

# Interventions for American cutaneous and mucocutaneous leishmaniasis (Review)

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[Intervention Review]

# Interventions for American cutaneous and mucocutaneous leishmaniasis

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## ABSTRACT

### Background

Pentavalent antimonial drugs are the most prescribed treatment for American cutaneous and mucocutaneous leishmaniasis. Other drugs have been used with varying success.

### Objectives

To assess the effects of therapeutic interventions for American cutaneous and mucocutaneous leishmaniasis.

### Search strategy

We searched the Cochrane Skin Group Specialised Register (January 2009), the Register of Controlled Clinical Trials in *The Cochrane Library* (Issue 1,2009), MEDLINE (2003 to January 2009), EMBASE (2005 to January 2009), LILACS (from inception to January 2009), CINAHL (1982-May 2007) and other databases.

### Selection criteria

Randomised controlled trials (RCTs) assessing treatments for American cutaneous and mucocutaneous leishmaniasis.

### Data collection and analysis

Two authors independently assessed trial quality and extracted data.

### Main results

We included 38 trials involving 2728 participants. Results are based on individual studies or limited pooled analyses. There was good evidence in:

*Leishmania braziliensis* and *L. panamensis* infections:

Intramuscular (IM) meglumine antimoniate (MA) was better than oral allopurinol for 28 days (1RCT n=127, RR 0.39; 95% CI 0.26, 0.58). Intravenous (IV)MA for 20-days was better than 3-day and 7-day IVMA plus 15% paromomycin plus 12% methylbenzethonium

chloride (PR-MBCL) or 7-day IVMA (1RCT n= 150, RR 0.24; 95% CI 0.11, 0.50; RR 0.69; 95% CI 0.53, 0.90; RR 0.64; 95% CI 0.44, 0.92 respectively). Oral allopurinol plus antimonials was better than IV antimonials (2RCT n= 168, RR 1.90; 95% CI 1.40, 2.59;  $I^2=0\%$ ).

*L. braziliensis* infections:

Oral pentoxifylline plus IV sodium stibogluconate (SSG) was better than IVSSG (1RCT n= 23, RR 1.66; 95% CI 1.03, 2.69); IVMA was better than IM aminosidine sulphate (1RCT n= 38, RR 0.05; 95% CI 0.00, 0.78) and better than IV pentamidine isethionate (1RCT n= 80, RR 0.45; 95% CI 0.29, 0.71). Intramuscular MA was better than Bacillus Calmette-Guérin (1RCT n= 93, RR 0.46; 95% CI 0.32, 0.65).

*L. panamensis* infections:

Oral allopurinol was better than IVMA (1RCT n= 58, RR 2.20; 95% CI 1.34, 3.60). Aminosidine sulphate at doses of 12mg/kg/day and 18mg/kg/day for 14 days were better than aminosidine sulphate 12mg/kg/day for 7 days (1RCT n= 60, RR 0.23; 95% CI 0.07, 0.73; RR 0.23; 95% CI 0.07, 0.73 respectively). Oral ketoconazole for 28 days, oral miltefosine and topical PR-MBCL were better than placebo.

### Authors' conclusions

Most trials have been designed and reported so poorly that they are inconclusive. There is a need for large well conducted studies that evaluate long-term effects of current therapies to improve quality and standardization of methods.

## PLAIN LANGUAGE SUMMARY

### Interventions for American cutaneous and mucocutaneous leishmaniasis.

American cutaneous and mucocutaneous leishmaniasis, a disfiguring and stigmatising disease affecting Central and South American regions, is caused by a parasite transmitted by sandflies. Pentavalent antimonial drugs (sodium stibogluconate (Pentostam, Stibanate, SSG) and meglumine antimoniate (Glucantime, MA)) have been used since the 1940s as first-line therapeutic agents for cutaneous leishmaniasis worldwide. However, other treatments have been used because these are expensive, toxic and painful, and because resistance is emerging.

We assessed 38 trials involving different interventions.

In *L. braziliensis* and *L. panamensis* infections there was good evidence that intramuscular (IM) MA was better than oral allopurinol for 28 days, that 20-day intravenous (IV) MA was better 7-day IVMA and also better than 3 or 7-day IVMA with paromomycin plus 12% methylbenzethonium chloride (PR-MBCL). Oral allopurinol plus intravenous antimonials was better than intravenous antimonials.

There was reasonable randomised controlled trial (RCT) evidence in *L. braziliensis* infections that oral pentoxifylline plus IVSSG was better than IVSSG alone; IVMA was better than IM aminosidine sulphate and IV pentamidine isethionate; and IMMA was better than the Bacillus Calmette-Guérin vaccine. Regarding *L. panamensis* infections, oral ketoconazole for 28 days and oral miltefosine and topical PR-MBCL were all better than placebo; oral allopurinol better than IVMA, aminosidine sulphate 12mg/kg/day and 18mg/kg/day for 14 days were better than aminosidine sulphate 12mg/kg/day for 7 days.

There was complete absence of RCT evidence on alternative treatments, surgery, oral itraconazole and fluconazole, oral antibiotics like rifampicin, metronidazole and cotrimoxazole, intravenous or topical amphotericin B, oral dapsone, photodynamic therapy, promoting healing therapies, laser, and cryotherapy treatments. Moreover, none of the studies reported quality of life, "microbiological or histopathological cure of skin lesions", changes in ability to detect the parasite by diagnostic methods (e.g. smear or culture) or mortality.

No general consensus on optimal treatment has been achieved but alternatives to intramuscular or intravenous treatments are under active investigation.

The evidence base for the treatment of American cutaneous and mucocutaneous leishmaniasis has many limitations due to poor design and reporting of clinical trials. Because resources are limited for clinical research into neglected diseases, there is a need for prioritising properly designed clinical trials. Therefore, we suggest the creation of an international strategy to improve the quality and standardization of future trials for a better evidence-based strategic approach in the future.

## BACKGROUND

### Description of the condition

The leishmaniasis are a group of diseases caused by protozoan parasites of the genus *Leishmania*. The parasite is transmitted by bites from sand-flies infected with the parasite. Different female sand-flies may act as carriers of the parasites, and the parasite may be transmitted from person to person or from a range of animals to humans (Desjeux 1996).

Leishmaniasis presents in three main clinical forms (cutaneous, mucocutaneous and visceral), which are associated with a broad range of signs, symptoms and degrees of severity (Herwaldt 1999; Reithinger 2007):

#### Cutaneous leishmaniasis

Cutaneous leishmaniasis is a public health and a social problem in many developing countries worldwide. In fact, *Leishmania* species are widespread in 88 countries in the New (America) and Old (Europe, Asia and Africa) World, affecting the skin and mucous membranes.

In American cutaneous leishmaniasis (ACL) the parasite is confined to the skin. After an incubation period of one to 12 weeks a painless papule or pimple develops at the site of the insect bite. The papule grows and turns into an ulcer with an adherent crust of dried exudate. Most patients have one or two lesions varying in size from 0.5 to 3 cm in diameter, usually on exposed parts of the body such as the face, arms or legs. There is, however, considerable variation: patients may have several skin lesions; some lesions grow but do not ulcerate (nodules); and some *Leishmania* species also infect the lymphatic system producing lesions along the lymphatic channels (nodular lymphangitis). Secondary bacterial infection is common, causing pain and serious disability.

Most lesions heal spontaneously (re-epithelialise) over a period of a few to many months (sometimes over more than 12 months). Scarring of leishmaniasis is typical with a depigmented centre and a pigmented border with skin thinning (Reithinger 2007). This is the most common presentation of ACL, which is mainly seen in large parts of Central and South America.

#### Mucocutaneous leishmaniasis

Mucocutaneous leishmaniasis is a chronic form of leishmaniasis (Amato 2007). It is mainly seen in South America. In fact, *L. braziliensis* and also other strains of the parasite such as *L. panamensis*, *L. guyanensis*, and *L. amazonensis* may spread to the mucous membranes, especially those of the nose, mouth and throat, and cause extensive damage and disfiguration.

#### Visceral or kala-azar leishmaniasis

The parasite affects internal organs, in particular the spleen, liver, bone marrow and lymph nodes. It is a potentially deadly disease if left untreated. This form of leishmaniasis may present as an opportunistic infection in people with a defect in the immunological

defences, such as those with HIV infection (Alvar 2008). However, for this review we were only focused on the cutaneous and mucocutaneous form of leishmaniasis.

### Causes and impact

In many tropical and subtropical developing countries protozoan parasites are amongst the most common infectious agents and have serious consequences for socio-economic development (WHO 2002; Alvar 2006). Because the World Health Organisation (WHO) considers leishmaniasis to be one of the most serious parasitic diseases, the World Health Assembly has advocated a concerted effort for its control (WHO 2007). The overall prevalence is 12 million with an estimated incidence of 1.5 million new cases of cutaneous leishmaniasis per year. Approximately 350 million people, who are often impoverished, are at risk of contracting the disease (WHO 2001; Alvar 2006). The disease appears to be currently underestimated and on the rise in several countries.

The geographical distribution of ACL is from the United States-Mexico border, through Central America and the northern part of South America, and down to the region of Rio de Janeiro (Soto 2004). The most common causative agents of ACL are *L. braziliensis*, *L. guyanensis*, *L. panamensis*, and *L. mexicana*. Each species has distinct epidemiological and demographic patterns and all are transmitted through animals, which are the reservoir hosts (Navin 1992).

Cutaneous and mucocutaneous leishmaniasis caused by *L. braziliensis* and *L. panamensis* are considered a major health problem in Latin American countries such as Brazil, Bolivia, Peru, Venezuela and Guatemala, (Herwaldt 1999; WHO 2001). Some patients develop mucocutaneous leishmaniasis and possible risk factors are male gender, age, length of disease, nutritional status, genetics, site of skin lesions, concomitant diseases, and no treatment of previous cutaneous leishmaniasis (Passos 2001; Machado-Coelho 2005). The mucocutaneous form typically begins with nasal inflammation and stuffiness followed by ulceration of the nasal mucosa and perforation of the nasal septum. In some cases, the lips, cheeks, soft palate, pharynx, or larynx are also affected. Mucocutaneous leishmaniasis never heals spontaneously, it is very difficult to treat and secondary bacterial infections are common (Reithinger 2007). If mucocutaneous leishmaniasis is not treated early, it can cause disfiguration and death in some cases (Vélez 1997; Reithinger 2007). In some areas of South America, mucocutaneous leishmaniasis represents approximately 12.5% of the reported cases of ACL (Davies 2000). However, a prospective study in north-east Brazil found a lower proportion of cases developing mucocutaneous disease (Brandao 1999). Furthermore, suicide attempts have occurred due to the social stigma associated to the disease. American cutaneous leishmaniasis caused by *L. mexicana* infections often resolves spontaneously (within three months) and does not lead to mucocutaneous lesions. American cutaneous leishmaniasis is also increasingly seen in immigrants, military personnel, humanitarian aid workers, tourists and travellers from endemic areas. However, ACL is still poorly recognised

by most Western physicians who must analyse skin lesions with biopsies and tissue smears when faced with a possible leishmanial skin lesion (Reithinger 2007).

### Diagnosis

Diagnosis of ACL is based mostly on clinical findings. Confirmation by laboratory tests is not always feasible and the available tests are not entirely reliable (Aviles 1999). Identification of the parasite by histopathology can be used to confirm the diagnosis, but the sensitivity of histopathology is low because parasite concentrations are usually low (Dimier-David 1991). Cultures allow identification and characterisation of the infecting species, but it is expensive and time consuming. A polymerase chain reaction test (PCR) is useful in diagnosing cutaneous leishmaniasis because it enhances sensitivity and aids the identification of the infecting species and it obviates the need for parasite culture (Pirmez 1999; Uezato 1988). The Leishmanin Montenegro skin test is simple to use and highly specific but produces false negative results in some affected patients and it does not distinguish between previous and present infections (Escobar 1992). Immunologic tests, which identify specific antibodies, are of little diagnostic use.

### Description of the intervention

Issues of treatment in ACL are difficult to tackle because of the factors that influence the efficacy of drugs: intrinsic and acquired variation in the sensitivity of the different *Leishmania* species, host factors such as immunity, variable clinical response to treatments, age of the lesions treated, drug toxicity, co-infection and compliance (Tuon 2008). There is no single effective treatment for all species of *Leishmania*. The choice of treatment strategy is based on geographical location and the infecting species (Croft 2003). Direct comparisons are therefore difficult.

### Systemic Treatments

Systemic treatments are administered for infections caused by *L. panamensis* and *L. braziliensis* to accelerate the cure, to avoid relapses or to prevent development of mucocutaneous lesions. *L. mexicana* infections may or may not be treated.

Pentavalent antimonial drugs (sodium stibogluconate (SSG) and meglumine antimoniate (MA)) are the most frequently prescribed treatments in ACL (Hepburn 2001). They cannot be given orally and must be injected either into a muscle (intramuscular IM) or vein (intravenous IV). The WHO recommends treating ACL with IM or IV pentavalent antimonial drugs i.e., SSG or MA at a dose of 20 mg/kg daily for 28 days (WHO 1990; Reithinger 2007). Because of the regional variability in response to treatment, doses of antimonials cannot be standardised and local physicians determine appropriate dosages based on experience (Tuon 2008). Where *L. mexicana* coexists with *L. braziliensis* and remains indistinguishable by presentation, the lesions are normally treated with systemic antimonials as a standard therapy (Soto 2004).

Antimonials are contraindicated in individuals with drug sensitivity, certain chronic conditions, very young children, and pregnant or breast feeding women (Arévalo 2007). The major drawback, associated with injected systemic antimonials is local pain that causes important patient discomfort. The main adverse effects that occur in systemic administration of antimonials are arthralgias, myalgias, anorexia, nausea, vomiting, lack of appetite, malaise, tremors, diarrhoea, fever, urticaria, headache, rash, phlebitis, mild to moderate muscle and joint stiffness, itch, cough, herpes zoster, mild leucopenia, thrombocytopenia, jaundice, albuminuria, and pneumonia (Navin 1992). Other serious side effects associated with the administration of pentavalent antimonial drugs include pancreatitis, liver-enzyme abnormalities, cardiac and electrocardiographic malfunctions and severe renal toxic effects (Sampaio 1997; Berman 1996; Santos 2004; Seaton 1999).

Azole antifungal drugs are potential therapeutic agents in ACL available for oral administration. The first reports of oral ketoconazole for the treatment of ACL came out in the early 1980s (Urcuyo 1982; Jolliffe 1986). The drug is well tolerated although the adverse effects associated with it are nausea, abdominal pain, headache, dizziness and rash. Reports of hepatotoxicity boosted the search for other oral azoles as itraconazole and fluconazole.

Other systemic drugs have been considered as second-line treatments (M-Verástegui 2005) or the drug of choice for antimonial failures (Berman 2005):

- oral allopurinol, generally used to prevent high uric acid levels, and allopurinol riboside (Nelson 1979). Only a few patients had transient headache, myalgias, abdominal pain and minor itch associated with headaches, transient increase of liver enzymes, and myalgia (Ghanem 1996);
- oral miltefosine was originally developed as an anticancer drug (Berman 2005; Croft 2006; Chappuis 2007; Minodier 2007) despite its teratogenic potential (Sundar 2005). It has variable efficacy depending on geographical areas even for the same *Leishmania* species (Soto 2004B);
- intramuscular or intravenous aminosidine is an aminoglycoside antibiotic identical to paromomycin (Jha 1998; Hepburn 1994; Llanos-Cuentas 2007). Aminoglycoside sulphate is associated with pain at the injection site that improves with the application of local heat. Other side effects included mild proteinuria, elevated serum creatinine, fever, asthenia, chills, arthralgia, anorexia, and myalgia (Romero 1996; Llanos-Cuentas 2007);
- intramuscular or intravenous pentamidine (isethionate or methanesulfonate) is a conventional, costly, second-line drug for treating visceral leishmaniasis. However it is gradually being abandoned because of its unacceptable toxic effects including damage to the pancreas that may lead to irreversible insulin dependent diabetes mellitus, to the kidney or bone marrow; and its declining

efficacy in India (Sundar 2006);

- Amphotericin B was first used in 1963 with a deoxycholate formulation, but acute and chronic toxic side-effects have promoted the use of lipid formulations including a liposomal form which is much better tolerated despite its prohibitive cost in underdeveloped countries (Bern 2006; WHO 2008).

Other drugs such as oral azithromycin (Prata 2003; Modabber 2007), water-soluble phosphate prodrugs of buparvaquone (Mäntylä 2004), and oral sitamaquine (Singh 2004) are under development or investigation.

### Local treatments

The dogma that systemic treatment is required to prevent development of mucocutaneous lesions has been questioned by some authors and the administration of topical treatment on *L. braziliensis*-lesions needs to be evaluated with respect to risk/benefit and cost/benefit (Modabber 2007). Therefore, topical treatment of some forms of ACL is probably both ethical and desirable. Topical and local treatments often offer significant advantages such as easier administration, less adverse effects and sometimes cost effectiveness, but absorption of topical treatments through the skin is not always successful. Intralesional treatments are used on a regular basis in Old World cutaneous leishmaniasis but not in ACL. Other topical preparations are currently available for cutaneous leishmaniasis: 15% paromomycin sulphate dissolved in a soft white paraffin base, either with 12% methylbenzethonium chloride (MBCL) or with 10% urea, a gel formulation of paromomycin (10% paromomycin in 1.5% hydroxyethylcellulose in water) (Gonçalves 2005, Modabber 2007) and paromomycin (15%) plus gentamicin (0.5%) (Grogil 1999).

Contamination and infection of skin lesions are major problems encountered in patients with cutaneous leishmaniasis. In fact, development of novel therapies aims at preventing the occurrence of chronic wounds and at enhancing their healing by accelerating the naturally occurring processes (Vaneau 2007). Nonetheless, methods used in promoting wound healing should be employed in ulcerative lesions of ACL to accelerate cure, normalise epithelialisation and reduce scarring, especially at cosmetic sites.

### Physical methods

Surgical excision of lesions is generally not recommended because of the high risk of local relapse and disfigurement. Thermotherapy (heat therapy) devices deliver localised heat directly to a lesion and can be convenient for use in primary health care facilities. In the 1980s, studies showed that *Leishmania* parasites do not readily multiply at temperatures greater than 39°C *in vitro* (Berman 1981; Sacks 1983). These findings led to studies investigating the efficacy of thermotherapy treatment with hot-water baths (Neva 1984), infrared light (Junaid 1986), laser light (Rodríguez 1990; Babajev 1991; Meawad 1997; Asilian 2004), and radio-frequency waves (Navin 1990; Levine 1992; V-Castrejon 1997). Patients treated with heat do not have significant adverse effects but some

patients can develop moderate to severe local cellulitis during heat and superficial secondary burns where the electrodes were applied (Navin 1990) and secondary bacterial infection after treatment (Lobo 2006).

### Immuno-chemotherapy

Immuno-chemotherapy is the use of “therapeutic” vaccines (killed promastigotes of a strain of *Leishmania*) or immunomodulators such as Bacillus Calmette-Guerin (BCG), pentoxifylline (Lessa 2001), imiquimod cream (Arevalo 2001), intradermal recombinant Interferon-gamma (IFN- $\gamma$ ) (Falcoff 1994) or granulocyte macrophage colony-stimulating factor (GM-CSF) (Al-Zamel 1996) alone or combined with pentavalent antimonial drugs (chemotherapy). Immuno-chemotherapy has strong potential to shorten/reduce treatment duration and dosage, thus preventing resistance of pentavalent antimonial drugs. This may mean they could be available in developing countries despite their prohibitive cost (Flynn 2005; Badaro 2006).

### Why it is important to do this review

Control of cutaneous leishmaniasis currently depends on case management including early detection and rapid treatment (Modabber 2007). Global health development policies are mainly focused on new and innovative tools to tackle neglected tropical diseases (NTDs). However, the WHO also prioritises the delivery of currently available drugs and existing resources that reduce mortality, morbidity, and disability of NTDs in low-income countries (Savioli 2006). Therefore, in accordance with the priorities set by the WHO, we consider that in order to improve current methods of disease management it is important to know the evidence for the efficacy of the different treatment strategies as well as for their safety and cost-effectiveness.

Given that a wide range of systemic treatments are currently being used not only in developing countries but also in developed ones due to economic globalisation and the increased volume of international travel, their effectiveness and safety needs to be well established.

This systematic review has focused on addressing the effects of the existing treatments for American cutaneous and mucocutaneous leishmaniasis. Treatments for Old World cutaneous leishmaniasis (González 2008) and prevention measures (Title stage) for all types of cutaneous leishmaniasis are addressed in separate Cochrane reviews.

### OBJECTIVES

Main objective: to assess the effects of therapeutic interventions for American cutaneous and mucocutaneous leishmaniasis. Secondary objective: to ascertain whether response to treatment is

species-dependent or associated with their geographical distribution.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled clinical trials (RCTs).

#### Types of participants

All immuno-competent people who have cutaneous leishmaniasis and/or mucocutaneous leishmaniasis that has been diagnosed by clinical presentation and *Leishmania* infection confirmed by histopathology, polymerase chain reaction (PCR) analysis or culture of lesions. If *Leishmania* parasites could not be seen, diagnosis was based on a clinical presentation and at least two of the following criteria: suggestive histopathology, serologic reaction, positive Leishmanin Montenegro skin test, or negative tests for other diseases that compromise the oral or nasal mucous membranes, especially leprosy and paracoccidioidomycosis.

#### Types of interventions

The interventions were either single therapy, or combination therapy. The comparators were either no treatment, vehicle only, or another active compound.

#### 1. Antimonials

##### 1.1 Meglumine Antimoniate (Glucantime)

##### 1.2 Stibogluconate

#### 2. Non-antimonial systemic treatments

##### 2.1 Antifungals

##### 2.2 Allopurinol

##### 2.3 Miltefosine

##### 2.4 Aminosidine sulphate

##### 2.5 Pentamidine isethionate

#### 3. Non-antimonial topical or intralesional therapies

##### 3.1 Paromomycin (aminosidine)

##### 3.2 Aminoglycosides

#### 4. Physical therapies

##### 4.1 Thermotherapy

#### 5. Immuno-chemotherapy

##### 5.1 Vaccines

##### 5.2 *Bacillus Calmette-Guerin* (BCG)

##### 5.3 Pentoxifylline

#### 5.4 Imiquimod

##### 5.5 Granulocyte macrophage colony-stimulating factor (GM-CSF)

##### 5.6 Interferon-gamma (IFN- $\gamma$ )

### Types of outcome measures

#### Primary outcomes

Percentage of participants “cured” at least three months after the end of treatment.

By “cured”, we mean that all inflammatory signs have disappeared (either skin oedema or hardening, or both), and that scarring or epithelialization has occurred in ulcerative lesions. Lesions were considered not to be healed if there was no re-epithelialized skin, or inflammatory signs remain after follow-up.

We considered that data on the percentage of participants “cured” recorded for less than three months showed a short term benefit, and although we described them we excluded them from statistical analysis.

#### Secondary outcomes

- Recurrence: duration of remission and/or percentage of people with treated lesions that recur within six months, one, two and three years.
- Degree of functional and aesthetic impairment and/or prevention of scarring.
- Quality of life.
- Adverse effects.

#### Tertiary outcomes

- Speed to healing.
- Change in isolation or PCR of *Leishmania* and emergence of resistance (defined as a decline in the efficacy of a drug against a population of parasites previously susceptible to that compound (Ponte-Sucre 2003). The definition assumes that the original susceptibility of the population is known, which is not always the case for *Leishmania*).
- Only microbiological or histopathological cure of skin lesions.
- Development of cell-mediated immunity (i.e. positive leishmanin skin test).
- Mortality.

### Search methods for identification of studies

#### Electronic searches

We searched the Cochrane Skin Group Specialised Register in January 2009 using the following terms:

((mucocutan\* or mucos\* or nose or pharynx or palat\* or cartila\* or nas\* or larynx or ear or nariz or faring\* or laring\* or paladar or oreja) and leish\*) OR (solitary or limited or (old and world) or localised) AND (\*cutaneous and leishmania\*)

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) from *The Cochrane Library* (Issue 1, 2009) using the strategy in [Appendix 1](#)

We searched MEDLINE (OVID) (2003 to January 2009) using the strategy in [Appendix 2](#)

We searched EMBASE (OVID) (2005 to January 2009) using the strategy in [Appendix 3](#)

The UK Cochrane Centre has an ongoing project to systematically search MEDLINE and EMBASE for reports of trials which are then included in the Cochrane Central Register of Controlled Trials. Searching has currently been completed in MEDLINE to 2003 and in EMBASE to 2005. Further searching has been undertaken for this review by the Cochrane Skin Group to cover the years that have not been searched by the UKCC.

We searched CINAHL (1982-May 2007) using the strategy in [Appendix 4](#)

We searched LILACS from its inception to January 2009 using the strategy in [Appendix 5](#)

We searched the American College of Physicians (ACP) journal club (from 1991 to May 2007) using the terms: cutaneous and leishmaniasis.

#### Ongoing trials

We searched the following ongoing trials registers in January 2009 using the terms “Leishmaniasis, cutaneous” and “Leishmaniasis, mucocutaneous”

The metaRegister of Controlled Trials [www.controlled-trials.com](http://www.controlled-trials.com)

The U.S. National Institutes of Health ongoing trials register [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

The Australian and New Zealand Clinical Trials Registry [www.anzctr.org.au](http://www.anzctr.org.au)

The World Health Organisation International Clinical Trials Registry platform [www.who.int/trialsearch](http://www.who.int/trialsearch)

The Ongoing Skin Trials register on [www.nottingham.ac.uk/ongoingskintrials](http://www.nottingham.ac.uk/ongoingskintrials)

#### Searching other resources

##### References from published studies.

We looked at the bibliographies of all papers identified by these strategies and relevant articles were obtained.

##### Unpublished literature

We wrote to National Programme Managers, General Co-ordinators, Directors, clinicians, WHO-EMRO (Eastern Mediterranean Regional Office), Regional Officers of endemic countries, pharmaceutical companies and authors for further information about unpublished and ongoing trials.

Unpublished and grey literature was obtained via correspondence with authors and pharmaceutical companies.

The following Tropical Medicine Centres were contacted: Department of Infectious Diseases and Tropical Medicine at the University of Munich, Germany; Swiss Tropical Institute, Switzerland;

Prince Leopold Institute of Tropical Medicine, Belgium; McGill Centre for Tropical Disease, Canada; Tulane University School of Public Health & Tropical Medicine, USA; London School of Hygiene & Tropical Medicine, UK; Tropical Medicine at the Liverpool School of Tropical Medicine, UK; Department of Public Health and Tropical Medicine James Cook, University of North Queensland, Australia; Institute Pasteur, France; Bernhard Nocht Institute, Germany; TropEdEurop, Spain; and Centro Dermatológico Federico Lleras Acosta, Colombia.

#### Adverse effects

We searched MEDLINE (OVID) (1950 to 2007) for adverse or side effects using the strategy in [Appendix 6](#).

#### Language

We imposed no language restrictions when searching for publications, and translations were sought where necessary.

## Data collection and analysis

### Selection of studies

Titles and abstracts identified from the searches were checked by at least two authors (UG, MP). If it was clear that the study did not refer to a RCT on American cutaneous and mucocutaneous leishmaniasis; it was excluded. If it was unclear, then the full text study was obtained for independent assessment by two authors (AM, JT). The authors decided which trials fitted the inclusion criteria. Any disagreements were resolved by discussion between the authors, with referral to a third author (UG) if necessary. We listed the excluded studies and stated the reasons for exclusion in the [Characteristics of excluded studies](#).

### Data extraction and management

At least two of the authors (AM, MP, MR, JT) independently carried out the data extraction by using a pre-designed data extraction form. We extracted reported data pertaining to cure rates for all evaluated drugs, paying attention particularly to the doses and therapeutic frequencies. We resolved any disagreements by discussion. We obtained missing data from trial authors whenever possible.

### Assessment of risk of bias in included studies

The quality assessment included an evaluation of the following components for each included study, since there is some evidence that these are associated with biased estimates of treatment effect ([Jüni 2001](#)):

- the method of generation of the randomisation sequence;
- the method of allocation concealment - it was considered 'adequate' if the assignment could not be foreseen;
- who was blinded / not blinded (participants, clinicians, outcome assessors);

- how many participants were lost to follow up in each arm (split into post-randomisation exclusions and later losses if possible), and whether participants were analysed in the groups to which they were originally randomised (intention-to-treat).

In addition the quality assessment also included:

- calculation of sample size;
- inclusion and exclusion criteria clearly defined;
- reporting of *Leishmania* species involved;
- time of follow-up;
- baseline comparability of severity of infection, age, sex and duration of complaint;
- conflict of interest.

The information was recorded in the Risk of Bias table and a description of the quality of each study was given based on a summary of these components.

#### Measures of treatment effect

We expressed the results as Relative Risk (RR and 95% confidence intervals (CI)) for dichotomous outcomes. The percentage of lesions “cured” at least three months after the end of treatment was the primary outcome measure if available. If this was not available, secondary and tertiary outcomes were used. Pooled analyses

were performed by using a random effect model. Where it was not possible to perform a meta-analysis, we summarised the data for each trial. The secondary objective was tackled qualitatively.

We have analysed the results using the intention-to-treat (ITT) analysis. Only six of the trials explicitly stated intention-to-treat (ITT) analysis. In those cases where this was not provided we used the numbers originally randomised to the groups.

#### Assessment of heterogeneity

We used sensitivity or subgroup analyses for low methodological quality, *Leishmania* species, location and severity of infection, geographical setting, diagnostic techniques, type of treatment (topical, systemic or combination), and relapse or re-infection provided that we found substantial heterogeneity ( $I^2 > 50\%$ ) between pooled studies for the primary outcome.

We did not take cross-over trials into consideration in this review because they are an inappropriate design for treatments which can potentially cure an infectious disease. We listed the quasi-randomised and non-randomised controlled studies in Table 1, but were not discussed further. We described adverse events qualitatively in the results and discussion sections. We did not find any additional information of interest in our specific search for adverse effects relating to treatments.

**Table 1. Quasi-randomised and non-randomised controlled trials**

Authors	Title of the study	Journal citation	Observations
Arevalo I, Ward B, Miller R, Meng TC, Najar E, Alvarez E, Matlashewski G, Llanos-Cuentas A	Successful treatment of drug-resistant cutaneous leishmaniasis in humans by use of imiquimod, an immunomodulator	CID 2001; 33 (11): 1847-1851	Non-randomised trial
de Paula CD, Sampaio JH and Cardoso DR	A comparative study between the efficacy of pentamidine isethionate given in three doses for one week and N-methylglucamine in a dose of 20 mgSbV/kg/day for 20 days to treat cutaneous leishmaniasis	Rev Soc Bras Med Trop 2003; 36 (3): 365-371	Non-randomised trial
Harms G, Zwingenberger K, Chehade AK, Talhari S, Racz P, Mouakeh A, Douba M, Näkel L, Naiff RD, Kreamsner PG, Feldmeier H and Bienzle U	Effects of intradermal gamma-interferon in cutaneous leishmaniasis	Lancet 1989; 10: 1287-1292	Non-randomised and mixed Old and New World cutaneous leishmaniasis

**Table 1. Quasi-randomised and non-randomised controlled trials** (Continued)

Monjour L, Silva OA, Vouldoukis I, Neogy AB, Brito ME, Filho SP and Jardim ML	Immunoprophylaxis in cutaneous leishmaniasis	Lancet 1992; 340 (8827): 1098-9	Non-randomised trial
Saldanha AC, Romero GA, Merchan-Hamann E, Magalhaes AV and Macedo V de O	Comparative study between sodium stibogluconate BP 88R and meglumine antimoniate for cutaneous leishmaniasis treatment: I. Efficacy and safety	Rev Soc Bras Med Trop 1999; 32 (4): 383-387	Non-randomised trial
Soto J, Toledo J, Valda L, Balderrama M, Rea I, Parra R, Ardiles J, Soto P, Gomez A, Molleda F, Fuentelsaz C, Anders H, Sindermann H, Engel J, Berman J	Treatment of Bolivian mucosal leishmaniasis with miltefosine	CID 2007; 44(3): 350-356	Non-randomised trial
Saenz RE, Paz HM, Johnson CM, Marr JJ, Nelson DJ, Pattishall KH and Rogers MD	Treatment of American cutaneous leishmaniasis with orally administered allopurinol riboside	J Infect Dis 1989; 160: 153-158	Non-randomised and non-comparative trial
Toledo VPCP, Mayrink W, Gollob KJ, Oliveira MA, Costa, CA DA, Genaro O, Pinto JA, Alfonso LCC	Immunochemotherapy in American cutaneous leishmaniasis: immunological aspects before and after treatment	Mem Inst Oswaldo Cruz 2001; 96 (1): 89-98	Non-randomised trial
Romero, Gustavo Adolfo Sierra.	Study of the cutaneous illness caused by leishmania (Viannia) Braziliensis and Leishmania (Viannia) Guyanensis/ Estudo da doença cutânea causada por leishmania (Viannia) Braziliensis e Leishmania (Viannia) Guyanensis	Brasília; s.n; 2000. 222 p. mapas, tab. (doctoral thesis)	Non-randomised trial

CL: cutaneous leishmaniasis; MCL: mucocutaneous leishmaniasis; OD: once daily; TD: twice daily

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting assessment](#); [Characteristics of ongoing studies](#).

### Results of the search

We identified 72 RCTs from our searches, of which we included 38 that overall randomised 2728 participants. We excluded 18 RCTs which are presented in the [Characteristics of excluded studies](#) table. We found 14 RCTs that are ongoing trials and two that are awaiting assessment, which are listed in [Characteristics of ongoing studies](#) and [Characteristics of studies awaiting classification](#) tables, respectively. We will include these RCTs in future updates of this review.

## Included studies

The 38 included RCTs (of which 10 were placebo-controlled and 28 had active controls) are detailed in the [Characteristics of included studies](#) table.

The RCTs included in this review were conducted throughout different countries, mainly in Central and South America. Eight were performed in Brazil, six in Peru, two in Ecuador, four in Guatemala, two were carried out in Venezuela, two in Panama, one in El Salvador, and one in Honduras. We found nine studies in Colombia, of which two were performed also in Bolivia and in Guatemala. There were also two RCTs that were conducted in North America (USA) and one in Edinburgh (UK). These latter three RCTs recruited active-duty military personnel who had contracted leishmaniasis in endemic areas when deployed abroad.

### 1. Antimonials

We found 16 RCTs on the use of systemic antimonials as the experimental group. Systemic antimonials were used at a dose of 20 mg/kg/day, unless otherwise stated. We also found 25 RCTs using antimonials either as the control group or as a combined treatment with other interventions, 16 of which are referred in this section on 'Included studies', eight in the 'Ongoing Studies' and one in the 'Studies awaiting classification' reference lists.

#### 1.1 Meglumine Antimoniate (Glucantime)

Two RCTs compared IMMA for 20 days with placebo (Vélez 1997; Saenz 1990) and one with IMMA for 10 days (Palacios 2001). A RCT (Navin 1990) compared low dose IMMA (850 mg/daily) for 15 days with placebo. A RCT (Martínez 1992) compared IVMA for 15 days with no treatment. Another RCT (Soto 1998) compared IVMA for 20 days with IVMA for one week. A RCT (Arana 1994) compared IVMA for 20 days with IVMA for 10 days plus placebo for 10 days. A RCT (Figueiredo 1999) compared IVMA 14 mg/kg/day in 2 series of 20 days, separated with intervals of 15 days for cutaneous leishmaniasis, and three series of 30 days each, separated with intervals of 15 days in the mucocutaneous form, with IVMA (28 mg/kg/day) for 10 days at the same dosage schedule. A RCT (Oliveira-Neto 1997) compared IVMA 5 mg/kg/day for 30 days with IVMA 20mg/kg/day for 30 days.

#### 1.2 Stibogluconate (Pentostam)

We found RCTs comparing IMSSG with no treatment (Guderian 1991), with IMMA (Saenz 1987) and with IMSSG or IMMA for 20 days (Soto 2004A). A RCT of military participants from the USA (Balou 1987) compared IVSSG 10 mg/kg/day for 20 days, with IVSSG. A RCT (Franke 1994) compared IVSSG for 28 days with IVSSG for 40 days. A RCT from the USA (Oster 1985) compared IVSSG 600 mg once daily for 10 days, IVSSG continuous infusion of 600 mg over 24 hours, with IVSSG infusion of 200 mg every 8 hours each day for 9 days. A RCT (Navin 1992) compared IVSSG with oral ketoconazole.

## 2. Non-antimonial systemic treatments

### 2.1 Antifungals

We found two RCTs comparing oral ketoconazole 600 mg/day for 28 days with IMMA for 20 days (Saenz 1990) and with IVSSG for 20 days (Navin 1992). We found no studies on the use of otherazole antifungals.

### 2.2 Allopurinol

We found six RCTs on the use of oral allopurinol alone or in combination: adjuvant therapy with 20 mg/kg/day oral allopurinol for 15 days in IVMA (Martínez 1992); 20 mg/kg oral allopurinol three times a day for 20 days compared with 10 mg/kg/day IVMA for 20 days (D'Oliveira 1997); 300 mg oral allopurinol for 28 days compared with IMMA for 20 days and placebo (Vélez 1997); adjuvant oral allopurinol for 15 days in IVSSG for 15 days (Martínez 1997); adjuvant 20 mg/kg/day oral allopurinol in IVSSG for 28 days (Llanos-Cuentas 1997); and oral allopurinol ribonucleoside (1.500 mg QID) plus oral probenecid for 28 days compared with IMSSG for 20 days, and with no treatment (Guderian 1991). In the study by D'Oliveira (D'Oliveira 1997), we interpreted the authors statement that they recruited "randomly selected patients" as meaning that eligible patients were randomly allocated to the two treatment groups, although the method for generating and concealment such as randomisation schedule was unclear. We will follow-up this assumption up by further contact with the original authors.

### 2.3 Miltefosine

A RCT (Soto 2004B) compared oral miltefosine (50 mg) for 28 days with placebo.

### 2.4 Aminosidine sulphate

We found four RCTs on the use of aminosidine sulphate. A RCT of the Colombian army (Soto 1994) compared aminosidine sulphate 12 mg/kg/day for 7 days, aminosidine sulphate 12 mg/kg/day for 14 days, and aminosidine sulphate 18 mg/kg/day for 14 days. A RCT of British soldiers (Hepburn 1994) compared IV aminosidine 14 mg/kg/day for 20 days and IVSSG for 20 days. Another RCT (Correia 1996) compared IM aminosidine sulphate 20 mg/kg/day for 20 days, IM pentamidine isethionate 4 mg/kg every two days and IMMA 10 mg/kg/day for 20 days. Another RCT (Llanos-Cuentas 2007) compared IM aminosidine sulphate 20 mg/kg/day for 21 days and IVMA for 28 days.

### 2.5 Pentamidine isethionate

We found two RCTs on the use of pentamidine: 2 mg/kg IV pentamidine isethionate on alternate days for 7 doses compared with IVMA for 20 days (Andersen 2005) and 4 mg/kg IM pentamidine

isethionate every 2 days for 8 doses compared with 10 mg/kg/day IMMA for 20 days (Correia 1996).

### 3. Non-antimonial topical or intralesional therapies

#### 3.1 Paromomycin (aminosidine)

We found four RCTs on the use of topical paromomycin: 15% paromomycin in 12% MBCL ointment (PR-MBCL) twice a day for 20 days compared with placebo (Arana 2001); 15% paromomycin ointment three times daily for 4 weeks compared with placebo (Neva 1997); PR-MBCL twice daily for 30 days compared with 15% paromomycin in 10% urea same regimen and with IMMA for 10 days (Armijos 2004). In the (Soto 1998) study four treatment comparisons were made: PR-MBCL for 10 days combined with IVMA for 7 days; PR-MBCL for 10 days combined with IVMA for 3 days; placebo with IVMA for 7 days and IVMA for 20 days

#### 3.2 Aminoglycosides

We found one RCT (Soto 2002) that compared a topical aminoglycoside (WR279396) applied topically for 20 days with placebo.

