rubiano 2012 (Colombia); Machado 2010 (Brazil); Vélez 2010 (Colombia); Soto 2008 (Bolivia)												
5	Randomized trials	Not serious	Serious[3]	Not serious	Not serious	None	90/364 (24.7%)	64/277 (23.1%)	RR 0.88 (0.44 - 1.74)	28 (129 to 171)	MODERATE	Important
								0%		–		

[1] Meglumine antimoniate: doses used - 20 mg Sb^{+5}/kg/day for 20 days with maximum dose of 3 ampoules; 20 mg Sb^{+5}/kg/day for 20 days with no maximum dose and 15 mg Sb^{+5}/kg/day for 20 days with maximum dose of 3 ampoules.
[2] Studies used photography for evaluation of outcome, but did not state who did the evaluation and whether it was blinded.
[3] Three species of *Leishmania* (*L. braziliensis*, *L. panamensis* and *L. guyanensis*) were identified in these studies and outcomes were different among species and within the same species, but in different geographic regions.
[4] Three different Leishmania species were identified in 3 different geographic areas. I^2 = 0%.
[5] Study in different geographic areas, different circulating species (*L. braziliensis* and *L. guyanensis*), and different populations (general and military) I^2 = 83%.
[6] Study in 2 geographic regions and different Leishmania species (*L. braziliensis*, *L. panamensis*, and *L. guyanensis*).
[7] Wide confidence interval when studies analyzed in meta-analysis RR 1.55 (0.23–10.56).

Note: Three *Leishmania* species (*L. braziliensis*, *L. panamensis*, and *L. guyanensis*) were identified in these studies and outcomes were different among species and within the same species, but in different geographic regions. I^2 = 79%. Studies with small "n" included adult and child populations.
Updated evidence: Search carried out for period January 2009 to July 2012 to supplement the systematic review by González, 2009.

TABLE 2

Authors: Chrusciak-Talhari 2011 (Brazil); Rubiano, 2012 (Colombia); Machado 2010 (Brazil); Vélez 2010 (Colombia). ***Date:*** 30 Nov. 2012. ***Question:*** Miltefosine versus meglumine antimoniate for cutaneous–species Leishmania guyanensis and panamensis 1. ***Outcome:*** Cure. ***Reference:*** Interventions for American Cutaneous and Mucocutaneous Leishmaniasis: A Systematic Review Update.

EVALUATION OF QUALITY							NUMBER OF PATIENTS		EFFECT			
No. of studies	Design	Risk of bias	Inconsistency	Indirect	Imprecision	Other considerations	Miltefosine	Meglumine antimoniate	Relative (95% CI)	Absolute/ 1000	QUALITY	IMPORTANCE
Complete cure (ITT) *Leishmania guyanensis* and *panamensis* Chrusciak-Talhari, 2011 (Brazil); Rubiano, 2012 (Colombia)												
2	Randomized trials	Not serious	No inconsistency[4]	No grave indirecto	Not serious	None	89/118 (75.4%)	56/88 (63.6%)	RR 1.22 (1.02 - 1.46)	140 (13 to 293)	HIGH	Important
Complete cure (ITT) *Leishmania braziliensis* Machado, 2010 (Brazil); Vélez, 2010 (Colombia)												
2	Randomized trials	Not serious	Serious[5]	No grave indirecto	Not serious	None	56/92 (60.8%)	48/71 (67.6%)	RR 0.88 (0.64 - 1.21)	81 (-243 to 142)	MODERATE	Important

[1] Studies in the Americas: 1 in Brazil and 1 in Colombia.

[2] Meglumine antimoniate: doses used—20 mg Sb^{+5}/kg/day for 20 days with maximum dose of 3 ampoules and 15 mg Sb^{+5}/kg/day for 20 days with maximum dose of 3 ampoules. Miltefosine: 2.5 mg/kg max. 150 mg /28 days.

[3] Studies used photography for evaluation of outcome, but did not state who did the evaluation and whether it was blinded.

[4] Studies in different geographic areas and different circulating species *L. guyanensis* and *L. panamensis* and I2 = 0%.

[5] Studies in different geographic areas and same circulating species, *L. braziliensis*, with different populations: general and military, I2 = 46%.

Note: Updated evidence: Search carried out for period January 2009 to July 2012 to supplement the systematic review by González, 2009.

TABLE 3

Authors: Andersen, 2005; Neves, 2012; Correia, 1996. ***Date:*** 30 Nov. 2012.