### 4. Physical therapies

#### 4.1 Thermotherapy

We found two RCTs on the use of thermotherapy: localized heat at 7 day intervals compared with IMMA 850 mg daily for 15 days, and placebo (Navin 1990) and a single session of heat therapy combined with IVMA for 20 days compared with IVMA at the same dosage schedule (Lobo 2006).

### 5. Immuno-chemotherapy

#### 5.1 Vaccines

We found three RCTs on the use of vaccines in comparison with IMMA. A RCT (Convit 1987) compared vaccine of *L. mexicana amazonensis* combined with intradermal Bacille Calmette Guerin (BCG) and IMMA at a dosage of 50 mg/kg in series of 20 daily injections with 15 days between series. A RCT (Convit 1989) compared intradermal vaccine of *L. mexicana amazonensis* combined with BCG and IMMA 50 mg/kg/day in series of 20 daily injections with intervals of 15 days between successive series. A RCT (Machado-Pinto 2002) compared vaccine of *L. amazonensis* combined with IMMA (8.5 mg/kg) for 10 days with IMMA at the same dosage schedule.

#### 5.2 Bacillus Calmette-Guerin (BCG)

A RCT (Convit 1989) compared BCG with IMMA, 50 mg/kg/day in a series of 20 daily injections with intervals of 15 days between successive series.

#### 5.3 Pentoxifylline

We found a RCT on adjuvant therapy with oral pentoxifylline 400 mg three times daily in IVSSG for 30 days (Machado 2007).

#### 5.4 Topical imiquimod

We found two RCTs on adjuvant therapy with 7.5% imiquimod cream every other day for 20 days in IVMA for 20 days (Arévalo 2007) and with 5% imiquimod cream every other day for 20 days in IMMA for 20 days (M-Verástegui 2005).

#### 5.5 Granulocyte macrophage colony-stimulating factor (GM-CSF)

A RCT (Santos 2004) compared GM-CSF combined with IVMA for 20 days and only IVMA for 20 days. The other RCT (Almeida 1999) compared GM-CSF combined with IVSSG for 20 days and only IVSSG for 20 days.

#### 5.6 Interferon-gamma (IFN- $\gamma$ )

A RCT (Arana 1994) compared 10-day IVMA combined with IFN- $\gamma$  and 10-day and 20-day IVMA treatment.

### Excluded studies

We have excluded 18 RCTs for several reasons: use of vaccines alone; inadequate generation of randomisation sequence; no assessment of clinical outcomes; non-comparative studies; and mixing Old World and American forms of cutaneous leishmaniasis (Characteristics of excluded studies).

#### Ongoing studies

We have found 14 registered ongoing RCTs (NCT00004755; NCT00111514; NCT00111553; NCT00121862; NCT00233545; NCT00257530; NCT00317629; NCT00317980; NCT00469495; NCT00471705; NCT00487253; NCT00537953; NCT00600548; NCT00682656). See Characteristics of ongoing studies for details.

#### Awaiting assessment studies

We have found two RCTs that await assessment. One RCT (Krolewiecki 2007) compared oral azithromycin (500 mg/day) in 22 participants with IMMA (10 mg/kg/day) in 23 participants both for 28 days and followed-up for one year after completion of treatment. The other RCT (Soto 2008) compared oral miltefosine (2.5 mg/Kg/day) for 28 days in 44 participants with IMMA (20 mg/kg/day) for 20 days in 18 participants, followed-up for 6 months after completion of treatment (see Characteristics of studies awaiting classification for more details).

### Risk of bias in included studies

Our assessment of the risk of bias in the included studies has broadly followed the criteria set in the protocol. We thought that the quality of RCTs was generally poor for the following reasons:

### Allocation

#### The method of generation of the randomisation sequence

All included studies were randomised clinical trials (stated or implied that treatment allocation was randomised); however there were only 13 RCTs that stated an adequate randomisation method (see [Characteristics of included studies](#) for more details).

#### The method of allocation concealment

Only five of the included studies ([Arana 2001](#); [Armijos 2004](#); [Neva 1997](#); [Soto 2004A](#); [Vélez 1997](#)) adequately reported allocation concealment.

### Blinding

#### Who was blinded / not blinded (participants, clinicians, outcome assessors)

Fifteen of the 38 RCTs included in this review were double-blinded; five were single-blinded and 18 did not use any blinding at all or at least did not mention it (see [Characteristics of included studies](#) for details).

### Follow up and exclusions

#### How many participants were lost to follow up in each arm and whether participants were analysed in the groups to which they were originally randomised

##### Drop outs

The overall number of participants lost to follow-up was 220, i.e. 8.06% of the total number of study participants included in the meta-analysis. Only 13 studies specified post randomisation losses and later losses. All the studies reported within which arm the losses occurred. We categorised the drop-outs into groups according to the percentage of evaluable participants ([Characteristics of included studies](#)).

##### Intention-to-treat analyses

Losses to follow-up occurred in 23 studies, and the other 15 reported no drop-outs. However, 17 of the 23 studies did not carry out an intention to treat analyses (ITT) or rather they just assessed participants that completed treatment. Only six of the trials explicitly stated intention-to-treat (ITT) analysis. For each study, we have taken all randomised participants into account when introducing the data in our tables. We assumed that missing data were treatment failures.

### Other potential sources of bias

In addition, other 'quality' indicators that may lead to bias but that were not assessed within the risk of bias domain are the following:

#### Calculation of sample size

Only six studies reported a sample size calculation ([Balou 1987](#); [Convit 1987](#); [Convit 1989](#); [Llanos-Cuentas 1997](#); [Llanos-Cuentas 2007](#); [Palacios 2001](#)). The studies were further classified into 3 main groups (small, medium and large) according to their size (see [Characteristics of included studies](#) for more details).

#### Inclusion and exclusion criteria clearly defined

The main criterion for inclusion was parasitological confirmation of cutaneous leishmaniasis. None of the included RCTs reported immunodeficiency, co-infections with HIV, or use of immunosuppressants. For the majority of the studies, the most common reason for exclusion was previous treatment with anti-*Leishmania* therapy prior to entering the trial, as well as suffering from any chronic or concomitant disease. Additional reasons for excluding female participants were pregnancy, potential for pregnancy or breast feeding.

#### Reporting of *Leishmania* species involved

Four RCTs out of the 38 failed to mention the causative parasite. Six trials mentioned the endemic nature of the parasite in the area and therefore assumed that was the type of parasite causing the development of the disease ([Arévalo 2007](#); [M-Verástegui 2005](#); [Lobo 2006](#); [Machado 2007](#); [Machado-Pinto 2002](#); [Santos 2004](#)). Another two trials accepted that the type of parasites were the same as in previous studies ([Almeida 1999](#); [Arana 2001](#)). On the other hand, 26 RCTs confirmed the type of the causative organism. Of the 26 studies which analysed the *Leishmania* parasite, eight RCTs treated participants suffering from cutaneous leishmaniasis caused by *L. braziliensis*, five caused by *L. panamensis* and the rest were caused by two species or more. See [Characteristics of included studies](#) for more details. The majority of RCTs evaluated the cutaneous form of leishmaniasis. However, only four RCTs ([Franke 1994](#); [Llanos-Cuentas 1997](#); [Llanos-Cuentas 2007](#); [Machado 2007](#)) evaluated the mucocutaneous form and one RCT ([Figueiredo 1999](#)) assessed participants with both forms of leishmaniasis.

With regard to the geographic distribution of the species, the only species found in Brazil and Venezuela was *L. braziliensis*. In Colombia there was *L. braziliensis* and *L. panamensis*, in Guatemala *L. braziliensis* and *L. mexicana* and in Peru although *L. braziliensis* was confirmed, but *L. peruviana*, *L. amazonensis* and *L. mexicana* were endemic. None of the RCTs from Panama and Honduras found *L. braziliensis* species but did find *L. panamensis* or *L. mexicana* species. Only Brazil and Peru assessed the mucocutaneous form of leishmaniasis in *L. braziliensis* species. One RCT conducted in Brazil assessed both disease forms from unknown *Leishmania* species but the interventions evaluated were of the same benefit in both forms. Some of the RCTs did not report the *Leishmania* species and some others based their studies on endemic species or previous studies. This added a limitation and the fact that we found many different interventions with different regimens, made it impossible to determine the overall efficacy of drugs according to every species causing leishmaniasis. For more details see [Table 2](#).

**Table 2. Geographic distribution of *Leishmania***

Reference	Country	Form of <i>Leishmania</i>	Type of parasite	Interventions
Soto 2004A	Bolivia & Colombia	CL	<i>L. panamensis</i> (confirmed)	T1: IMSSG 20 mg/Kg/day; T2: IMMA 20 mg/Kg/day (for 20 days)
Almeida 1999	Brazil	CL	<i>L. braziliensis</i> (previous studies)	T1: GM-CSF (2 injections of 200 µg at entry and 1 week later) + IVSSG at 20 mg/kg/d for 20 days; T2: IVSSG (20 mg/kg daily for 20 days) + Saline
Correia 1996	Brazil	CL	<i>L. braziliensis</i> (confirmed)	T1: IMPI 4 mg/kg/every 2 days for 8 applications; T2: IMAS 20 mg/kg/day for 20 days; T3: IMMA 10 mg/kg/day for 20 days
Figueiredo 1999	Brazil	CL+ MCL	NR	T1: MA 15% (14 mg SBV/kg/day) + placebo; T2: MA 30% (28 mg SBV/kg/day) for 10 days +10 days placebo *CL: 2 series of 20 days; MCL: 3 series of 30 days
Lobo 2006	Brazil	CL	<i>L. braziliensis</i> (endemic)	T1: Single session heat therapy; T2: IVMA 20 mg/kg/d for 20 days
Machado 2007	Brazil	MCL	<i>L. braziliensis</i> (NR but stated that MCL is caused by <i>L. brasiliensis</i> )	T1: Oral pentoxifylline 400 mg 3 times/day for 30 days + IVSSG 20 mg/kg/d; T2: Oral placebo + IVSSG 20 mg/kg/d
Oliveira-Neto 1997	Brazil	CL	<i>L. braziliensis</i> (confirmed)	T1: IVMA 5 mg/kg/day; T2: IVMA 20 mg/kg/day *during 30 days

**Table 2. Geographic distribution of *Leishmania* (Continued)**

Santos 2004	Brazil	CL	<i>L. braziliensis</i> (endemic)	T1: GM-CSF+ IV MA 20 mg/kg/d for 20 days; T2: Placebo + IVMA 20 mg/kg/d for 20 days
Machado-Pinto 2002	Brazil	CL	<i>L. braziliensis</i> (endemic)	T1: Subcutaneous injection of <i>L. amazonensis</i> strain vaccine (0.5 ml) daily + IMMA; T2: Subcutaneous injection of Placebo daily+ IMMA *(8.5 mg/kg) for 10 d and 10 d of rest
Martínez 1992	Colombia	CL	<i>L. panamensis</i> (confirmed)	T1: Oral AL 20 mg/kg/day in 4 doses for 15 d; T2: IVMA 20 mg/kg/day for 15 d; T3: AL+ MA same doses; T3: no treatment
Martínez 1997	Colombia	CL	<i>L. braziliensis</i> (confirmed)	T1: Oral AL 20 mg/kg/day in 4 doses for 15 days+ IVSSG; T2: IVSSG *20 mg/kg/day for 15 days
Palacios 2001	Colombia	CL	<i>L. braziliensis; L. panamensis</i> (confirmed)	T1: IMMA 20 mg/kg/day OD for 10 days; T2: IMMA 20 mg/kg/day OD for 20 days
Soto 2002	Colombia	CL	<i>L. panamensis</i> (confirmed)	T1: Topical WR279396 TD for 20 days; T2: Topical placebo
Soto 1994	Colombia	CL	<i>L. panamensis</i> (confirmed)	T1: AS 12 mg/Kg/day for 7 d; T2: AS 12 mg/Kg/day for 14 d; T3: AS 18 mg/Kg/day for 14 d
Soto 1998	Colombia	CL	<i>L. braziliensis; L. panamensis</i> (confirmed)	T1: Topical 15% PR sulphate 12% MBCL TD for 10 days + IVMA for 7 days; T2: Topical placebo TD for 10 days + IVMA for 7 days; T3: Topical

**Table 2. Geographic distribution of *Leishmania* (Continued)**

				15% PR sulphate 12% MBCL TD for 10 days+ IV MA for 3 days; T4: IVMA for 20 days
Vélez 1997	Colombia	CL	<i>L. braziliensis</i> ; <i>L. panamensis</i> (confirmed)	T1: Oral AL 300 mg 4 times daily for 28 days; T2: IMMA 20 mg/kg/day for 20 days; T3: Oral placebo 4 times daily for 28 days
Soto 2004B	Colombia & Guatemala	CL	<i>L. panamensis</i> ; <i>L. braziliensis</i> ; <i>L. mexicana</i> (confirmed)	T1: Oral miltefosine orally for 28 days; T2: Placebo
Armijos 2004	Ecuador	CL	NR	T1: Topical PR 15%+12% MBCL TD for 30 d; T2: Topical PR 15%+10% urea TD for 30 d; T3: IMMA 20 mg/kg/day for 10 d
Guderian 1991	Ecuador	CL	<i>L. panamensis</i> ; <i>L. guyanensis</i> ; <i>L. braziliensis</i> ; <i>L. mexicana</i> (confirmed)	T1: Oral AL ribonucleoside (1.500 mg QID) plus probenecid (500 mg QID) for 28 days; T2: IMSSG (20 mg/Kg/day) for 20 days; T3: no treatment
Hepburn 1994	Edinburgh(Belize)	CL	<i>L. braziliensis</i> ; <i>L. mexicana</i> (confirmed)	T1: IVAS 14 mg/kg/day; T2: IVSSG 20 mg/kg/day for 20 day
D'Oliveira 1997	El Salvador	CL	<i>L. braziliensis</i> (confirmed)	T1: Oral AL 20 mg/kg 3 times/day for 20 days; T2: IVMA 10 mg/kg OD for 20 days
Arana 2001	Guatemala	CL	<i>L. braziliensis</i> ; <i>L. mexicana</i> (previous studies)	T1: Topical 15% PR plus 12% MBCL; T2: Topical placebo *TD for 20 days

**Table 2. Geographic distribution of *Leishmania* (Continued)**

Arana 1994	Guatemala	CL	<i>L. braziliensis</i> ; <i>L. mexicana</i> (confirmed)	T1: IVMA 20 mg/kg/d for 20 days; T2: IVMA 20 mg/kg/d for 10 days + 10 days of a saline infusion; T3: IVMA 20 mg/kg/d for 10 days + IFN- $\gamma$
Navin 1990	Guatemala	CL	<i>L. braziliensis</i> ; <i>L. mexicana</i> (confirmed)	T1: IMMA 850 mg daily for 15 days; T2: Localized heat 50°C for 30 sec, 3 treatments at 7 day intervals; T3: Placebo
Navin 1992	Guatemala	CL	<i>L. braziliensis</i> ; <i>L. mexicana</i> (confirmed)	T1: Oral ketoconazole 600 mg/day for 28 days; T2: IVSSG 20 mg/kg/day for 20 days; T3: Placebo
Neva 1997	Honduras	CL	<i>L. chagasi</i> ; <i>L. mexicana</i> (confirmed)	T1: Topical 15% PR + 10% urea; T2: Topical placebo *3 times/day for 4 weeks
Saenz 1987	Panama	CL	<i>L. panamensis</i> (confirmed)	T1: IMSSG 20 mg/kg/d; T2: IMMA 20 mg/kg/d *for 20 days
Saenz 1990	Panama	CL	<i>L. panamensis</i> ; <i>L. mexicana</i> (confirmed)	T1: Oral ketoconazole 3 (200-mg tablets) each day for 28 d; T2: IMMA 20 mg/Kg for 20 days; T3: Oral placebo 3 tablets for 28 d
Andersen 2005	Peru	CL	<i>L. braziliensis</i> (confirmed)	T1: IVPI 2 mg/kg on alternate days for 7 doses; T2: IVMA 20 mg/kg/day for 20 days
Arévalo 2007	Peru	CL	<i>L. braziliensis</i> ; <i>L. peruviana</i> ; <i>L. mexicana</i> ; <i>L. amazonensis</i> (endemic)	T1: Topical imiquimod 7.5% every other day for 20 days; T2: Topical imiquimod 7.5 % + IVMA 20 mg/kg/d for 20 days; T3: IVMA 20 mg/kg/d for 20 days

**Table 2. Geographic distribution of *Leishmania* (Continued)**

Franke 1994	Peru	MCL	<i>L. braziliensis</i> (confirmed)	T1: IVSSG 20 mg Sb/Kg/d for 28 d; T2: IVSSG 20 mg/Kg/d for 40d
Llanos-Cuentas 2007	Peru	MCL	<i>L. braziliensis</i> (endemic)	T1: IMAS 14 mg/kg OD for 21 d; T2: IVMA 20 mg/kg OD for 28 d
Llanos-Cuentas 1997	Peru	MCL	NR	T1: IVSSG (20 mg/kg/d)+ oral AL (20 mg/kg/d in 4 doses); T2: IVSSG (20 mg/kg/d) for 28 days
M-Verástegui 2005	Peru	CL	<i>L. braziliensis</i> ; <i>L. peruviana</i> (endemic)	T1: Topical imiquimod cream 5% every other day for 20 days + IMMA; T2: Topical placebo + IMMA as in T1
Balou 1987	USA (mainly Panama)	CL	<i>L. panamensis</i> ; <i>L. chagasi</i> (confirmed)	T1: IVSSG 10 mg/kg (P10); T2: IVSSG 20 mg/kg (P20) *OD for 20 days
Oster 1985	USA(Panama or Brazil)	CL	<i>L. braziliensis</i> ; <i>L. mexicana</i> ; <i>L. chagasi</i> (confirmed)	T1: IVSSG 600 mg OD for 10 days; T2: IVSSG loading dose of 600 mg SB + continuous infusion of 600 mg 24 h/9 days; T3: IVSSG loading dose of 600 mg SB + continuous infusion of 200 mg 8 h/day for 27 doses/9 days
Convit 1987	Venezuela	CL	<i>L. braziliensis</i> (confirmed)	T1: IMMA 50 mg/kg in series (2-3) of 20 daily injections with 15 days between series; T2: Vaccine
Convit 1989	Venezuela	CL	<i>L. braziliensis</i> (confirmed)	T1: Vaccine+BCG; T2: BCG alone intradermally in 2 sites 3 doses at 6-8 weeks intervals; T2: IMMA 50 mg/kg/day in

CL: cutaneous leishmaniasis; MCL: mucocutaneous leishmaniasis; NR: not reported; OD: once daily; TD: twice daily; T1,2,3,4: Treatment groups; \*: dosage schedule for all groups



### Time of follow-up period

The follow-up period ranged from 28 days (Lobo 2006) to 7 years (Oliveira-Neto 1997). In only one study (Machado 2007) the length of follow-up period was not reported. Although the most common follow-up period was 12 months, one study performed a 3 month follow-up (Arévalo 2007), 6 studies (Almeida 1999; Andersen 2005; Neva 1997; Soto 2002; Soto 2004A; Soto 2004B) performed a 6 month or up-to 6 month follow-up post treatment period, one a 40 week follow-up (Convit 1987), and 2 studies a 2 year follow-up period (Convit 1989; Figueiredo 1999).

### Baseline comparability of severity of infection, age, sex and duration of complaint

With regard to the baseline characteristics of sex, age, infection severity, and symptom/sign duration, not all studies reported comparability between arms or provided detailed information: only one study did not compare baseline characteristics at all or at least did not mention if there was comparability among groups (Oster 1985). With regard to age, most people enrolled into the studies included in this review were over 12 years old. One study included participants as young as one year of age (M-Verástegui 2005), or three years (Neva 1997). The ages of older participants ranged from 36 to 87 years old. Six studies (Balou 1987; Hepburn 1994; Navin 1992; Soto 1994; Soto 2002; Soto 2004B) recruited soldiers. Lesions were mainly located in the extremities (arms and legs) and limbs but also head (lips, nose (septum, turbinates), ears, mouth, vocal cords, palate-uvula-pharynx and larynx-epiglottis), neck and trunk. Not all the RCTs provided the male/female ratio. However, the overall ratio was 5.44:1 (1301/239). Eleven RCTs included only male participants (Arana 1994; Balou 1987; Franke 1994; Hepburn 1994; LLanos-Cuentas 1997; LLanos-Cuentas 2007; Navin 1990; Oster 1985; Saenz 1990; Soto 1994; Soto 2002). The types of lesions were mainly ulcerative and also infiltrative, proliferative, verrucose, nodular, papular, plaque, regional adenopathy, satellite lesion, edematous or erythematous to a lesser extent.

### Conflict of interest

Nine of the 38 studies failed to mention a potential conflict of interest or any funding for the investigators. Nine trials were supported by Boehringer Ingelheim (Arana 1994), 3M Pharmaceuticals (M-Verástegui 2005), Farmitalia Carlo Erba (Soto 1994), AB Foundation for Medical Research (Soto 1998; Soto 2002; Soto 2004A), and Zentaris (Soto 2004B), Petroleros de Venezuela S.A (Convit 1987; Convit 1989) and Camara venezolana de la Industria de la Cerveza (Convit 1989). Five trials were supported by the USA army (Andersen 2005; Franke 1994; Navin 1992; Neva 1997; Soto 2002). Twenty trials were granted by Institutional (academic and/or governmental/WHO/PAHO) grants.

### Effects of interventions

We did not always find the primary outcome measure as we had expected when we wrote the protocol. We defined our primary outcome measure as the percentage of lesions "cured" at least three months after the end of treatment. However, all the RCTs reported the percentage in terms of participants cured, and only one also reported it in terms of the number of lesions (Soto 2002). Thus, we modified our primary outcome to assess participants.

Only 23 RCTs reported the timing for the primary outcome (long-term): two RCTs reported the percentage of participants cured at three months follow-up and 21 RCT reported a timing over three months (mainly 6 months or one year). Overall the timing ranged from just at the end of treatment to two years after completion of treatment.

Our secondary outcome measure, recurrence, where duration of remission and/or percentage of people with treated lesions recurring after 6 months was reported in 15 studies. Adverse effects were reported in all except six studies. We have described them below. Four studies did not report secondary outcomes. We found no RCTs with measurements of degree of functional and aesthetic impairment and/or prevention of scarring nor with quality of life. Of our tertiary outcome measures speed of healing (time taken to be 'cured') was reported in nine studies; development of cell-mediated immunity (i.e. positive leishmanin skin test) or emergence of resistance was reported in two studies and microbiological or histopathological cure of skin lesions in three studies. We have described them below. Twenty-five studies did not report tertiary outcomes. We did not find any RCT which evaluated other tertiary outcomes such as change in ability to detect *Leishmania* by parasitological diagnostic methods (e.g. smear, PCR or culture), and mortality.

Compliance assessment: only 6 out of the 38 studies stated that compliance was assessed but only one RCT showed the results (Soto 2004B).

We found only five trials that reported the mucocutaneous form of leishmaniasis. For example, we have seen that oral allopurinol combined with intravenous antimonials was efficacious in the cutaneous leishmaniasis form (Martínez 1992; Martínez 1997) but not in the mucocutaneous form (LLanos-Cuentas 1997). Conversely, cutaneous or mucocutaneous forms of leishmaniasis responded similarly to high and low doses of intravenous meglumine antimoniate (Figueiredo 1999). So a treatment useful for the cutaneous form might not always be successful for the treatment of the mucocutaneous form.

## I. Antimonials

### I.1 Meglumine antimoniate

#### IM meglumine antimoniate *versus* placebo

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

Two RCTs (Vélez 1997; Saenz 1990) compared IMMA for 20 days with oral placebo in Colombia and Panama, respectively. One year and 3 months after treatment, cure rates were higher in the IMMA group although the effect was not statistically significant in *L. braziliensis* and *L. panamensis* infections (RR of 4.23; 95% CI 0.84, 21.38;  $I^2=46\%$  Analysis 1.1)

Another RCT (Navin 1990) from Guatemala that compared IMMA for 15 days with placebo, reported complete cure of participants in 16/22 (73%) and in 6/22 (27%) two months after treatment, respectively (short-term primary outcome, excluded from analysis).

Secondary outcomes: Remission

One RCT (Vélez 1997) reported that relapse or mucocutaneous disease (1.5-3 months after healing in the MA group and 12 months after healing in the placebo group) was seen in 3% (2/67) and 1.67% (1/60) in the MA and placebo (was mucocutaneous) groups respectively.

Secondary outcomes: Adverse effects

One RCT (Vélez 1997) reported that 79% (53/67) of participants in MA group had moderate side effects and 52.2% (35/67) had severe adverse effects (myalgias, arthralgias, anorexia, nausea, and headache). Regarding the placebo group, 10% (6/60) of the participants had moderate to severe side effects. One RCT (Saenz 1990) recorded laboratory abnormalities in 47% (9/19) participants in the MA group, consisting of mild elevations of liver enzymes which partially or completely resolved despite continued therapy in five participants; 84% (16/19) complained of pain at the IM injection site; 58% (11/19) complained of myalgia, 21% (4/19) had headache or arthralgia, and 11% (2/19) had nausea or fever. One RCT (Navin 1990) reported that no participant complained of symptoms related to treatment.

#### 10-day versus 20-day treatment with IM meglumine antimoniate

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Palacios 2001) from Colombia compared IMMA for 10 days with IMMA for 20 days. One year after treatment, there was no significant difference in cure rates between 10-day and 20-day treatment with IMMA in *L. braziliensis* and *L. panamensis* infections (RR 1.17; 95% CI 0.76, 1.79 Analysis 2.1).

Secondary outcomes: Adverse effects

The most common adverse effects but with no statistical significance were anorexia (RR 1.00; 95% CI 0.52, 1.94 Analysis 2.2), myalgias (RR 1.08; 95% CI 0.55, 2.12 Analysis 2.2) in the 10-day IMMA treatment group. However, headache (RR 0.55; 95% CI 0.29, 1.01 Analysis 2.2), malaise (RR 0.56; 95% CI 0.27, 1.18 Analysis 2.2) and arthralgias (RR 0.36; 95% CI 0.14, 0.94 Analysis 2.2) were mostly observed in the 20-day IMMA treatment group.

#### IV meglumine antimoniate versus no treatment

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Martínez 1992) from Colombia compared IVMA for 15 days with no treatment. One year after treatment, cure rates were higher in the IV group compared with no treatment but the effect was not statistically significant in *L. panamensis* infections (RR 13.24; 95% CI 0.83, 210.87 Analysis 3.1).

Secondary outcomes: Remission

One year after treatment, there was no statistical difference in relapse between the two groups (RR 1.55; 95% CI 0.35, 6.85 Analysis 3.2).

#### 7-day versus 20-day IV meglumine antimoniate

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Soto 1998) from Colombia compared IVMA for 20 days with IVMA for 7 days. One year after treatment, cure rates were significantly higher in the 20-day IVMA group compared with the 7-day IVMA treatment group in *L. braziliensis* and *L. panamensis* infections (RR 0.64; 95% CI 0.44, 0.92 Analysis 4.1).

#### Different regimens of IV N-methyl-glucamine antimoniate (MA)

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

An RCT (Figueiredo 1999) from Brazil compared IVMA (14 mg /kg/day in two series of 20 days for the cutaneous leishmaniasis form or three series of 30 days in the mucocutaneous form) with IVMA (28 mg /kg/day for 10 days). Two years after treatment, there was no significant difference in cure rates between IVMA (14 mg /kg/day) and IVMA (28 mg /kg/day) (RR 1.49; 95% CI 0.88, 2.54 Analysis 5.1). When the clinical forms were analysed separately, there was no significant difference in either the cutaneous leishmaniasis form (RR 1.50; 95% CI 0.81, 2.78 Analysis 5.2) or in the mucocutaneous form (RR 1.43; 95% CI 0.53, 3.86 Analysis 5.3).

A RCT (Oliveira-Neto 1997) from Brazil compared a low dose IVMA with high dose IVMA over a period of 30 days. Complete cure occurred in 83% (10/12) and 82% (9/11) of participants in the respective groups at the end of treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Adverse effects

One study (Oliveira-Neto 1997) reported that in the high dose group; 54.5% (6/11) presented with arthralgias, myalgias, asthenia, malaise, nausea, itch, herpes zoster, and augmentation of the QT interval (which is the period that extends from the beginning of ventricular depolarisation until the end of ventricular repolarisation) in an electrocardiogram. In contrast, 16% (2/12) of the participants receiving a low dosage, complained of arthralgias, pruritus and malaise.

### **10-day IV meglumine antimoniate combined with placebo for 10 days versus 20-day IV meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Arana 1994) from Guatemala compared IVMA for 10 days with IVMA for 20 days. One year after treatment, there was no significant difference in cure rates between 10-day and 20-day IVMA (RR 0.95; 95% CI 0.73, 1.23 Analysis 6.1).

Secondary outcomes: Remission

Two of 22 (12.1%) participants receiving MA for 20 days did not respond: one participant who was infected with *L. braziliensis*, responded initially by 13 weeks but reactivation of the lesion occurred five months after the start of treatment; the other participant was removed from the study at 13 weeks. Two of the participants 12% (2/22) receiving MA for 10 days had reactivations: one participant had an initial response but reactivation of the lesion occurred at 11 months and the other participant was also removed at 13 weeks.

Secondary outcomes: Adverse effects

Twenty-three per cent of the participants (5/22) who received MA for 20 days developed six episodes of mild adverse reactions, which included four episodes of arthralgias and one episode each of anorexia and phlebitis at the site of injection. In the group receiving MA for 10 days, only one episode of arthralgia was observed in one participant.

## **1.2 Stibogluconate**

### **IM sodium stibogluconate versus no treatment**

A RCT (Guderian 1991) from Ecuador compared IMSSG for 20 days with no treatment. Complete cure occurred in 90% (27/30) and 60% (9/15) of participants in the respective groups 1.5 months after treatment (short-term primary outcome, excluded from analysis).

### **IM sodium stibogluconate versus IM meglumine antimoniate**

Primary outcome: Percentage of participants cured at three months after the end of treatment.

A RCT (Soto 2004A) from Bolivia and Colombia compared IMSSG (branded and generic) for 20 days with IMMA for 20 days. Six months after treatment, there was no significant difference in cure rates between IMSSG and IMMA (RR 1.07; 95% CI 0.88, 1.30 Analysis 7.1). Similarly, there was no significant difference in cure rates between branded and generic IMSSG (RR 1.11; 95% CI 0.82, 1.51 Analysis 8.1) in *L. panamensis* infections.

A RCT (Saenz 1987) from Panama compared IMSSG for 20 days with IMMA for 20 days. Complete cure occurred in 46.7% (14/30) and 72.4% (21/29) of participants in the respective groups at the end of treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Remission

One RCT (Saenz 1987) reported that 22% (13/59), 23.3% (7/30) and 20.7% (6/29) of cured participants had reactivation of lesions after 6-12 months of follow-up in the branded, generic SSG and MA groups, respectively.

Secondary outcomes: Adverse effects

One RCT (Soto 2004A) reported myalgias in SSG and MA groups respectively (RR 0.78; 95% CI 0.50, 1.22 Analysis 7.2) but more myalgias were observed in the generic SSG than in the branded SSG group (RR 1.93; 95% CI 1.04, 3.58 Analysis 8.2). There was no significant difference in headache between the SSG and MA groups (RR 0.68; 95% CI 0.37, 1.26 Analysis 7.2) or between the branded and generic SSG groups (RR 1.67; 95% CI 0.65, 4.25 Analysis 8.2). A metallic taste was observed more in the SSG than in the MA group (RR 0.49; 95% CI 0.27, 0.92 Analysis 7.2) but no differences were observed between the branded and generic SSG groups (RR 2.14; 95% CI 0.79, 5.82 Analysis 8.2). There was no difference in abdominal pain in the SSG and MA groups (RR 0.78; 95% CI 0.32, 1.94 Analysis 7.2) or between the branded and generic SSG groups (RR 3.00; 95% CI 0.85, 10.63 Analysis 8.2).

One RCT (Saenz 1987) reported that 63.3% (19/30) and 51.7% (15/29) of the participants in the SSG and MA groups respectively, had mild to moderate adverse events such as myalgias, arthralgias, headaches, pain at the site of injection, allergy and fever. There were no cases reporting hepatic, renal, hematologic or cardiac toxicity.

Tertiary outcomes: Microbiological or histopathological cure of skin lesions

One RCT (Saenz 1987) reported that at the end of treatment, the cultures were parasitologically negative in 90% (27/30) and 89.7% (26/29) of the participants in the SSG and in the MA groups, respectively.

### **IV sodium stibogluconate versus placebo**

A RCT (Navin 1992) from Guatemala compared IVSSG for 20 days with placebo. In *L. braziliensis* infections, complete cure occurred in 96% (24/25) and 20% (3/15) of participants in the respective groups two months after treatment. All participants (7/7) infected by *L. mexicana* in the SSG group were completely cured by six weeks but two had subsequent reactivations two months after treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Remission

In the SSG group, none of the participants 96% (24/25) infected with *L. braziliensis* and who responded to treatment had reactivations of their lesions between the 13- and 52-week examinations. Sixty-seven per cent of *L. braziliensis*-infected participants (2/3) who received placebo that responded clinically had reactivations of their lesions, one at 14 weeks and the other at five months. Regarding *L. mexicana* none of the participants had reactivations of their lesions between the 13- and 52-weeks follow-up examinations.

Secondary outcomes: Adverse effects

In the SSG group, 5/29 participants had nausea; 4/29 anorexia; 3/29 headache; 1/29 had rash; 6/29 had arthralgias and 10/29 had phlebitis. In the placebo group, 1/5 each had nausea and anorexia and 3/5 had abdominal pain.

#### Different doses of IV sodium stibogluconate

A RCT (Balou 1987) from the USA compared low dose IVSSG for 20 days with high dose IVSSG for 20 days. Complete cure occurred in 76% (16/21) and 100% (19/19) of participants in the respective groups 1.5 months after treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Adverse effects

Mild to moderate muscle and joint stiffness were experienced by 62% (13/21) participants in the low-dose group and 58% (11/19) participants in the high-dose group. Laboratory abnormalities were limited to increases in liver enzymes in 48% (10/21) and 53% (10/19), respectively; mild leucopenia in 9.5% (2/21) and 5.3% (1/19), respectively; and electrocardiographic abnormalities in 19% (4/21) and 21% (4/19), respectively.

#### Different regimens of IV sodium stibogluconate

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Franke 1994) from Peru compared IVSSG for 28 days with IVSSG for 40 days. One year after treatment, there was no significant difference in cure rates between 28 and 40 days of IVSSG (RR 0.83; 95% CI 0.47, 1.47 Analysis 9.1) in *L. braziliensis* infections.

Secondary outcomes: Adverse effects

None of the subjective complaints were severe enough to warrant cessation of treatment. Although more participants of the 40-day regimen complained of arthralgias and myalgias, most complaints began before day 28. Side effects were arthralgias, myalgias, itch, rash, nausea, anorexia, abdominal pain, cough and headache.

#### Different doses and regimens of IV sodium stibogluconate

A RCT (Oster 1985) from the USA treated participants with IVSSG for 10 days at a dose of 600mg per day by 1 of 3 schedules: once daily by rapid infusion for 10 days; a loading dose of 600 mg followed by a continuous infusion of 600 mg for 24 hours each day for 9 days; or a loading dose of 600 mg followed by 200 mg every 8 hours for 9 days. Complete cure occurred in 100% (12/12), 50% (6/12) and 42% (5/12) of participants in the respective groups at the end of treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Adverse effects

Despite the lack of side-effects reported by the participants, there was an equal distribution of mildly elevated liver enzymes, triglycerides and creatine phosphokinase (CPK) in the three groups.

## 2. Non-antimonial systemic treatments

### 2.1 Oral antifungals

#### Ketoconazole versus IM meglumine antimoniate

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Saenz 1990) from Panama compared oral ketoconazole for 28 days with IMMA for 20 days. Three months after treatment, there was no significant difference in cure rates between oral ketoconazole and 20mg/kg/day IMMA for 20 days (RR 1.06; 95% CI 0.71, 1.58 Analysis 10.1) in *L. panamensis* and *L. mexicana* infections.

Secondary outcomes: Adverse effects

The laboratory abnormalities recorded in 27% (6/22) of ketoconazole-treated participants were mild elevations of liver transaminase values that normalized during or after therapy. Subjective complaints consisted of headache (4/22), abdominal pain (2/22), fever (2/22), nausea (1/22) and malaise (1/22). Laboratory abnormalities were recorded in 47% (9/19) participants in the MA group, consisting of mild elevations of liver enzymes which partially or completely resolved despite continued therapy in five participants. Eighty-four per cent (16/19) complained of pain at the IM injection site. In addition, 58% (11/19) complained of myalgia, 21% (4/19) had headache or arthralgia, and 11% (2/19) had nausea or fever.

Tertiary outcomes: Speed of healing

In the ketoconazole group complete re-epithelization occurred by three months after the end of therapy. Fifty-four per cent of participants (7/13) in the MA group demonstrated complete re-epithelialization of lesions by the end of approximately 1 month of therapy.

Tertiary outcomes: Microbiological or histopathological cure of skin lesions

For the 73% (16/22) participants who were cured by the end of therapy in the ketoconazole group, lesions were parasitologically sterile in all attempted tests for only 56% (9/16) of participants at the end of therapy. In the MA group 69% (9/13) of the participants who were cured, had a negative diagnostic test result for leishmanial organisms at the end of therapy.

#### Ketoconazole versus IV sodium stibogluconate

A RCT (Navin 1992) from Guatemala compared oral ketoconazole for 28 days with IVSSG for 20 days. Complete cure occurred in 52% (12/23) and 96% (24/25) of participants in the respective groups 2 months after treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Remission

In the ketoconazole group, 17% (2/12) responders infected with *L. braziliensis* had reactivations of their lesions, 1 at 17 weeks and 1 at 11 months. In the SSG group, none of the 96% (24/25) of

the participants infected with *L. braziliensis* and who responded to treatment by 13 weeks had reactivations of their lesions at the 52-week examinations. With regard to *L. mexicana*, all participants who had responded in all treatment groups had no reactivations of their lesions at the 52-week follow-up examinations.

Secondary outcomes: Adverse effects

In the ketoconazole group, 2/8 had nausea, abdominal pain and headache and 1/8 each had dizziness and rash. In the SSG group, 5/29 participants had nausea; 4/29 anorexia; 3/29 headache; 1/29 had rash; 6/29 had arthralgias and 10/29 had phlebitis.

### **Ketoconazole versus placebo**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Saenz 1990) from Panama compared oral ketoconazole for 28 days with oral placebo. Three months after treatment, cure rates were significantly higher in the oral ketoconazole group compared with placebo (RR 17.22; 95% CI 1.13, 262.82 Analysis 11.1) in *L. panamensis* and *L. mexicana* infections.

A RCT (Navin 1992) from Guatemala compared oral ketoconazole for 28 days with placebo. Complete cure occurred in 52% (12/23) and 20% (3/15) of participants in their respective groups two months after treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Remission

In a study (Navin 1992) 17% (2/12) responders in the ketoconazole group infected with *L. braziliensis* had reactivations of their lesions, one at 17 weeks and one at 11 months. Sixty-seven per cent of *L. braziliensis*-infected participants (2/3) who received placebo that responded clinically had reactivations of their lesions, 1 at 14 weeks and the other at 5 months. With regard to *L. mexicana*, all participants who had responded in the two treatment groups had no reactivations of their lesions.