Question: Pentamidine isethionate versus meglumine antimoniate for cutaneous leishmaniasis?[1,2] ***Outcome:*** Cure and adverse events

References: Interventions for American cutaneous and mucocutaneous (Review), González, 2009 and Interventions for American Cutaneous and Mucocutaneous Leishmaniasis: A Systematic Review Update.

EVALUATION OF QUALITY							NUMBER OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirect	Imprecision	Other considerations	Miltefosine	Meglumine antimoniate	Relative (95% CI)	Absolute/ 1000		
Cure in 6 months–*L. guyanensis* and *L. braziliensis* (mean follow-up 6 months; evaluated by clinic) Andersen, 2005; Neves, 2012												
2	Randomized trials	Serious[3]	Very serious[4]	Not serious	Not serious	None	58/113 (51.3%)	72/112 (64.3%)	RR 1.42 (0.61 - 3.29)	270 (-251 to 1000)	VERY LOW	Important
								0%		–		
Failure (mean follow-up 6 months; evaluated by clinic) Andersen 2005, Neves 2012												
2	Randomized trials	Serious[5]	Very serious[5]	Not serious	Not serious	None	48/113 (42.5%)	30/112 (26.8%)	RR 0.52 (0.14 - 1.94)	129 (230 to 252)	VERY LOW	Important
								0%		–		
Adverse events (mean follow-up 6 months; evaluated by clinic) Andersen, 2005												
1	Randomized trials	Serious[5]	Not applicable	Not serious	Serious[6]	None	2/113 (1.8%)	1/112 (0.89%)	RR 0.49 (0.04 - 5.6)	5 (9 to 41)	VERY LOW	Important
Cure in 6 months *L. braziliensis* (mean follow-up 6 months; evaluated by clinic) Andersen, 2005												
1	Randomized trials	Serious	Not applicable	Not serious	Not serious	None	14/40 (35%)	31/40 (77.5%)	RR 2.21 (1.41 - 3.49)	938 (318 to 1000)	LOW	Important
								0%		–		
Cure in 1 year *L. braziliensis* (1 year follow-up; evaluated by clinic) Correia, 1996												
1	Randomized trials	Serious[7]	Not applicable	Not serious	Not serious	None	13/15 (86.7%)	14/16 (87.5%)	RR 0.99 (0.75 - 1.30)	9 (219 to 272)	LOW	Important
								0%		–		

[1] Pentamidine isethionate—three studies: *L. guyanensis*—4 mg/kg every 72 hours in 3 doses; *L. braziliensis*—2 mg/kg on alternate days for 7 doses, and *L. braziliensis*—4 mg/kg on alternate days for 8 doses.

[2] Meglumine antimoniate—two studies: 15 mg Sb+5/kg/day for 20 days and 20 mg Sb+5/kg/day for 20 days.

[3] Authors did not mention how randomization sequence was generated and concealed. The study was open and did not report on evaluation process.

[4] The studies were conducted in different geographic regions and on different species of parasite: *L. braziliensis* and *L. guyanensis*: I2 = 90%.

[5] The studies were conducted in different geographic regions and on different species of parasite: *L. braziliensis* and *L. guyanensis* I2 = 88%.

[6] González, 2012 classified as risk of bias, due to lack of information on generation and concealment of randomization sequence.

[7] Performance bias and detection bias. Small number of participants.

Note: Updated evidence: Search carried out for period January 2009 to July 2012 to supplement the systematic review by González, 2009.

TABLE 4

Author: López, 2012 ***Date:*** 30 Nov. 2012

Question: Thermotherapy versus meglumine antimoniate for cutaneous leishmaniasis?[1,2] ***Outcome:*** Cure

Reference: Interventions for American Cutaneous and Mucocutaneous Leishmaniasis: A Systematic Review Update