Secondary outcomes: Adverse effects

In one study (Saenz 1990) the laboratory abnormalities recorded in 27% (6/22) of ketoconazole-treated participants were mild elevations of liver transaminase values that normalized during or after therapy. Subjective complaints consisted of headache (4/22), abdominal pain (2/22), fever (2/22), nausea (1/22), and malaise (1/22).

In the other study (Navin 1992) reported that in the ketoconazole group, 2/8 each had nausea, abdominal pain and headache and 1/8 had dizziness and rash. In the placebo group, 1/5 had nausea and anorexia and 3/5 had abdominal pain.

## **2.2 Oral allopurinol**

### **Oral allopurinol versus allopurinol combined with IM meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Martínez 1992) from Colombia compared oral allopurinol for 15 days with oral allopurinol plus IVMA in the same regimen. One year after treatment, there was no significant difference in cure rates between oral allopurinol alone and oral allopurinol in combination with IVMA (RR 1.08; 95% CI 0.82, 1.42 Analysis 12.1) in *L. panamensis* infections.

Secondary outcomes: Remission

After 12 months the difference in relapse after cure was not statistically significant between the 2 groups (RR 0.70; 95% CI 0.07, 7.30 Analysis 12.2).

### **Oral allopurinol versus IV meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Martínez 1992) from Colombia compared oral allopurinol for 15 days with IVMA for 15 days. One year after treatment, cure rates were significantly higher in the oral allopurinol group compared with the IVMA group (RR 2.20; 95% CI 1.34, 3.60 Analysis 13.1).

A RCT (D'Oliveira 1997) from Ecuador compared oral allopurinol with IVMA, both for 20 days. There was no complete cure for the first nine participants of the allopurinol group, two months after treatment. The other nine participants in this group were not included in the evaluation because the protocol was stopped due to some participants getting worse, antimonial was administered to some of this group. There was complete cure in 50% (8/16) of the MA group two months after treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Remission

One study (Martínez 1992) reported that a 12 month relapse after cure was seen in 4% (1/25) and 6% (2/33) of the allopurinol and MA groups respectively (RR 0.66; 95% CI 0.06, 6.88 Analysis 13.2).

Secondary outcomes: Adverse effects

The other study (D'Oliveira 1997) reported that 11.1% (1/9) of participants developed mucocutaneous disease within three months although the groups are unknown.

### **Oral allopurinol combined with IV meglumine antimoniate versus IV meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Martínez 1992) from Colombia compared oral allopurinol for 15 days combined with IVMA for 15 days with IVMA monotherapy for 15 days. One year after treatment, oral allopurinol had a significant synergistic effect with IVMA for 15 days (RR 2.04; 95% CI 1.25, 3.34 Analysis 14.1).

Secondary outcomes: Remission

Relapse after cure was not statistically significant (RR 0.94; 95% CI 0.14 to 6.31 Analysis 14.2).

### Oral allopurinol *versus* IM meglumine antimoniate

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Vélez 1997) from Colombia compared oral allopurinol for 28 days with IMMA for 20 days. One year after treatment, oral allopurinol showed lower cure rates compared with IMMA (RR 0.39; 95% CI 0.26, 0.58 Analysis 15.1).

Secondary outcomes: Remission

Relapse or mucocutaneous disease was seen in 5% (3/60) of the allopurinol group: 1 was seen 5 months after healing and 2 mucocutaneous cases were seen at the end of treatment and 1.5 months later. Relapse or mucocutaneous disease was seen 1.5-3 months after healing in 3% (2/67) of MA group.

Secondary outcomes: Adverse effects

Twenty-five per cent of participants in the allopurinol group (15/60) had moderate to severe side effects. The only side effects attributable to allopurinol were headache and epigastric pain. Seventy-nine per cent of participants (53/67) in the MA group had moderate side effects and 52.2% (35/67) had severe adverse effects. Myalgias, arthralgias, anorexia, nausea, and headache were common adverse effects.

### Oral allopurinol combined with IV sodium stibogluconate *versus* IV sodium stibogluconate

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Martínez 1997) from Colombia compared oral allopurinol combined with IVSSG with IVSSG alone, both for 15 days. One year after treatment, oral allopurinol had a significant synergistic effect with IVSSG (RR 1.82; 95% CI 1.23, 2.70 Analysis 16.1).

When pooling two RCTs (*L. braziliensis*) (Martínez 1992; Martínez 1997) where oral allopurinol combined with IV antimonials (20 mg/kg/day for 15 days) was compared with IV antimonials, the results showed that oral allopurinol had a significant synergistic effect (RR 1.90; 95% CI 1.40, 2.59;  $I^2=0%$  Analysis 16.2).

A RCT (LLanos-Cuentas 1997) from Peru compared oral allopurinol combined with IVSSG with IVSSG alone, both for 28 days. One year after treatment, there was no significant difference in cure rates between oral allopurinol plus IVSSG and 20 mg /kg/d IVSSG for 28 days (RR 0.62; 95% CI 0.38, 1.03 Analysis 17.1).

Secondary outcomes: Remission

One RCT (Martínez 1997) reported that at 12 months, relapse after cure was seen in 14% (7/51) and 14% (7/49) of the oral allopurinol combined with IVSSG and the IVSSG groups, respectively. The other RCT (LLanos-Cuentas 1997) reported that at 12 months relapses were seen in 45% (18/40) and 37% (15/41) of the oral allopurinol combined with IVSSG and the IVSSG groups respectively.

Secondary outcomes: Adverse effects

One RCT (Martínez 1997) reported that clinically important side-effects were observed only for the group of participants who received SSG monotherapy. Two per cent of participants (1/49) developed severe chemical hepatitis with neurological manifestations, and treatment was stopped after 7 days. The cause of this adverse event is unclear, but it was not believed to be related to antileishmanial therapy. There was an increase in the frequency of eosinophilia and rash in the group receiving allopurinol (18% (9/51) eosinophilia and 28% (14/51) rash). In the SSG-alone group 2% (1/49) had eosinophilia and the same results for rash. The rashes were generally macular or erythematous. There was no urticaria or desquamation. These cutaneous manifestations were mild, did not require treatment, and were consistent with the known side effects of allopurinol. The other RCT (LLanos-Cuentas 1997) reported that the more frequent symptoms were headache (81.5% of participants), arthralgia (75.3%), myalgia (67.9%), chills (42%), fever (39.5%), abdominal pain (33.3%), and anorexia (25.9%). Three participants developed Herpes Zoster (2 in the allopurinol combined with SSG group and 1 in the SSG-alone group), and they were treated with acyclovir but one developed partial blindness as a consequence. The most frequent laboratory adverse event was hematologic abnormality: the rate of thrombocytopenia was higher among the allopurinol combined with SSG group.

### Oral allopurinol ribonucleoside combined with probenecid *versus* IM sodium stibogluconate

A RCT (Guderian 1991) from Ecuador compared oral allopurinol ribonucleoside combined with probenecid for 28 days with IMSSG for 20 days. Complete cure occurred in 30% (9/30) and 60% (9/15) of participants in the respective groups 1.5 months after treatment (short-term primary outcome, excluded from analysis). The authors also compared the experimental intervention with no treatment, and they reported complete cure of 30% (9/30) and 90% (27/30) participants in the respective groups 1.5 months after treatment.

### Oral allopurinol *versus* no treatment

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Martínez 1992) from Colombia compared oral allopurinol for 15 days with no treatment. One year after treatment, oral allopurinol had significantly higher cure rates compared with no treatment (RR 28.38; 95% CI 1.83, 439.72 Analysis 18.1).

Secondary outcomes: Remission

This study (Martínez 1992) reported that at 12 months, relapse after cure not statistically significant (RR 0.34; 95% CI 0.03, 3.46 Analysis 18.2).

### Oral allopurinol *versus* placebo

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Vélez 1997) from Colombia compared oral allopurinol for 28 days with placebo. One year after treatment, there was no significant difference in cure rates between oral allopurinol and placebo (RR 1.06; 95% CI 0.61, 1.85 Analysis 19.1).

Secondary outcomes: Remission

Relapse or mucocutaneous disease was seen in 5% (3/60) of the allopurinol group: 1 was seen 5 months after healing and 2 mucocutaneous cases were seen at the end of treatment and 1.5 months later. Relapse was seen in 1.67% (1/60) of the placebo group - this participant had developed mucocutaneous disease 12 months after healing.

Secondary outcomes: Adverse effects

Moderate to severe side effects were observed in 25% (15/60) in the allopurinol group. The only side effects attributable to allopurinol were headache and epigastric pain. Seventy-nine per cent of participants (53/67) in the MA group had moderate side effects and 52.2% (35/67) had severe adverse effects. Myalgias, arthralgias, anorexia, nausea, and headache were common adverse effects.

### **Oral allopurinol combined with IV meglumine antimoniate versus no treatment**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Martínez 1992) from Colombia compared oral allopurinol combined with IVMA for 15 days with no treatment. One year after treatment, oral allopurinol had significantly higher cure rates than no treatment (RR 26.50; 95% CI 1.71, 410.42 Analysis 20.1).

Secondary outcomes: Remission

Relapse after cure at 12 months was not statistically significant (RR 0.49; 95% CI 0.07, 3.16 Analysis 20.2).

### **2.3 Oral miltefosine**

#### **Oral miltefosine versus placebo**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Soto 2004B) from Colombia and Guatemala compared oral miltefosine for 28 days with placebo in *L. braziliensis* and *L. panamensis* and *L. mexicana* infections. Six months after treatment, oral miltefosine had significantly higher cure rates than placebo in the Colombian site (RR 2.18; 95% CI 1.28, 3.71 Analysis 21.1) but not in the Guatemalan site (RR 2.50; 95% CI 0.99, 6.33 Analysis 21.1).

Secondary outcomes: Remission

Relapses occurred within 6 months in 4.1% (2/49) and 0% (0/24) of the respective treatments in the Colombian site, and 10% (4/40) and 5% (1/20) of the respective treatments from the Guatemala site.

Secondary outcomes: Adverse effects

Nausea was observed more in the miltefosine group (RR 3.96; 95% CI 1.49, 10.48 Analysis 21.2), motion sickness was not statistically significant (RR 1.29; 95% CI 0.68, 2.42 Analysis 21.2), headache was not statistically significant (RR 1.32; 95% CI 0.67, 2.59 Analysis 21.2), vomiting was observed more in the miltefosine group (RR 6.92; 95% CI 2.68, 17.86 Analysis 21.2) and diarrhoea was not statistically significant (RR 2.47; 95% CI 0.57, 10.80 Analysis 21.2). The creatinine level increased towards the normal range in the miltefosine recipients (RR 3.58; 95% CI 1.34, 9.56 Analysis 21.2). Aspartate aminotransferase was not statistically significant (RR 0.43; 95% CI 0.17, 1.12 Analysis 21.2), nor alanine aminotransferase (RR 0.89; 95% CI 0.32, 2.50 Analysis 21.2).

### **2.4 Aminosidine sulphate**

#### **Different regimens of aminosidine sulphate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Soto 1994) from Colombia compared aminosidine sulphate (AS) 12 mg/kg/day for 7 days, and for 14 days, with AS 18 mg/kg/day for 14 days. One year after treatment, AS 12 mg/kg/day for 7 days had significantly lower cure rates than AS 12 mg/Kg/day for 14 days (RR 0.23; 95% CI 0.07, 0.73 Analysis 22.1); and 18 mg/Kg/day for 14 days (RR 0.20; 95% CI 0.06, 0.62 Analysis 22.2). There was no significant difference between AS 12 mg/Kg/day and AS 18 mg/Kg/day, both for 14 days (RR 0.87; 95% CI 0.50, 1.49 Analysis 22.3) in *L. panamensis* infections.

Secondary outcomes: Adverse effects

The aspartate aminotransferase (AST) value was at 50% above the upper limit of normal in 23.3% (1/30) of participants in the aminosidine sulphate 12 mg/kg/day for 14 days group. Of the participants in the aminosidine sulphate 12 mg/kg/day for 7 days group, 6.6% (2/30) had AST values between 100% and 200% above the upper limit.

#### **IV aminosidine sulphate versus IV sodium stibogluconate**

A RCT (Hepburn 1994) conducted in British soldiers deployed in Belize compared IVAS with IVSSG, both for 20 days. Complete cure occurred in 59% (10/17) and 88% (15/17) of participants in the respective groups 1.5 months after treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Adverse effects

SSG was not well tolerated; all participants reported aching muscles and joint stiffness which started after 12-17 days of treatment and persisted for 2-4 days after treatment had stopped. Six soldiers reported loss of appetite and three reported headaches. One soldier developed an erythematous macular rash after 17 days of treatment, which resolved 2 days after the course finished.

### **IM aminosidine sulphate versus IM meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Correia 1996) from Brazil compared IMAS with IMMA, both for 20 days. One year after treatment, there was no significant difference in cure rates between IMAS 20 mg/kg/day for 20 days and IMMA 10 mg/kg/day for 20 days (RR 1.22; 95% CI 0.94, 1.58 Analysis 23.1) in *L. braziliensis* infections.

Secondary outcomes: Adverse effects

Adverse events were not statistically significant with regard to myalgias (RR 0.27; 95% CI 0.07, 1.06 Analysis 23.2), anorexia (RR 1.07; 95% CI 0.44, 2.59 Analysis 23.2), asthenia (RR 0.71; 95% CI 0.25, 2.03 Analysis 23.2), and arthralgias (RR 0.10; 95% CI 0.01, 1.61 Analysis 23.2).

### **IM aminosidine sulphate versus IM pentamidine isethionate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Correia 1996) from Brazil compared IMAS for 20 days with IM pentamidine isethionate (PI) for eight applications. One year after treatment, there was no significant difference in cure rates between IMAS 20 mg/kg/day for 20 days and IMPI 4 mg/kg/every 2 days, for 8 doses (RR 1.15; 95% CI 0.91, 1.44 Analysis 24.1) in *L. braziliensis* infections.

Secondary outcomes: Adverse effects

Adverse events were not statistically significant with regard to myalgias (RR 0.33; 95% CI 0.08, 1.39 Analysis 24.2), anorexia (RR 0.86; 95% CI 0.38, 1.95 Analysis 24.2), asthenia (RR 0.80; 95% CI 0.27, 2.41 Analysis 24.2), and arthralgias (RR 0.20; 95% CI 0.01, 3.85 Analysis 24.2).

### **IM aminosidine sulphate versus IV meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Llanos-Cuentas 2007) from Peru compared IMAS for 21 days with IVMA for 28 days. One year after treatment, IMAS 14 mg/kg/day for 21 days had significantly lower cure rates than IVMA 20 mg/kg/day for 28 days (RR 0.05; 95% CI 0.00, 0.78 Analysis 25.1).

Secondary outcomes: Adverse effects

Participants from the MA group had transient and mild electrocardiograph abnormalities that did not need therapeutic intervention. Aminosidine sulphate was associated with pain at the injection site that improved with the application of local heat. Fever, chills, arthralgia, anorexia, and myalgia were seen equally in both groups.

## **2.5 Pentamidine isethionate**

### **IV Pentamidine isethionate versus IV meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Andersen 2005) from Peru compared IVPI for 7 doses with IVMA for 20 days. Six months after treatment, IVPI 2 mg/kg on alternate days for 7 doses, showed significantly lower cure rates than IVMA 20 mg/kg/day for 20 days (RR 0.45; 95% CI 0.29, 0.71 Analysis 26.1) in *L. braziliensis* infections.

Secondary outcomes: Remission

The number of relapses at six months follow-up was 12.5% (5/40) of the participants in each group.

Secondary outcomes: Adverse effects

Adverse events were not statistically significant with regard to gastrointestinal events (RR 1.44; 95% CI 0.90, 2.29 Analysis 26.2) and musculoskeletal events (RR 0.80; 95% CI 0.49, 1.31 Analysis 26.2), but headache was mostly seen in the IVPI group (RR 0.61; 95% CI 0.43, 0.85 Analysis 26.2). Other minor side effects were lesion pain, paraesthesia, fever or chills, bad taste and cough.

Tertiary outcomes: Microbiological or histopathological cure of skin lesions

There were no parasites found in the MA group (0/40) but in the PI group 35% (14/40) had parasites at 2 weeks and 7.5% (3/40) at three months post-therapy

### **IM pentamidine isethionate versus IM meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Correia 1996) from Brazil compared IMPI with IMMA for 20 days. One year after treatment, there was no significant difference between IMPI 4 mg/kg/every 2 days, for 8 doses and IMMA 10 mg/kg/day for 20 days (RR 0.99; 95% CI 0.75, 1.30 Analysis 27.1) in *L. braziliensis* infections.

Secondary outcomes: Adverse effects

Adverse events were not statistically significant with regard to myalgias (RR 0.80; 95% CI 0.36, 1.76 Analysis 27.2), anorexia (RR 1.24; 95% CI 0.54, 2.86 Analysis 27.2), asthenia or weakness (RR 0.89; 95% CI 0.34, 2.31 Analysis 27.2), and arthralgias (RR 0.43; 95% CI 0.10, 1.88 Analysis 27.2).

## **3. Non-antimonial topical or intralesional therapies**

### **3.1 Topical paromomycin (aminosidine)**

#### **Paromomycin versus placebo**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Arana 2001) from Guatemala compared topical 15% paromomycin in 12% MBCL ointment (PR-MBCL) for 20 days with placebo. One year after treatment, topical paromomycin in MBCL had significantly higher cure rates than placebo (RR 2.38;

95% CI 1.50, 3.80 [Analysis 28.1](#)) in *L. braziliensis* and *L. mexicana* infections.

A RCT ([Neva 1997](#)) from Honduras compared topical 15% paromomycin in 10% urea (PR-U) ointment for four weeks with placebo. Complete cure occurred in 4.3% (1/23) and 3.3% (1/30) of participants in the respective groups 2.5 months (11 weeks) after treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Remission

One study ([Arana 2001](#)) reported that between weeks 13 and 52, only 3.1% (1/32) of participants in the paromomycin group and none (0/13) in the placebo group with healed clinical lesions at the 13-week follow-up examination experienced reactivation of the lesion, however reactivation occurred in that one individual around 26 weeks.

In the other study ([Neva 1997](#)), the 10 participants recruited to the trial had already had the condition for 9 months. Their lesions persisted regardless whether they received drug or placebo, although there was no change with regard to size.

Secondary outcomes: Adverse effects

One study ([Arana 2001](#)) reported that of the 38 participants receiving PR-MBCL ointment, 57.9% (22) had a total of 30 adverse effects. These effects included local itch 42.1% (16/38), sensation of burning 28.9% (11/38), local pain 21% (8/38) and local edema 2.6% (1/38). All adverse effects disappeared within one week after finishing the treatment. In the other study ([Neva 1997](#)) no untoward effect of either the paromomycin or placebo ointment was reported or observed.

#### **Paromomycin-MBCL versus IM meglumine antimoniate**

A RCT ([Armijos 2004](#)) from Ecuador compared topical PR-MBCL for 30 days, topical PR-U for 30 days, with IMMA for 10 days. Complete cure occurred in 47.5% (19/40), 47.5% (19/40) and 70% (28/40) of participants in the respective groups 2 months after treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Remission

During the 52 week observation period, 10% (4/40), 5% (2/40) and 12.5% (5/40) of participants experienced infection relapse in the PR-MBCL, PR-U and MA groups respectively.

Secondary outcomes: Adverse effects

Inflammation and soreness were only reported in the paromomycin groups. However, the adverse effects reported in the MA group were epigastric pain, anxiety, nausea, dizziness, joint discomfort, shortness of breath, abdominal and muscular pain. In all three groups a number of side-effects were experienced including local application site reactions such as itch, burning, redness, heat and exudation and systemic reactions including headache and weakness.

Tertiary outcomes: Speed of healing

The days required for initial healing were 43.1 14.4 (Mean SD),

43.5 17 and 29.5 12.2 in the PR-MBCL, PR-U and MA groups respectively (the original paper reported that the time to cure was faster for participants treated with IMMA compared with PR-MBCL (P= 0.001) or PR-U (P= 0.002) by the Students' t- test).

#### **Paromomycin- MBCL combined with 7 days of IM/IV meglumine antimoniate versus paromomycin in MBCL combined with 3 days of IM/IV meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT ([Soto 1998](#)) from Colombia compared PR-MBCL for ten days combined with a short course of IVMA for seven days with PR-MBCL for ten days combined with a short course of IVMA for three days. One year after treatment, PR-MBCL plus IVMA for seven days had significantly higher cure rates compared with PR-MBCL plus IVMA for three days (RR 2.88; 95% CI 1.36, 6.09 [Analysis 30.1](#)) in *L. braziliensis* and *L. panamensis* infections.

#### **Paromomycin-MBCL combined with 7 days of IM/IV meglumine antimoniate versus 7 days of IM/IV meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

In the same RCT ([Soto 1998](#)) from Colombia PR-MBCL for ten days combined with a short course of IVMA for seven days was compared with IVMA for seven days. One year after treatment, there was no significant difference in cure rates between PR-MBCL plus IVMA for 7 days and IVMA for 7 days (RR 1.08; 95% CI 0.72, 1.61 [Analysis 29.1](#)).

#### **Paromomycin-MBCL combined with three days of IM/IV meglumine antimoniate versus seven days of IM/IV meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

This RCT ([Soto 1998](#)) from Colombia also compared topical PR-MBCL for ten days combined with a short course of IVMA for three days with IVMA for seven days. One year after treatment, PR-MBCL plus IVMA for 3 days had significantly lower cure rates than IVMA for 7 days (RR 0.38; 95% CI 0.17, 0.83 [Analysis 31.1](#)).

#### **Paromomycin combined with IV meglumine antimoniate (for 3 and 7 days) versus IM/IV meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

The same RCT ([Soto 1998](#)) from Colombia compared topical PR-MBCL for ten days combined with a short course of IVMA for seven days, with topical PR-MBCL for ten days combined with a short course of IVMA for three days with IVMA for 20 days. One year after treatment, IVMA for 20 days had significantly higher

cure rates than topical PR-MBCL plus IVMA for 7 days (RR 0.69; 95% CI 0.58, 0.90 [Analysis 32.1](#)) and topical PR-MBCL plus IVMA for 3 days (RR 0.24; 95% CI 0.11, 0.50 [Analysis 33.1](#)) in *L. braziliensis* and *L. panamensis* infections.

### 3.2 Topical aminoglycosides

#### Formulation of aminoglycosides (WR279396) versus placebo

A RCT ([Soto 2002](#)) from Colombia compared topical WR279396 for 20 days with placebo. Complete cure occurred in 51.5% (17/33) and 41.7% (5/12) of participants in the respective groups 2 months (70 days) after treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Adverse effects

In the WR279396 group, 55% (18/33) of participants experienced mild local reactions lasting a mean of 3.6 days, except for 1 participant who had moderate erythema for only 1 day. In the placebo group, 33% (4/12) reported mild side-effects for a mean of 2.5 days each. No participant demonstrated an increase in creatinine values (nephrotoxicity) to higher than normal values.

Tertiary outcomes: Speed of healing

The speed of healing occurred in 35–21 days in the WR279396 group and 56–28 days in the placebo group (the original paper reported that the time to cure was faster for participants treated with topical WR279396 ( $P=0.04$ ) by the Students' *t*-test).

## 4. Physical therapies

### 4.1 Thermotherapy

#### Thermotherapy versus placebo

A RCT ([Navin 1990](#)) from Guatemala applied 3 treatments of localized heat at 50°C for 30 seconds, at 7 day intervals compared with placebo. Complete cure occurred in 73% (16/22) and 27% (6/22) of participants in the respective groups 2 months after treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Adverse effects

No participant complained of symptoms related to treatment. Four participants developed moderately severe local cellulitis during heat despite routine treatment with dicloxacillin one hour before and three days after each heat application. Participants treated with heat usually had superficial 2<sup>nd</sup> degree burns where the electrodes were applied.

Tertiary outcomes: Microbiological or histopathological cure of skin lesions

In the heat-treated group, by week 13, 73% (16/22) participants were parasitologically negative for *Leishmania*. By week 13, 27% (6/22) of participants in the placebo group had negative cultures.

#### Thermotherapy versus IM meglumine antimoniate

A RCT ([Navin 1990](#)) from Guatemala applied 3 treatments of localized heat at 50°C for 30 sec, at 7 day intervals compared with IMMA for 15 days. Complete cure occurred in 59% (13/22) and 73% (16/22) of participants in the respective groups 2 months after treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Adverse effects

Described above.

Tertiary outcomes: Microbiological or histopathological cure of skin lesions

In the heat-treated group, by week 13, 73% (16/22) of participants were parasitologically negative for *Leishmania*. By week 9, 73% (16/22) of participants in the MA group had negative cultures.

#### Thermotherapy combined with IV meglumine antimoniate versus IV meglumine antimoniate

A RCT ([Lobo 2006](#)) from Brazil compared heat therapy given in a single session combined with IVMA after day 28, with IVMA, both for 20 consecutive days. Complete cure occurred in 5.9% (1/17) and 10% (2/20) of participants in the respective groups at the end of treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Adverse effects

No significant adverse effect was seen or reported by participants who submitted to heat therapy, except for secondary bacterial infection after treatment (seven in the heat therapy group and one in the MA group).

## 5. Immunochemotherapy

### 5.1 Vaccines

#### Vaccine versus IM meglumine antimoniate

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

Two RCTs from Venezuela ([Convit 1987](#); [Convit 1989](#)) compared intradermal vaccine of the *L. mexicana amazonensis* strain combined with Bacille Calmette Guerin (BCG) with IMMA. Six months after treatment, there was no significant difference in cure rates between the vaccine and IMMA (RR 0.96; 95% CI 0.90, 1.04;  $I^2=0\%$  [Analysis 34.1](#)) in *L. braziliensis* infections.

Secondary outcomes: Remission

One study ([Convit 1989](#)) reported that no relapses were seen in the two groups.

Secondary outcomes: Adverse effects

One study ([Convit 1987](#)) reported that for the vaccine group 5.2% (3/58) reported slight side-effects (shallow necrosis and ulceration at the inoculation site between 1.5 and 1.9 cm in diameter). For the MA group 50% (22/44) reported side-effects, and some were severe. The commonest moderate side-effects were bone and muscle pain, headache and fever. The nine participants

with severe side-effects had one or more of the following: severe bone and muscle pain (five), hypotension (three), alteration of cardiac rhythm (one), severe colic (one), and paraesthesia (one). One study (Convit 1989) reported that side-effects in the vaccine group occurred in approximately 5% of participants and were limited to local lesions >10 mm at injection sites or slight fever. Forty-nine per cent of the participants (25/51) receiving MA showed secondary effects including bone and muscle pain, headache and fever. The severe side effects observed in 17.6% (9/51) of participants included one or more of the following: cardiovascular alterations, such as hypotension or alterations in heart rhythm (four participants), paraesthesia and colic (one participant), and severe osteomuscular pain (five participants). Temporary suspension of treatment was required in the participants with severe side-effects. Tertiary outcomes: Speed of healing

One study (Convit 1987) reported that the average time from start of treatment to cure was 18.3 weeks for the vaccine group and 16.1 weeks for MA group (the original paper reported that the time to cure was not significant ( $P > 0.05$ ) by the Students' *t*-test). In the other study (Convit 1989) the average times required for healing were 18.3 weeks in the vaccine group and 16.1 weeks in the MA group (the original paper reported that the difference was not statistically significant by variance analysis).

Tertiary outcomes: Development of cell-mediated immunity

One study (Convit 1987) reported that both groups showed changes in immunological reactivity after treatment, but the differences between them were not statistically significant. Montenegro skin test reactions increased from a mean of 21.88 mm before treatment to 26.8 mm in the vaccine group and from 20.50 mm to 24.7 mm in the MA group. In the other study (Convit 1989) the average size of the Montenegro reaction increased slightly in the two groups (from 21.6 mm before treatment to 25.4 mm in the vaccine-treated group and from 20.4 mm to 20.8 mm in the MA group) but the differences among the groups and within each group were not statistically significant. While these increases are not significant, they clearly suggest stimulation of the participants' immune system.

### **Vaccine combined with IM meglumine antimoniate versus IM meglumine antimoniate**

In a RCT (Machado-Pinto 2002) from Brazil subcutaneous vaccination of *L. amazonensis* strain combined with IMMA was compared with IMMA, both for ten days followed by ten days of rest. Complete cure occurred in 92.15% (47/51) and 7.84% (4/51) of participants in the respective groups at the end of treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Remission

No relapses were observed at one year after cessation of treatment.

Secondary outcomes: Adverse effects

Apart from occasional complaints of pain at the site of injection, no side-effects were observed in either group.

Tertiary outcomes: Speed of healing

The time taken to be cured was 43 days (CI: 40-47) in the vaccine combined with MA group compared with 102 days (CI: 97-107) in the placebo plus MA groups (the original paper reported that the time to cure was faster for participants treated with vaccine plus MA ( $P < 0.0001$ ) by the log rank test).

### **5.2 Intradermal Bacillus Calmette-Guerin (BCG)**

#### **BCG versus IM meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Convit 1989) from Venezuela compared three doses of intradermal BCG with IMMA. Six months after treatment, intradermal BCG had significantly lower cure rates than IMMA (RR 0.46; 95% CI 0.32, 0.65 Analysis 35.1) in *L. braziliensis* infections.

Secondary outcomes: Remission

Only one relapse was observed in the BCG alone group between 3 months to 2.5 years. No relapses were seen in the other group.

Secondary outcomes: Adverse effects

For the BCG alone group approximately 5% of participants experienced side-effects which were limited to local lesions > 10 mm at injection sites or slight fever. In the group receiving MA, 48.9% (25/51) of the participants showed secondary effects including bone and muscle pain, headache and fever. The severe side-effects observed in 17.6% (9/51) of participants included one or more of the following: cardiovascular alterations, such as hypotension or alterations in heart rhythm (four participants), paraesthesia and colic (one participant), and severe osteomuscular pain (five participants). Temporary suspension of treatment was required in the participants with severe side-effects.

Tertiary outcomes: Development of cell-mediated immunity

The average size of the Montenegro reaction increased slightly in the two groups (from 18.6 mm to 22.4 mm in the BCG group, and from 20.4 mm to 20.8 mm in the MA group), but the differences among the groups and within each group were not statistically significant. While these increases are not significant, they clearly suggest stimulation of the participants' immune system.

### **5.3 Oral pentoxifylline**

#### **Pentoxifylline combined with IV sodium stibogluconate versus IV sodium stibogluconate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

In a RCT (Machado 2007) from Brazil oral pentoxifylline combined with IVSSG was compared with IVSSG, both for 30 days. Four months after treatment, oral pentoxifylline had a significant synergistic effect with IVSSG 20 mg/Kg/day for 30 days (RR 1.66; 95% CI 1.03, 2.69 Analysis 36.1) in *L. braziliensis* infections.

Secondary outcomes: Adverse effects

Mild adverse effects were observed more frequently in the pentoxifylline combined with SSG group, including nausea (three participants); arthralgias (one); and dizziness, abdominal pain, and diarrhoea (one). In the SSG group, one participant complained of anorexia, nausea, and myalgias. No participants in either group discontinued treatment because of these adverse effects.

Tertiary outcomes: Speed of healing

The speed of healing was 83.36 days (Mean SD) and 145.99 days in the pentoxifylline combined with SSG and the SSG groups, respectively (the original paper reported that the time to cure was significantly shorter for participants treated with pentoxifylline plus SSG;  $P=0.049$ , by the Mann-Whitney U test).

#### 5.4 Topical imiquimod

##### **Imiquimod combined with IV/IM meglumine antimoniate versus IV/IM meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

In a RCT (Arévalo 2007) from Peru topical 7.5% imiquimod cream combined with IVMA was compared with IVMA, both for 20 days. Three months after treatment, there was no significant difference in cure rates between topical 7.5% imiquimod plus 20 mg/kg/d IVMA for 20 days and 20 mg/kg/d IVMA for 20 days (RR 1.67; 95% CI 0.88, 3.15 Analysis 37.1) in *L. braziliensis*, *L. amazonensis*, *L. mexicana*, *L. peruviana* infections.

A RCT (M-Verástegui 2005) from Peru compared topical 5% imiquimod cream combined with MA (IM in children and IV in older subjects) with MA (IM in children and IV in older subjects), both for 20 days. One year after treatment, there was no significant difference in cure rates between topical 5% imiquimod plus 20 mg/kg/d IMMA for 20 days and 20 mg/kg/d IMMA for 20 days (RR 0.87; 95% CI 0.58, 1.30 Analysis 38.1) in *L. peruviana* and *L. braziliensis* infections.

Secondary outcomes: Adverse effects

In one study (Arévalo 2007), among participants treated with imiquimod, 77% (10/13) reported mild adverse effects (localised itch, erythema and edema). In participants treated with MA, adverse effects were more severe as 86% (12/14) reported arthralgia, myalgia, and flu-like symptoms. Nine of the 14 participants treated with imiquimod had elevated liver enzyme levels, none of which resulted in the discontinuation of therapy. However, 1 participant voluntarily discontinued treatment with MA on day 15 of re-treatment because of flu-like symptoms, arthralgia, and myalgia. In the other study (M-Verástegui 2005), adverse events were not statistically significant with regard to edema (RR 0.88; 95% CI 0.39, 1.95 Analysis 38.2), itching (RR 0.67; 95% CI 0.12, 3.57 Analysis 38.2) and burning (RR 3.00; 95% CI 0.34, 26.45 Analysis 38.2), and/or local pain were reported with equal frequency by subjects treated with imiquimod and those treated with the placebo cream. Only mild erythema was more common

among subjects in the imiquimod group and was evident during most of the 20-day treatment period (RR 2.75; 95% CI 1.05, 7.20 Analysis 38.2).

##### **Imiquimod versus IV meglumine antimoniate**

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Arévalo 2007) from Peru compared topical 7.5% imiquimod cream with IVMA, both for 20 days. Three months after treatment, there was no significant statistical difference in cure rates between topical 7.5% imiquimod and 20 mg/kg/d IVMA for 20 days (RR 0.13; 95% CI 0.01, 1.97 Analysis 39.1).

Secondary outcomes: Adverse effects

Among participants treated with imiquimod, adverse effects are described above. In addition, one participant voluntarily discontinued treatment with MA on day 15 of retreatment because of flu-like symptoms, arthralgia, and myalgia.

#### 5.5 Topical or intralesional granulocyte macrophage colony-stimulating factor (GM-CSF)

##### **GM-CSF combined with IV meglumine antimoniate versus placebo**

In a RCT (Santos 2004) from Brazil topical GM-CSF (for a total of nine applications over three weeks) combined with IVMA was compared with IVMA, both for 20 days. Complete cure occurred in 91% (10/11) and 45.5% (5/11) of participants in the respective groups 40 days after treatment (short-term primary outcome, excluded from analysis).

Secondary outcomes: Adverse effects

No side effects were detected in participants of the GM-CSF combined with IVMA group.

Tertiary outcomes: Speed of healing

The speed of healing occurred in 43.14 (Mean SD) days in the GM-CSF combined with IVMA group and 104.79 days in the placebo group (the original paper reported that the time to cure was faster for participants treated with topical GM-CSF ( $P=0.043$ ) by the Mann-Whitney U test).

##### **GM-CSF combined with IV sodium stibogluconate versus IV sodium stibogluconate**

A RCT (Almeida 1999) from Brazil compared intralesional GM-CSF combined with IVSSG and IVSSG, both for 20 days. Complete cure occurred in 70% (7/10) and 10% (1/10) of participants in the respective groups 20 days after treatment (short-term primary outcome, excluded from analysis).

Tertiary outcomes: Speed of healing

The speed of healing reported was 49.32.8 (Mean SD) days in the GM-CSF group and 110.61.6 days in the placebo groups, respectively after beginning therapy (the original paper reported

that the time to cure was faster for participants treated with topical GM-CSF ( $P < 0.05$ ) by the Mann-Whitney U test).

## 5.6 Subcutaneous interferon-gamma (IFN- $\gamma$ )

### 10-day IV meglumine antimoniate combined with subcutaneous IFN- $\gamma$ versus 10-day and 20-day IV meglumine antimoniate

Primary outcome: Percentage of participants cured at least three months after the end of treatment.

A RCT (Arana 1994) from Guatemala compared IVMA for 20 days, IVMA for 10 days with IVMA for 10 days combined with 10 days of IFN- $\gamma$ . There was no significant difference in cure rates between 10-day adjuvant subcutaneous IFN- $\gamma$  to 10-day IVMA therapy (RR 1.22; 95% CI 0.99, 1.50 Analysis 40.1) or 20-day IVMA therapy (RR 1.15; 95% CI 0.96, 1.39 Analysis 40.2) either.

Secondary outcomes: Adverse effects

A total of 50% (11/22) participants receiving IFN- $\gamma$  complained of mild malaise, headache, fever, and/or chills.

### Results from the MEDLINE search for adverse effects

A MEDLINE search was made for adverse or side effects combined with therapeutic terms. However, we could only find general papers reporting known adverse effects derived from the evaluated drugs. These are summarised in the background under the "description of the intervention" section.

## DISCUSSION

### Summary of main results

The RCTs included in this review have assessed a broad range of treatments and many different clinical questions, however they resulted in limited opportunities to describe and pool useful data. We have some concerns regarding the precision of data reported in several studies. Furthermore, because the majority of RCTs had a high risk of bias, it was difficult to conclude whether one treatment was more beneficial than the comparator much of the time. Many interventions discarded as ineffective in an essentially inconclusive study, could still prove to have some benefit if they were evaluated in an adequately powered study. Nonetheless, this review accurately documents the existing RCT evidence on the usefulness of treatments and that relevant information can be extracted for practice and future research.

We found 38 RCTs that covered at least 16 different interventions, which could be broadly categorised into five main groups: antimonial drugs, non-antimonial systemic treatments, non-antimonial topical and intralesional treatments, physical therapies

and immuno-chemotherapy. The fact that sample size, a source of potential imprecision, may lead to bias, does not necessarily mean that small-sized studies cannot provide some useful information about drug efficacy.

Thirty two RCTs assessed the cutaneous form, four assessed the mucocutaneous form enrolling participants with symptoms that basically affected the lips, nose, palate-uvula-pharynx and larynx-epiglottis, and one RCT mixed both forms of leishmaniasis. These RCTs assessed a broad range of treatments and many different clinical questions.

Limited statistical pooling after data transformation was only possible for intramuscular meglumine antimoniate (IMMA) for 20 days versus placebo; for adjuvant oral allopurinol combined with intravenous antimonials for two weeks; and for immuno-chemotherapy with vaccine combined with IMMA.

### Evidence for antimonial therapy

IMMA did not show statistically significant higher cure rates than placebo in Colombia (*L. braziliensis* and *L. panamensis*) and Panama (*L. panamensis*). Intravenous meglumine antimoniate (IVMA) did not show statistically significant higher cure rates than no treatment in *L. panamensis* infections.

There were no significant differences in cure rates between:

- 10-day and 20-day IVMA in *L. braziliensis* and *L. mexicana* infections;
- 10-day and 20-day IMMA in *L. braziliensis* and *L. panamensis* infections;
- 28 day and 40 day of intravenous sodium stibogluconate (IVSSG) in *L. braziliensis* infections.

20-day IVMA had significantly higher cure rates than 7-day IVMA in *L. braziliensis* and *L. panamensis* infections.

There was no significant difference in cure rates between IVMA (14 mg /kg/day in two series of 20 days for the cutaneous form or three series of 30 days in the mucocutaneous form) and IVMA (28 mg /kg/day for ten days) in unreported species (Brazil).

In *L. panamensis* infections, there were no significant differences in cure rates between:

- intramuscular sodium stibogluconate (IMSSG) and IMMA;
- branded and generic IMSSG.