EVALUATION OF QUALITY							NUMBER OF PATIENTS		IMPORTANCE			
No. of studies	Design	Risk of bias	Inconsistency	Indirect	Imprecision	Other considerations	Miltefosine	Meglumine antimoniate	Relative (95% CI)	Absolute/ 1000	QUALITY	IMPORTANCE
Complete cure 6 months—ITT *L. braziliensis* and *L. panamensis* (average monitoring 6 months; evaluated by clinical examination and photography)												
1	Randomized trials	Not serious	Not applicable	Not serious	Not serious	None	86/149 (57.7%)	103/143 (72%)	RR 0.80 (0.68 to 0.95)	144 (36 to 230)	MODERATE	Important
								0%		–		
Complete cure 6 months ITT - *L. panamensis* (average monitoring 6 months; evaluated by clinical examination and photography)												
1	Randomized trials	Not serious	Not applicable	Not serious	Not serious	None	14/24 (58.3%)	23/32 (71.9%)	RR 0.81 (0.54 to 1.21)	137 (-331 to 151)	MODERATE	Important
								0%		–		
Complete cure 6 months ITT - *L. braziliensis* (average monitoring 6 months; evaluated by clinical examination and photography[3])												
1	Randomized trials	Not serious	Not applicable	Not serious	Not serious	None	31/59 (52.5%)	34/52 (65.4%)	RR 0.80 (0.59 to 1.1)	131 (- 268 to 65)	MODERATE	Important
								0%		–		
Cure 3 months (average monitoring 3 months; evaluated by clinic)												
1	Randomized trials	Not serious	Not applicable	Serious[4]	None	None	16/22 (72.7%)	16/22 (72.7%)	RR 1 (0.70 to 1.44)	0 (218 to 320)	LOW	Important
								0%		–		
Cures 3 months *L. braziliensis* - ITT (average monitoring 6 months; evaluated by clinical examination												
1	Randomized trials	Not serious	Not applicable	Serious[4]	Serious[4]	None	11/14 (78.6%)	9/14 (64.3%)	OR 2.04 (0.38 to 10.94)	143 (309 to 343)	LOW	Important
								0%		–		

[1] Application of 50°C for 30 seconds. Number of applications depends on size of lesion.

[2] 20 mg Sb+5/kg/day for 20 days

[3] Different species: Thermotherapy (29% *L. panamensis* and 71 *L. braziliensis*) and meglumine antimoniate (38% *L. panamensis* and 62 *L. braziliensis*).

[4] Specific population: army soldiers.

Note: Updated evidence: Search carried out for period January 2009 to July 2012 to supplement the systematic review by González, 2009.

TABE 5

Author: Palacios, 2001 ***Date:*** 30 Nov. 2012

Question: Meglumine antimoniate 20 days versus meglumine antimoniate 10 days for cutaneous leishmaniasis?[1,2] ***Outcome:*** Complete cure and adverse events

Reference: Interventions for American cutaneous and mucocutaneous (Review), González, 2009

EVALUATION OF QUALITY							NUMBER OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirect	Imprecision	Other considerations	Miltefosine	Meglumine antimoniate	Relative (95% CI)	Absolute/ 1000		
Complete cure 1 year (average monitoring 12 months; evaluated by clinic[3])												
1	Randomized trials	Not serious	Not applicable	Not serious	Serious	None	28/68 (41.2%)	24/68 (35.3%) 0%	RR 1.17 (0.76 to 1.79)	60 (-85 to 279) –	MODERATE	Important
Adverse event - Arthralgia (average monitoring 12 months; evaluated by clinic)												
1	Randomized trials	Not serious	Not applicable	Not serious	Serious[4]	None	5/68 (7.4%)	14/68 (20.6%) 0%	RR 0.36 (0.14 to 0.94)	132 (12 177) –	MODERATE	Critical

[1] Meglumine antimoniate dose of 20 mg Sb+5/kg/day for 10 days.
[2] Meglumine antimoniate dose of 20 mg Sb+5/kg/day for 20 days.
[3] Clinical examiner responsible for evaluation was blinded.
[4] In 95% of patients the Leishmania species identified was *L. panamensis*; in all others it was *L. braziliensis*.

TABLE 6

Author: Soto, 2004/A ***Date:*** 30 Nov. 2012

Question: Generic sodium stibogluconate versus patented sodium stibogluconate for cutaneous leishmaniasis? ***Outcome:*** Complete cure and adverse events

Reference: Interventions for American cutaneous and mucocutaneous (Review), González, 2009

EVALUATION OF QUALITY							NUMBER OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirect	Imprecision	Other considerations	Miltefosine	Meglumine antimoniate	Relative (95% CI)	Absolute/ 1000		
Complete cure (average monitoring 6 months; evaluated by clinic)												
1	Randomized trials	Not serious	Not applicable	Not serious	Serious	None	12/16 (75%)	40/48 (83.3%)	RR 1.11 (0.82 to 1.51)	92 (150 to 425) –	MODERATE	Important
Adverse event - abdominal pain (average monitoring 6 months; evaluated by clinic)												
1	Randomized trials	Not serious	Not applicable	Not serious	Serious[1]	None	4/48 (8.3%)	4/16 (25%)	RR 3.00 (0.85 to 10.63)	500 (37 to 1000) –	MODERATE	Critical

[1] Wide confidence interval.