There was significant synergistic effect of:

- oral allopurinol in combination with IVMA for 15 days and with IVSSG for 15 days, but not for 28 days in *L. panamensis* and *L. braziliensis* infections
- oral pentoxifylline in combination with IVSSG for 30 days in *L. braziliensis* infections.

There was no significant synergistic effect of:

- 10-day subcutaneous IFN-gamma combined with 10-day or 20-day IVMA therapy in *L. braziliensis* and *L. mexicana* infections.

- topical 7.5% imiquimod combined with IVMA in *L. braziliensis*, *L. amazonensis*, *L. mexicana*, *L. peruviana* infections.
- topical 5% imiquimod combined with IMMA in *L. peruviana* and *L. braziliensis* infections.
- Paramomycin-MBCL combined with IVMA for 3 or 7 days in *L. braziliensis* and *L. panamensis* infections.

#### **Evidence for non-antimonial treatments**

Of the 38 studies assessed, only five RCTs (Arana 2001; Neva 1997; Soto 1994; Soto 2002; Soto 2004B) evaluated non-antimonial treatments in all study arms.

**Oral allopurinol** alone had significantly higher cure rates than no treatment and IVMA, but no significant differences were seen when it was combined with IVMA in *L. panamensis*. Conversely in another RCT, oral allopurinol showed lower cure rates compared with IMMA and there was no significant difference in cure rates when compared with placebo in *L. braziliensis* and *L. panamensis* infections.

There was no significant difference in cure rates between **oral ketoconazole** and IMMA but cure rates were significantly higher in the oral ketoconazole group compared with placebo, in *L. panamensis* and *L. mexicana* infections.

**Oral miltefosine** had significantly higher cure rates than placebo in the Colombian site but not in the Guatemalan site (*L. braziliensis*, *L. panamensis* and *L. mexicana*).

**Intramuscular aminosidine sulphate (IMAS)** 12 mg/kg/day for 7 days had significantly lower cure rates than 12 or 18 mg/kg/day of IMAS for 14 days.

There was no significant difference in cure rates between:

- 12 and 18 mg/kg/day of IMAS for 14 days in *L. panamensis*;
- 10 and 20 mg/kg/day of IMMA for 20 days in *L. braziliensis*.

**Intravenous pentamidine isethionate (IVPI)** (2 mg/kg on alternate days for 7 doses) showed significantly lower cure rates than IVMA in *L. braziliensis* but there was no significant difference between intramuscular pentamidine isethionate (IMPI) (4 mg/kg on alternate days for 8 doses) and 10 mg/kg/day IMMA for 20 days in *L. braziliensis*. There was no significant difference in cure rates between IMAS (20 mg/kg/day for 20 days) and IMPI (4 mg/kg on alternate days for 8 doses) and IMAS (14 mg/kg/day for 21 days) had significantly lower cure rates than IVMA for 28 days, in *L. braziliensis* infections.

**Topical paramomycin in MBCL** had significantly higher cure rates than placebo in *L. braziliensis* and *L. mexicana*.

**Topical 7.5% imiquimod** had significantly lower cure rates than IVMA in *L. braziliensis*, *L. amazonensis*, *L. mexicana*, and *L. peruviana*.

There was no significant difference in cure rates between **vaccine plus BCG** and IMMA in *L. braziliensis*.

**Intradermal *Bacillus Calmette Guerin* (BCG)** had significant lower cure rates than IMMA in *L. braziliensis*.

Although the rest of the studies did report cure, they were not statistically assessed because they were characterised by too short-term assessment of the primary outcome, or rather they did not report cure rates in our pre-specified time period for the primary outcome. Thus, there was insufficient RCT evidence to make recommendations on topical aminoglycosides, thermotherapy, vaccine combined with IMMA, and topical or intralesional granulocyte macrophage colony-stimulating factor (GM-CSF).

We found no disparities of response to pentavalent antimonial drugs amongst the studied species (*L. braziliensis*, *L. amazonensis*, and *L. guyanensis*). The other species did not respond differently either, but were not analysed specifically because of the small number of studies (*L. mexicana*, *L. chagasi*, *L. peruviana*, and *L. panamensis*). What's more, some of the included articles did not identify the species responsible for the illness, making a detailed review of the benefits of each therapeutic option difficult. Some other studies reported epidemiologic information without any identification of the species causing the disease, and this might be considered a methodological bias.

#### **Overall completeness and applicability of evidence**

Not all the trials provided information regarding the primary, secondary and tertiary outcome measures evaluated for this review. The timing of the primary outcome was variable. The main secondary outcome reported was the description of adverse events and recurrence. Several RCTs also reported other secondary outcomes but none reported the degree of functional and aesthetic impairment, prevention of scarring, or quality of life. The main tertiary outcome reported was speed of healing and "microbiological or histopathological cure of skin lesions" but none reported changes in ability to detect either *Leishmania* or mortality.

Whilst the majority of RCTs evaluated the cutaneous form, the evidence for the treatment of the mucocutaneous form of leishmaniasis is limited. Only five RCTs evaluated the clinical mucocutaneous form of leishmaniasis.

There was complete absence of RCT evidence on fluconazole, itraconazole, amphotericin B, promoting healing therapies, alternative therapy or surgery, photodynamic therapy, laser and cryotherapy treatments.

Amphotericin B is a second-line treatment which has been widely used in the lipid or deoxycholate formulations for those cutaneous leishmaniasis cases that have switched into the mucocutaneous form and are resistant to antimonial drugs. However, there are no RCTs in the literature that compare lipid-based drugs and deoxycholate formulations nor any evaluating amphotericin *versus* pentavalent antimonial drugs (Amato 2007). In fact, we found only one RCT (Rodriguez 1995) comparing systemic amphotericin B

and amphotericin B combined with itraconazole, although we excluded this trial because it did not report cure rates.

### Quality of the evidence

Adequate randomisation method was reported in 29% (11/38) of the studies. Only 13% (5/38) had an adequate reporting of allocation concealment. Double-blinding was found in 39.5% (15/38) of the studies. Overall, few participants withdrew or were lost to follow up. An inadequate description of baseline characteristics was found in one study. Calculation of sample size was performed in 16% (6/38) of the studies. The majority of trial authors stated that they had performed a compliance assessment but results were seldom shown in the assessed studies. In fact, only one study assessed compliance.

The causative parasite was not mentioned in 10.5% (4/38) of the studies. Sixteen per cent (6/38) of the trials mentioned the endemic nature of the parasite in the area and assumed that was the species causing the disease. Five per cent (2/38) RCTs accepted that the type of parasites were the same as that of previous studies, and 68% (26/38) confirmed the type of the causative organism.

We found only two trials (Neva 1997; Soto 2004A) of high quality that fulfilled randomisation, allocation concealment, blinding and ITT adequately. One of the two RCTs assessed interventions in *L. mexicana* and *L. chagasi* infections (Neva 1997) and the other one in *L. panamensis* infections (Soto 2004A). Thus, better evidence is needed for the different *Leishmania* species affecting American countries.

We found many mistakes in the write-up of published manuscripts and also the quality of reporting was poor. Thus, it is essential that submitted journal manuscripts undergo rigorous peer-review.

### Potential biases in the review process

The difficulties in determining the appropriate time point for cure in terms of significant clinical findings in the assessed studies, was due to an nonexistent universal measure of successful cure for American cutaneous and mucocutaneous leishmaniasis. The majority of the included RCTs measured cure rates beyond the three-month time frame we had pre-specified as our primary outcome. In fact, the time frame for the assessment of the primary outcome ranged from the end of treatment to 2 years after completion of treatment. RCTs are needed to explore long-term effects across a group of participants of defined disease severity and duration based on the maximum length of time after the event during which, if improvement occurs, you are prepared to attribute it to the intervention (Goodman 2007).

Some readers might think that our exclusion of non-randomised controlled studies was a bit harsh, especially for studies of antimonials where some reports show high cure rates. Selective reporting of dramatic effects from non-randomised trials without any

control group is likely to be very misleading. Although RCTs are widely accepted as the ideal way of obtaining unbiased estimates of treatment effects, we acknowledge that RCTs are sometimes not needed for treatments which have dramatic and persistent effects that are highly unlikely to reflect inadequately controlled biases (Glasziou 2007). In other words, the relation between a treatment and its effects is sometimes so dramatic that bias can be ruled out as an explanation without the need of performing RCTs.

Studies with more positive effects are more likely to be published than those with less conclusive results that normally remain unpublished because authors fail to write manuscripts and submit them to journals, or those written in languages other than English (Bygby 2003). Seemingly, the first study to be published on a particular intervention is more likely to show positive results. To tackle the problem of this publication bias we wrote to authors from endemic countries and the WHO asking for information. Besides, we searched databases of ongoing trials and others as well.

### Agreements and disagreements with other studies or reviews

Amato and co-workers (Amato 2007) and Tuon and his colleagues (Tuon 2008) performed non-Cochrane systematic reviews on the cutaneous and mucocutaneous forms of leishmaniasis in Latin America, respectively. Both reviews classified the studies as comparative, dose-finding and non-comparative and therefore not all the studies included were RCTs. The first review included 22 studies with a total of 635 participants. No meta-analyses were performed due to an insufficient number of controlled and randomised studies. The latter, included 54 articles with 2969 participants, but only 12 were included in the meta-analyses. Both reviews agreed with the fact that before determining the best treatment to manage the disease, several aspects such as cost, adverse effects, local experience and availability of the drugs must be considered in developing countries. However, they failed to emphasize the need for properly designed randomised clinical trials in an attempt to improve their quality and to provide better evidence. Our findings regarding the geographic distribution of the species and treatment effects are similar to those reported in the above mentioned non-Cochrane systematic reviews.

## AUTHORS' CONCLUSIONS

### Implications for practice

We have produced an updated coverage of randomised controlled trials of treatments for American cutaneous and mucocutaneous leishmaniasis by summarising the best available evidence using quantitative and qualitative methods. We have endeavoured to provide information to help clinicians choose the most appropriate

treatment. We have been careful not to be too prescriptive because the purpose of this systematic review is to present information, rather than offer advice. In addition, the lack of standardisation of the measurements used to judge success or failure of a treatment, as well as different regimens of the same tested drug, meant meta-analyses could not be carried out. This is important since our results and conclusions are based on individual studies or limited pooled analyses.

It seems that antimonials (sodium stibogluconate and meglumine antimoniate) administered intramuscularly showed similar efficacy in *L. panamensis* infections. Moreover, branded and generic intramuscular sodium stibogluconate were of equal efficacy. It also seems that a 10-day treatment is of as efficacious as a 20-day treatment of systemic meglumine antimoniate in *L. braziliensis*, *L. panamensis* and *L. mexicana* infections. Some of the alternative drugs showed synergistic effects with antimonials such as oral allopurinol and oral pentoxifylline in *L. braziliensis* infections. Others failed to show synergistic effects with antimonials such as subcutaneous IFN-gamma, topical imiquimod cream (5 or 7.5%) and topical paromomycin (15%) plus methylbenzethonium chloride (12%). Moreover, antimonials were more efficacious than intravenous pentamidine isethionate, intramuscular aminosidine sulphate, intradermal Bacillus Calmette-Guerin and topical 7.5% imiquimod cream alone. Oral allopurinol monotherapy has been compared with meglumine antimoniate and it seems that the way of administering the antimonial was important. In fact, oral allopurinol was more efficacious when meglumine was administered intravenously but less efficacious when it was administered intramuscularly. The efficacy of oral miltefosine seems to be species-dependent as it was more efficient in *L. panamensis* infections (from the Colombian site) than in *L. braziliensis* and *L. mexicana* infections (from the Guatemalan site).

Before starting treatment, people with cutaneous leishmaniasis infected with *L. mexicana*, need to be informed of the possibility of spontaneous healing and the lack of evidence for some treatments.

To summarise, antimonials seem to be a good treatment option despite their toxicity and prohibitive cost especially in developing countries. Generic sodium stibogluconate can be administered instead of the branded option, and this may reduce costs. Nonetheless, care must be exercised as the number of participants treated with the generic treatment was smaller than the number of participants treated with the branded treatment. Oral allopurinol and oral pentoxifylline seem to be effective as an adjuvant to antimonials, and miltefosine can be used depending on the species causing the infection.

## Implications for research

Few treatments for American cutaneous and mucocutaneous leishmaniasis have been well evaluated in randomised trials and we found no RCT with measurements of quality of life nor change

in ability to detect *Leishmania* by parasitological diagnostic methods (e.g. smear, PCR or culture), or mortality. Addressing these deficiencies by means of high quality clinical trials has to be a priority and one of the main conclusions from our review. There is a need for more evidence of the effectiveness and safety of different anti-*Leishmania* drugs compared with placebo in self-healing forms of leishmaniasis or with traditional first-line antimonials in the mucocutaneous form, as the base to recommend alternative safe, efficacious and affordable treatments. Authors also need to standardise the measurements used to judge success or failure of a treatment and so a guide should be offered by future panels of experts.

Clinical research on *L. braziliensis* and *L. panamensis* are the highest priority since both lead to the mucocutaneous form. However, the diagnostic tools for *Leishmania* identification are not always feasible or reliable, which delays the onset of treatment due to false negative results. Thus, there is a need to improve detection methods to avoid false negative results, speed up the identification of the parasite at a species level and the choice and start of treatment. As the WHO recommends use of antimonials as first line treatment despite their toxicity, future trials on antimony-alternative treatments need to be designed in such a way to guarantee to distinguish efficacy between treatments.

We found no or few RCT evidence for oral and local treatments that have been used in the Old World cutaneous leishmaniasis including antifungals, antibiotics and local treatments as photodynamic therapy, laser, cryotherapy treatments or alternative therapies. Besides, we have not found any RCT on methods used in promoting wound healing as a form of care that appears promising in cutaneous leishmaniasis. The paucity of evidence based on different types of wound healing management in American cutaneous and mucocutaneous leishmaniasis makes the plea for more research. It is recommended that The Burn Scar Index, often called the Vancouver Scar Scale (Baryza 1995) is used to assess cosmetic impact. These are widely used in clinical practice and research to document change in scar appearance. Ideally measurements are taken 6 months after cessation of treatment (Modabber 2007).

Cost and licensing entanglements (freedom to use in affected countries) need to be considered before spending money conducting new trials. It is important to consider that the choice of regimens depends not only on efficacy and safety (that can be tested in clinical trials) but also on cost-effectiveness in real life and other variables as indirect costs, real-life implementation studies and continuous monitoring of the effects.

The evidence base for the treatment of American cutaneous and mucocutaneous leishmaniasis has many limitations because it is characterised by poor quality of reporting and design. To encourage the execution of properly designed clinical trials specifically aimed at the development of effective therapies (both primary and adjuvant), we suggest that future trials should add the following

features:

- adequacy of generation of randomisation sequence, allocation concealment, calculation of sample size and ITT analysis provided
- confirmation of type of causative *Leishmania* species and the form (cutaneous or mucocutaneous)
- baseline characteristics should be clearly reported on a table describing age, gender, nationality, history of travel in an endemic area, duration of disease, number and morphology of lesions, sites and severity of lesions, previous treatment taken, and past history of disease scheme for outcome evaluation
- compliance assessment should be described and all information provided
- time to follow-up should be stated and outcomes should be described accordingly.
- all trials should be conducted with the same clinical and/or parasitological endpoint.
- detailed definition of inclusion and exclusion criteria: eligible participants should have the presence of lesions parasitologically confirmed as leishmaniasis by direct slit smears and/or skin-punch biopsies of the active, infiltrated edge of a representative lesion, and non-use of anti-*Leishmania* therapy during previous two months. Participants should be excluded if they have multiple or disseminated lesions, pregnancy or potential for pregnancy or breast feeding, chronic illness (particularly any affecting the kidney, liver, heart, lungs or haemopoietic system), an immunologically compromised con-

dition, hyperallergic reaction to the trial drugs, treatment with regular medications (such as antituberculous agents and steroids) which may affect specific therapy, treatment with anti-*Leishmania* drugs within the previous six months, and presence of scars of previously healed lesions.

The ideal schedule of administration is with a single dose (with the shortest regimen for improving compliance), systemic (oral) and self administered with no or minimal supervision. The route of administration can be topical or systemic but oral is preferred. Last but not least, it should be safe to use in women of childbearing age, co-morbid conditions and in immunocompromised participants with no drug interactions.

A more evidence-based strategic approach based on the findings of our systematic review may help to plan and prioritise global treatment recommendations and clinical research (Remme 2002a; Remme 2002b).

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Almeida 1999

Methods	FU: 180 days after treatment onset. D: Randomised clinical trial	
Participants	Brazil n=20 Px were recruited at an ambulatory clinic in an endemic region in Brazil. Px of both groups were similar in age, sex, and ulcer size and duration. The majority of the lesions were below the waist and on the lower limbs in 15 (75%) Px. In the GM-CSF group there were 8 males and 2 females whereas in the saline group there were equally divided (5 each). M/F: 13/7. Incl: Age between 10 and 50 years, presence of a single typical CL ulcer for < 60 days duration, and confirmation of CL by compatible histology and either a positive serology or positive intradermal skin test for <i>Leishmania</i> antigen. Excl: pregnancy, other associated acute or chronic illnesses, and history of allergy to GM-CSF and/or antimonial. <i>Leishmania</i> species: Previous studies have shown <i>L. braziliensis</i> to be aetiologic agent in this area.	
Interventions	T1:GM-CSF received 2 local injections of 200 µg of hr-GM-CSF at entry and 1 week later + IV SSG at 20 mg/kg/d for 20 days N= 10. MNL: 1. MSL: 18.8 mm. MDLBT: 36.10 days. T2: IVSSG (20 mg/kg daily for 20 days) + Saline (2 local injections of saline at entry and 1 week later N= 10. MNL:1. MSL: 17.9 mm. MDLBT: 25.80 days. Co-treatment: All Px received IVSSG at 20 mg/kg/d for 20 days.	
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" 20 days after therapy <i>Secondary outcomes</i> None reported <i>Tertiary outcomes</i> Speed of healing (time taken to be 'cured')	
Notes	Sample size: Small/NC	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Blinding? All outcomes	Yes	Double-blinded. The research team was blinded to the administered drug. Two medical doctors examined the Px and questions on possible side effects of the treatment were deferred to a third medical doctor.

Almeida 1999 (Continued)

Intention-to-treat/Drop-outs?	Yes	ND
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**Andersen 2005**

Methods	FU: 6 months D: Randomised clinical trials	
Participants	Peru n=80 Px lived in and around the city of Cusco, Peru and presented with clinical diagnosis of CL. The average Px was 30-year-old man weighing 57 kg. The average number of lesions was two (1/3 of which were on the arms and 1/2 of which were on the legs). M/F: 65/15. Incl: An age between 18 and 60 years old; a parasitological diagnosis of CL from a lesion; no evidence of mucosal involvement of oropharynx; no previous use of anti-leishmanial drugs; no previously confirmed leishmaniasis (by scar or clinically compatible history); no use of hypoglycaemic, nephrotoxic, or pancreatitis-inducing drugs; no acute or chronic medical condition; and not being pregnant or not nursing. <i>Leishmania species</i> : culture from 70 Px were typed by isoenzyme electrophoresis and all were <i>L. braziliensis</i> . They were also identified by stained smears.	
Interventions	T1: IVPI 2 mg/kg on alternate days for 7 doses. N= 40. MNL: 2.3. MDLBT: 119 days. T2: IVMA 20 mg (Sb)/kg/day for 20 days. N= 40. MNL: 2.1. MDLBT: 134 days.	
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" 6 months after therapy <i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within six months Adverse effects <i>Tertiary outcomes</i> Microbiological or histopathological cure of skin lesions	
Notes	Sample size: Medium/NC	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Blinding? All outcomes	No	Open
Intention-to-treat/Drop-outs?	Yes	6 out of 80 (7.5%)

**Arana 1994**

Methods	FUt: 52 weeks. D: Randomised clinical trials	
Participants	Guatemala n=66 They were all Guatemalan male soldiers. Incl: Guatemalan soldiers with parasitologically proven CL <i>Leishmania</i> species: <i>L. braziliensis</i> (33/66; 50%) and <i>L. mexicana</i> (8/66; 12.1%) by cultures.	
Interventions	T1: IVMA infusion over 15 minutes, 20 mg Sb/kg body weight/d for 20 days N= 22. MNL: 1.2. MSL: 1 cm2. MDLBT: 56.8 days. T2: IVMA infusion over 15 minutes, 20 mg Sb/kg body weight/d for 10 days + 10 days of a saline infusion N= 22. MNL: 1.2. MSL: 0.8 cm2. MDLBT: 64.1 days. T3: IVMA infusion over 15 minutes, 20 mg Sb/kg body weight/d for 10 days + IFN- $\gamma$ (1 ml solution containing 0.2 mg of recombinant IFN- $\gamma$ /ml given subcutaneously in the forearm every other day for 5 doses) N= 22. MNL: 1.4. MSL: 1.4 cm2. MDLBT: 78.4 days.	
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" one year after therapy <i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 1 year Adverse effects <i>Tertiary outcomes</i> None reported	
Notes	Px whose lesions were not completely reepithelialized by the 13-week examination were removed from the study and treated with additional MA. Sample size: Medium/NC	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Blinding? All outcomes	Yes	Double-blind: only stated but not reported who was blinded
Intention-to-treat/Drop-outs?	No	3 out of 66 (4.5%)

## Arana 2001

Methods	FU: 12 months. D: Randomised clinical trials	
Participants	<p>Guatemala n=76</p> <p>Px in the paromomycin group aged 22.3 years and in the placebo group, Px aged 20.3 years. Regarding ethnicity, 47.4% (18/38) of the participants in the paromomycin group were Indian while a 52.5% (20/38) were ladinos. In the placebo group, 42.1% (16/38) and 57.9% (22/38) were Indian and ladinos respectively. Lesions were mainly localized in the extremities (arms and legs) and thorax.</p> <p>Incl: Either male or female sex, aged 10-60 years, and parasitologically confirmed CL. Further, all Px had to provide written informed consent to participate in the study, and they had to be available for FU examinations for 12 months.</p> <p>Excl: &gt; 4 lesions or an active lesion measuring &gt; 5 cm in diameter; previous use of antimony-containing drugs; serious concomitant medical problems; and evidence of mucosal involvement of leishmaniasis.</p> <p><i>Leishmania</i> species: According to their own previous studies, most of the Px (75%) were infected with <i>L. braziliensis</i> and the rest (25%) with <i>L. mexicana</i>.</p>	
Interventions	<p>T1: Topical 15% PR plus 12% MBCL n= 38. MNL: 1.1, MDLBT: 101.2 days.</p> <p>T2: Topical placebo (white soft paraffin) ointment n=38. MNL: 1.3, MDLBT: 105.1 days.</p> <p>Frequency: TD for 20 days across the lesions in 2 different directions at 90° to each other</p>	
Outcomes	<p><i>Primary outcome</i> Percentage of Px “cured” one year after therapy</p> <p><i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 6 months Adverse effects <i>Tertiary outcomes</i> None reported</p>	
Notes	Sample size: Medium/NC	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	The PR ointment (15% PR sulphate plus 12% MBCL), and the placebo ointment tubes were prepared and randomly numbered by Teva Pharmaceutical Industries, Petach, Tikva, Israel, and provided to the investigators by Dr. F. Modabber (Tropical Diseases Research/World Health organisation [TDR/WHO]). Both active and placebo ointment were identical in appearance and marked only by a consecutive number. These codes were kept in

**Arana 2001** (Continued)

		Geneva by the TDR/WHO representative (FM) until completion of the study.
Blinding? All outcomes	Yes	Double-blind (Px and Physicians)
Intention-to-treat/Drop-outs?	No	8 out of 76 (10.5%)

**Armijos 2004**

Methods	FU: at week 52 after the start of treatment. D: Randomised clinical trial
Participants	Ecuador n=120 Px were recruited at the National Leishmaniasis Reference Laboratory clinic located in the Central University of Ecuador School of Medicine (Quito, Ecuador). The subjects reported that they had acquired their CL infections in tropical and subtropical areas of Pichincha, Napo and Sucumbios Provinces. Incl: If the <i>Leishmania</i> parasite was demonstrated to be present in their ulcerated lesions, lesion evolution time was at least 4 months prior to enrolment in the study, they had 1-3 CL lesions, their age was between 5 and 60 years, and they gave their informed written consent. Excl: If they were pregnant or lactating, had at least 3 lesions, lesions that were of a non-ulcerative form, showed evidence of mucocutaneous or disseminated leishmaniasis infection, had active tuberculosis or PPD hyperreactivity (>20 mm induration at 48 h), other serious infections (e.g., malaria, dengue, and fever), chronic illnesses or immunosuppression. had prior CL infection, were being treated with steroid or other immunosuppressant drugs, and had acute malnutrition. <i>Leishmania</i> species: not reported.
Interventions	T1: Topical PR 15% plus 12% MBCL ointment TD for 30 days. N= 40. MNL: 1.5. MSL: 259 mm <sup>2</sup> . MDLBT: 3 months. T2: Topical PR 15% plus 10% urea (PR- U) TD for 30 days. N= 40. MNL: 1.8. MSL: 308 mm <sup>2</sup> . MDLBT: 3.2 months. T3: IMMA 20 mg of Sb/kg/day for 10 days N= 40. MNL: 1.7. MSL: 418 mm <sup>2</sup> . MDLBT: 2.7 months.
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" 2 months after therapy <i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 1 year Adverse effects <i>Tertiary outcomes</i> Speed of healing (time taken to be 'cured')

**Armijos 2004** (Continued)

Notes	Sample size: Medium/NC	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Computer-generated random numbers table
Allocation concealment?	Yes	The codes marked on the preparations were kept secured in a locked file cabinet until data analysis
Blinding? All outcomes	Yes	Double-blinded. The 2 preparations were identical in appearance except for codes marked on the outside which were not known to clinicians, laboratory technologists, and other study personnel involved in selection, treatment and follow-up. Double-blind for the two groups treated with PR. It was not possible to blind the control group (MA) whose treatment was administered IM rather than topically
Intention-to-treat/Drop-outs?	No	25 out of 120 (20.83%)

**Arévalo 2007**

Methods	FU: 3 months. D: Randomised clinical trial
Participants	Peru n=20 This study was carried out at Cayetano Heredia Hospital in Lima, Peru. Px were from cities in Peru where CL is endemic. The clinical diagnosis of CL had been confirmed in all Px by direct smear, by culture, and/or by PCR prior to enrolment; 18 (90%) of 20 Px had positive direct smear and PCR results. 11 (55%) had positive Montenegro Skin test results. 9 (45%) had a culture positive for <i>Leishmania</i> . The mean age was 34.9 years (18-87). M/F: 11/9. The majority of Px were farmers. Lesions were nearly equally distributed in the face and upper and lower extremities. 17 of the 20 lesions were ulcerative and the remaining 3 were nodular. Incl: adult Px (>18 years of age) with a confirmed diagnosis of CL and who had newly referred to the outpatient <i>Leishmania</i> clinic were enrolled in the study after signing written informed consent. Excl: Px with mucosal involvement, other known diseases, immunodeficiency, lesions > 25 cm <sup>2</sup> in area, women who were breast-feeding or pregnant, and those with a history of previous treatment for leishmaniasis. <i>Leishmania</i> species: <i>L. braziliensis</i> , <i>L. peruviana</i> , <i>L. mexicana</i> , and <i>L. amazonensis</i> endemic in the area.

**Arévalo 2007** (Continued)

Interventions	<p>T1: Topical imiquimod 7.5% cream every other day for 20 days  n= 6. MNL: 1.1. MSL: 4.0 cm<sup>2</sup> (0.4-12.5). MDLBT: 4.2 months (1-6).  T2: Topical imiquimod 7.5 %cream every other day for 20 days plus IVMA 20 mg/kg/d over a 10-min period for 20 days  n= 7. MNL: 1.28. MSL: 8.1 cm<sup>2</sup> (0.9-33). MDLBT: 6.2 months (1.5-26).  T3: IVMA 20 mg/kg/d over a 10-min period for 20 days  n= 7. MNL: 1.1. MSL: 7.1 cm<sup>2</sup> (0.18-25.5). MDLBT: 5.07 months (1-12).</p>	
Outcomes	<p><i>Primary outcome</i>  Percentage of Px “cured” 3 months after therapy  <i>Secondary outcomes</i>  Adverse effects  <i>Tertiary outcomes</i>  None reported</p>	
Notes	<p>If bacterial superinfection of a lesion was observed, the Px was administered a regimen of daily cleansing and an oral antibiotic prior to the start of study medication. Only present in 2 Px (1 from the MA group and 1 from the imiquimod plus MA).  Sample size: Small/NC</p>	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors’ judgement</b>	<b>Description</b>
Blinding? All outcomes	Unclear	Not mentioned
Intention-to-treat/Drop-outs?	Yes	ND

**Balou 1987**

Methods	<p>FU: 12 months.  D: Randomised clinical trial</p>	
Participants	<p>USA  n=40  Conducted at the Walter Reed Army Medical Center in Washington. During the study period all active-duty military Px seen at army health care facilities with clinically suspected CL were referred to the centre for diagnosis and treatment. In the P10 group Px were 27.9 years of age and in the P20, 28.5. Lesions were located mainly in the extremities, head and neck and trunk. All were healthy young male soldiers on active duty when they acquired their infections in the Republic of Panama (38 Px) or elsewhere in Central America (2 Px).  Incl: Diagnosis established by culture of promastigotes from lesion aspirates or biopsy specimens (26 Px), by identification of amastigotes and granulomatous inflammation in biopsy material (26 Px,</p>	

**Balou 1987** (Continued)

	<p>including 13 with positive cultures), or by identification of granulomatous inflammation in biopsy material without demonstrable parasites but with a serum IFA titre &gt; 1:8 (1 Px);</p> <p>Excl: No evidence of underlying cardiac, hepatic, or renal diseases; no previous treatment with pentavalent antimonial drugs; at least 18 years of age; and informed consent to participation in the trial.</p> <p><i>Leishmania</i> species: 22 isolates of <i>L. panamensis</i> and 1 of <i>L. chagasi</i> by isoenzyme analysis.</p>	
Interventions	<p>T1: IVSSG 10 mg Sb/kg (P10) N= 21. MNL: 2.9. MSL: 22.8 mm. MDLBT: 10.8 weeks.</p> <p>T2: IVSSG 20 mg Sb/kg (P20) N= 19. MNL: 2.7. MSL: 22.1 mm. MDLBT: 9.7 weeks.</p> <p>Frequency: OD for 20 consecutive days</p>	
Outcomes	<p><i>Primary outcome</i> Percentage of Px "cured" 1.5 months after therapy</p> <p><i>Secondary outcomes</i> Adverse effects <i>Tertiary outcomes</i> None reported</p>	
Notes	Sample size: Small/C	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Blinding? All outcomes	Yes	Double-blind: only stated but not reported who was blinded
Intention-to-treat/Drop-outs?	Yes	ND

**Convit 1987**

Methods	<p>FU: 40 weeks of treatment. D: Randomised clinical trial</p>
Participants	<p>Venezuela n=102 In this study, 19/58 (32.76%) and 14/44 (31.8%) were females in the vaccine and IM MA groups respectively.</p> <p>Incl: Over 12 years of age, localised clinical trial form of leishmaniasis &lt; 1 year in evolution, written agreement to participate in the trial, and no contraindication to either chemotherapy or immunotherapy.</p> <p><i>Leishmania</i> species: <i>L. braziliensis</i> by use of monoclonal and polyclonal antibodies, and restriction fragment polymorphisms of kinetoplast DNA.</p>

**Convit 1987** (Continued)

Interventions	<p>T1: IMMA 50 mg/kg in series of 20 daily injections, with a maximum of three and a minimum of two series, and with 15 days between series N= 44.</p> <p>T2: Vaccine group: Promastigotes of the strain <i>L. mexicana amazonensis</i> (6.4 x 10E8) in 0.4 ml of PBS per dose, were heat-killed by autoclaving + viable bacille Calmette Guerin (BCG). The amount used in the first dose depended on the response to a previous tuberculin skin test, read at 48 h. The mixture was prepared immediately before use and the vaccine was injected intradermally, half in each deltoid region (0.25 ml in each of two sites). A second dose was given 6-8 weeks after the first and, in a proportion of participants, a third dose 12-18 weeks after the second. N=58</p>	
Outcomes	<p><i>Primary outcome</i> Percentage of Px "cured" 6 months after therapy</p> <p><i>Secondary outcomes</i> Adverse effects</p> <p><i>Tertiary outcomes</i> Speed of healing Development of cell-mediated immunity (i.e. positive leishmanin skin test)</p>	
Notes	Sample size: Medium/C	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Blinding? All outcomes	Yes	Single-blind. Groups were classified as cured or not, by an experienced dermatologist who did not know to which group they belonged. For this examination the Px were asked to keep their deltoid regions covered and not to mention the kind of treatment they were receiving; health workers were trained to assist in this blinding.
Intention-to-treat/Drop-outs?	No	8 out of 102 (7.8%)

**Convit 1989**

Methods	<p>FU: 24-month period. D: Randomised clinical trial</p>	
Participants	<p>Venezuela n=217 Px with localized CL from a single endemic focus in Miranda State, Venezuela. Incl: Over 12 years of age, localised clinical trial form of leishmaniasis &lt; 1 year in evolution, written agreement to participate in the trial, and no contraindication to either chemotherapy or immunotherapy.</p>	

**Convit 1989** (Continued)

	<p>Excl: Pregnant women and Px suffering from malnutrition or other diseases affecting the general state of health.</p> <p><i>Leishmania</i> species: All isolates of parasites from these Px were identified as <i>L. braziliensis</i> using monoclonal antibodies, enriched polyclonal sera, and kinetoplast DNA hybridisation studies using restriction enzymes and specific DNA probes</p>	
Interventions	<p>T1: Combined vaccine was carried out by the intradermal injection of a mixture of <math>6.4 \times 10^8</math> heat-killed promastigotes of <i>L. mexicana amazonensis</i> and variable amounts of BCG in a volume of 0.5 ml. The mixture was injected intradermally in two sites in the deltoid regions; 3 doses were applied at 6 to 8-week intervals N= 124. MSL: 21.6 mm.</p> <p>T2: IMMA, 50 mg/kg/day in series of 20 daily injections, with a maximum dose of 3 g/d and with intervals of 15 d between successive series. 2 or 3 series were administered unless otherwise stated N= 51. MSL: 20.4 mm.</p> <p>T3: BCG alone (in a volume of 0.5 ml) intradermally in 2 sites in the deltoid regions, 3 doses at 6 to 8 weeks intervals. N= 42. MSL: 18.6 mm.</p>	
Outcomes	<p><i>Primary outcome</i> Percentage of Px "cured" 6 months after therapy</p> <p><i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 3 months to 2.5 years Adverse effects</p> <p><i>Tertiary outcomes</i> Speed of healing Development of cell-mediated immunity (i.e. positive leishmanin skin test)</p>	
Notes	<p>0.2 mg of BCG was used if the reaction to PPD (purified protein derivative of tuberculin) was &lt;10 mm in diameter. 0.02 mg was used in Px with reactions of 10-20 mm. 0.01 mg if reaction was &gt;20 mm. In successive doses, 0.01 mg of BCG was used in all Px. Sample size: Large/C</p>	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Px were given serial numbers and were assigned randomly to one of the three study groups
Blinding? All outcomes	Yes	Single-blind. Outcome assessor blinded.