TABLE 7

Author: Saenz 1990 ***Date:*** 30 Nov. 2012

Question: Ketoconazole - *Leishmania panamensis* and *L. mexicana* versus meglumine antimoniate for cutaneous leishmaniasis?[1] ***Outcome:*** complete cure

Reference: Interventions of cutaneous and mucocutaneous leishmaniasis in the Americas, González, 2009

EVALUATION OF QUALITY							NUMBER OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirect	Imprecision	Other considerations	Miltefosine	Meglumine antimoniate	Relative (95% CI)	Absolute/ 1000		
Complete cure (average monitoring 3 months; evaluated by clinic)												
1	Randomized trials	Serious[2]	Not applicable	Not serious	Serious[3]	None	16/22 (72.7%)	13/19 (68.4%)	RR 1.06 (0,7 to 1.58)	41 (205 to 397)	LOW	Important

[1] 20 mg Sb^{+5}/kg/day for 20 days with maximum of 850 mg (2 ampoules).
[2] Blinding and evaluation process not mentioned.
[3] Small number of participants.

TABLE 8

Author: Figueiredo, 1999 ***Date:*** 30 Nov. 2012

Question: Meglumine antimoniate 14 mg/Sb^{+5}/kg/day versus meglumine antimoniate 14 mg/Sb^{+5}/kg/day in mucosal or mucocutaneous leishmaniasis? ***Outcome:*** Complete cure

Reference: Interventions for American cutaneous and mucocutaneous (Review), González, 2009

EVALUATION OF QUALITY							NUMBER OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirect	Imprecision	Other considerations	Miltefosine	Meglumine antimoniate	Relative (95% CI)	Absolute/ 1000		
Complete cure (monitoring 1 year; evaluated by clinic)												
1	Randomized trials	Not serious	Not applicable	Not serious	Serious[1,2]	None	4/10 (40%)	4/7 (57.1%)	RR 1.43 (0.53 to 3.86)	246 (-269 to 1000)	LOW	Crítical

[1] Type of *Leishmania* unreported.
[2] Limited number of participants.

TABLE 9

Author: Franke, 1994 ***Date:*** 30 Nov. 2012

Question: Sodium stibogluconate 28 days versus sodium stibogluconate 40 days for mucosal or mucocutaneous leishmaniasis? ***Outcome:*** complete cure

Reference: Interventions for American cutaneous and mucocutaneous (Review), González, 2009

EVALUATION OF QUALITY							NUMBER OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirect	Imprecision	Other considerations	Miltefosine	Meglumine antimoniate	Relative (95% CI)	Absolute/ 1000		
Cura completa 1 año (seguimiento 1 año; evaluado con: clínica)												
1	Randomized trials	Serious[1]	Not applicable	Not serious	Serious[2]	None	12/20 (60%)	10/20 (50%)	RR 0.83 (0,47 to 1,47)	-85 (265 to 235)	VERY LOW	Crítical

[1] No information on risk of bias.
[2] Small number of participants, evaluation without intention to treat (ITT).

TABLE 10

Author: Machado, 2007 ***Date:*** 30 Nov. 2012

Question: Oral pentoxifylline + sodium stibogluconate versus placebo + sodium stibogluconate for mucosal leishmaniasis?[1,2] ***Outcome:*** cure

Reference: Interventions for American cutaneous and mucocutaneous (Review), González, 2009

EVALUATION OF QUALITY							NUMBER OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirect	Imprecision	Other considerations	Oral pentoxifylline + Sodium stibogluconate	Placebo + Sodium stibogluconate	Relative (95% CI)	Absolute/ 1000		
Cure in 4 months *L. braziliensis* (average monitoring 6 months; evaluated by clinic and by ENT)												
1	Randomized trials	Serious[3]	Not applicable	Not serious	Serious[4]	None	11/11 (100%)	7/12 (58.3%)	RR 1.66 (1.03 to 2.69)	385 (17 986)	LOW	Crítical

[1] Doses: Oral pentoxifylline 400 mg 3/day for 30 days plus sodium stibogluconate 20 mg Sb^{+5}/kg/day for 20 days.