**Convit 1989** (Continued)

Intention-to-treat/Drop-outs?	Yes	ND
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**Correia 1996**

Methods	FU: 1 year. D: Randomised clinical trial
Participants	Brazil (Corte de Pedra -Bahia) n=46 Px were recruited in a Health Center of Corte de Pedra, Bahia, an endemic area of American tegumentary leishmaniasis (ATL). Age ranged from 12 to 56 years, male sex occurred in 65% (30/46) and females 34.8% (16/46) of the enrolled Px, and most of them worked as farmers 72% (33/46). 78% (36/46) of Px had 1 lesion and 22% (10/46) had 2 lesions. Incl: Primary cutaneous lesions compatibles with ATL, aged between 12 and 60 years, maximum number of 5 ulcers and duration of the disease < 6 months. <i>Leishmania</i> species: <i>L. braziliensis</i> by means of monoclonal antibodies and isoenzymes.
Interventions	T1: IMPI 4 mg/kg/every 2 days, for 8 applications N=15. MNL: 1.2. MDLBT: 40.5 days. T2: IMAS 20 mg/kg/day for 20 days N=15. MNL: 1.33. MDLBT: 35.1 days. T3: IMMA 10 mg/kg/day for 20 days N= 16. MNL: 1.13. MDLBT: 63.8 days.
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" one year after therapy <i>Secondary outcomes</i> Adverse effects <i>Tertiary outcomes</i> None reported
Notes	Sample size: Small/NC

**Risk of bias**

Item	Authors' judgement	Description
Blinding? All outcomes	No	Open
Intention-to-treat/Drop-outs?	Yes	ND

**D'Oliveira 1997**

Methods	FU: 12 months. D: Randomised clinical trial
Participants	El Salvador (Corte de Pedra) n=34 Aged 12 to 45 years. Incl: With leishmania-positive skin test and a maximum of 3 ulcerated lesions (with a minimum lesion diameter of 10 mm and a maximum of 50 mm) who had received no previous treatment. Excl: chronic disease, use of other drugs, history of allergy to allopurinol, pregnancy, breast feeding, or forms of leishmaniasis other than cutaneous. <i>Leishmania</i> species: <i>L. braziliensis</i> by culture and histologic assessment.
Interventions	T1: Oral AL 20 mg/kg 3 times a day for 20 days. N= 18. MNL: 15 Px had 1, 2 had 2 and 1 had 3 lesions. MDLBT: 38 days. T2: IVMA 10 mg/kg OD for 20 days. N= 16. MNL: 10 Px had 1, 5 had 2 and 1 had 3 lesions. MDLBT: 31.9 days.
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" two months (70 days) after therapy <i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 3 months <i>Tertiary outcomes</i> None reported
Notes	The other 9 Px of the AL group were not included in the evaluation because the protocol was broken and MA was administered before 90 days of treatment. Sample size: Small/NC

***Risk of bias***

Item	Authors' judgement	Description
Blinding? All outcomes	No	Open
Intention-to-treat/Drop-outs?	Yes	ND

**Figueiredo 1999**

Methods	FU: 2 years. D: Randomised clinical trial
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**Figueiredo 1999** (Continued)

Participants	<p>Brazil n=43 Px recruited developed CL (26) or mucocutaneous leishmaniasis (17). All cutaneous treatments were performed in health centres of SUCAM, in Caratinga (MC), which is located in the Valley of Rio Doce, and Px were residents in areas situated at 100 km from the city. All mucocutaneous treatments were performed in a hospital (Santa Casa de Misericordia) situated in the city of Belo Horizonte or in the hospital das Clinicas of UFMG, and these Px were mainly residents in regions of the state of Minas Gerais and 3 of other states. All Px diagnosed with CL had ulcerative lesions, and Px diagnosed with MCL had infiltrative or ulcerative lesions located in the nasal mucosae or orofarigean mucosae. Incl: Px were aged between 15 and 60 years, with no history of previous treatment, with no abnormalities in organ functions, negative reaction of Machado-Guerreiro skin test, with cutaneous lesions clinically diagnosed by direct examination, and Px with muco-cutaneous leishmaniasis clinically diagnosed by biopsy, epidemiology, positive Montenegro's Skin test or RIFI and by histopathology. Excl: Pregnancy, history of previous specific treatment, evidence of underlying cardiac, hepatic, or renal diseases, alterations in laboratory data, pregnancy, mucocutaneous lesions, and taking immunosuppressive drugs. <i>Leishmania</i> species: not reported.</p>	
Interventions	<p>T1: IVMA (14 mg/kg/day) alternated with placebo N= 24 (10 having mucocutaneous leishmaniasis and 14 CL). T2: IVMA (28 mg/kg/day) for 10 days and the other 10 days with placebo N= 19 (7 having mucocutaneous leishmaniasis and 12 CL). Frequency: in 2 series of 20 days, separated with intervals of 15 days for the CL, and 3 series of 30 days each, separated with intervals of 15 days in the mucocutaneous form</p>	
Outcomes	<p><i>Primary outcome</i> Percentage of Px "cured" two years after therapy <i>Secondary and tertiary outcomes</i> None reported</p>	
Notes	<p>Sample size: Small/NC</p>	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Blinding? All outcomes	Yes	Double-blind (Px and physicians). Tubes provided by Rodhia were identical in appearance
Intention-to-treat/Drop-outs?	No	4 out of 43 (9.3%)

**Franke 1994**

Methods	FU: 12 months. D: Randomised clinical trial	
Participants	Peru n=40 Px were from the villages of Ocongata ad Sicuani in the Department of Cusco, Peru. Men acquired their disease through occupational exposure in the jungles of the Department of Madre de Dios. All Px were male. <i>Leishmania</i> was found in the lips, nose (septum, turbinates), palate-uvula-pharynx, and larynx-epiglottis and was classified as ulcerated, infiltrated, edematous, or erythematous. Incl: If cultures prepared by inoculating aspirates from mucocutaneous lesions into Senekji's blood agar medium were positive for <i>Leishmania</i> . Excl: If they had received antimonials for treatment of leishmaniasis in the previous 12 months, had significant concomitant disease of any organ, or had abnormalities on subsequent baseline tests. <i>Leishmania</i> species: All cultured 35 strains were <i>L. braziliensis</i> by isoenzyme analysis.	
Interventions	T1: IVSSG 20 mg Sb/Kg/d for 28 days N= 20. MDLBT: 7.4 years (cutaneous) or 2.9 (mucocutaneous). T2: IVSSG 20 mg Sb/Kg/d for 40 days N= 20. MDLBT: 8.7 years (cutaneous) or 2.9 (mucocutaneous). Frequency: (the daily dose was administered in 50 ml of 5% dextrose in water by intravenous infusion over a 30-45 min period) with no upper limit on the daily dose	
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" one year after therapy <i>Secondary outcomes</i> Adverse effects <i>Tertiary outcomes</i> None reported	
Notes	Sample size: Small/NC	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Blinding? All outcomes	Unclear	Not mentioned
Intention-to-treat/Drop-outs?	No	5 out of 40 (12.5%)

**Guderian 1991**

Methods	FU: 12 months. D: Randomised clinical trial
Participants	Ecuador n=75 29/61 Px were male. The mean age of all Px was 29 years. The mean ages of Px groups were: AL (25 years), SSG (29 years), and untreated (36 years). Incl: Ecuadorians with cutaneous lesions clinically diagnosed as leishmaniasis and who signed informed consent. Excl: If they had facial or mucocutaneous lesions, significant concomitant disease of any organ, or abnormalities on subsequent baseline laboratory tests. <i>Leishmania</i> species: culture from 23 Px were typed and 12 were <i>L. panamensis</i> , (5) <i>L. guyanensis</i> , (3) <i>L. braziliensis</i> and (3) <i>L. mexicana</i> by monoclonal antibody staining, haematoxylin and eosin staining or Giemsa staining.
Interventions	T1: Oral AL ribonucleoside (1.500 mg QID) plus probenecid (500 mg QID) for 28 days N= 30. MNL: 30. MSL: 4.4 cm <sup>2</sup> . MDLBT: 3.5 months. T2: IMSSG (20 mg Sb/Kg/day) with no upper limit on daily dose, for 20 days N= 30. MNL: 46. MSL: 3.8 cm <sup>2</sup> . MDLBT: 3.9 months. T3: Untreated controls (the end of therapy was defined as 20 days after entering into the study) N= 15. MNL: 16. MSL: 1.2 cm <sup>2</sup> . MDLBT: 3.2 months.
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" 1.5 months after therapy <i>Secondary and Tertiary outcomes</i> None reported
Notes	In the AL and the untreated group, the Px that failed to heal, were successfully treated with SSG. Sample size: Medium/NC

**Risk of bias**

Item	Authors' judgement	Description
Blinding? All outcomes	Unclear	Not mentioned
Intention-to-treat/Drop-outs?	No	14 out of 75 (18.67%)

**Hepburn 1994**

Methods	FU: for at least 6 months (mean follow-up period 11.4 months). D: Randomised clinical trial
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**Hepburn 1994** (Continued)

Participants	<p>Edinburgh n= 34</p> <p>It was carried out at the army medical facility in Edinburgh, UK. All Px were British soldiers who had contracted CL in Belize. Lesions were located mainly on the limbs.</p> <p>Incl: All Px were British soldiers who had contracted CL in Belize and who had not received any anti-leishmanial therapy for at least 3 months.</p> <p><i>Leishmania</i> species: In the AS group 53% (9/17) were infected with <i>L. braziliensis</i> and 18% (3/17) with <i>L. mexicana</i>. In the SSG group, 41% (7/17) were infected with <i>L. braziliensis</i> and 18% (3/17) with <i>L. mexicana</i> via culture or histologically. The rest of Px their culture was negative.</p>	
Interventions	<p>T1: IVAS 14 mg/kg/day (max 1g daily) N=17. MNL: 1.58 (1-5). MSL: 18.6 mm. MDLBT: 15.7 weeks.</p> <p>T2: IVSSG 20 mg/kg/day N= 17. MNL: 1.76 (1-3). MSL: 11.8 mm. MDLBT: 10.9 weeks.</p> <p>Frequency: for 20 days</p>	
Outcomes	<p><i>Primary outcome</i> Percentage of Px "cured" 1.5 months after therapy</p> <p><i>Secondary outcomes</i> Adverse effects</p> <p><i>Tertiary outcomes</i> None reported</p>	
Notes	Sample size: Small/NC	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Blinding? All outcomes	No	Open
Intention-to-treat/Drop-outs?	Yes	ND

**LLanos-Cuentas 1997**

Methods	<p>FU: 12 months. D: Randomised clinical trial</p>	
Participants	<p>Peru n= 81</p> <p>Px were recruited from two Px associations and 2 medical centres in Cusco, Peru. The study was divided into 2 phases because the rate of cure of MCL varies with the severity of the disease. Px in phase I had severe lesions and Px in the phase II study had moderate disease. Px were admitted</p>	

LLanos-Cuentas 1997 (Continued)

	<p>to the Hospital Regional del Cusco during the administration therapy. They were all males with a mean age around 34 years.</p> <p>Incl: Px with severe or moderate MCL who were 15 to 60 years were eligible for study enrolment if they had a documented history of MCL with proven presence of parasites by culture and/or PCR analysis and gave written informed consent.</p> <p>Excl: Clinically similar diseases, serious concomitant diseases, pregnancy, known or suspected allergy to Sb5+ or AL, and use of Sb5+, AL, amphotericin B, or ketoconazole in the last 6 months before the study.</p> <p><i>Leishmania</i> species: not reported.</p>	
Interventions	<p>T1: IVSSG (20 mg of Sb 5+/kg/d) plus oral AL (20 mg/kg/d in 4 divided doses) N= 40 (n=11 in phase I and n=29 in phase II). MNL: 2.8 in the phase I and 2.5 in phase II. MDLBT: 71.9 months in phase I and 75.9 in phase II.</p> <p>T2: IVSSG (20 mg of Sb 5+/kg/d) N= 41 (n=11 in phase I and n=30 in phase II). MNL: 2.1 in the phase I and 2.4 in phase II. MDLBT: 105.1 months in phase I and 79.9 in phase II. Frequency: for 28 days</p>	
Outcomes	<p><i>Primary outcome</i> Percentage of Px "cured" one year after therapy</p> <p><i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 1 year Adverse effects</p> <p><i>Tertiary outcomes</i> None reported</p>	
Notes	Sample size: Medium/C	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	According to a permuted-blocks scheme with a block size of 10 Px
Blinding? All outcomes	No	Open
Intention-to-treat/Drop-outs?	No	11 out of 81 (13.6%)

## Llanos-Cuentas 2007

Methods	FU: 1 year. D: Randomised clinical trial	
Participants	<p>Peru n= 38</p> <p>All Px were men and the study was conducted in the city of Cuzco, Peru. The mean age of Px was 32.6 years in the AS group and 33.2 years in the MA group. More Px with severe laryngeal and vocal cord involvement were enrolled in the aminosidine group, but the difference did not reach statistical significance.</p> <p>Incl: Adults between 18 and 60 years of age with moderate MCL, defined as involvement of the nasal and pharyngeal mucosa with or without laryngeal affection but without respiratory distress and with proven presence of parasites by culture, histology, and/or PCR on a biopsy specimen.</p> <p>Excl: Px who had received treatment in the previous 6 months with antileishmanial agents or who had failed to a course of treatment with amphotericin B, Px with known or suspected allergy to aminoglycosides or antimonials, pregnant or nursing women, and Px not willing to return for FU evaluations. Also Px with severe concurrent illnesses such as tuberculosis, renal, liver, or heart disease, or alcoholism.</p> <p><i>Leishmania</i> species: not reported, but they stated that MCL caused by <i>L. braziliensis</i> is a significant health problem in rural areas of Central and South America.</p>	
Interventions	<p>T1: IMAS 14 mg/kg body weight OD for 21 days n= 21.</p> <p>T2: IVMA 20 mg/kg body weight in 250 ml 5% dextrose in water infused over a 20-minute period OD for 28 days n= 17.</p>	
Outcomes	<p><i>Primary outcome</i> Percentage of Px "cured" one year after therapy</p> <p><i>Secondary outcomes</i> Adverse effects</p> <p><i>Tertiary outcomes</i> None reported</p>	
Notes	Sample size: Small/C	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Computer-generated random table in a 1:1 ratio
Blinding? All outcomes	No	Open
Intention-to-treat/Drop-outs?	Yes	ND

**Lobo 2006**

Methods	FU: 28 days after onset of treatment. D: Randomised clinical trial	
Participants	<p>Brazil n= 37</p> <p>The same physician in a health care clinic in Laje attended Px from Laje and neighbourhood towns in the Jirquiriça Valley, in the southwest of Bahia State, Brazil. Age ranged from 18-67 years but mean age was around 35 years.</p> <p>Incl: Px had to be at least 18 years old, have no more than 2 cutaneous lesions and none larger than 10 cm. They had to have no signs and/or symptoms of mucous leishmanial involvement and no previous history of leishmaniasis or specific leishmanial treatment. Px had to be willing to return for clinical and laboratory evaluation 14 and 28 d after initiating treatment and continue for clinical FU.</p> <p>Excl: Pregnant participants, those who had contraindications for MA treatment, such as severe renal or cardiovascular disease.</p> <p><i>Leishmania</i> species: <i>L. braziliensis</i> endemic in the area.</p>	
Interventions	<p>T1: Heat therapy given in a single session. The Thermosurgery instrument placed at the edge of the lesion pointing toward the centre and heat at 50°C was applied for 30 s, then the applicator was moved to an adjacent area until the lesion had been completely covered, taking 4-5 min. N= 17. Total number of lesions: 16/17 (94%) had 1 lesion. MSL: 23 mm. MDLBT: 45 days (15-180).</p> <p>T2: IVMA 20 mg/kg/d for 20 consecutive days N=20. Total number of lesions: 13/20 (65%) had 1 lesion. MSL: 23 mm. MDLBT: 50 days (20-240).</p> <p>Co-treatment: T2 after day 28 to all Px in the heat therapy group.</p>	
Outcomes	<p>Primary outcome Percentage of Px “cured” at the end of therapy</p> <p>Secondary outcomes Adverse effects Tertiary outcomes None reported</p>	
Notes	Sample size: Small/NC	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors’ judgement</b>	<b>Description</b>
Blinding? All outcomes	No	
Intention-to-treat/Drop-outs?	No	1 out of 37 (2.7%)

**M-Verástegui 2005**

Methods	FU: 12 months. D: Randomised clinical trial	
Participants	<p>Peru n=40</p> <p>Px with CL were identified in rural health centres in regions of the Peruvian Andes (1500-2500 m above sea level) and the Peruvian jungle where CL is endemic, including the provinces of Churin, Barranca, Yauyos, Satipo, Chachapoyas, Cusco, and Madre de Dios. Subjects were referred for evaluation and treatment at the Instituto de Medicina Tropical Alexander von Humbolt, Unversidad Peruana Cayetano Heredia, in Lima. A total of 75 lesions were evaluated: 35 lesions in the imiquimod group and 40 in the placebo group. The median lesion size was 0.5 cm<sup>2</sup> for both groups, and lesions duration was 8.8 months for the imiquimod group <i>versus</i> 5.2 months for the placebo group. M/F: 17/13.</p> <p>Incl: Each Px must have had parasitologically confirmed CL and a history of &gt; or 1 failed course of treatment with MA.</p> <p>Excl: Mucosal involvement, pregnancy, breast-feeding, &gt; or 1 lesion with the area &gt; 25 cm<sup>2</sup>, a history of liver or renal disease, allergy to antimony or imiquimod, or the presence of another significant medical condition (e.g., liver failure, renal failure, AIDS, or tuberculosis).</p> <p><i>Leishmania</i> species: They considered that Px from the Andean valley regions were infected with <i>L. peruviana</i> and Px from the lower Amazonian jungle regions were infected with <i>L. braziliensis</i>.</p>	
Interventions	<p>T1: Topical imiquimod cream 5% applied to each lesion every other day for 20 days + IMMA in children or by slow IV (&gt;15 min) in older subjects for 20 days N= 20. MNL: 1.75. MSL: 1.3 cm<sup>2</sup>. MDLBT: 13.4 months.</p> <p>T2: Topical placebo cream applied to each lesion every other day for 20 days + IMMA same as in T1 N= 20. MNL: 2. MSL: 2.3 cm<sup>2</sup>. MDLBT: 11.4 months.</p>	
Outcomes	<p><i>Primary outcome</i> Percentage of Px "cured" one year after therapy</p> <p><i>Secondary outcomes</i> Adverse effects</p> <p><i>Tertiary outcomes</i> None reported</p>	
Notes	Sample size: Small/NC	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Blinding? All outcomes	Unclear	Double-blind (Px and physicians). Each numbered treatment package had 10 sachets that were identical in appearance and contained either imiquimod or vehicle cream
Intention-to-treat/Drop-outs?	No	2 out of 40 (5%)

**Machado 2007**

Methods	FU: 2 years. D: Randomised clinical trial
Participants	Brazil n=23 Px were living in Corte de Pedra, an endemic area of <i>L. braziliensis</i> . There were M/F: 19/4. Incl: Px who were eligible for enrolment after providing informed consent were aged 18-65 years and had severe mucocutaneous leishmaniasis (defined as the presence of deep mucosal ulcers and/or septal infiltration or perforation). Excl: Px who had superficial mucosal ulcers, prior therapy for mucocutaneous disease, diabetes, or coinfection with HIV, or who were unavailable to FU. <i>Leishmania</i> species: Corte de Pedra is an area of endemicity of <i>L. braziliensis</i> transmission.
Interventions	T1: Oral pentoxifylline 400 mg three times daily for 30 days plus IV SSG 20 mg/kg/d N= 11. MSL: 352 mm <sup>2</sup> . MDLBT: 6 months (0.5-120). T2: Oral placebo orally 3 times daily for 30 days plus IVSSG 20 mg/kg/d N= 12. MSL: 451 mm <sup>2</sup> . MDLBT: 12 months (2-240).
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" 4 months after therapy <i>Secondary outcomes</i> Adverse effects <i>Tertiary outcomes</i> Speed of healing (time taken to be 'cured')
Notes	Sample size: Small/NC

***Risk of bias***

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation table
Blinding? All outcomes	Yes	Double-blind (Both the otolaryngologist and Px were blinded to treatment assignment during all the steps of the study)
Intention-to-treat/Drop-outs?	Yes	ND

**Machado-Pinto 2002**

Methods	FU: 12 months D: Randomised clinical trial
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Machado-Pinto 2002 (Continued)

Participants	<p>Brazil n= 102</p> <p>All Px lived in a highly endemic area for ACL in the state of Minas Gerais, Brazil. Baseline characteristics do not include the Px that dropped-out, however: in the vaccine group the median age was 16 years (5-65), mean weight was 47.5 Kg and 53.2% were males. In the MA (control) group the median age was 29 years (7-82), mean weight was 60.3 Kg and 65.3% were males.</p> <p>There was a significant difference between the two groups with regard to age (medians were 16 and 29 years for the vaccine and MA groups respectively). Nonetheless, in multivariate analysis, age had no influence on the outcome.</p> <p>Incl: An age of 5 years, a parasitologically confirmed diagnosis of CL, and an informed consent form signed by the Px or the parents/guardians of those under 16 years of age.</p> <p><i>Leishmania</i> species: <i>L. braziliensis</i> endemic in the area.</p>	
Interventions	<p>T1: Subcutaneous injection of <i>L. amazonensis</i> strain (IFLA/BR/1967/PH8) vaccine (0.5 ml) daily plus IMMA (8.5 mg/kg) for 10 days followed by 10 days of rest. N= 51. MNL: 1 (1-8). MSL: 34.2 mm (25.8). MDLBT: 60 days.</p> <p>T2: Subcutaneous injection of Placebo (0.5 ml) daily plus IMMA (8.5 mg/kg) for 10 days followed by 10 days of rest. N= 51. MNL: 1 (1-7). MSL: 34.5 mm (25.6). MDLBT: 60 days.</p>	
Outcomes	<p><i>Primary outcome</i> Percentage of Px "cured" at the end of therapy</p> <p><i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 1 year Adverse effects</p> <p><i>Tertiary outcomes</i> Speed of healing (time taken to be 'cured')</p>	
Notes	Sample size: Medium/NC	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Blinding? All outcomes	Yes	Double-blind: only stated but not reported who was blinded
Intention-to-treat/Drop-outs?	No	6 out of 102 (6%)

**Martínez 1992**

Methods	FU: 12 months. D: Randomised clinical trial (Px in the AL alone group and in the no treatment group were not randomised but self-selected)	
Participants	Colombia (village called Lopez de Micay on the souther pacific coast and an endemic area of <i>L. panamensis</i> ) n=110 Except for 2 girls aged 8 and 10, the Px were male, ranging age from 11 to 40. Most of the Px had 1-3 lesions and only 3 had > 4. Incl: Px who had the disease proved by examination of a smear, culture, or biopsy; who had received no previous therapy and if their lesions were confined to the upper portion of the trunk or the arms. To be enrolled Px had to have a body weight within 20% of the ideal body weight for their height. Excl: If they or their parents did not give written informed consent; if they had a known or suspected allergy to antimony or AL; if they were pregnant or nursing; if they had serious concomitant diseases or any disease other than leishmaniasis requiring treatment; or if they had pre-existing skin rash or another disease of the skin. <i>Leishmania</i> species: <i>L. panamensis</i> by smear or biopsy.	
Interventions	T1: Oral AL 20 mg/kg/day in 4 divided doses for 15 days. N= 25 T2: IVMA 20 mg/kg/day for 15 days. N= 33. T3: AL+ MA same dosage. N= 35. T4: No treatment N= 17.	
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" one year after therapy <i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 1 year <i>Tertiary outcomes</i> None reported	
Notes	Sample size: Medium/NC	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	A master randomisation list was generated by a computer
Blinding? All outcomes	No	Open

**Martínez 1992** (Continued)

Intention-to-treat/Drop-outs?	Yes	ND
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**Martínez 1997**

Methods	FU: 12 months. D: Randomised clinical trial
Participants	Colombia n=100 M/F: 86/14. Their aged ranged from 18 to 57 years. All Px were from the southern Pacific coast of Colombia. Approximately 1/2 (47%) of the Px were farmers, 35% were soldiers, and the remaining 18% had diverse occupations. 2/3 (68/100) were black; 1/4 (24/100) were white; and the remaining 9% (87/100) were of native origin. Incl: Evidence of <i>Leishmania</i> in a smear, a biopsy specimen, or a culture was required. To be enrolled Px had to have a body weight within 20% of the ideal body weight for their height. Excl: If they did not give written informed consent; if they had a known or suspected allergy to antimony or AL; if they were pregnant or nursing; if they had serious concomitant diseases or any disease other than leishmaniasis requiring treatment; or if they had pre-existing skin rash or another disease of the skin. <i>Leishmania</i> species: <i>L. braziliensis</i> by smear or culture.
Interventions	T1: Oral AL 20 mg/kg/day in 4 divided doses for 15 days+ IVSSG 20 mg/kg/day for 15 days. N= 51. MDLBT: < 3 months. T2: IVSSG 20 mg/kg/day for 15 days. N= 49. MDLBT: < 3 months.
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" one year after therapy <i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 1 year Adverse effects <i>Tertiary outcomes</i> None reported
Notes	Sample size: Medium/NC

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A master randomisation list was generated by a computer at the Department of Statistics at Cauca University

**Martínez 1997** (Continued)

Blinding? All outcomes	No	Open
Intention-to-treat/Drop-outs?	Yes	3 out of 100 (3%)

**Navin 1990**

Methods	FU: 52 weeks after the start of therapy. D: Randomised clinical trial
Participants	Guatemala n= 66 Px were all men (average age 20 years). The average weight of Px who received MA was 56.1 Kg; they received an average of 15.2 mg antimony/kg body weight. Px were evenly divided between persons of Indian ancestry and those of mixed or other ancestry. Px had up to 6 lesions at the time of diagnosis, but most (68%) had only one lesion. The mean area of ulceration was 5.2 cm <sup>2</sup> . On average, their lesions had been apparent for 58 days when they first came to our clinic. Incl: Px were 18-60 years of age and had diagnoses of leishmaniasis confirmed by positive thin smear or cultures, no previous treatment with antimonials, no serious concomitant medical problems, lesions < 25 cm <sup>2</sup> in size, and no visual evidence of mucosal involvement. Excl: Px with lesions in locations that would have been difficult to treat with the heat device, such as lesions of the ear, near the eye, and on the finger, and unilateral lymphadenopathy or subcutaneous nodules in an area of lymph drainage from the lesion. <i>Leishmania</i> species: <i>Leishmania</i> was isolated in 53 Px by smear or culture; 13 (25%) were <i>L. mexicana</i> and 40 (75%) were <i>L. braziliensis</i> .
Interventions	T1: IMMA 850 mg daily for 15 days N= 22. MNL: 1.7. MSL: 6.2 cm <sup>2</sup> . MDLBT: 49 days. T2: Localized heat 50°C for 30 sec, 3 treatments at 7 day intervals (The apparatus heated the skin to 50°C in approx 20 sec, and maintained the temperature at 49-51°C for 30 sec) N= 22. MNL: 1.3. MSL: 4.6 cm <sup>2</sup> . MDLBT: 62.3 days. T3: Placebo treatment N= 22. MNL: 1.5. MSL: 4.9 cm <sup>2</sup> . MDLBT: 63 days.
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" 2 months after therapy <i>Secondary outcomes</i> Adverse effects <i>Tertiary outcomes</i> None reported
Notes	They found in a pilot study, that some Px developed what appeared to be bacterial cellulitis after heat treatments. To reduce the risk of subsequent cellulitis in this study, Px who were not allergic to penicillins received 500 mg oral dicloxacillin TD for 14 days before treatment. Px allergic to

Navin 1990 (Continued)

	penicillins received erythromycin at the same dose. All Px received 500 mg of dicloxacillin (or erythromycin) 1 hr before and TD after each heat or placebo treatment. Sample size: Medium/NC	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Blinding? All outcomes	Yes	Single-blinded. Px did not know whether they were receiving heat or sham treatments.
Intention-to-treat/Drop-outs?	Yes	ND

Navin 1992

Methods	FU: 48 weeks after the end of treatment or 52 weeks after the start of therapy. D: Randomised clinical trial	
Participants	Guatemala n= 120 The study included 21 civilians and 99 soldiers. In the SSG group 15% (6/40) were infected with an unknown infecting species, 63% (25/40) were infected with <i>L. braziliensis</i> , 18% (7/40) with <i>L. mexicana</i> and 5% (2/40) with both. In the ketoconazole group 16% (6/38) were infected with an unknown infecting species, 61% (23/38) were infected with <i>L. braziliensis</i> , 24% (9/38) with <i>L. mexicana</i> and 0% (0/38) with both. In the placebo group 23% (9/40) were infected with an unknown infecting species, 38% (15/40) were infected with <i>L. braziliensis</i> , 40% (16/40) with <i>L. mexicana</i> and 0% (0/40) with both. Incl: Confirmed diagnosis of leishmaniasis, no previous treatment with antimonials or imidazoles, no serious concomitant medical problems, availability for FU for 12 months, and no visible evidence of mucosal involvement. <i>Leishmania</i> species: <i>L. braziliensis</i> (53%) and <i>L. mexicana</i> (27%) by smear or culture.	
Interventions	T1: Oral ketoconazole 600 mg/day for 28 days N=40. MNL: 1.5. MSL: 2.2 cm <sup>2</sup> . MDLBT: 68.3 days. T2: IVSSG 20 mg of antimony/kg/day for 20 days N=40. MNL: 1.6. MSL: 1.5 cm <sup>2</sup> . MDLBT: 73.7 days. T3: Placebo. Half of the Px assigned to the placebo group received saline infusions similar to the SSG infusions and the other half received tablets similar in form to ketoconazole. N=40. MNL: 1.5. MSL: 2.0 cm <sup>2</sup> . MDLBT: 59.1 days.	
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" 2 months after therapy <i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 1 year	

Navin 1992 (Continued)

	Adverse effects Tertiary outcomes None reported
Notes	Sample size: Medium/NC
<b>Risk of bias</b>	
<b>Item</b>	<b>Authors' judgement</b> <b>Description</b>
Adequate sequence generation?	Yes According to a preexisting list produced by a computer programme that differed from a random number generation only in that it assigned equal number of Px into each treatment group.
Blinding? All outcomes	Unclear Not mentioned
Intention-to-treat/Drop-outs?	No 7 out of 120 (5.83%)

Neva 1997

Methods	FU: 11 weeks after completion of the 4-week topical treatment . They also stated that the study lasted for 4-5 months. D: Randomised clinical trial
Participants	Honduras ( 2 sites: village of San Juan Bautista, municipality of Pespire, Department of Choluteca and the village of Coyolito, municipality of Ampala, Department of Valle) n=53 26 Px came from San Juan Bautista and 27 from Coyolito. Cases were equally divided by sex and ranged in age from 3 to 36 years (only 4 participants were >20 years old, 1 was 18, and the remainder 16 years or less). 70-90% of the cases had 1 or 2 lesions (multiple lesions were more common in Px from Coyolito: 8/27 having 3 or more). The most prominent lesion on each Px was aspirated and cultured in NNN medium. Incl: Only those Px with positive cultures were enrolled in the study. <i>Leishmania</i> species: <i>L. mexicana</i> and <i>L. chagasi</i> by culture and isoenzyme typing.
Interventions	T1: Topical 15% PR + 10% urea n= 23. (10 Px having <i>L. mexicana</i> and 13 <i>L. chagasi</i> ) T2: Topical placebo (white soft paraffin) ointment n=30. (8 Px having <i>L. mexicana</i> and 22 <i>L. chagasi</i> ) Frequency: 3 times daily for 4 weeks

Neva 1997 (Continued)

Outcomes	<p><i>Primary outcome</i> Percentage of Px "cured" 2.5 months (11 weeks) after therapy</p> <p><i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 4-5 months Adverse effects</p> <p><i>Tertiary outcomes</i> None reported</p>
Notes	Sample size: Medium/NC

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A list of random numbers generated by Epi-Info software
Allocation concealment?	Yes	The code identifying the contents of each tube was know only to the Geneva participants (FM and PO)
Blinding? All outcomes	Yes	Double-blind. Tubes prepared by Farmitalia Carlo Erba and provided to the WHO TDR programme, containing the drug or placebo were identical in appearance and marked only by a number
Intention-to-treat/Drop-outs?	Yes	ND

**Oliveira-Neto 1997**

Methods	FU: 7 years. D: Randomised clinical trial
Participants	<p>Brazil n= 23</p> <p>Of the 23 Px proceeding from known endemic foci of ACL in Rio de Janeiro, M/F: 14/9. Ages ranged from 11 to 66 years. All Px presented cutaneous lesions: 16 one single lesion and 7 with multiple lesions. Single lesions were always rounded ones of the ulcerative type with raised borders. In cases of multiple lesions, some were papular and others ulcerative. Lesions were located mainly in exposed areas, face and limbs. Leg lesions were present in 15 Px. Duration of the disease ranged from 1 to 11 months.</p> <p>Incl: Clinical appearance of lesions, positive Montenegro's skin test and the presence of parasites either in in-prints, histological examination or isolation in culture.</p> <p><i>Leishmania</i> species: <i>L. braziliensis</i> (parasites were found in 18 Px by monoclonal antibodies and zymodeme analysis).</p>

Oliveira-Neto 1997 (Continued)

Interventions	T1: IVMA 5 mg/kg/day N= 12. MNL: 1-4 lesions. MSL: 3.73 cm <sup>2</sup> . MDLBT: 3.25 months. T2: IVMA 20 mg/kg/day N= 11. MNL: 1-7 lesions. MSL: 3.89 cm <sup>2</sup> . MDLBT: 2.54 months. Frequency: during 30 consecutive days
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" at the end of therapy <i>Secondary outcomes</i> Adverse effects <i>Tertiary outcomes</i> None reported
Notes	Random distribution of high and low doses were in charge of the Chief-nurse only in order to preserve the seal over the dosage employed. Sample size: Small/NC

**Risk of bias**

Item	Authors' judgement	Description
Blinding? All outcomes	Unclear	Not mentioned
Intention-to-treat/Drop-outs?	Yes	ND

**Oster 1985**

Methods	FU: 12 months. D: Randomised clinical trial
Participants	USA n= 36 Incl: The diagnosis was confirmed by demonstrating amastigotes in histological sections of skin biopsies and/or by culturing promastigotes from lesion aspirates or biopsies; the Px had not previously been treated with antileishmanial drugs; and the Px was at least 18 years of age and gave informed consent to participate in the trial. <i>Leishmania</i> species: Only in 26 Px <i>Leishmania</i> parasite was identified by culture or biopsies: 14 Px were infected with <i>L. braziliensis</i> , 9 with <i>L. mexicana</i> and 3 with <i>L. chagasi</i> .
Interventions	T1: IVSSG 600 mg OD for 10 days N=12. MSL: 3.0 cm. T2: IVSSG loading dose of 600 mg followed by 600mg/day continuous infusion for 9 days. N=12. MSL: 2.8 cm. T3: IVSSG loading dose of 600 mg followed by 200mg every 8 hour for 9 days

**Oster 1985** (Continued)

	N=12. MSL: 2.5 cm.
Outcomes	<p><i>Primary outcome</i> Percentage of Px “cured” at the end of therapy</p> <p><i>Secondary outcomes</i> Adverse effects</p> <p><i>Tertiary outcomes</i> None reported</p>
Notes	<p>Px who had initially been randomised to one of the three experimental treatment groups and were not cured, were randomised for re-treatment with one of the two treatment regimens they had not received, and Px failing this second course of therapy were then treated with the regimen they had not yet received.</p> <p>Sample size: Small/NC</p>

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	They stated that assignment to one of the three treatment groups was made according to predetermined randomised schedule which was balanced for every three Px
Blinding? All outcomes	Unclear	Not mentioned
Intention-to-treat/Drop-outs?	Yes	ND

**Palacios 2001**

Methods	<p>FU: 52 weeks after initiation of treatment.</p> <p>D: Randomised clinical trial</p>
Participants	<p>Colombia n= 136</p> <p>Carried out at the Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM) in Cali and Tumaco. Tumaco is an endemic area on the Colombian Pacific Coast where most of the recruited Px live in rural areas. Cali is the largest city in the southwestern region, and Px residing in non-endemic areas are often referred to Cali for diagnostic tests and medical attention.</p> <p>The 2 groups were comparable in socio-demographic and principal clinical characteristics, although Px randomised to receive 20 days of treatment bore lesions with median areas that were significantly larger and had less frequent regional adenopathies than Px who received 10 days of treatment.</p> <p>Incl: Px who had a parasitological diagnosis of cutaneous leishmaniasis.</p>

**Palacios 2001** (Continued)

	<p>Excl: Px who had been treated previously with antimonials, ketoconazole, or another imidazole, amphotericin B or pentamidine, as well as those with mucocutaneous leishmaniasis, severe cardiovascular, renal, hepatic, or pancreatic disease, and pregnant or nursing women.</p> <p><i>Leishmania</i> species: Of the 88 parasite isolates obtained, 84 were due to <i>L. panamensis</i>, and 4 cases were due to <i>L. braziliensis</i> by means of monoclonal antibodies and/or isoenzyme analysis.</p>
Interventions	<p>T1: IMMA 20 mg/kg/day (with no upper limit on the daily dose) OD during 10 days. N= 68. MNL: 2. MDLBT: 2 months.</p> <p>T2: IMMA 20 mg/kg/day (with no upper limit on the daily dose) OD during 20 days. N=68. MNL: 2. MDLBT: 2 months.</p>
Outcomes	<p><i>Primary outcome</i> Percentage of Px "cured" one year after therapy</p> <p><i>Secondary outcomes</i> Adverse effects</p> <p><i>Tertiary outcomes</i> None reported</p>
Notes	Sample size: Medium/C

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation was performed using permuted block randomisation as described previously (Spilker 1991)
Blinding? All outcomes	Yes	Single-blinded. Masked examiners evaluated clinical responses
Intention-to-treat/Drop-outs?	Yes	54 out of 136 (39.7%)

**Saenz 1987**

Methods	<p>FU: 12 months.</p> <p>D: Randomised clinical trial</p>
Participants	<p>Panama n= 59</p> <p>Most of the Px came from rural areas of the provinces of Panama and Colon, and were male. M/F was higher in the MA-treated group than the SSG-treated group (9:1 versus 2:1). Mean age in the MA group was 29.6 and 26.4 years in the SSG group. Lesions were ulcerative in all Px. Number of lesions in the SSG was 30 and in the MA was 29.</p> <p>Incl: Px were included if <i>Leishmania</i> organisms were cultured from lesion material or seen in smears of lesion material, and had not received previous antileishmanial therapy.</p>

**Saenz 1987** (Continued)

	<i>Leishmania</i> species: <i>L. panamensis</i> by culture or biopsy.	
Interventions	T1: IMSSG 20 mg/kg/d N= 30. MDLBT: 7.5 weeks. T2: IMMA 20 mg/kg/d N= 29. MDLBT: 8.3 weeks. Frequency: (maximum daily dose of 850 mg) for 20 days	
Outcomes	<p><i>Primary outcome</i> Percentage of Px “cured” at the end of therapy</p> <p><i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 6 to 1 year Adverse effects</p> <p><i>Tertiary outcomes</i> Microbiological or histopathological cure of skin lesions</p>	
Notes	Sample size: Medium/NC	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors’ judgement</b>	<b>Description</b>
Blinding? All outcomes	Unclear	Not mentioned
Intention-to-treat/Drop-outs?	No	9 out of 59 (15.3%)

**Saenz 1990**

Methods	FU: 12 months. D: Randomised clinical trial
Participants	<p>Panama n= 52</p> <p>They were all male. For the Ketoconazole group the age range was 16 to 48 years and the mean age was 25. For the MA group the age range was 17 to 67 years and the mean age was 34. The weight range for the ketoconazole group was 36 to 74 kg and 41 to 77 kg for the MA group. 66% (23/35) and 51% (25/49) of lesions were on the upper extremities in the ketoconazole and the MA groups respectively. The placebo-treated group were between 16 and 43 years of age and the mean age was 31 years old. 61% of lesions were in the upper extremities).</p>

Saenz 1990 (Continued)

	<p>Incl: Panamians with cutaneous lesions clinically diagnosed as leishmaniasis and who gave informed consent. Px were included if <i>Leishmania</i> organisms were cultured from lesion material or seen in smears of lesion material.</p> <p>Excl: If they had facial or mucocutaneous lesions, significant concomitant disease of any organ, or abnormalities on subsequent baseline tests.</p> <p><i>Leishmania</i> species: <i>L. panamensis</i>. Except one isolate in the ketoconazole group that was <i>L. mexicana</i></p>
Interventions	<p>T1: Oral ketoconazole 3 (200-mg tablets) before sleep each day (600 mg/kg/day) for 28 days N= 22. MNL: 2.1. MSL: 333 mm<sup>2</sup>. MDLBT: 8.2 weeks.</p> <p>T2: IMMA 20 mg/Kg with a maximum of 850 mg/day for 20 days N=19. MNL: 2.6. MSL: 350 mm<sup>2</sup>. MDLBT: 12.5 weeks.</p> <p>T3: Oral placebo 3 tablets each night for 28 days. N=11. MNL: 2.1. MSL: 95 mm<sup>2</sup>. MDLBT: 7.4 weeks.</p>
Outcomes	<p><i>Primary outcome</i> Percentage of Px "cured" 3 month after therapy</p> <p><i>Secondary outcomes</i> Adverse effects</p> <p><i>Tertiary outcomes</i> Speed of healing Microbiological or histopathological cure of skin lesions</p>
Notes	<p>Px in whom ketoconazole MA or placebo therapy failed were retreated with the local standard of care, pentavalent antimony in the form of Glucantime or Pentostam (20 mg Sb/Kg, with a maximum of 850 mg Sb/day, IM for 12 days) and all were cured.</p> <p>Sample size: Medium/NC</p>

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	By card drawing
Blinding? All outcomes	Unclear	Not mentioned
Intention-to-treat/Drop-outs?	Yes	ND

**Santos 2004**

Methods	<p>FU: 1 year. D: Randomised clinical trial</p>
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Participants	Brazil n=22 Px were referred to the health post of Corte de Pedra, Bahia, Brazil, an area where <i>L. braziliensis</i> infection is endemic. In this study there were M/F: 16/4. The average age was approx 29 years. Incl: An age of 15-50 years and a diagnosis of CL within 60 days of the beginning of the cutaneous lesion, confirmed either by parasitologic (culture or histopathologic) examination or by positive results of at least 2 of the following: compatible histopathologic examination, serologic examination, or delayed-type hypersensitivity test (Montenegro skin test) to <i>Leishmania</i> antigen. Excl: Pregnancy, an age of < 15 or > 50 years, other associated acute or chronic illness, and a history of allergy to GM-CSF and/or antimony. <i>Leishmania</i> species: <i>L. braziliensis</i> is endemic in the area.	
Interventions	T1: GM-CSF (final concentration of 10 µg/ml). The GM-CSF working solution was reapplied and dressings changed 3 times/week, on Mondays, Wednesdays, and Fridays, for 3 weeks (for a total of 9 GM-CSF applications) + IV MA 20 mg/kg/d for 20 days N= 11. MSL: 25 mm. MDLBT: 28 days. T2: Placebo (saline applied locally instead of GM-CSF) + IVMA 20 mg/kg/d for 20 days N= 11. MSL: 24 mm. MDLBT: 34 days.	
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" one month (40 days) after therapy <i>Secondary outcomes</i> Adverse effects <i>Tertiary outcomes</i> Speed of healing (time taken to be 'cured')	
Notes	Sample size: Small/NC	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	By use of a randomisation table performed by a statistician
Blinding? All outcomes	Yes	Double-blind (Both the Px and the physicians). Two independent physicians examined the Px on all visits and questions on possible side effects of the treatment were deferred to a third medical doctor who was conversant with the known side effects of GM-CSF.
Intention-to-treat/Drop-outs?	No	2 out of 22 (9%)