[2] Placebo + sodium stibogluconate 20 mgSb^{+5}/kg/day for 20 days.

[3] Forms of concealment of randomization sequence not mentioned.

[4] Limited number of participants.

TABLE 11
Characteristics of intervention studies for treatment of visceral leishmaniases, according to criteria for grading risk of bias, Cochrane

Author	Year	Country	Part.	Parasite diagnosis without species identification	Intervention	Outcome	Risk of Bias						Overall risk of bias grade
							Generation of randomization sequence	Concealment of randomization sequence	Blinding	Incomplete data	Selective description	Other biases	
Dietze	1993	Brazil	20	Yes	T1: Amphocil ® (lipid amphotericin B) 2 mg/kg/day for 10 days T2: Amphocil ® 2 mg/kg/day for 7 days	**Primary outcome:** "cured" with 6- and 12-month follow-up; **Secondary outcomes:** adverse effects.	No information. **Uncertain**	Two cohorts, but inclusion criteria/ randomization in cohorts not reported. **Uncertain**	Open, phase 1/2. Did not address additional information that enables evaluation. **Uncertain**	Similar cure. Suggests that 7-day treatment was as effective as 10-day. Cohort 2 loss: 1/10 (10%). Information missing. **Uncertain**	Outcomes available but with limited information. **Uncertain**	Patient characteristics between groups uniform, but information is insufficient for evaluation. **Uncertain**	**Uncertain**
Dietze	1995	Brazil	10	Yes	T1: Amphocil® 2 mg/kg/d 5 d	**Primary outcome:** "cured" with 12-month follow-up; **Secondary outcomes:** adverse effects	No information. **Uncertain**	No information. **Uncertain**	Open, phase 1/2. Did not address additional information. **Uncertain**	Observed recurrence: 1/10. Information missing. **Uncertain**	Outcomes available but with limited information. **Uncertain**	Information missing. **Uncertain**	**Uncertain**
Berman	1998	Brazil, cohort 1	13	Yes	T1: Anfotericina B Lipossomal 14 mg/kg (total)	**Primary outcome:** "cured" with 6-month follow-up; **Secondary outcomes:** adverse effects	No information. **Uncertain**	Three cohorts in only one study site. **Uncertain**	Open, phase 2. Insufficient information for evaluation. **Uncertain**	Cure 62% (8/13) failure and recurrence (5/13) Cure 100% (4/4), mentions that these patients had adverse events, thus, dose reduced to 10 mg. Cure reported in cohort 1. Cure 87%. (13/15) Recurrence (2/15) Adverse events: 5/15 in T4: fever in infusion 3/32: Respiratory failure and/or heart arrhythmia in infusion - Low	Outcomes available but with limited information. **Uncertain**	Authors state that there are differences among the groups, but information is insufficient for evaluation. **Uncertain**	**Uncertain**
		Brazil, cohort 2	4	Yes	T2: Anfotericina B Lipossomal 10 mg/kg (total)								
		Brasil, cohort 3	15	Yes	T4: Anfotericina B Lipossomal 20 mg/kg (total)								

Studies of treatment of visceral leishmaniasis in humans included in the systematic review: Romero & Boelaer, 2010.

Study of visceral leishmaniasis in process in Brazil: Clinical Trials Registry: NCT01310738

TABLE 12
Frequency of clinical, laboratory, and electrocardiographic adverse effects in patients with cutaneous leishmaniases treated with pentavalent antimonials and pentamidine isethionate

	Prevalent antimonials 20 mg/kg/day		Pentamidine isethionate 2-4 mg/kg/day	
Signs and symptoms	No.	%	No.	%
Myalgia/arthralgia	848	48.6	289	24,9
Gastrointestinal disorders	361	17.4	312	21,5
Headache	632	23.6	224	15,2
Anorexia	257	19.4	15	46,7
Astheni/fatigue	127	18.9	128	21,1
Fever	430	16.7	103	8,7
Skin reactions	238	5.9	38	5,3
Cardivascular disorders	254	6.7	77	7,8
Respiratory disorders	76	10.5	40	5
Local pain	42	64.3	526	31,6
Itching	23	8.7	–	–
Changes in taste	154	25.3	40	17,5
Neurological disorders	103	2.9	281	4,6
Balance disorders	77	5.2	88	22,7
Behavior disorders	–	–	38	5,3
↑ AST/ALT	268	43.3	–	–
↑ Lipase/amylase	157	59.9	–	–
Leucopenia	52	7.7	–	–
Thrombocytopenia	42	7.1	–	–
Hypoglycemia	–	–	83	2,4
QTc interval prolongation	162	16	–	–
Vrd	124	25	–	–
Arrythmia	61	3.3	–	–

N: Number of patients evaluated; Vrd: Ventricular repolarization disturbance.
AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Source: L.F. Oliveira et al. Acta Tropica. 118(2011):87–96.