**Soto 1994**

Methods	FU: 12 months. D: Randomised clinical trial	
Participants	Colombia n=90 Members of Colombian army. The Px were infected during military duty in the regions of Uraba and Llanos Orientales, Colombia. 90 consecutive Px who met eligibility requirements, presented with disease when standard antileishmanial agents were no longer in stock at the field medical dispensary, and received permission from the local commander to relocate to Bogota for treatment, constituted the study population. All treatment was performed at Bogota Military Hospital. Incl: If they were 18-60 years old, had CL proven parasitologically, had not used putative antileishmanial compounds in the previous 9 months, and gave written informed consent to participate. Excl: If there were serious concomitant problems in their medical history or abnormalities in baseline laboratory tests. <i>Leishmania</i> species: 30/90 of the Px had <i>L. panamensis</i> by Giemsa smears, monoclonal antibody. Also a separate biopsy was taken to be cultured in NNN and Schneider's media and further identified by isoenzyme electrophoresis.	
Interventions	T1: IMAS 12 mg/Kg/day (maximum 850 mg/day) for 7 days. N= 30. Total number of lesions: 69. MSL: 143 mm <sup>2</sup> . T2: IMAS 12 mg/Kg/day (maximum 850 mg/day) for 14 days. N= 30. Total number of lesions: 55. MSL: 305 mm <sup>2</sup> . T3: IMAS 18 mg/Kg/day (maximum 850 mg/day) for 14 days. N=30. Total number of lesions: 48. MSL: 288 mm <sup>2</sup> .	
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" one year after therapy <i>Secondary outcomes</i> Adverse effects <i>Tertiary outcomes</i> None reported	
Notes	Sample size: Medium/NC	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Unclear	The original intention was to compare AS 12 mg base for 7 days with AS for 14 days, the first 60 Px were randomly allocated equally between the 2 groups. When 50 Px had been entered, it became clear the AS efficacy was less than expected. Therefore a 3rd group was added and the final 40 Px were randomly allocated to the three groups in the ratio 5:5:30
Blinding? All outcomes	Unclear	Not mentioned

**Soto 1994** (Continued)

Intention-to-treat/Drop-outs?	Unclear	1 out of 90 (1.1%)
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**Soto 1998**

Methods	FU: 12 months. D: Randomised clinical trial
Participants	Colombia n=150 The Px acquired their disease in the Colombian regions of Uraba, Magdalena Medio, and Llanos Orientales. Incl: If they were 18-60 years old, had cutaneous leishmaniasis proven parasitologically by visualization or culture of organisms, and were otherwise healthy. Excl: If there were serious concomitant problems in their medical history or abnormalities in baseline laboratory tests (in the levels of white blood cells and haemoglobin, serum levels of aspartate aminotransferase, and concentrations of glucose and blood urea nitrogen). <i>Leishmania</i> species: Of the 69/150 cultures strains, 49 were <i>L. panamensis</i> , and 20 were <i>L. braziliensis</i> by isoenzyme electrophoresis.
Interventions	T1: Topical 15% PR sulphate TD for 10 days+ 12% MBCL and a short course of IV MA for 7 days N= 59. MNL: 1.4. MSL: 224 mm <sup>2</sup> . T2: Topical placebo TD for 10 days plus IVMA for 7 days N= 30. MNL: 1.4. MSL: 202 mm <sup>2</sup> . T3: Topical 15% PR sulphate TD for 10 days+ 12% MBCL and a short course of IVMA for 3 days N= 30. MNL: 1.4. MSL: 302 mm <sup>2</sup> . T4: IVMA for 20 days N= 31. MNL: 1.2. MSL: 267 mm <sup>2</sup> .
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" one year after therapy <i>Secondary and tertiary outcomes</i> None reported
Notes	The inclusion and exclusion criteria definitions were identical to those reported in our previous study (Soto et al., 1995) Sample size: Medium/NC

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Px were randomly assigned in unequal allocation (2:1:1:1) to four groups

**Soto 1998** (Continued)

Blinding? All outcomes	Yes	Partially double-blinded: only stated but not reported who was blinded
Intention-to-treat/Drop-outs?	Yes	2 out of 150 (1.3%)

**Soto 2002**

Methods	FU: 6 months after initiation of treatment. D: Randomised clinical trial
Participants	Colombia n=45 Colombian soldiers acquired their disease in the Colombian regions of Uraba and Magdalena Medio. Most Px were evacuated to the Central Military Hospital in Bogota for diagnosis and treatment. Some Px were diagnosed and treated at the Instituto Colombiano de Medicina Tropical in Uraba. All Px were men aged approx. 25 years. The pre-therapy lesion sizes were a mean of 166 mm <sup>2</sup> . The mean number of lesions was 1.6 per Px. Incl: If the total ulcer lesion size was < 2000 mm <sup>2</sup> , lymphadenopathy was < 1 cm in diameter, there was no disease of the oronasal mucosa, screening laboratory values (serum levels of creatinine) were within normal limits and the Px had not concomitant medical problems. <i>Leishmania</i> species: determination of <i>Leishmania</i> was successfully detected in 5 of the 45 Px, and they were all <i>L. panamensis</i> via Giemsa smears or monoclonal antibody staining.
Interventions	T1: Topical WR279396 with 0.0005 ml/mm <sup>2</sup> TD for 20 days N= 33. MNL: 1.70. MSL: 155 mm <sup>2</sup> . T2: Topical placebo with 0.0005 ml/mm <sup>2</sup> TD for 20 days N= 12. MNL: 1.42. MSL: 203 mm <sup>2</sup> .
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" 2 months (70 days) after therapy <i>Secondary outcomes</i> Adverse effects <i>Tertiary outcomes</i> Speed of healing (time taken to be 'cured')
Notes	The reason for the lack of exact 2:1 assignment was that randomisation was performed for a possible total of 60 Px to allow for drop-outs, and a relatively large number of active treatments were randomised to the first 45 Px. Sample size: Small/NC

**Risk of bias**

Item	Authors' judgement	Description
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**Soto 2002** (Continued)

Adequate sequence generation?	Unclear	Randomly assigned in a 2:1 allocation
Blinding? All outcomes	Yes	Single-blind. Outcome assessor (determination of lesion cure and failure was made by a clinician blinded as to the treatment group of the Px)
Intention-to-treat/Drop-outs?	No	8 out of 45 (17.8%)

**Soto 2004A**

Methods	FU: 6 months. D: Randomised clinical trial
Participants	Bolivia and Colombia n= 114 45 consecutive Bolivian Px from the province of La Paz had parasitologically proven CL and 69 consecutive Colombian Px from the provinces of Urabá and Carmen de Chucurí, aged at least 18 years (age range 18-65) were eligible for the study. Diagnosis and treatment were performed in local hospitals in Apartade and Carmen de Chucurí, Colombia. In 45 Bolivian Px, the mean number of lesions per Px was 1.8 and the mean lesion size was 397 mm <sup>2</sup> . In 69 Colombian Px, the mean number of lesions per Px was 1.9 and the mean lesion size was 328 mm <sup>2</sup> . Incl: Parasitologically proven CL and Px who were at least 18 years of age. Excl: Mucocutaneous disease, previous treatment with antimonials, concurrent treatment with hepatotoxic, pancreaticotoxic, or cardiotoxic drugs, and any concurrent systemic medications except common drugs for symptomatic relief. <i>Leishmania</i> species: <i>L. panamensis</i> by direct Giemsa stain of the smear. In Colombia when motile promastigotes were seen, the parasite was determined by monoclonal antibody binding.
Interventions	T1: IMSSG 20 mg/Kg/day N= 48. MNL: 49.5. MSL: 366.5 mm <sup>2</sup> . T2: IMSSG (Pentostam) 20 mg/Kg/day N= 16. MNL: 14. MSL: 474.5 mm <sup>2</sup> . T3: IMMA 20 mg/Kg/day N= 50. MNL: 48. MSL: 307 mm <sup>2</sup> . Frequency: for 20 consecutive days (there was no upper limit on the daily dose)
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" 6 months after therapy <i>Secondary outcomes</i> Adverse effects <i>Tertiary outcomes</i> None reported
Notes	Sample size: Medium/NC

Soto 2004A (Continued)

<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Px were randomised by playing cards
Allocation concealment?	Yes	The Colombian allocation ratios were chosen to achieve a final allocation ratio for both sites for generic stibogluconate, Pentostam, and Glucantime of approximately 3:1:3. The Px code was broken only after all efficacy and toxicity evaluations had been completed
Blinding? All outcomes	Yes	Double-blind (neither Px, administering medical personnel, or evaluator knew the identity of the agent)
Intention-to-treat/Drop-outs?	Yes	10 out of 114 (8.8%)

Soto 2004B

Methods	FU: 6 months. D: Randomised clinical trial
Participants	Colombia and Guatemala n= 133 In Colombia, the Px were both civilians and soldiers who acquired infection in the provinces of provinces of Uraba and Carmen de Chucuri and who were evaluated in local hospitals for diagnosis and treatments. In Guatemala, the Px were civilians who presented, received diagnoses, and were treated at 2 clinics operated by the Universidad del Valle de Guatemala, which is located in Poptun, El Peten, Guatemala. On average, Px were in the third decade of life, weighed approx. 60 kg, and had 1 lesion. The ulcer size was approx. 200 mm <sup>2</sup> . M/F: 119/ 14. Incl: Px were of either sex, aged > 12 years, had parasitologically confirmed CL, and did not have mucosal involvement. Previous treatment for the disease was permitted if the therapy had stopped > or 4 weeks earlier and the lesions were not improving. Normal complete blood cell counts, liver transaminase levels, and kidney function test results. Excl: Pregnancy and lactation, and significant concomitant diseases. <i>Leishmania</i> species: In Colombia, all parasites were <i>L. panamensis</i> via monoclonal antibody binding. In Guatemala, 63% were <i>L. braziliensis</i> , and 37% of speciated parasites were <i>L. mexicana</i> via PCR. Compliance assessment: Drugs were administered under observation of study staff. 6/133 (4.5%) treated Px did not receive the full 28 days of medication. All 6 partially treated Px are included with the 127 fully treated Px in the efficacy and tolerance evaluations below.
Interventions	Colombia: T1: Miltefosine orally (50 mg) for 28 days. N= 49. MNL: 1 (1-8). MSL: 171 (72-1775) mm <sup>2</sup> . T2: Placebo administered like miltefosine for 28 days N= 24. MNL: 1 (1-5). MSL: 238 (6-2110) mm <sup>2</sup> .

**Soto 2004B** (Continued)

	<p>Guatemala:            T1: same as in Colombia            N= 40. MNL: 1 (1-10). MSL: 165 (6-1650) mm<sup>2</sup>.            T2: same as in Colombia            N= 20. MNL: 1 (1-3). MSL: 154 (6-3300) mm<sup>2</sup>.</p>	
Outcomes	<p><i>Primary outcome</i>            Percentage of Px "cured" 6 months after therapy  <i>Secondary outcomes</i>            Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 6 months            Adverse effects  <i>Tertiary outcomes</i>            None reported</p>	
Notes	<p>Sample size: Medium/NC</p>	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Blinding? All outcomes	Yes	Double-blind: only stated but not reported who was blinded
Intention-to-treat/Drop-outs?	Yes	8 out of 133 (6%)

**Vélez 1997**

Methods	<p>FU: 12 months.            D: Randomised clinical trial</p>	
Participants	<p>Colombia ( 11 regions of Colombia in which cutaneous leishmaniasis is endemic: Arma, Dabeiba, Herveo, La Mesa, Marquetalia, Medellin, San Carlos, San Luis, Taraza, Valdivia and Victoria)            n=187            Incl: If they were 6 to 60 years of age, had CL as confirmed by the presence of parasites, had not received treatment for leishmaniasis with recognised agents during the previous 6 months, did not have lesions close to the eyes or on the mucosa, had body weight that was appropriate for height, and were amenable to prolonged FU.            Excl: The presence of concomitant diseases that required medical intervention, abnormalities in the complete blood count, abnormal glutamate oxoacetate aminotransferase levels, abnormal creatinine levels, abnormal uric acid levels, and pregnancy.  <i>Leishmania</i> species: For the 182 analysable Px, 84% (153/182) had documented infection with <i>L. panamensis</i> and 16% (29/182) had infection with <i>L. braziliensis</i> by culture or Gimesa staining.</p>	

Vélez 1997 (Continued)

	Compliance assessment: Oral therapy was self-administered and compliance self-recorded. At each monitoring session, a 10-day supply of pills was dispensed and the Px's compliance record was checked and verified by counting the number of pills. MA was administered by medical support personnel. However, figures are not reported.
Interventions	T1: Oral AL 300 mg ( three 100-mg tablets) 4 times daily for 28 days, (dosage given was approx 5 mg/kg). N= 60. MNL: 2.8. MDLBT: 3.1 months. T2: Oral placebo, 3 tablets 4 times daily for 28 days. N= 56 (60 ITT). MNL: 3.3. MDLBT: 2.7 months. T3: IMMA, 20 mg/kg/day (no maximum daily dose) for 20 days. N= 66 (67 ITT). MNL: 2.9. MDLBT: 2.6 months.
Outcomes	<i>Primary outcome</i> Percentage of Px "cured" one year after therapy <i>Secondary outcomes</i> Recurrence: duration of remission and/or percentage of people with treated lesions that recur within 1 year Adverse effects <i>Tertiary outcomes</i> None reported
Notes	Sample size: Large/NC

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Yes	After the end of follow-up for the last Px, 3 independent, blinded evaluators determined the efficacy and reached consensus for each Px. The randomisation code was then broken. Toxicity was determined by one evaluator before the code was broken
Blinding? All outcomes	Yes	Partially double-blinded (only Px in the allopurinol and placebo groups were assigned to treatment in a double-blinded manner (Px, study investigators and monitors were blinded)
Intention-to-treat/Drop-outs?	No	30 out of 187 (16%)

FU: follow-up; D: design; Px: participants; M/F: male/female ratio; Incl: inclusion criteria; Excl: exclusion criteria; m/f:male/female; T1: treatment 1; T2: Treatment 2; T3: treatment 3; T4: treatment 4; IM: intramuscular; IL: intralesional; IV: intravenous; OD: once daily; TD: twice daily; MNL: Median number of lesions; MSL: Median size of lesions; MDLBT: Median duration of lesions before therapy; GM-CSF: Granulocyte macrophage colony-stimulating factor; MA: meglumine antimoniate; SSG: sodium stibogluconate; AL: allopurinol; PR: paromomycin; MBCL: methylbenzethonium chloride; AS: aminosidine sulphate; PI: pentamidine isethionate; Drop-outs: ND= no drop-outs; Sample size: Small= <50 participants; Medium= 51-150 participants; Large= >150 participants; C: Calculated; NC: Not calculated

### Characteristics of excluded studies *[ordered by study ID]*

Armijos 2004B	Use of vaccines alone
De Luca 1999	Use of vaccines alone
De Luca 2001	Use of vaccines alone
De Luca 2003	Use of vaccines alone
Deps 2000	Method of randomisation inadequate (order of arrival)
Fagundes 2007	A therapeutic but not a clinical trial
Hepburn 1994B	No mention about clinical cure rates but hepatotoxic parameters
Laguna-Torres 1999	In the text they mentioned that 10 Px were randomly distributed into 2 groups. Authors were contacted and clarified that 5 random Px were picked up and assigned to group 1 and another 5 Px picked up randomly were assigned to the other group. Thus, this is a quasi-randomised clinical trial.
Llanos 1991	No mention about clinical cure rates but nephrotoxic parameters
Monjour 1994	Use of vaccines alone
Nascimento 1990	Use of vaccines alone
Oliveira-Neto 2000	Non-comparative although randomised study
Rodriguez 1995	This RCT did not provide cure rates.
Saldanha 2000	No mention about clinical cure rates but hepatotoxic parameters
Soto 1993	Randomisation method of generation of allocation sequence was inadequate. Randomisation of the first 80 Px was accomplished by assigning Px 1, 5, 9, etc., to receive MA; Px 2, 6, 10, etc., to receive pentamidine; Px 3, 7, 11, etc., to receive itraconazole; and Px 4, 8, 12, etc., to receive no treatment. Px 81-92 were randomly assigned to receive MA or pentamidine but we were unable to distinguish the outcomes from these participants.
Soto 1994 A	Method of randomisation inadequate: the first 94 consecutive Px were entered. The first 38 Px constituted group 1. The other 56 Px constituted group 2.
Velez 2005	Use of vaccines alone
Wortmann 2002	Mixed Old World and New World forms of CL

## Characteristics of studies awaiting assessment [ordered by study ID]

### Krolewiecki 2007

Methods	Follow up: one year after completion of treatment
Participants	45 Px from Argentina Species of <i>Leishmania</i> : <i>L. braziliensis</i> was identified in all of them
Interventions	T1: Oral azithromycin, 500 mg/day n=22. T2: IM MA 10 mg Sb/kg/day n=23. Frequency: for 28 days, with a second cycle of 15 days if necessary. All Px who failed treatment with azithromycin were treated with MA and clinically cured.
Outcomes	Efficacy, defined as complete re-epithelization without relapse for 12 months after completing therapy, was 82.6% (95% confidence interval [CI] = 67-98%) for MA and 45.5% (95% CI = 25-66%) for azithromycin. Azithromycin was well tolerated; MA caused arthralgias and local symptoms in 78% of the Px.
Notes	Efficacy, defined as complete healing of all lesions by 6 months after completing therapy, was miltefosine 82% (36/44) and IM MA 83% (15/18). During therapy, the primary adverse event for the miltefosine group was gastrointestinal symptoms, experienced by 27/44 (61%) of Px for a median of 3 days (range 1-10 days). For the MA group, 13/18 (72%) of Px reported arthralgias and/or local pain at the injection site for a median of 7 days (range 5-14 days).

### Soto 2008

Methods	Follow up: one year after completion of treatment
Participants	62 Px from Bolivia 25-30 years of age with a median of 1 ulcer per Px with an average area of 300mm <sup>2</sup> . Species of <i>Leishmania</i> : <i>L. braziliensis</i> in the area Drop-outs: 5/62 (8%)
Interventions	T1: Miltefosine orally 2.5 mg/kg daily for 28 days n=44 T2: IMMA at 20 mg/kg/d for 20 days n=18
Outcomes	Six months after end of therapy, cure rates were of 88% (36/41) in the miltefosine group and of 94% (15/16) in the IMMA group. Speed of healing: more rapid in the IMMA group. Adverse effects: gastrointestinal in the miltefosine group and arthralgias and/or local pain in the injection site in the IMMA group.
Notes	

Px= participants

## Characteristics of ongoing studies [ordered by study ID]

NCT00004755

Trial name or title	Phase II Randomized Study of Allopurinol Versus Glucantime Versus Allopurinol/Glucantime for Cutaneous Leishmaniasis in Brazil
Methods	Treatment, Randomized, Open Label, Parallel Assignment, Safety/Efficacy Study
Participants	<p>Total Enrollment: 375            Participants are followed at 3, 6, and 9 months, then annually for at least 5 years.            Ages Eligible for Study: 12 Years and above, Genders Eligible for Study: Both            Criteria            PROTOCOL ENTRY CRITERIA:            --Disease Characteristics--            Parasitologically confirmed cutaneous leishmaniasis (lesion of &lt; 3 months duration)            No mucocutaneous leishmaniasis            No prior leishmaniasis            --Prior/Concurrent Therapy--            No prior treatment for leishmaniasis            --Px Characteristics--            Hepatic: No clinical or laboratory evidence of hepatic disease            Renal: No clinical or laboratory evidence of renal disease No hyperuricaemia or gout            Cardiovascular: No clinical, electrocardiographic, or laboratory evidence of cardiac disease            Other: No allergy or other contraindication to allopurinol or glucantime; No concurrent medication that might interact with study drugs, e.g.: probenecid, warfarin, azathioprine; No skin rash; No malnutrition; No other medical contraindication to protocol therapy; No pregnant or nursing women</p>
Interventions	<p>Group 1: IMMA daily. Px with less than a complete response on Day 21 continue treatment until lesions heal completely or for a maximum of 60 days. Px with progressive disease on Day 40 are removed from study.            Group 2: Daily oral allopurinol. Px with a partial response on Day 21 continue treatment until lesions heal completely. Px with stable or progressive disease on Day 21 or unhealed lesions on Day 56 cross to glucantime therapy. Accrual into this group was closed in 6/96.            Group 3: Oral allopurinol plus IMMA</p>
Outcomes	Not reported
Starting date	Study start: September 1995 Study completed
Contact information	<p>James H. Maguire, Study Chair, Harvard School of Public Health            More Information Study ID Numbers: 199/11679; HSPH-11679            Last Updated: June 23, 2005            Record first received: February 24, 2000            ClinicalTrials.gov Identifier: NCT00004755            Health Authority: United States: Federal Government</p>

**NCT00004755** (Continued)

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**NCT00111514**

Trial name or title	A Phase 1, Randomised, Double-Blind, Placebo-Controlled, Dose-Escalating Study to Evaluate Safety, Tolerability, and Immunogenicity of Leish-111f + MPL-SE Vaccine in Combination With Pentavalent Antimony in Treatment of Mucocutaneous Leishmaniasis
Methods	Treatment, Randomised, Double-Blind, Placebo Control, Parallel Assignment, Safety Study
Participants	Total Enrollment: 48 Ages Eligible for Study: 18 Years - 60 Years, Genders Eligible for Study: Both  Inclusion Criteria: Px with mucocutaneous leishmaniasis confirmed by a positive smear, in vitro culture or PCR test Exclusion Criteria: Mucocutaneous leishmaniasis must not involve the vocal cords or cause respiratory distress, and there must be no evidence of other disease
Interventions	This study is a phase 1, randomised, double-blind, placebo controlled, sequential dose-escalating trial to evaluate the safety and immunogenicity of three injections of 5, 10, or 20 µg of Leish-111f protein + 25 µg of MPL-SE adjuvant given at 4 week intervals as an adjunct to standard chemotherapy with pentavalent antimony (20 mg/kg/day for 28 days) in Px with mucocutaneous leishmaniasis
Outcomes	Further study details as provided by Infectious Disease Research Institute: Primary Outcome Measures: <ul style="list-style-type: none"> <li>● Occurrence of dose-limiting toxicity</li> <li>● Adverse events</li> </ul> Secondary Outcome Measures: <ul style="list-style-type: none"> <li>● IgG and T-cell response to Leish-111f vaccine</li> <li>● Leish-111f skin test reactivity</li> <li>● Safety of the vaccine with respect to the clinical course of mucocutaneous leishmaniasis</li> </ul>
Starting date	Study start: July 2004 Study completed
Contact information	Universidad Peruana Cayetano Heredia, Lima, 100, Peru Clínica de Leishmaniasis, Hospital Nacional Sur Este EsSalud, Cusco, Peru Study chairs or principal investigators Alejandro Llanos-Cuentas, MD, Principal Investigator, Universidad Peruana Cayetano Heredia Franco M Piazza, MD, MPH, Study Director, Infectious Disease Research Institute More Information Study ID Numbers: IDRI-LMVTC-102 Last Updated: February 13, 2007 Record first received: May 20, 2005 ClinicalTrials.gov Identifier: NCT00111514

**NCT00111514** (Continued)

	Health Authority: Peru: General Directorate of Pharmaceuticals, Devices, and Drugs; United States: Food and Drug Administration
Notes	

**NCT00111553**

Trial name or title	Randomised, Double-Blind, Adjuvant- and Placebo-Controlled, Dose-Escalating Study to Evaluate Safety, Tolerability, and Immunogenicity of Leish-111f + MPL-SE Vaccine With Meglumine Antimoniate (Glucantime) in Cutaneous Leishmaniasis
Methods	Treatment, Randomised, Double-Blind, Active Control, Parallel Assignment, Safety Study
Participants	Total Enrollment: 45 Ages Eligible for Study: 18 Years - 60 Years, Genders Eligible for Study: Both Inclusion Criteria: <ul style="list-style-type: none"> <li>● Confirmed diagnosis of cutaneous leishmaniasis defined as positive identification of parasite from lesion biopsy</li> <li>● Normal lab values and electrocardiogram (ECG)</li> <li>● Negative for HIV, hepatitis B and C, and Chagas disease</li> </ul> Exclusion Criteria: <ul style="list-style-type: none"> <li>● Nine or more active cutaneous lesions</li> <li>● Lesion diameter &gt;60 mm</li> <li>● Previous exposure to Leishmania vaccines or to MPL-SE</li> <li>● Pregnant or breast feeding female</li> </ul>
Interventions	This study is a phase 1, randomised, double-blind, placebo controlled, sequential dose-escalating trial to evaluate the safety and immunogenicity of three injections of 5, 10, or 20 µg of Leish-111f protein + 25 µg of MPL-SE adjuvant given at 4 week intervals as an adjunct to the standard chemotherapy with Glucantime cycles, as described above in Px with CL.
Outcomes	Further study details as provided by Infectious Disease Research Institute: Primary Outcome Measures: <ul style="list-style-type: none"> <li>● Occurrence of dose limiting toxicity</li> <li>● Adverse events</li> </ul> Secondary Outcome Measures: <ul style="list-style-type: none"> <li>● IgG and T-cell response to Leish-111f vaccine</li> <li>● Leish-111f skin test reactivity</li> <li>● Safety of the vaccine with respect to the clinical course of cutaneous leishmaniasis</li> </ul>
Starting date	Study start: October 2004 Study completed

**NCT00111553** (Continued)

Contact information	<p>Study chairs or principal investigators            Evaldo Nascimento, MD, Principal Investigator, Universidade Federal de Minas Gerais            Franco M Piazza, MD, MPH, Study Director, Infectious Disease Research Institute (IDRI)            More Information            Study ID Numbers: IDRI-LCVTC-101            Last Updated: February 13, 2007            Record first received: May 23, 2005            ClinicalTrials.gov Identifier: NCT00111553            Health Authority: United States: Food and Drug Administration; Brazil: Committee of Ethics in Research</p>
Notes	

**NCT00121862**

Trial name or title	A Study to Evaluate the Safety, Tolerability, and Immunogenicity of the Leish-111f + MPL-SE Vaccine Compared to the Leish-111f Protein Alone in Montenegro Skin Test-Negative Healthy Adults
Methods	Prevention, Randomised, Double-Blind, Placebo Control, Parallel Assignment, Safety Study
Participants	<p>Total Enrollment: 60            Ages Eligible for Study: 18 Years - 40 Years, Genders Eligible for Study: Both            Accepts Healthy Volunteers            Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Must have negative Montenegro skin test (0 mm)</li> <li>• Must be in good general health with normal lab values</li> <li>• Negative for HIV, hepatitis B and C</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>• History of leishmaniasis or exposure to Leishmania vaccine or MPL-SE</li> <li>• Nursing or pregnant female</li> </ul>
Interventions	The vaccine, identified as Leish-111f + MPL-SE, consists of a recombinant three-antigen Leishmania polyprotein (Leish-111f, 10 µg) together with the adjuvant MPL-SE (25 µg). In addition, the safety and immunogenicity of the vaccine will be compared to that of the Leish-111f protein (10 µg) given alone. The vaccine, Leish-111f protein alone or placebo will be given to each study subject three times at 4 week intervals.
Outcomes	<p>Further study details as provided by Infectious Disease Research Institute:            Primary Outcome Measures:</p> <ul style="list-style-type: none"> <li>• Adverse events</li> <li>• Dose-limiting toxicities: hematology and serum chemistry evaluations at Screening, Days 7, 35, 63, 84</li> <li>• T-cell IFN-γ response to the Leish-111f protein: immunology evaluations at Days 0, 84, 168</li> </ul> <p>Secondary Outcome Measures:</p> <ul style="list-style-type: none"> <li>• T-cell IL-5 response to the Leish-111f protein</li> <li>• Antibody responses to the Leish-111f protein</li> <li>• Skin test reactivity to the Leish-111f protein at Days 84, 168</li> </ul>

**NCT00121862** (Continued)

Starting date	Study start: August 2005 Study completed
Contact information	Franco M Piazza, MD, MPH, Study Director, Infectious Disease Research Institute More Information Study ID Numbers: IDRI-LCVPX-201 Last Updated: May 4, 2006 Record first received: July 18, 2005 ClinicalTrials.gov Identifier: NCT00121862 Health Authority: United States: Food and Drug Administration; Colombia: INVIMA Instituto Nacional de Medicamentos y Alimentos
Notes	

**NCT00233545**

Trial name or title	Miltefosine to Treat Cutaneous Leishmaniasis in Bolivia
Methods	Treatment, Randomised, Open Label, Active Control, Parallel Assignment, Efficacy Study
Participants	Puesto de Salud, Campamento OSCAR,, Palos Blancos,, Bolivia Total Enrollment: 80 Ages Eligible for Study: 3 Years and above, Genders Eligible for Study: Both Criteria Presentation: At least 1 lesion must be ulcerative. Parasitology: Parasitological confirmation of 1 lesion will be made by visualization or culture of leishmania from the biopsy or aspirate of the lesion. Previous RX: No specific or putatively specific therapy for leishmaniasis (Sb, pentamidine, amphotericin B, imidazoles, allopurinol)  Other diseases: No concomitant diseases by history and by approximately normal complete blood counts (white blood count, haemoglobin, platelet count), values of liver transaminases (SGOT) and kidney function tests (creatinine).
Interventions	Standard dose regimens will be used for both drugs.
Outcomes	Primary Outcome Measures: cure rate
Starting date	Study start: September 2005
Contact information	J Soto, MD, Principal Investigator, FADER More Information Study ID Numbers: 01-2005 Last Updated: September 18, 2006 Record first received: September 28, 2005 ClinicalTrials.gov Identifier: NCT00233545

**NCT00233545** (Continued)

	Health Authority: Bolivia: Ethics Committee
Notes	

**NCT00257530**

Trial name or title	Randomised Double Blind Clinical Trial of Imiquimod (Aldara) Versus Placebo Used in Combination With Pentavalent Antimony (Glucantime) in Peruvian Cutaneous Leishmaniasis Patients
Methods	Treatment, Randomised, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study
Participants	<p>Total Enrollment: 80  Ages Eligible for Study: 5 Years - 65 Years, Genders Eligible for Study: Both</p> <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>● Males/Females between 5 and 65 yrs</li> <li>● CL diagnosis confirmed</li> <li>● &gt;4 weeks time disease</li> <li>● no prior anti-leishmanial therapy for CL</li> <li>● negative pregnancy test</li> <li>● informed written consent or parent consent for &lt;18yrs Px</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>● &gt;25cm<sup>2</sup> lesion(s)</li> <li>● &gt;6 cutaneous lesions</li> <li>● mucocutaneous lesion</li> <li>● previous exposure to Imiquimod or anti-leish treatment</li> <li>● participation in another protocol within 30 days prior study</li> <li>● other acute or chronic illness / medication that may interfere</li> <li>● significant psychiatric illness</li> <li>● anaphylaxis or severe allergic reaction to proposed drugs</li> <li>● Px unlikely to cooperate</li> <li>● concomitant infection</li> <li>● pregnancy or breast feeding</li> </ul>
Interventions	Not reported
Outcomes	<p>Further study details as provided by Drugs for Neglected Diseases:</p> <p>Primary Outcome Measures:</p> <ul style="list-style-type: none"> <li>● Time to healing</li> <li>● Reduction of scarring</li> </ul> <p>Secondary Outcome Measures:</p> <ul style="list-style-type: none"> <li>● Safety (measured by AE reporting) during treatment and follow up to 12 months</li> </ul>

**NCT00257530** (Continued)

Starting date	Study start: November 2005 Study completed
Contact information	Please refer to this study by ClinicalTrials.gov identifier NCT00257530 Alejandro Llanos-Cuentas, Dr +51 1482 7739 allanos@upch.edu.pe Peru UPCH, Cusco, Peru Alejandro Llanos-Cuentas, Dr +5114827739 IMT Alexander Von Humboldt, Lima, Peru Alejandro Llanos-Cuentas, Dr +51 1 482 7739 Study ID Numbers: DNDi-IMQ-05 Last Updated: November 22, 2005 Record first received: November 22, 2005 ClinicalTrials.gov Identifier: NCT00257530 Health Authority: Peru: UPHC (Universidad Peruana Cayetano Heredia); Canada: McGill University; Switzerland: Drugs for Neglected Diseases initiative
Notes	

**NCT00317629**

Trial name or title	Double Blind, Randomised Controlled Trial, to Evaluate the Effectiveness of a Controlled Nitric Oxide Releasing Patch Versus Meglumine Antimoniate in the Treatment of Cutaneous Leishmaniasis
Methods	
Participants	Double Blind, Randomised Controlled Trial, to Evaluate the Effectiveness of a Controlled Nitric Oxide Releasing Patch Versus MA in the Treatment of CL
Interventions	Group 1: During 20 days this group will receive simultaneously IMMA (Glucantime 20 mg/kg/day with a maximum dose of 3 ampoules per day); and a NOP placebo. Group 2: During 20 days this group will receive simultaneously placebo of IMMA (5-15cc/day) and an active NOP.
Outcomes	Further study details as provided by Fundación Cardiovascular de Colombia: Primary Outcome Measures: <ul style="list-style-type: none"> <li>• Complete reepithelization three months after the beginning of the treatment</li> <li>• Absence of reactivation and affections of the mucous membranes during the 6 months of the study</li> </ul> Secondary Outcome Measures: <ul style="list-style-type: none"> <li>• Incomplete reepithelization three months after the beginning of the treatment</li> <li>• Increase in the size of the ulcer by more than 50% in relation to the last clinical evaluation</li> <li>• Reactivation and/or affections of the mucous membranes during the 6 months of the study</li> </ul>
Starting date	Study start: May, 2006

**NCT00317629** (Continued)

Contact information	<p>Please refer to this study by ClinicalTrials.gov identifier NCT00317629            Patricio López-Jaramillo, MD, PhD +57-7-639292 Ext. 331 <a href="mailto:jplopezj@fcv.org">jplopezj@fcv.org</a>            Federico A Silva, MD +57-7-6399292 Ext. 345 <a href="mailto:fsilva@fcv.org">fsilva@fcv.org</a>            Study ID Numbers: fcv137            Last Updated: May 31, 2006            Record first received: April 21, 2006            ClinicalTrials.gov Identifier: NCT00317629            Health Authority: Colombia: Cardiovascular Foundation of Colombia; United States: University of Akron;            Colombia: University of Antioquia; Colombia: University of Santander</p>
Notes	

**NCT00317980**

Trial name or title	Phase IV Randomised Controlled Clinical Trial to Evaluate the Safety and Efficacy of Low-Dose Pentavalent Antimony Compared to the Standard Dose in Patients With Cutaneous Leishmaniasis Caused by <i>Leishmania (Viannia) Braziliensis</i>
Methods	Treatment, Randomised, Single Blind, Active Control, Parallel Assignment, Safety/Efficacy Study
Participants	<p>Total Enrollment: 324            Ages Eligible for Study: 7 Years - 50 Years, Genders Eligible for Study: Both            Accepts Healthy Volunteers            Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>● Presence of 1 to 9 cutaneous lesions clinically compatible with leishmaniasis</li> <li>● Disease duration of 2 to 20 weeks</li> <li>● Positive leishmanin skin test</li> <li>● Parasitological diagnosis confirmed through culture or genus-specific polymerase chain reaction (PCR) for <i>Leishmania</i> spp</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>● History of past episode of leishmaniasis</li> <li>● Mucocutaneous disease</li> <li>● Disseminated disease</li> <li>● Use of drugs with anti-leishmanial activity</li> <li>● Contraindications for using pentavalent antimony:               <ul style="list-style-type: none"> <li>○ pregnancy</li> <li>○ renal failure</li> <li>○ heart failure</li> <li>○ hepatic failure</li> </ul> </li> <li>● Other diseases: active tuberculosis, hanseniasis</li> </ul>
Interventions	<p>Group1: IVMA (calculated dose based on the concentration of pentavalent antimony) 5 mg/kg/d            Group2: IVMA (calculated dose based on the concentration of pentavalent antimony) 15 mg/kg/d            Frequency: for 20 days.</p>

**NCT00317980** (Continued)

Outcomes	The clinical outcomes of cure or failure will be evaluated until the third month of follow-up Primary Outcome Measures: <ul style="list-style-type: none"> <li>• Proportion of clinically cured Px at the third month after treatment</li> <li>• Proportion of Px with early failure during the first 3 months after treatment</li> </ul> Secondary Outcome Measures: <ul style="list-style-type: none"> <li>• Proportion of Px with adherence to the protocol prescribed drug</li> <li>• Proportion of Px with adverse events</li> <li>• Proportion of Px with late failure after the first 3 months of follow-up</li> </ul>
Starting date	Study start: February 2006 Study completed
Contact information	Gustavo S Romero, MD, Principal Investigator, University of Brasilia Study ID Numbers: NMT-LD-CP-2006 Last Updated: February 5, 2007 Record first received: April 21, 2006 ClinicalTrials.gov Identifier: NCT00317980 Health Authority: Brazil: National Health Surveillance Agency
Notes	

**NCT00469495**

Trial name or title	Empiric Antihelminthic Therapy Combined With Antimony in the Treatment of Cutaneous Leishmaniasis: A Randomised Controlled Trial in Subjects Co-Infected With Helminths and Leishmania Brasiliensis
Methods	Treatment, Randomised, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study
Participants	Number of arms in study: 2 Total Enrollment: 90 Ages Eligible for Study: 13 Years - 50 Years, Genders Eligible for Study: Both  Inclusion Criteria: <ul style="list-style-type: none"> <li>• Subjects with a diagnosis of CL based on the presence of typical skin lesions and a positive Montenegro skin test</li> <li>• Evidence of helminthic infection by parasitological examination of first stool sample</li> <li>• Males or females between 13 and 50 years of age</li> <li>• Maximum of 3 ulcers with no more than 2 body regions involved</li> <li>• Period of 15 to 60 days from the onset of the first ulcer</li> <li>• Subject agreement to follow-up visits and therapy</li> <li>• Ability to give informed consent</li> </ul> Exclusion Criteria: <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Breast feeding mothers</li> <li>• Presence of mucocutaneous disease</li> </ul>

**NCT00469495** (Continued)

	<ul style="list-style-type: none"> <li>• History of prior treatment with antimonial drugs.</li> <li>• History of prior treatment with anthelmintic drugs within the last 6 months.</li> <li>• History of allergy to pentavalent antimony or antihelminthic</li> <li>• Presence of underlying disease which affects the immune response, such as HIV and diabetes mellitus</li> </ul>
Interventions	Not reported
Outcomes	Further study details as provided by Hospital Universitário Professor Edgard Santos: Primary Outcome Measures: Bidirectional measurements will be taken of the subjects' lesions at each visit and will be categorized as active or healed by a dermatologist. [Time Frame: 90 days]
Starting date	Study start: February 2007
Contact information	Please refer to this study by ClinicalTrials.gov identifier NCT00469495 Edgar M Carvalho, MD 212-746-6320 edgar@ufba.br Marshall J Glesby, MD, PhD 212-746-6320 mag2005@med.cornell.edu Study ID Numbers: 0701008939 Last Updated: May 2, 2007 Record first received: May 2, 2007 ClinicalTrials.gov Identifier: NCT00469495 Health Authority: Brazil: Committee of Ethics in Research; United States: Institutional Review Board
Notes	

**NCT00471705**

Trial name or title	Phase 3 Open-Label Study of Efficacy and Safety of Miltefosine vs Glucantime for Cutaneous Leishmaniasis in Colombia.
Methods	Treatment, Randomised, Open Label, Active Control, Single Group Assignment, Safety/Efficacy Study In this phase III, randomised open trial, subjects meeting inclusion criteria of the trial will be randomly allocated into two groups according to a randomisation list.
Participants	Number of arms in study: 2 Total Enrollment: 288 Sample size The sample was calculated using a power of 80%, confidence of 95% establishing important differences from 12%. We expect a successful rate of 90% meglumine antimoniate (Glucantime) and 78% for miltefosine. We calculated that 288 will be needed. Population CL in is a remerging disease in Colombia affecting civilian and military population as well, sharing the same epidemiologic characteristics.

	<p>The selected population will be composed from National Army of Colombia soldiers from CL endemic areas (Caquetá, Meta, Guaviare, Putumayo, Córdoba, Antioquia and Chocó).</p> <p>Withdrawal criteria:</p> <ul style="list-style-type: none"> <li>● A serious adverse event occurs</li> <li>● Withdrawal of the consent</li> <li>● Withdrawn cases will be treated according to the investigators opinion and beneficial of the participants at no cost. All withdrawn Px will be evaluated in final analysis (intent-to-treat analysis).</li> </ul> <p>Ages Eligible for Study: 18 Years - 40 Years, Genders Eligible for Study: Male</p> <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>● Parasitologically proven cases of CL based on positive smear and/or culture.</li> <li>● Px belonging to the National Colombian Army.</li> <li>● Otherwise healthy subjects on the basis of medical history, physical examination and results of blood test (if seemed necessary by the physician)</li> <li>● Age 18-40 years.</li> <li>● Willing to participate in the study, sign the informed consent , to go to the scheduled visits and to the follow-up visits.</li> <li>● Abstain to receive any other treatment for CL during the trial and follow-up periods.</li> <li>● Non purulent lesions.</li> <li>● Mentally sane volunteers.</li> <li>● No Leishmaniasis treatment in the six months prior to the recruitment.</li> <li>● Number of lesions no more than 5</li> </ul> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>● None of the lesions must be close to the anal, oral and nasal mucosa, or next to the urogenital and anal canal.</li> <li>● Serious systemic illnesses (as judged by the physician)</li> <li>● Px with mucocutaneous compromise.</li> <li>● Px with diffuse Leishmaniasis (defined as 10 or more cutaneous lesions and negative Montenegro's test)</li> </ul>
Interventions	<p>Group 1:150 mg/day of oral miltefosine for 28 days                  Group 2: 20 mg/kg/day IMMA for 20 days.</p>
Outcomes	<p>Primary Outcome Measures:</p> <ul style="list-style-type: none"> <li>● Clinical response:Complete re-epithelization of all lesions with disappearance of induration (with or without scar). No parasitological evaluation will be done on clinically cured lesions determined until 45 days posttreatment. [Time Frame: Until 45 days posttreatment]</li> </ul> <p>Secondary Outcome Measures:</p> <ul style="list-style-type: none"> <li>● Treatment failure: No change or increase in the size of induration and ulcer. [Time Frame: Until 45 days posttreatment]</li> <li>● Absence of clinical response: Induration and ulcer area =50% compared with the immediately previous evaluation. [Time Frame: Until 45 days posttreatment]</li> </ul>
Starting date	<p>Study start: June 2006</p>

**NCT00471705** (Continued)

Contact information	Please refer to this study by ClinicalTrials.gov identifier NCT00471705 Laureano Mestra, MD. +574 210 65 02 laureanomestra@gmail.com Liliana López, BSc. +574 210 65 02 lililop14@yahoo.com Study ID Numbers: PECET001 Last Updated: May 8, 2007 Record first received: May 7, 2007 ClinicalTrials.gov Identifier: NCT00471705 Health Authority: Colombia: INVIMA Instituto Nacional de Vigilancia de Medicamentos y Alimentos; Colombia: Ministry of Social Protection.
Notes	

**NCT00487253**

Trial name or title	Randomized Clinical Trial of the Efficacy and Tolerability of Oral Miltefosine Versus Parenteral Antimony for the Treatment of Pediatric Cutaneous Leishmaniasis in Colombia
Methods	Interventional Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study
Participants	Ages Eligible for Study: 2 Years - 12 Years, Genders Eligible for Study: Both, Accepts Healthy Volunteers: No Inclusion Criteria: <ul style="list-style-type: none"> <li>• 2 to 12 years of age (inclusive)</li> <li>• Parasitologically confirmed CL</li> <li>• Availability to receive supervised treatment for 28 days (i.e., directly observed therapy, to ensure the therapy is appropriately administered and received - e.g., the miltefosine is “swallowed”)</li> <li>• Availability to return for follow-up visits for at least 6 months after treatment is initiated</li> </ul> Exclusion Criteria: <ul style="list-style-type: none"> <li>• Weight under 10kg</li> <li>• Previous use of SbV, miltefosine or other antileishmanial therapy</li> <li>• Simultaneous mucosal lesions suggestive of or proven to be mucosal leishmaniasis</li> <li>• If a girl, ability to reproduce (history of menarche)</li> <li>• Relative or absolute contraindications for the use of SbV drugs or miltefosine, including history of cardiac, renal or hepatic disease</li> <li>• Patients with pretreatment haemoglobin &lt;10g/dl or blood urea nitrogen (BUN), serum creatinine, ALT, AST or amylase values that exceed the upper limit of normal</li> <li>• If living in Malaria endemic areas (eg. Tumaco) only: A positive malaria thick smear</li> </ul>
Interventions	Estimated Enrollment: 150
Outcomes	Primary Outcome Measures: <ul style="list-style-type: none"> <li>• The primary outcome measure will be the proportion of “Therapeutic Failures” diagnosed during the final (week 26) visit or before, according to defined clinical criteria. [ Time Frame: 26 weeks (6 months) ]</li> </ul>

**NCT00487253** (Continued)

	<ul style="list-style-type: none"> <li>Evidence of clinical or laboratory toxicity during the treatment period. [ Time Frame: During the treatment period (20 or 28 days) ]</li> </ul> <p>Secondary Outcome Measures: Proportion of patients with “parasitologic” response 26 weeks after the initiation of treatment. [ Time Frame: 26 weeks ]</p>
Starting date	Study Start Date: July 2007
Contact information	Please refer to this study by ClinicalTrials.gov identifier NCT00487253 Maria Consuelo Miranda, MD, MSc (571)6682164 ext 216 clinico@cideim.org.co; Isabel Rodriguez, MD (571)6682164 ext 307 irodriguez@cideim.org.co; Study ID Numbers: 50100119; Study First Received: June 14, 2007; Last Updated: July 26, 2007; ClinicalTrials.gov Identifier: NCT00487253; Health Authority: Colombia: Institutional Review Board
Notes	

**NCT00537953**

Trial name or title	EFFICACY AND SAFETY OF A SHORT COURSE OF THE COMBINATION OF MILTEFOSINE AND ANTIMONY TO TREAT CUTANEOUS LEISHMANIASIS IN BOLIVIA
Methods	Interventional Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study
Participants	<p>Ages Eligible for Study: 18Years - 65 Years, Genders Eligible for Study: Male, Accepts Healthy Volunteers: No</p> <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>Gender: Male Age: Adults Presentation: At least 1 lesion must be ulcerative. Parasitology: Parasitological confirmation of 1 lesion will be made by visualization or culture of leishmania from the biopsy or aspirate of the lesion.</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>Previous treatment for leishmaniasis, specific or putatively specific therapy (Sb, pentamidine, amphotericin B, imidazoles, allopurinol)</li> <li>Other concomitant diseases by history and by approximately normal complete blood counts (white blood count, hemoglobin, platelet count), values of liver transaminases (SGOT), values of pancreatic function (lipase), kidney function tests (creatinine), and EKG.</li> </ul>
Interventions	Not reported
Outcomes	Not reported
Starting date	Not reported

**NCT00537953** (Continued)

Contact information	Jaime Soto, MD 571 348 2171 j.soto@medplus.org.co Julia Toledo, MD 571 347 6093 toledo.julia@yahoo.es Study ID Numbers: 2007-Bol/LC-1339 Study First Received and Last updated: September 28, 2007 ClinicalTrials.gov Identifier: NCT00537953 Health Authority: Bolivia: Ministry of Health
Notes	

**NCT00600548**

Trial name or title	Clinical Trial to Assess Efficacy and Safety of Orally Administered Miltefosine in Brazilian Patients With Cutaneous Leishmaniasis Compared to the Standard Care as Active Control
Methods	Interventional Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study
Participants	<p>Estimated Enrollment: 180 Ages Eligible for Study: 2 Years - 65 Years, Genders Eligible for Study: Both, Accepts Healthy Volunteers: No Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>● Newly diagnosed (untreated) cutaneous leishmaniasis with localized lesions and visualization of amastigotes in tissue samples or a positive culture or diagnosed by polymerase chain reaction (PCR) methods or by intradermal skin testing (Montenegro test).</li> <li>● Number of lesions: 1 to 5 ulcerative lesions.</li> <li>● Lesion's diameter: 1 to 5 cm.</li> <li>● Disease duration: up to three months.</li> </ul> <p>Exclusion Criteria: Safety concerns:</p> <ul style="list-style-type: none"> <li>● Thrombocyte count &lt;30 x 10<sup>9</sup>/l</li> <li>● Leukocyte count &lt;1 x 10<sup>9</sup>/l</li> <li>● Hemoglobin &lt;5 g/100 ml</li> <li>● ASAT, ALAT, AP &gt;3 times upper limit of normal range</li> <li>● Bilirubin &gt;2 times upper limit of normal range</li> <li>● Serum creatinine or BUN &gt;1.5 times upper limit of normal range</li> <li>● Evidence of serious underlying disease (cardiac, renal, hepatic or pulmonary)</li> <li>● Immunodeficiency or antibody to HIV</li> <li>● Any non-compensated or uncontrolled condition, such as active tuberculosis, malignant disease, severe malaria, HIV, or other major infectious diseases</li> <li>● Lactation, pregnancy (to be determined by adequate test) or inadequate contraception in females of childbearing potential for treatment period plus 2 months</li> </ul> <p>Lack of suitability for the trial:</p> <ul style="list-style-type: none"> <li>● Negative parasitology (aspirate/smear) or negative Montenegro test</li> <li>● Any history of prior anti-leishmania therapy</li> <li>● Any condition which compromises ability to comply with the study procedures</li> <li>● Concomitant serious infection other than cutaneous</li> </ul>

**NCT00600548** (Continued)

	<p>Administrative reasons:</p> <ul style="list-style-type: none"> <li>• Lack of ability or willingness to give informed consent (patient and/or parent / legal representative)</li> <li>• Anticipated non-availability for study visits/procedure</li> </ul>
Interventions	<p>Cutaneous leishmaniasis patients in Manaus-Amazonas:            Group1: Miltefosine: Capsules containing 10 mg or 50 mg miltefosine; administered orally for 28 days at dosage of 2.5 mg/kg body weight per day.            Group 2: Meglumine antimoniate administered by intravenous route for 20 days at the dosage of 20mg/kg/day.            Cutaneous leishmaniasis patients in Corte de Pedra-Bahia:            Group 1: same as above            Group2: same as above</p>
Outcomes	<p>Primary Outcome Measures:            Cure rate or complete cicatrization of the ulcer. [ Time Frame: 6 months after treatment. ] [ Designated as safety issue: Yes ]</p> <p>Secondary Outcome Measures:            Inicial cure rate or complete cicatrization of the ulcer. [ Time Frame: 2 months after treatment. ] [ Designated as safety issue: Yes ]</p>
Starting date	Study Start Date: March 2007
Contact information	<p>Principal Investigator: Paulo RL Machado, MD, PhD            Responsible Party: Universidade Federal da Bahia            Study ID Numbers: D-18506, 410559/2006-7            Study First Received: January 2, 2008            Last Updated: November 12, 2008            ClinicalTrials.gov Identifier: NCT00600548            Health Authority: Brazil: Universidade Federal da Bahia; Brazil: Fundação de Medicina Tropical do Amazonas; Brazil: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); Brazil: Ministério da Ciência e Tecnologia</p>
Notes	

**NCT00682656**

Trial name or title	Open Label Randomized Study to Assess Safety and Efficacy of Azithromycin Versus Meglumine Antimoniate to Treat Cutaneous Leishmaniasis
Methods	Interventional Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study

Participants	<p>Ages Eligible for Study: 14 Years - 65 Years, Genders Eligible for Study: Both, Accepts Healthy Volunteers: No</p> <p>Estimated Enrollment: 620</p> <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Patients older than 14 and younger than 65 years old</li> <li>• Skin lesions with clinical suggestion of cutaneous leishmaniasis and positive leishmanin skin test (Montenegro test)</li> <li>• Agreement to participate in the study and signed the informed consent</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Diabetes mellitus, kidney diseases, liver or cardiac diseases, tuberculosis, malaria.</li> <li>• Pregnancy</li> <li>• Breast feeding</li> <li>• Cutaneous lesion with bacterial infection for which antibiotics need to be prescribed</li> <li>• More than six cutaneous lesions</li> <li>• Previous history of cutaneous or mucosal leishmaniasis</li> <li>• Use of drugs with potential pharmacological interactions with antimonials as anti-arrhythmic or tricyclic anti-depressives</li> <li>• Previous intolerance to azithromycin or other macrolides or N-metilglucamine</li> <li>• Abusive alcohol ingestion according to the CAGE questionnaire</li> </ul>
Interventions	<p>Group1: metil glucamine (Glucantime-Aventis) 15mg Sb+5/Kg/day, during 20 days. Maximum dose: 15ml/day</p> <p>Group 2: Azithromycin (Zitromax/ Pfizer) 500 mg per os 1x day, during 20 days</p>
Outcomes	<p>Primary Outcome Measures:</p> <ul style="list-style-type: none"> <li>• Proportion of clinically cured patients [ Time Frame: at the third month after treatment ] [ Designated as safety issue: No ]</li> </ul> <p>Secondary Outcome Measures:</p> <ul style="list-style-type: none"> <li>• Proportion of patients with failure [ Time Frame: twelve months after treatment ] [ Designated as safety issue: No ]</li> <li>• Occurrence of mucosal lesions after treatment [ Time Frame: twelve months after treatment ] [ Designated as safety issue: No ]</li> <li>• Proportion of patients presenting new lesions [ Time Frame: 1st 2nd 3rd 6th 12th month after treatment ] [ Designated as safety issue: No ]</li> <li>• Proportion of adverse events on each treatment group [ Time Frame: 1st 2nd 3rd 6th 12th month after treatment. ] [ Designated as safety issue: Yes ]</li> </ul>
Starting date	Study Start Date: June 2008
Contact information	<p>Ana Rabello, MD, PhD 55-31-3349-7708 ana@cpqrr.fiocruz.br</p> <p>Mariana Pedras 55-31-3349-7712 mjpedras@cpqrr.fiocruz.br</p> <p>Responsible Party: Fundação Oswaldo Cruz</p> <p>Study ID Numbers:CEPSH/CPqRR 21/2006</p> <p>Study First Received:May 20, 2008</p> <p>Last Updated: October 8, 2008</p>

**NCT00682656** (Continued)

	ClinicalTrials.gov Identifier: NCT00682656 Health Authority: Brazil: National Health Surveillance Agency
Notes	

Px= participants

## DATA AND ANALYSES

**Comparison 1. IMMA (20 mg/kg/d for 20 d) vs placebo (3 tablets/4 times a day for 28 d) in *L. braziliensis* and *L. panamensis*; FU: 3 months and 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	2	157	Risk Ratio (M-H, Random, 95% CI)	4.23 [0.84, 21.38]

**Comparison 2. 10-day IMMA versus 20-day IMMA in *L. braziliensis* and *L. panamensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Anorexia	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Headache	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Myalgias	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Malaise	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.5 Arthralgias	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

**Comparison 3. IVMA 20 mg/kg/d for 15 d vs no treatment in *L. panamensis*; FU: 12 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Relapses	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 4. IVMA for 7 days + placebo topically TD for 10 d vs IVMA for 20 d in *L. braziliensis* & *L. panamensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 5. IVMA 15% (14 mg/kg/d) vs IVMA 30% (28 mg/kg/d) ; FU: 2 years**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure (CL plus MCL)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Complete cure CL form	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 complete cure MCL form	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 6. 10-day IVMA+ 10-day placebo versus 20-day IVMA in *L. braziliensis* and *L. mexicana*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 7. IMSSG 20 mg/kg/d for 20d vs IMMA (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Myalgias	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Headache	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Metallic taste	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

**Comparison 8. IMSSG (branded) vs IMSSG (generic). Dose: 20 mg/kg/d for 20 d in *L. panamensis*; FU: 6 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Myalgias	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Headache	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Metallic taste	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

**Comparison 9. IVSSG for 28 days versus IVSSG for 40 days in *L. braziliensis*; FU: 1 year**

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Complete cure</a>	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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**Comparison 10. Oral ketoconazole for 28 days versus IMMA for 20 days in *L. panamensis* and *L. mexicana*; FU: 3 months**

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Complete cure</a>	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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**Comparison 11. Oral ketoconazole versus oral placebo for 28 days in *L. panamensis* and *L. mexicana*; FU: 3 months**

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Complete cure</a>	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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**Comparison 12. Oral AL 20 mg/kg/d (4 doses) for 15d vs. AL + IVMA (same regimen) in *L. panamensis*; FU: 12 months**

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Complete cure</a>	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
<a href="#">2 Relapses</a>	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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**Comparison 13. Oral AL 20 mg/kg/d (4 doses) x 15d vs. IVMA (same regimen) in *L. panamensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Relapses	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 14. Oral AL + IVMA (20 mg/kg/d (4 doses) for 15d) vs. IVMA (same regimen) in *L. panamensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Relapses	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 15. Oral AL for 28d vs IMMA 20mg/kg/d for 20 d in *L. braziliensis* and *L. panamensis* ; FU: 12 month**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 16. Oral AL + IVSSG (20 mg/kg/d (4 doses) x 15d) vs IVSSG (same dose) in *L. braziliensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Oral AL plus IV antimonials vs. IV antimonials	2	168	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.40, 2.59]

**Comparison 17. Oral AL + IVSSG (20 mg/kg/d (4 doses) for 28d) vs IVSSG (same dose); FU: 12 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Complete cure</a>	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 18. Oral AL 20 mg/kg/d (4 doses) for 15 d vs no treatment in *L. panamensis*; FU: 12 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Complete cure</a>	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
<a href="#">2 Relapses</a>	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 19. Oral AL 28 days versus placebo in *L. braziliensis* and *L. panamensis*; FU: 12 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Complete cure</a>	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 20. Oral AL + IVMA (20 mg/kg/ d in 4 doses for 15d) vs no treatment in *L. panamensis*; FU: 12 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Complete cure</a>	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
<a href="#">2 Relapses</a>	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 21. Oral miltefosine 50 mg for 28 d vs. placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Colombia	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Guatemala	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Motion sickness	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Headache	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Vomiting	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.5 Diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.6 Creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.7 Aspartate aminotransferase	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.8 Alanine aminotransferase	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

**Comparison 22. Different regimens of IMAS in *L. panamensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AS 12-g base x 7 days versus AS 12-g base x 14 days	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 AS 12-g base x 7d versus AS 18-g base for 14 d	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 AS 12-g base x 14 d versus AS 18-g base x 14 d	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 23. IMAS for 20 days versus IMMA for 20 days in *L. braziliensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Myalgias	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Anorexia	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Asthenia	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Arthralgias	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

**Comparison 24. IMAS for 20 days versus IMPI x 8 applications in *L. braziliensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Myalgias	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Anorexia	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Asthenia	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Arthralgias	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

**Comparison 25. IM Aminosidine 20 mg/kg/d for 28 d vs IVMA 20 mg/kg for 28 d; *L. braziliensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 26. IVPI for seven doses versus IVMA for 20 days in *L. braziliensis*; FU: 6 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Gastrointestinal events	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Musculoskeletal events	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Headache	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

**Comparison 27. IMPI versus IMMA for 20 days in *L. braziliensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Myalgias	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Anorexia	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Asthenia	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Arthralgias	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

**Comparison 28. Topical PR-MBCL TD for 20d vs placebo TD for 20d in *L. panamensis* and *L. mexicana*; FU: 12 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 29. Topical PR-MBCL (TD x 10d) + IVMA x 7 d vs Placebo + IVMA x 7 d in *L. braziliensis* and *L. panamensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 30. Topical PR-MBCL (TD x 10d) + IVMA x 7 d vs PR-MBCL + IVMA x 3 d in *L. braziliensis* and *L. panamensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 31. Topical PR-MBCL (TD x 10d) + IVMA x 3 d vs Placebo + IVMA x 7 d in *L. braziliensis* and *L. panamensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 32. Topical PR-MBCL (TD x 10d) + IVMA x 7 d vs IVMA for 20 d in *L. braziliensis* and *L. panamensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 33. Topical PR-MBCL (TD x 10d) + IVMA x 3 d vs IVMA for 20 d in *L. braziliensis* and *L. panamensis*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 34. Vaccine vs IMMA (50 mg/kg in 2-3 series of 20 daily injections) in *L. braziliensis*; FU: 6 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	2	277	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.04]

**Comparison 35. BCG vs. IMMA in *L. braziliensis*; FU: 6 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 36. Oral pentoxifylline 400 mg 3 times daily for 30d + IVSSG 20 mg/kg /d vs. placebo + IVSSG in *L. braziliensis*; FU: 4 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 37. 7.5% imiquimod cream x 20 days plus IVMA for 20 days versus IVMA x 20 days in *L. braziliensis*, *L. peruviana*, *L. mexicana* and *L. amazonensis*; FU: 3 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 38. Topical imiquimod 5% + IVMA vs placebo + IM/IVMA in *L. braziliensis* and *L. peruviana*; FU: 1 year**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Edema	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Itching	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Burning	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Erythema	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

**Comparison 39. 7.5% imiquimod cream x 20 days versus IVMA x 20 days in *L. braziliensis*, *L. peruviana*, *L. mexicana* and *L. amazonensis*; FU: 3 months**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Comparison 40. IVMA combined or in different regimens in *L. braziliensis* and *L. mexicana*; FU: 1 year**

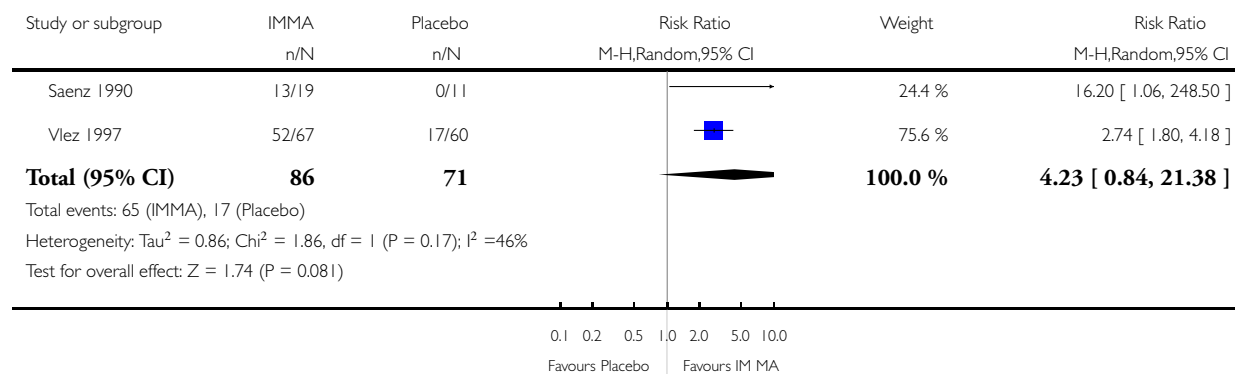
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 10-day IV MA+10-day IFN- $\gamma$ versus 10-day IV MA+10-day placebo	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 10-day IV MA+ 10-day IFN- $\gamma$ versus 20-day IV MA	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Analysis 1.1. Comparison 1 IMMA (20 mg/kg/d for 20 d) vs placebo (3 tablets/4 times a day for 28 d) in *L. braziliensis* and *L. panamensis*; FU: 3 months and 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 1 IMMA (20 mg/kg/d for 20 d) vs placebo (3 tablets/4 times a day for 28 d) in *L. braziliensis* and *L. panamensis*; FU: 3 months and 1 year

Outcome: 1 Complete cure

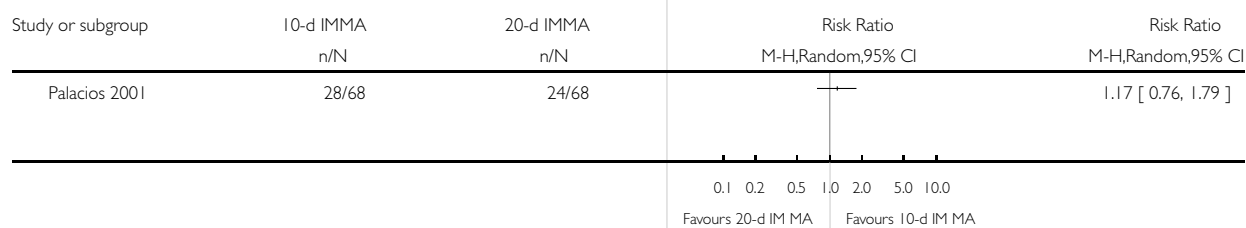


**Analysis 2.1. Comparison 2 10-day IMMA versus 20-day IMMA in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 2 10-day IMMA versus 20-day IMMA in *L. braziliensis* and *L. panamensis*; FU: 1 year

Outcome: 1 Complete cure

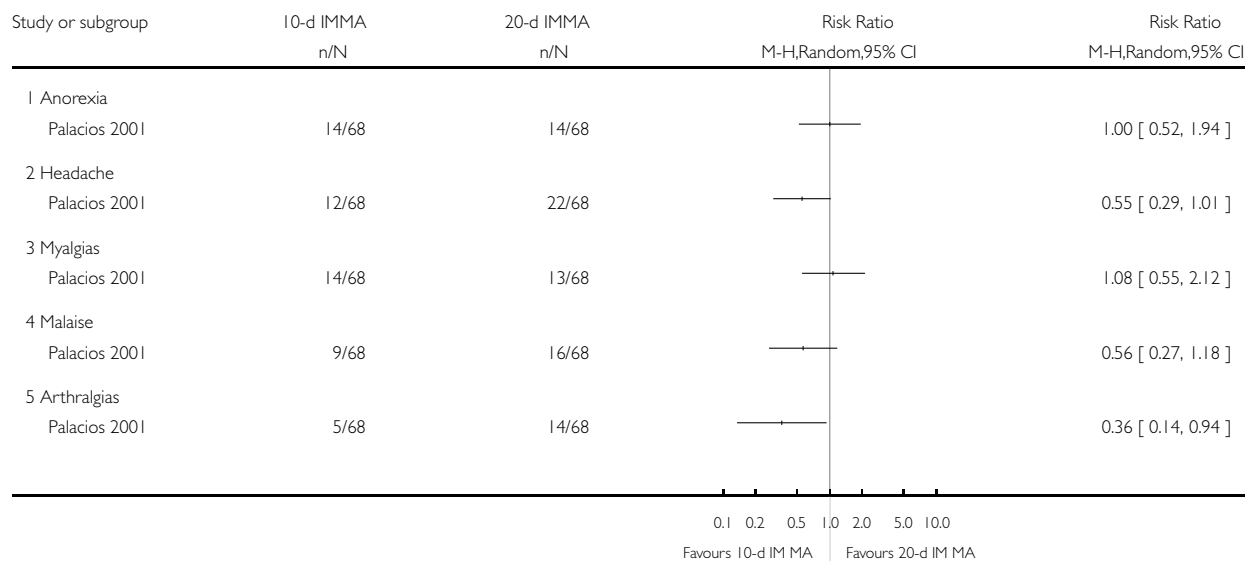


**Analysis 2.2. Comparison 2 10-day IMMA versus 20-day IMMA in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 2 Adverse effects.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 2 10-day IMMA versus 20-day IMMA in *L. braziliensis* and *L. panamensis*; FU: 1 year

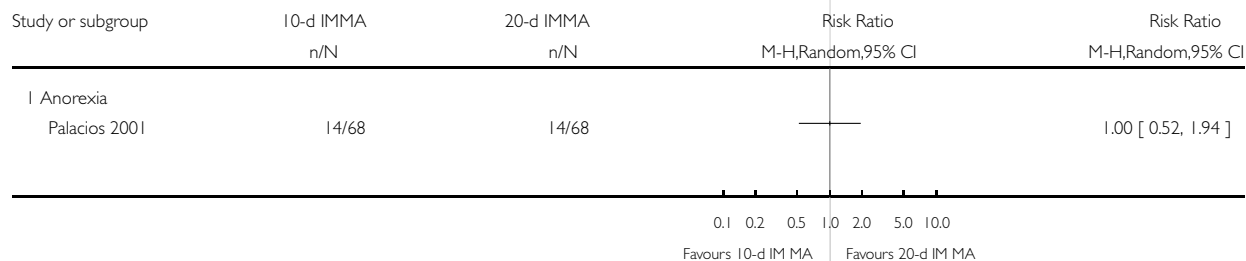
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 2 10-day IMMA versus 20-day IMMA in *L. braziliensis* and *L. panamensis*; FU: 1 year

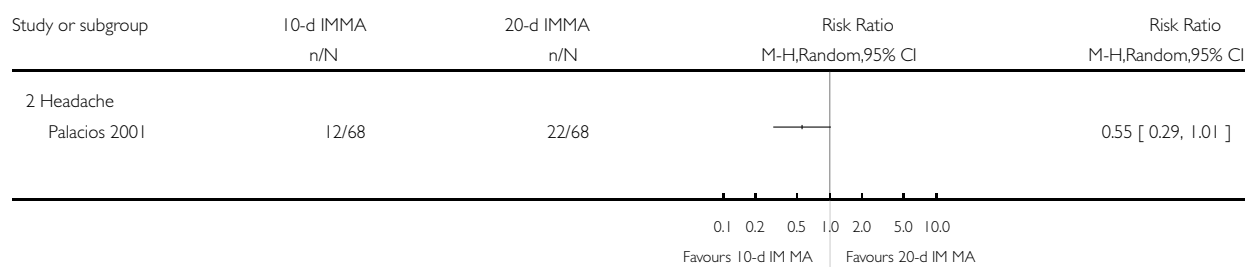
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 2 10-day IMMA *versus* 20-day IMMA in *L. braziliensis* and *L. panamensis*; FU: 1 year

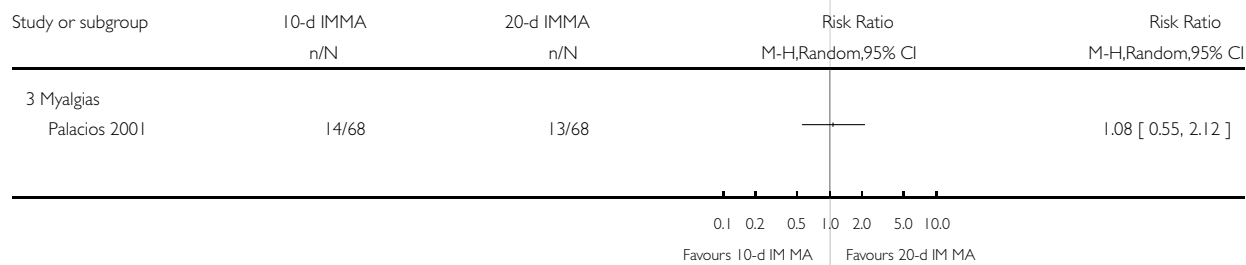
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 2 10-day IMMA *versus* 20-day IMMA in *L. braziliensis* and *L. panamensis*; FU: 1 year

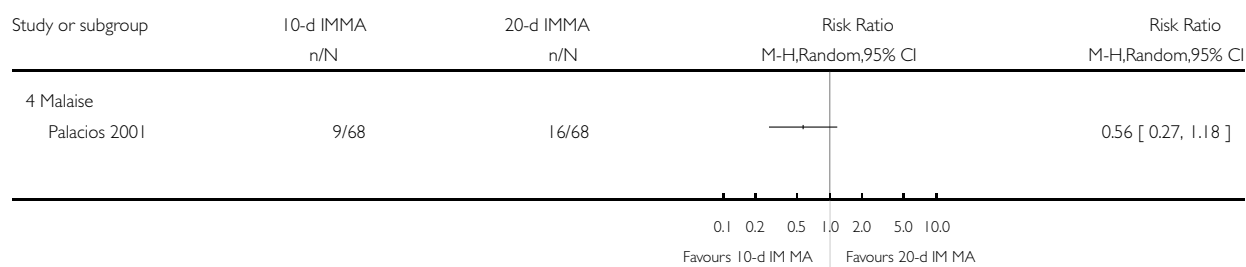
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 2 10-day IMMA *versus* 20-day IMMA in *L. braziliensis* and *L. panamensis*; FU: 1 year

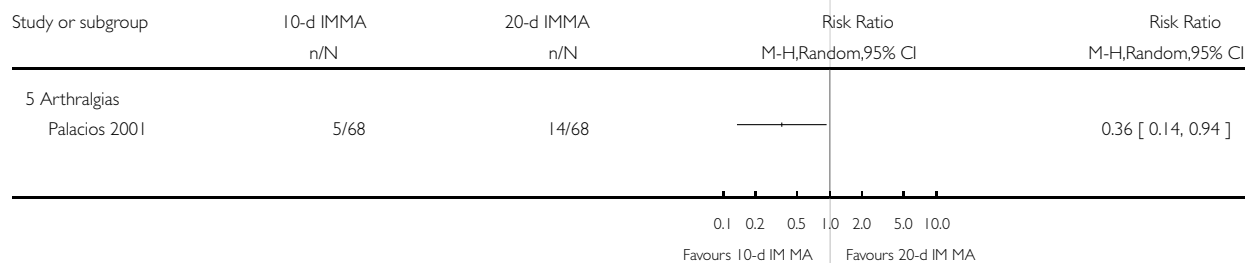
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 2 10-day IMMA *versus* 20-day IMMA in *L. braziliensis* and *L. panamensis*; FU: 1 year

Outcome: 2 Adverse effects



**Analysis 3.1. Comparison 3 IVMA 20 mg/kg/d for 15 d vs no treatment in *L. panamensis*; FU: 12 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 3 IVMA 20 mg/kg/d for 15 d vs no treatment in *L. panamensis*; FU: 12 months

Outcome: 1 Complete cure

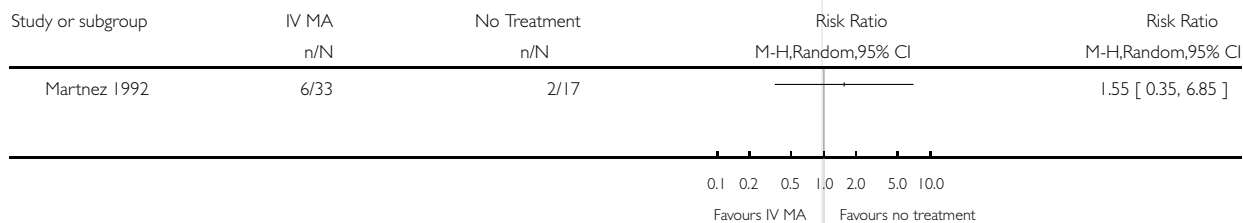


**Analysis 3.2. Comparison 3 IVMA 20 mg/kg/d for 15 d vs no treatment in *L. panamensis*; FU: 12 months, Outcome 2 Relapses.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 3 IVMA 20 mg/kg/d for 15 d vs no treatment in *L. panamensis*; FU: 12 months

Outcome: 2 Relapses

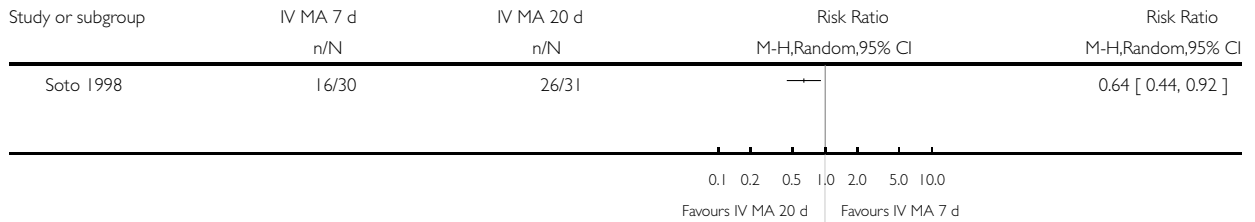


**Analysis 4.1. Comparison 4 IVMA for 7 days + placebo topically TD for 10 d vs IVMA for 20 d in *L. braziliensis* & *L. panamensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 4 IVMA for 7 days + placebo topically TD for 10 d vs IVMA for 20 d in *L. braziliensis* & *L. panamensis*; FU: 1 year

Outcome: 1 Complete cure



**Analysis 5.1. Comparison 5 IVMA 15% (14 mg/kg/d) vs IVMA 30% (28 mg/kg/d) ; FU: 2 years, Outcome 1 Complete cure (CL plus MCL).**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 5 IVMA 15% (14 mg/kg/d) vs IVMA 30% (28 mg/kg/d) ; FU: 2 years

Outcome: 1 Complete cure (CL plus MCL)

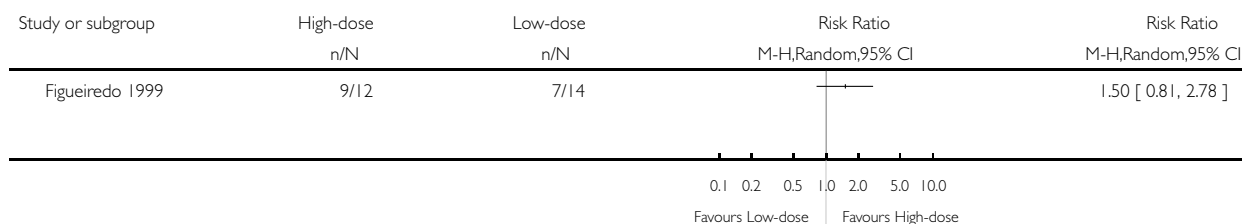


**Analysis 5.2. Comparison 5 IVMA 15% (14 mg/kg/d) vs IVMA 30% (28 mg/kg/d) ; FU: 2 years, Outcome 2 Complete cure CL form.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 5 IVMA 15% (14 mg/kg/d) vs IVMA 30% (28 mg/kg/d) ; FU: 2 years

Outcome: 2 Complete cure CL form

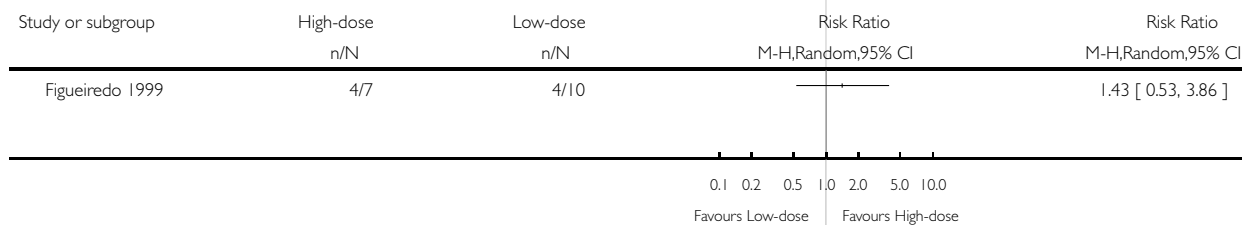


**Analysis 5.3. Comparison 5 IVMA 15% (14 mg/kg/d) vs IVMA 30% (28 mg/kg/d) ; FU: 2 years, Outcome 3 complete cure MCL form.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 5 IVMA 15% (14 mg/kg/d) vs IVMA 30% (28 mg/kg/d) ; FU: 2 years

Outcome: 3 complete cure MCL form

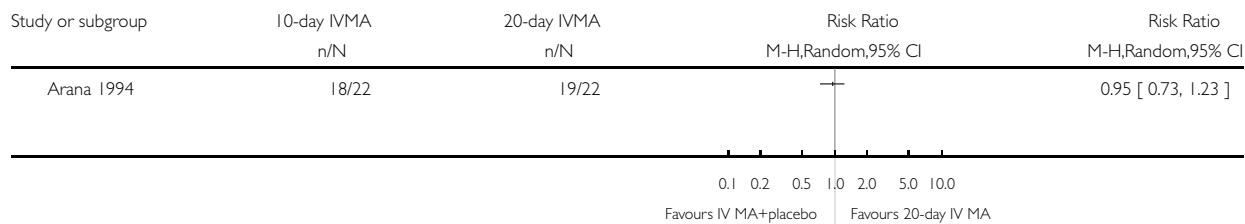


**Analysis 6.1. Comparison 6 10-day IVMA+ 10-day placebo versus 20-day IVMA in *L. braziliensis* and *L. mexicana*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 6 10-day IVMA+ 10-day placebo versus 20-day IVMA in *L. braziliensis* and *L. mexicana*; FU: 1 year