Note: The methodological structure of the systematic review by Oliveira et al. (2011) was not conducive to producing a GRADE table with outcomes for adverse events from treatment of cutaneous leishmaniasis presented in the included studies. The adverse events in Table 12 represent the overall prevalence of events observed with pentavalent antimonials and pentamidine isethionate, available in Table 4 of that systematic review (9).

ANNEX 3

Pan American Health Organization (PAHO) / World Health Organization

Internal Production Team

- Ana Nilce Silveira Maia-Elkhoury, Regional Advisor on Leishmaniasis, Health Surveillance, Disease Prevention and Control / Prevention and Control of Communicable Diseases (HSD/CD), PAHO/WHO, Rio de Janeiro, Brazil. Coordination, organization, preparation, and review of the evidence and of the development of the guide. Preparation of the systematic review update on therapeutic interventions for leishmaniases in the Americas.
- Rubén Santiago Nicholls, Consultant, Health Surveillance, Disease Prevention and Control / Prevention and Control of Communicable Diseases (HSD/CD/NTD), PAHO/WHO, Washington, D.C., United States. Organization and review of the evidence and of the development of the guide. Preparation of the systematic review update on therapeutic interventions for leishmaniases in the Americas.
- Zaida E. Yadón, Regional Advisor on Communicable Diseases Research, Health Surveillance, Disease Prevention and Control / Prevention and Control of Communicable Diseases (HSD/CD), PAHO/WHO, Rio de Janeiro, Brazil. Support for coordination, organization, and review of the evidence. Preparation of the systematic review update on therapeutic interventions for leishmaniases in the Americas.
- Ludovic Reveiz, Health Systems Based on Primary Health Care (HSH), PAHO/WHO, Washington, D.C., United States. Support for methodology and review of the evidence. Preparation of the systematic review update on therapeutic interventions for leishmaniases in the Americas.
- Jorge Alvar, Medical Officer, Leishmaniasis Control Programme, World Health Organization, Geneva, Switzerland. Technical review of the guide.

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ANNEX 4

Advisory groups for the development of this guide

The experts and decision-makers that contributed to the development of this guide are listed below.

Leishmaniasis experts

- Byron Alfredo Arana Figueroa, Researcher, Universidad del Valle de Guatemala, Guatemala[6]
- Gustavo Adolfo Sierra Romero, Researcher, Tropical Medicine Group, Universidade de Brasília, Brasilia, Distrito Federal, Brazil[6,7]
- Iván Darío Vélez, Researcher and Director, Program for the Study and Control of Tropical Diseases (PECET), Universidad de Antioquia, Medellín, Colombia[6]
- Jaime Soto, Researcher and Dermatology Professor Emeritus, Fundación Nacional de Dermatología, Santa Cruz de la Sierra, Bolivia[6]
- José Angelo Lauletta Lindoso, Researcher, Seroepidemiology and Immunobiology Laboratory of the Instituto de Medicina Tropical de São Paulo and Instituto de Infectologia Emílio Ribas, São Paulo, São Paulo, Brazil[6]
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- Nancy Gore Saravia, Scientific Director and Researcher, Centro Internacional de Entrenamiento e Investigaciones Medicas, WHO Collaborating Centre on Leishmaniasis Control, Cali, Colombia[6]
- Olga Zerpa, Researcher and Dermatologist, Institute of Biomedicine, Universidad Central de Venezuela, and Leishmaniasis Section Coordinator, Ministry of Health and Social Development, Caracas, Venezuela[6]
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Ministry of Health representatives

- Daniele Pelissari, Technical Group on Leishmaniasis, Secretariat of Health Surveillance, Ministry of Health, Brasília, Distrito Federal, Brazil[6]
- Martha Stella Ayala Sotelo, Coordinator, Parasitology Group and National Laboratory Network, National Institute of Health, Bogotá, Colombia[6]
- Pilar Zambrano, Expert, Vector-borne Diseases Group, National Institute of Health, Bogotá, Colombia[6]

[6] Participation in the meeting held in 2011, establishment of the scope and purpose of the guide, definition of the questions and outcomes of interest, review of the evidence, participation in the consensus on the recommendations, and review of the document.

[7] Preparation of the systematic review update on therapeutic interventions for leishmaniases in the Americas.

ANNEX 5

External reviewers

Technical reviewers

- Ana Rabello, MD, MSc, PhD, Researcher, René Rachou Research Center, Oswaldo Cruz Foundation (Fioruz), Belo Horizonte, MG, Brazil
- Elmer Alejandro Llanos Cuentas, MD, MSc, PhD, Researcher, National Institute of Health, Lima, Peru
- Gloria I. Palma, MD, PhD, Professor and Chair, Department of Microbiology, School of Health, University of Valle, Cali, Colombia
- Heidy Monastérios Torrico, Dermatologist and Researcher, Clinical Hospital at the Universidad Mayor de San Andrés Faculty of Medicine, La Paz, Bolivia
- Jackson Mauricio Lopes Costa, MD, MSc, PhD, Gonçalo Moniz Research Center, Oswaldo Cruz Foundation (Fiocruz), Salvador, BH, Brazil

Methodological reviewers

The reviewers used the AGREE II instrument[8] to evaluate the quality of the guide.

- Romina Brignardello-Petersen, DDS, MSc, PhD (c), Clinical Epidemiology and Health Care Research, University of Toronto, Toronto, ON, Canada, and Evidence-based Dentistry Unit, Faculty of Dentistry, Universidad de Chile, Santiago, Chile
- Alonso Carrasco-Labra, DDS, MSc, PhD (c), Health Research Methodology, McMaster University, Hamilton, ON, Canada, and Evidence-based Dentistry Unit, Faculty of Dentistry, Universidad de Chile, Santiago, Chile

[8] International tool for assessing quality and reporting of practice guidelines (www.agreetrust.org/resource-centre/agree-ii/).

ANNEX 6

Conflict of Interest statement

In accordance with WHO procedures, a conflict of interest statement and form were sent to all potential participants of the guideline development panel requesting their declaration of any relevant conflicts of interests. Three potential participants declared conflicts of interest, but it was determined by the group that the declared conflicts of interests did not have a direct bearing on or compromise in any way the deliberations or the recommendations reached by consensus during the meeting.

Dr. José Angelo Lauletta Lindoso declared that he received funding from Brazil's Financiadora de Estudos e Projetos (FINEP) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (public sector) for leishmaniasis research projects.

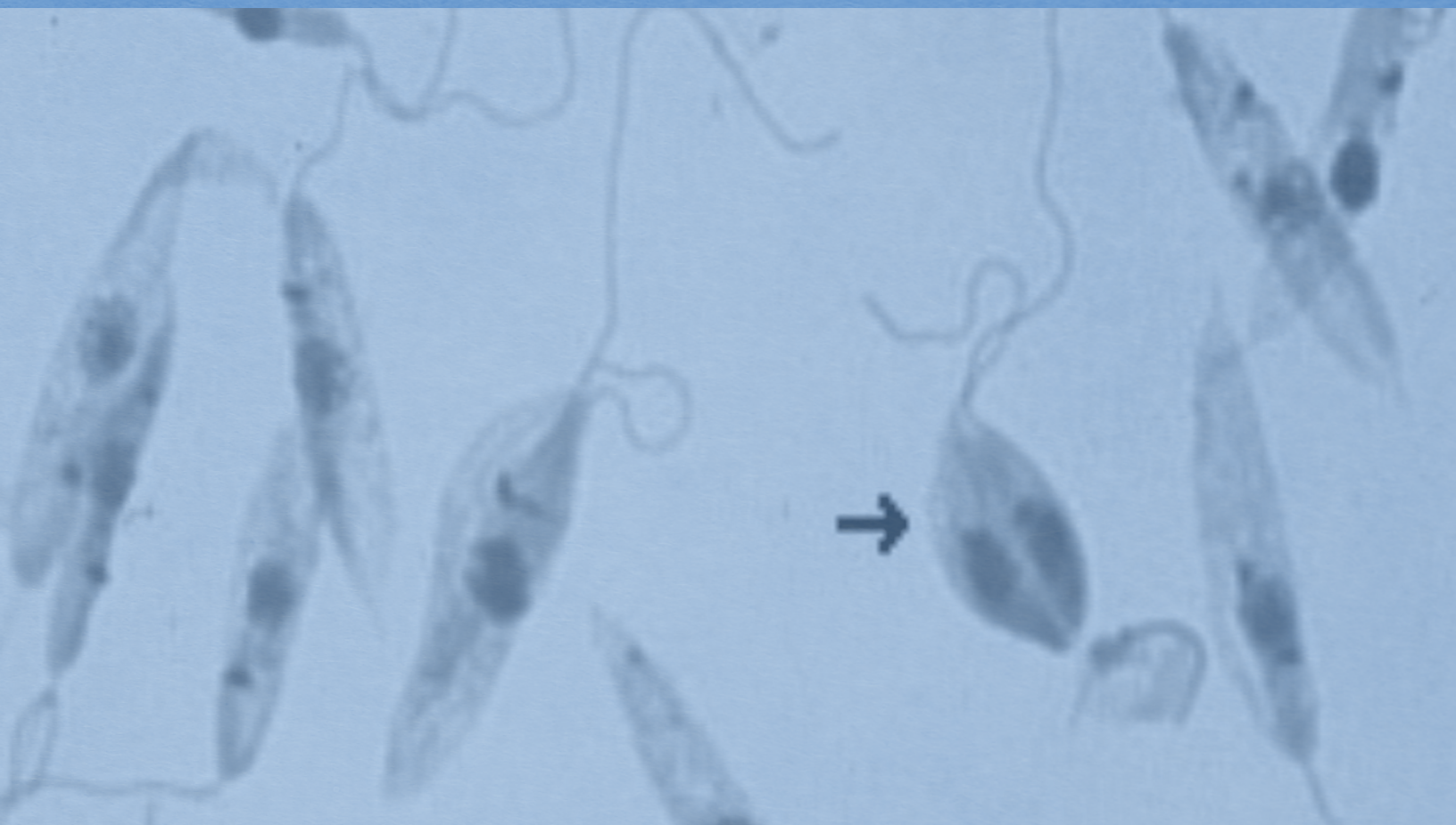
Dr. Jaime Soto declared that three years before the meeting he received a grant from the Sanofi S.A. (Paris, France) to produce multimedia materials on practical aspects of the management of leishmaniasis patients. He also declared that he has recently been in discussions with Paladin Labs Inc. (Montreal, Canada) about implementation of a telemedicine program on leishmaniasis, which had not been finalized as of the date of the meeting. In a second communication, the consultant stated that the project with Paladin had been indefinitely postponed, and as a result there was no conflict of interest.

Dr. Gustavo Adolfo Sierra Romero declared that he received funding from Brazil's Ministry of Health and the Oswaldo Cruz Foundation (Fiocruz) (Rio de Janeiro, Brazil) to conduct clinical studies on the efficacy and safety of drugs for the treatment of visceral leishmaniasis in Brazil and for a clinical study on the efficacy and safety of azithromycin for the treatment of cutaneous leishmaniasis.

ANEXO 7

PubMed search strategy for systematic leishmaniasis reviews in the Americas

(leishmaniasis [mh] OR leishma* [tw]) AND (review [pt] OR review OR meta-analysis) AND (Latinamerica* OR South America* OR Central America* OR Carribbean* OR America* OR ("New world") OR Anguilla OR (Antigua AND Barbuda) OR Argentina OR Aruba OR Bahamas OR Barbados OR Belize OR Bermuda OR Bolivia* OR Brazil* OR brasil* OR (British Virgin Islands) OR (Cayman Islands) OR Chile* OR Colombia* OR (Costa Rica) OR Cuba OR Dominica OR (Dominican Republic) OR El Salvador OR Ecuador OR (French Guiana) OR Grenada OR Guadalupe OR Guatemala OR Guyana OR Haiti OR Honduras OR Jamaica* OR Martinique OR Mexico OR Montserrat OR (Netherlands Antilles) OR Nicaragua OR Panama OR Paraguay OR Peru OR (Puerto Rico) OR (Saint Kitts and Nevis) OR (Saint Lucia) OR (Saint Vincent Grenadines) OR Suriname OR (Trinidad Tobago) OR Uruguay* OR Venezuela OR argentinean OR mexican OR bolive* OR costaric*)



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