Outcome: 1 Complete cure

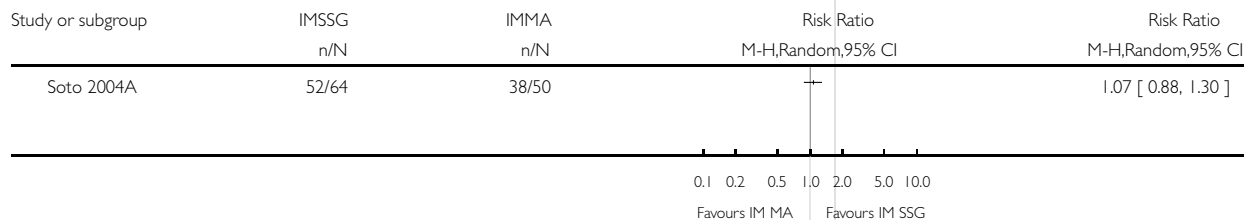


**Analysis 7.1. Comparison 7 IMSSG 20 mg/kg/d for 20d vs IMMA (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 7 IMSSG 20 mg/kg/d for 20d vs IMMA (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months

Outcome: 1 Complete cure

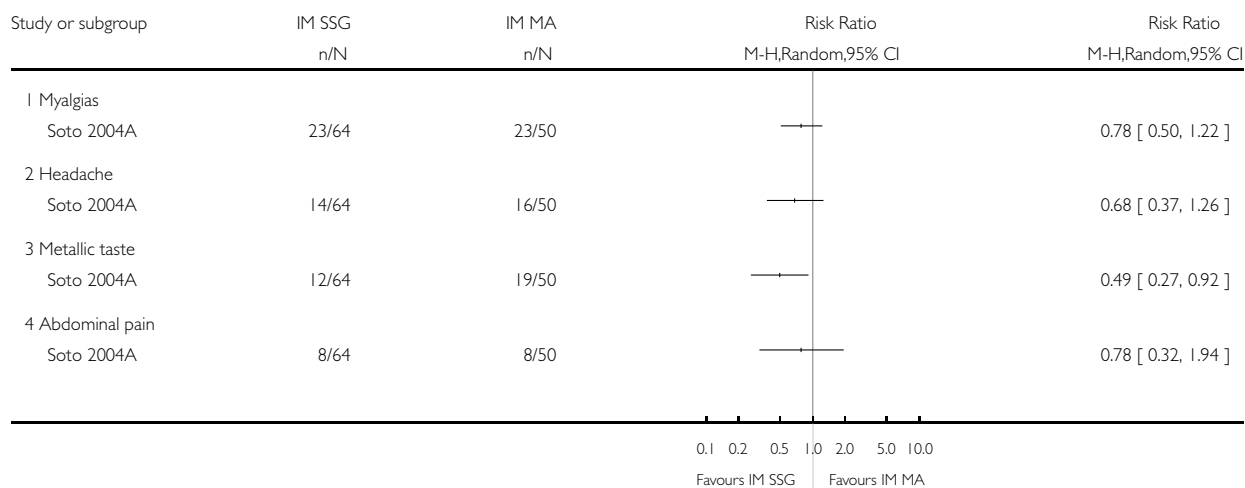


**Analysis 7.2. Comparison 7 IMSSG 20 mg/kg/d for 20d vs IMMA (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months, Outcome 2 Adverse effects.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 7 IMSSG 20 mg/kg/d for 20d vs IMMA (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months

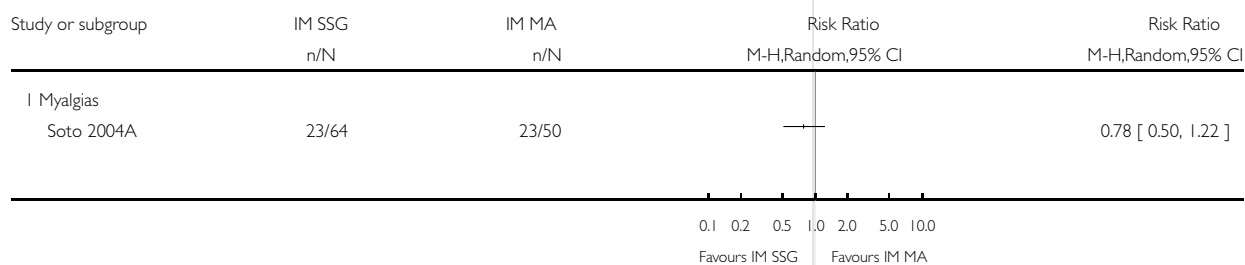
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 7 IMSSG 20 mg/kg/d for 20d vs IMMA (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months

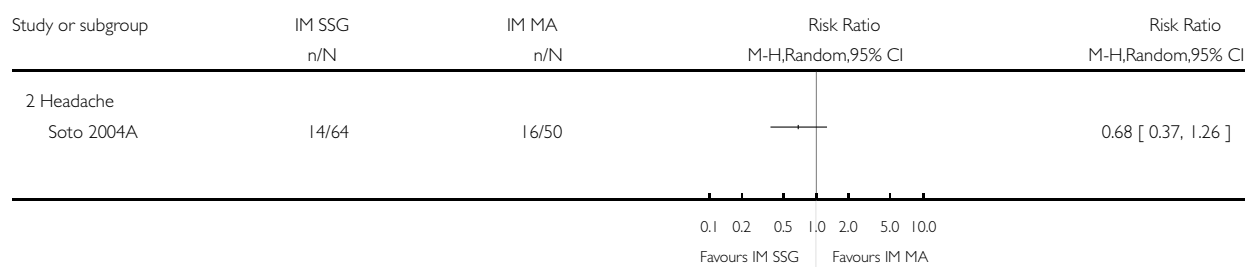
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 7 IMSSG 20 mg/kg/d for 20d vs IMMA (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months

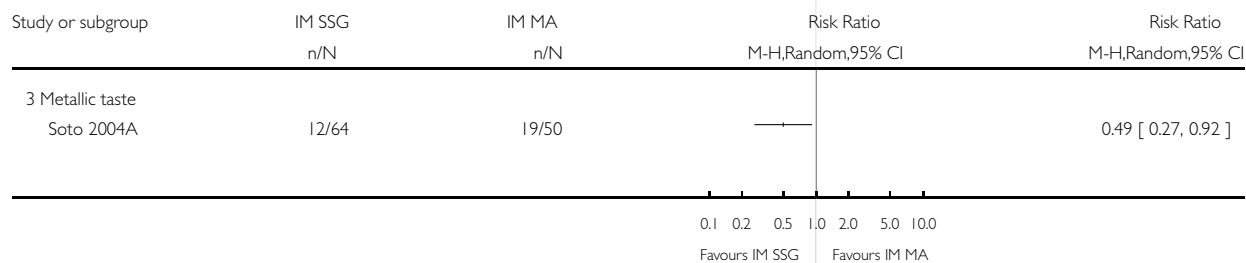
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 7 IMSSG 20 mg/kg/d for 20d vs IMMA (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months

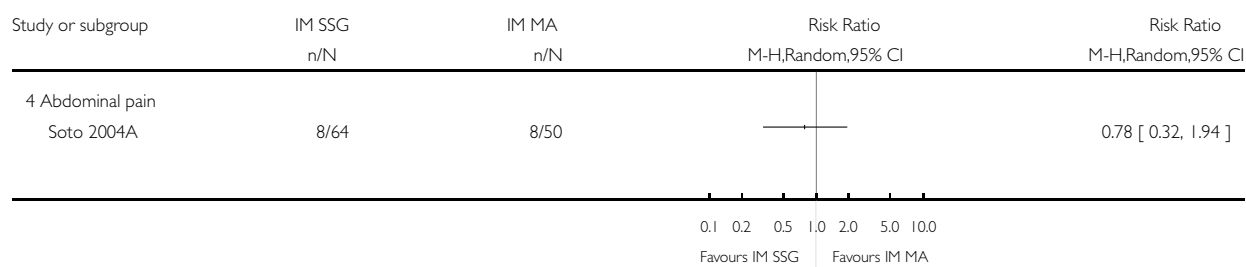
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 7 IMSSG 20 mg/kg/d for 20d vs IMMA (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months

Outcome: 2 Adverse effects



**Analysis 8.1. Comparison 8 IMSSG (branded) vs IMSSG (generic). Dose: 20 mg/kg/d for 20 d in *L. panamensis*; FU: 6 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 8 IMSSG (branded) vs IMSSG (generic). Dose: 20 mg/kg/d for 20 d in *L. panamensis*; FU: 6 months

Outcome: 1 Complete cure

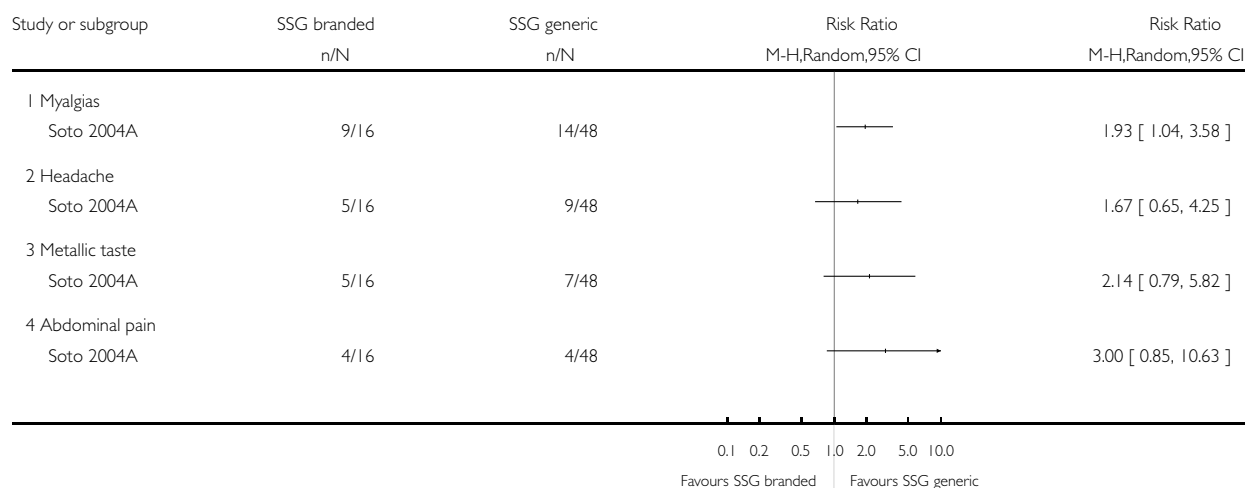


**Analysis 8.2. Comparison 8 IMSSG (branded) vs IMSSG (generic). Dose: 20 mg/kg/d for 20 d in *L. panamensis*; FU: 6 months, Outcome 2 Adverse effects.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 8 IMSSG (branded) vs IMSSG (generic). Dose: 20 mg/kg/d for 20 d in *L. panamensis*; FU: 6 months

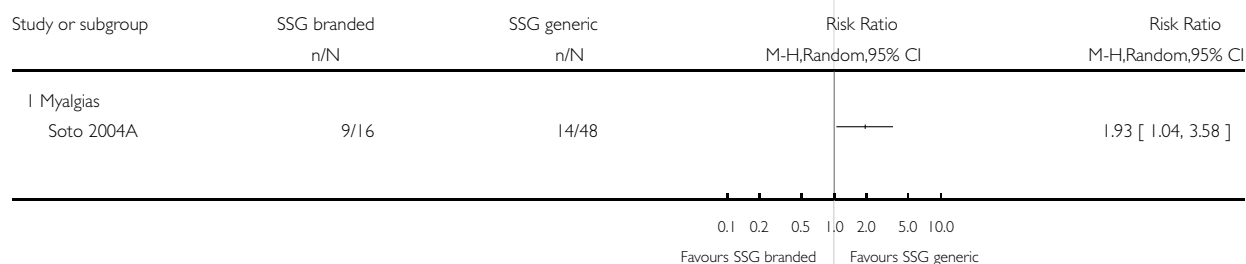
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 8 IMSSG (branded) vs IMSSG (generic). Dose: 20 mg/kg/d for 20 d in *L. panamensis*; FU: 6 months

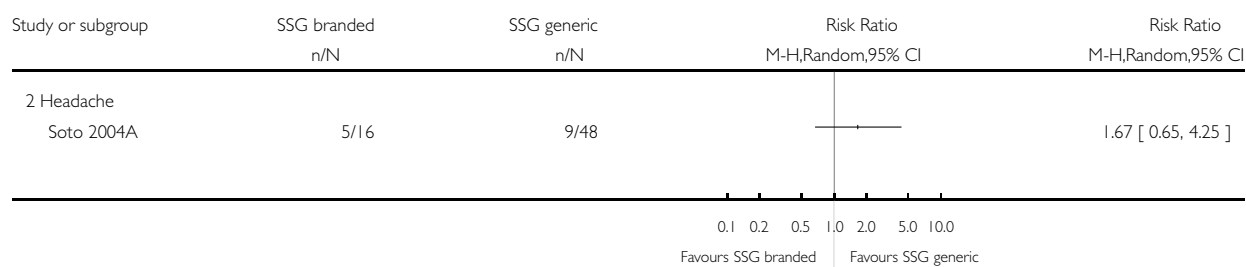
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 8 IMSSG (branded) vs IMSSG (generic). Dose: 20 mg/kg/d for 20 d in *L. panamensis*; FU: 6 months

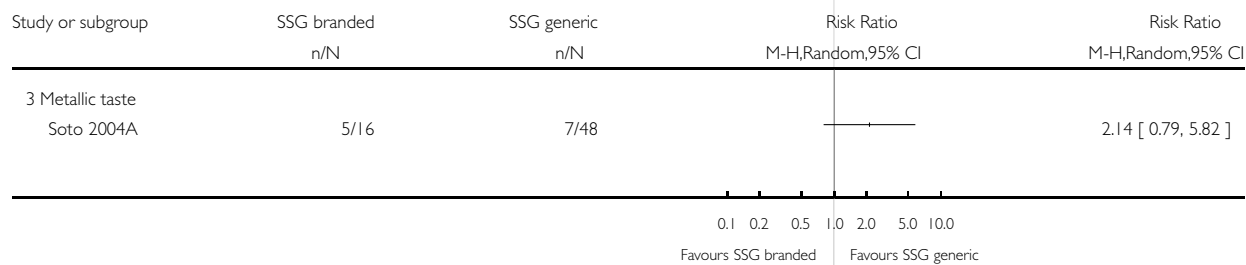
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 8 IMSSG (branded) vs IMSSG (generic). Dose: 20 mg/kg/d for 20 d in *L. panamensis*; FU: 6 months

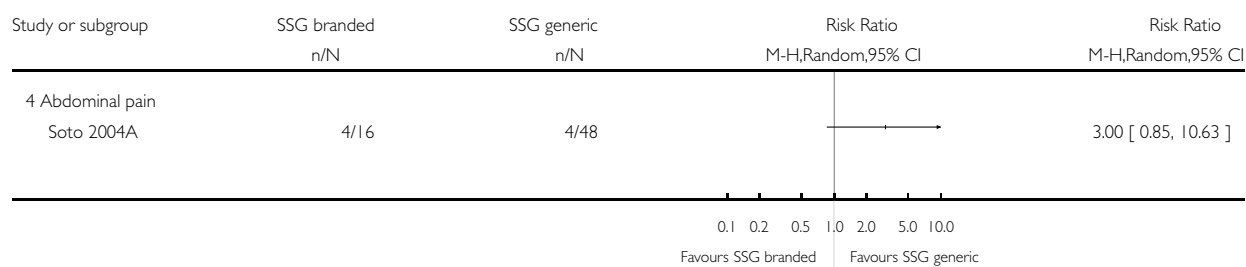
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 8 IMSSG (branded) *vs* IMSSG (generic). Dose: 20 mg/kg/d for 20 d in *L. panamensis*; FU: 6 months

Outcome: 2 Adverse effects

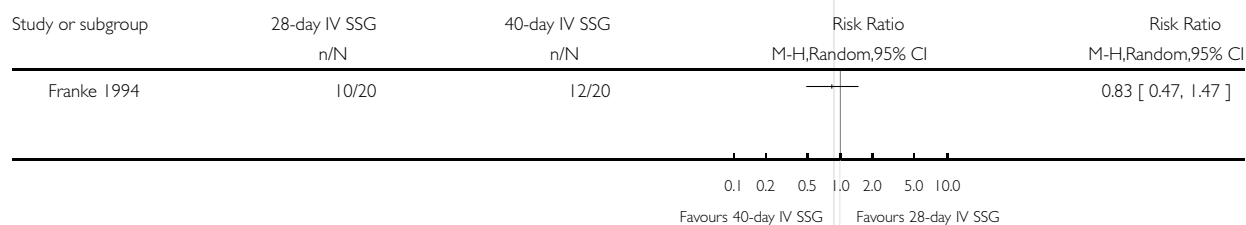


**Analysis 9.1. Comparison 9 IVSSG for 28 days *versus* IVSSG for 40 days in *L. braziliensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 9 IVSSG for 28 days *versus* IVSSG for 40 days in *L. braziliensis*; FU: 1 year

Outcome: 1 Complete cure

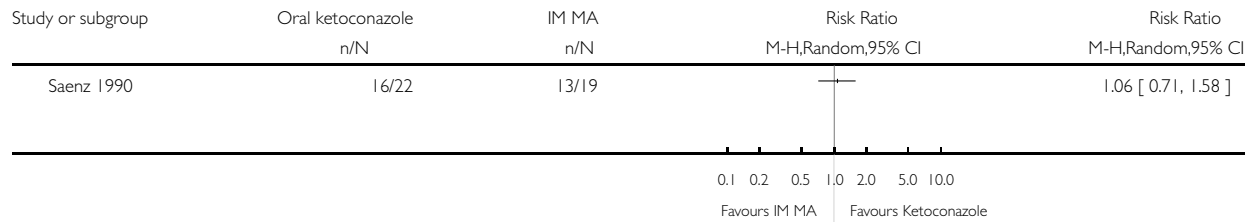


**Analysis 10.1. Comparison 10 Oral ketoconazole for 28 days versus IMMA for 20 days in *L. panamensis* and *L. mexicana*; FU: 3 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 10 Oral ketoconazole for 28 days versus IMMA for 20 days in *L. panamensis* and *L. mexicana*; FU: 3 months

Outcome: 1 Complete cure

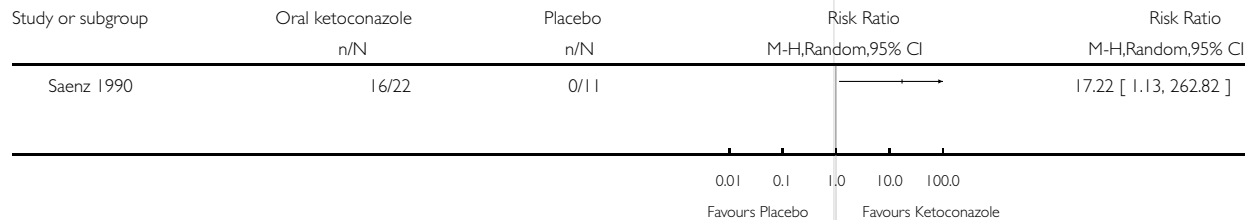


**Analysis 11.1. Comparison 11 Oral ketoconazole versus oral placebo for 28 days in *L. panamensis* and *L. mexicana*; FU: 3 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 11 Oral ketoconazole versus oral placebo for 28 days in *L. panamensis* and *L. mexicana*; FU: 3 months

Outcome: 1 Complete cure

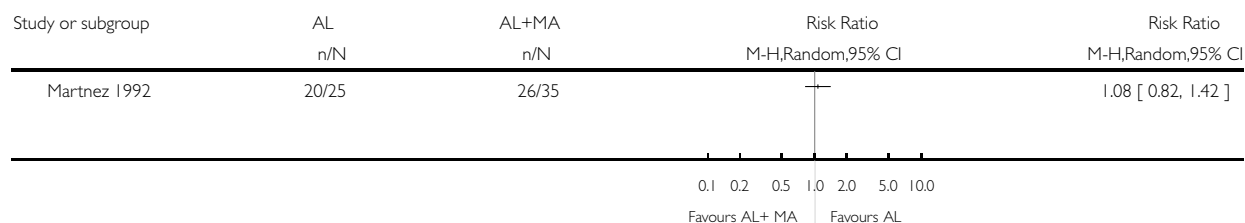


**Analysis 12.1. Comparison 12 Oral AL 20 mg/kg/d (4 doses) for 15d vs. AL + IVMA (same regimen) in *L. panamensis*; FU: 12 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 12 Oral AL 20 mg/kg/d (4 doses) for 15d vs. AL + IVMA (same regimen) in *L. panamensis*; FU: 12 months

Outcome: 1 Complete cure

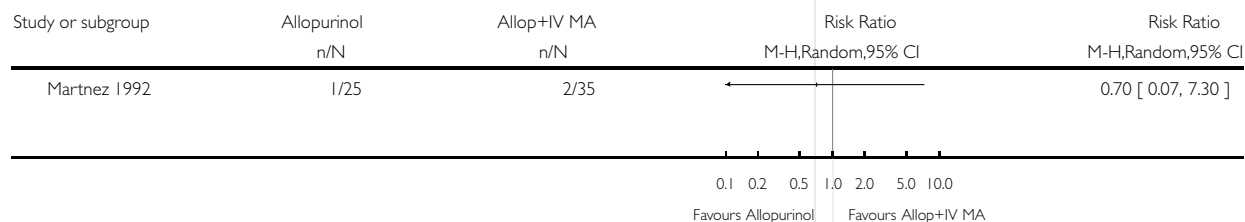


**Analysis 12.2. Comparison 12 Oral AL 20 mg/kg/d (4 doses) for 15d vs. AL + IVMA (same regimen) in *L. panamensis*; FU: 12 months, Outcome 2 Relapses.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 12 Oral AL 20 mg/kg/d (4 doses) for 15d vs. AL + IVMA (same regimen) in *L. panamensis*; FU: 12 months

Outcome: 2 Relapses

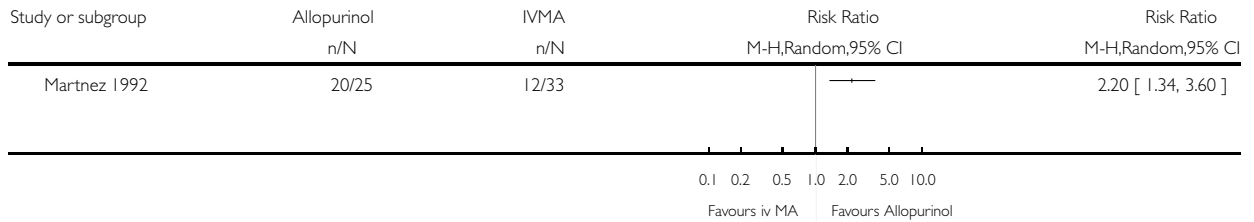


**Analysis 13.1. Comparison 13 Oral AL 20 mg/kg/d (4 doses) x 15d vs. IVMA (same regimen) in *L. panamensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 13 Oral AL 20 mg/kg/d (4 doses) x 15d vs. IVMA (same regimen) in *L. panamensis*; FU: 1 year

Outcome: 1 Complete cure

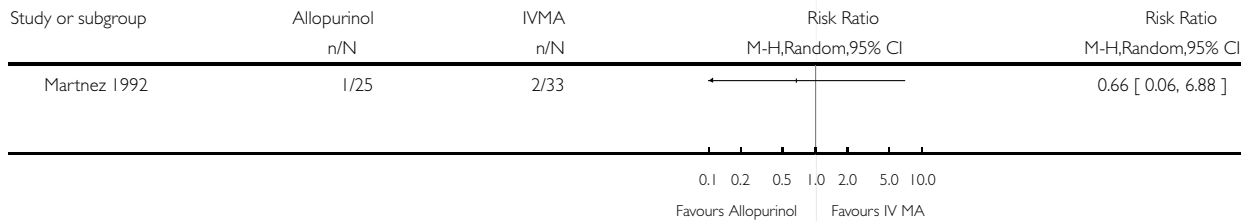


**Analysis 13.2. Comparison 13 Oral AL 20 mg/kg/d (4 doses) x 15d vs. IVMA (same regimen) in *L. panamensis*; FU: 1 year, Outcome 2 Relapses.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 13 Oral AL 20 mg/kg/d (4 doses) x 15d vs. IVMA (same regimen) in *L. panamensis*; FU: 1 year

Outcome: 2 Relapses



**Analysis 14.1. Comparison 14 Oral AL + IVMA (20 mg/kg/d (4 doses) for 15d) vs. IVMA (same regimen) in *L. panamensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 14 Oral AL + IVMA (20 mg/kg/d (4 doses) for 15d) vs. IVMA (same regimen) in *L. panamensis*; FU: 1 year

Outcome: 1 Complete cure



**Analysis 14.2. Comparison 14 Oral AL + IVMA (20 mg/kg/d (4 doses) for 15d) vs. IVMA (same regimen) in *L. panamensis*; FU: 1 year, Outcome 2 Relapses.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 14 Oral AL + IVMA (20 mg/kg/d (4 doses) for 15d) vs. IVMA (same regimen) in *L. panamensis*; FU: 1 year

Outcome: 2 Relapses

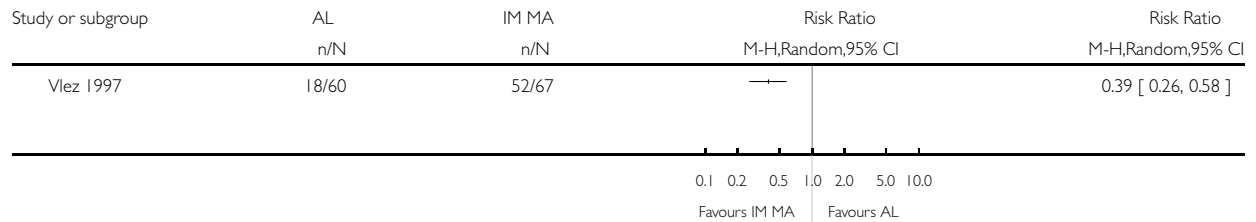


**Analysis 15.1. Comparison 15 Oral AL for 28d vs IMMA 20mg/kg/d for 20 d in *L. braziliensis* and *L. panamensis* ; FU: 12 month, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 15 Oral AL for 28d vs IMMA 20mg/kg/d for 20 d in *L. braziliensis* and *L. panamensis* ; FU: 12 month

Outcome: 1 Complete cure

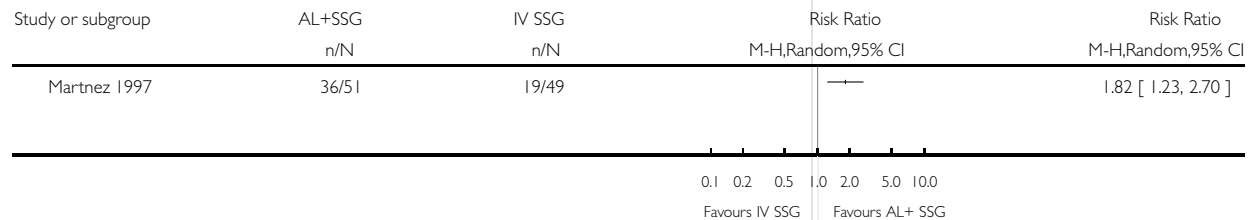


**Analysis 16.1. Comparison 16 Oral AL + IVSSG (20 mg/kg/d (4 doses) x 15d) vs IVSSG (same dose) in *L. braziliensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 16 Oral AL + IVSSG (20 mg/kg/d (4 doses) x 15d) vs IVSSG (same dose) in *L. braziliensis*; FU: 1 year

Outcome: 1 Complete cure

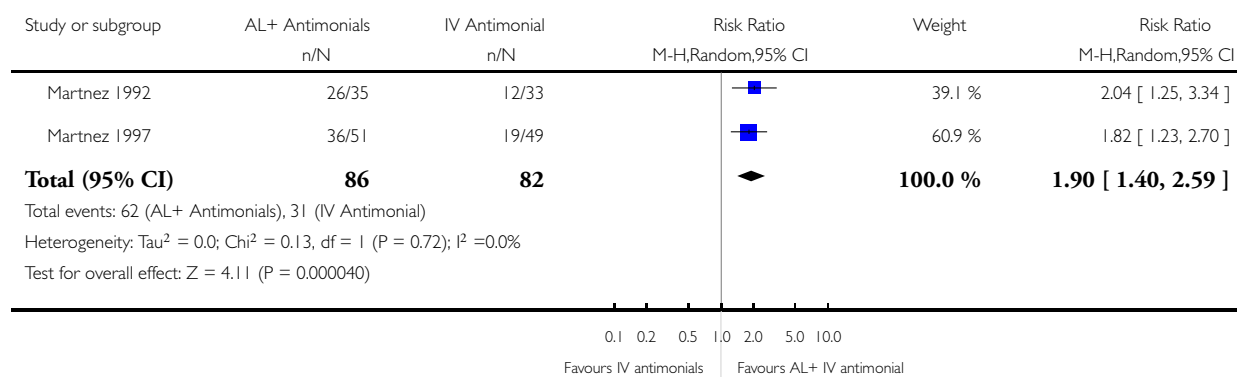


**Analysis 16.2. Comparison 16 Oral AL + IVSSG (20 mg/kg/d (4 doses) x 15d) vs IVSSG (same dose) in *L. braziliensis*; FU: 1 year, Outcome 2 Oral AL plus IV antimonials vs. IV antimonials.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 16 Oral AL + IVSSG (20 mg/kg/d (4 doses) x 15d) vs IVSSG (same dose) in *L. braziliensis*; FU: 1 year

Outcome: 2 Oral AL plus IV antimonials vs. IV antimonials

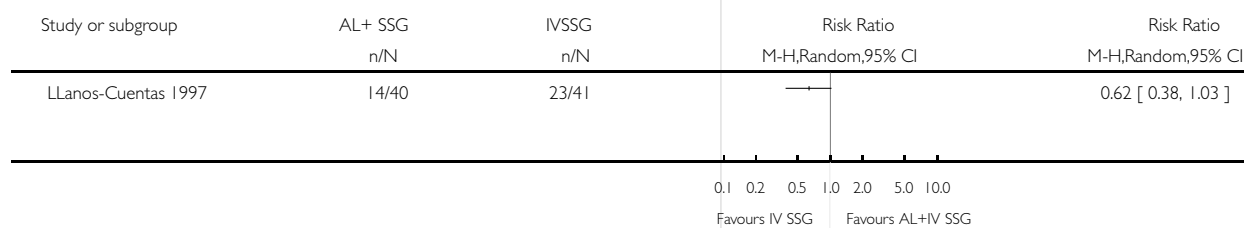


**Analysis 17.1. Comparison 17 Oral AL + IVSSG (20 mg/kg/d (4 doses) for 28d) vs IVSSG (same dose); FU: 12 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 17 Oral AL + IVSSG (20 mg/kg/d (4 doses) for 28d) vs IVSSG (same dose); FU: 12 months

Outcome: 1 Complete cure

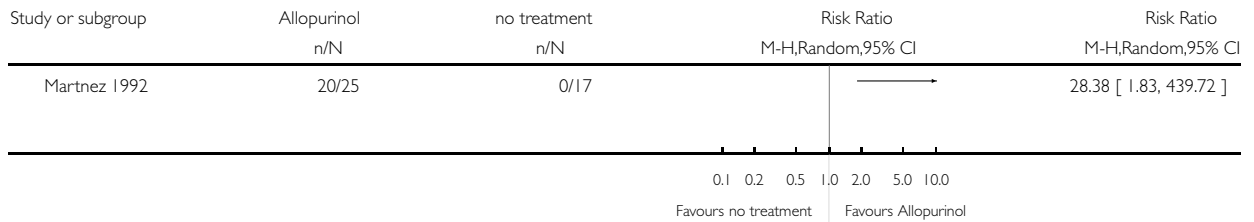


**Analysis 18.1. Comparison 18 Oral AL 20 mg/kg/d (4 doses) for 15 d vs no treatment in *L. panamensis*; FU: 12 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 18 Oral AL 20 mg/kg/d (4 doses) for 15 d vs no treatment in *L. panamensis*; FU: 12 months

Outcome: 1 Complete cure

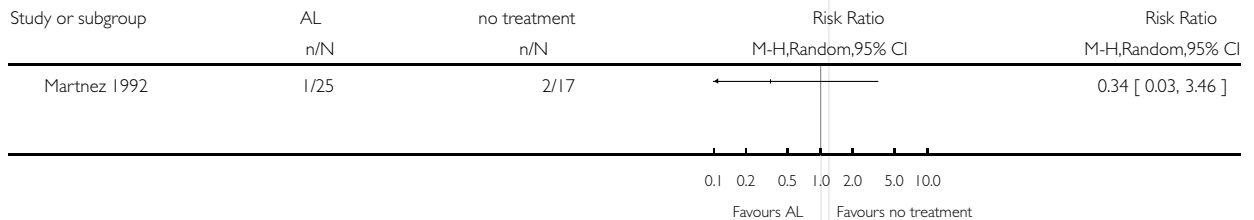


**Analysis 18.2. Comparison 18 Oral AL 20 mg/kg/d (4 doses) for 15 d vs no treatment in *L. panamensis*; FU: 12 months, Outcome 2 Relapses.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 18 Oral AL 20 mg/kg/d (4 doses) for 15 d vs no treatment in *L. panamensis*; FU: 12 months

Outcome: 2 Relapses

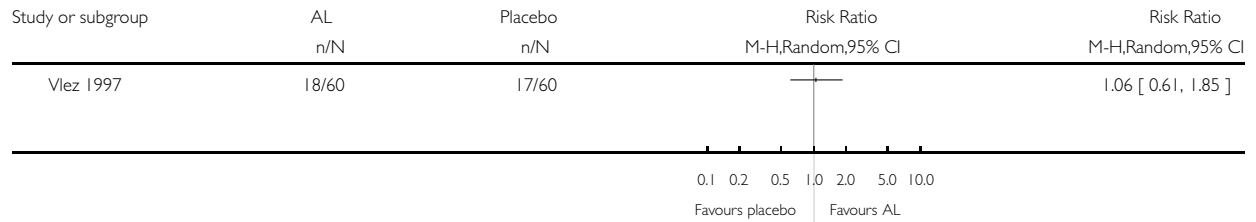


**Analysis 19.1. Comparison 19 Oral AL 28 days versus placebo in *L. braziliensis* and *L. panamensis*; FU: 12 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 19 Oral AL 28 days versus placebo in *L. braziliensis* and *L. panamensis*; FU: 12 months

Outcome: 1 Complete cure



**Analysis 20.1. Comparison 20 Oral AL + IVMA (20 mg/kg/ d in 4 doses for 15d) vs no treatment in *L. panamensis*; FU: 12 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 20 Oral AL + IVMA (20 mg/kg/ d in 4 doses for 15d) vs no treatment in *L. panamensis*; FU: 12 months

Outcome: 1 Complete cure



**Analysis 20.2. Comparison 20 Oral AL + IVMA (20 mg/kg/ d in 4 doses for 15d) vs no treatment in *L. panamensis*; FU: 12 months, Outcome 2 Relapses.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 20 Oral AL + IVMA (20 mg/kg/ d in 4 doses for 15d) vs no treatment in *L. panamensis*; FU: 12 months

Outcome: 2 Relapses

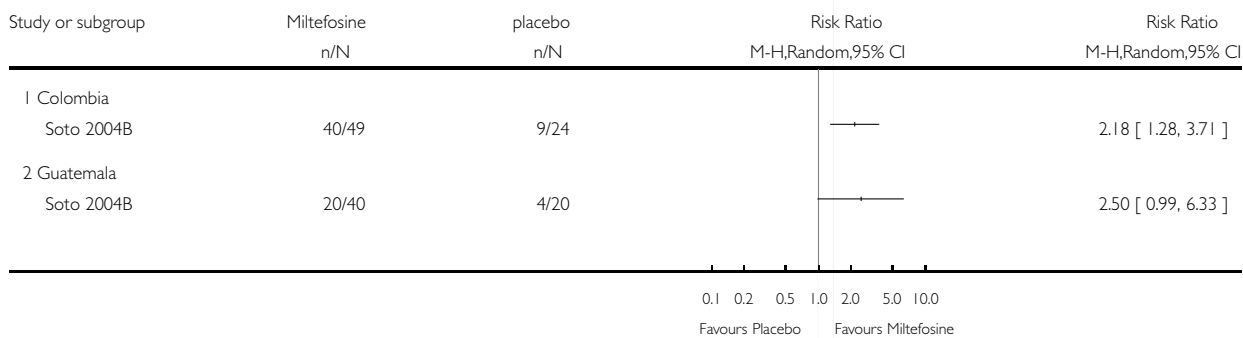


**Analysis 21.1. Comparison 21 Oral miltefosine 50 mg for 28 d vs. placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 21 Oral miltefosine 50 mg for 28 d vs. placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

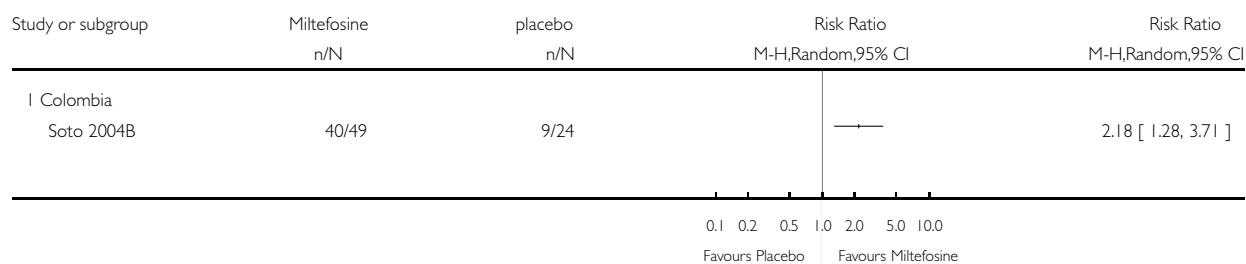
Outcome: 1 Complete cure



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 21 Oral miltefosine 50 mg for 28 d *vs.* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

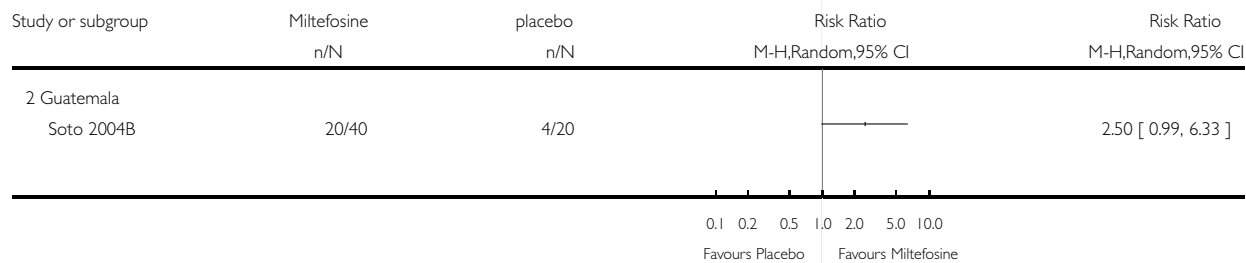
Outcome: 1 Complete cure



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 21 Oral miltefosine 50 mg for 28 d *vs.* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

Outcome: 1 Complete cure

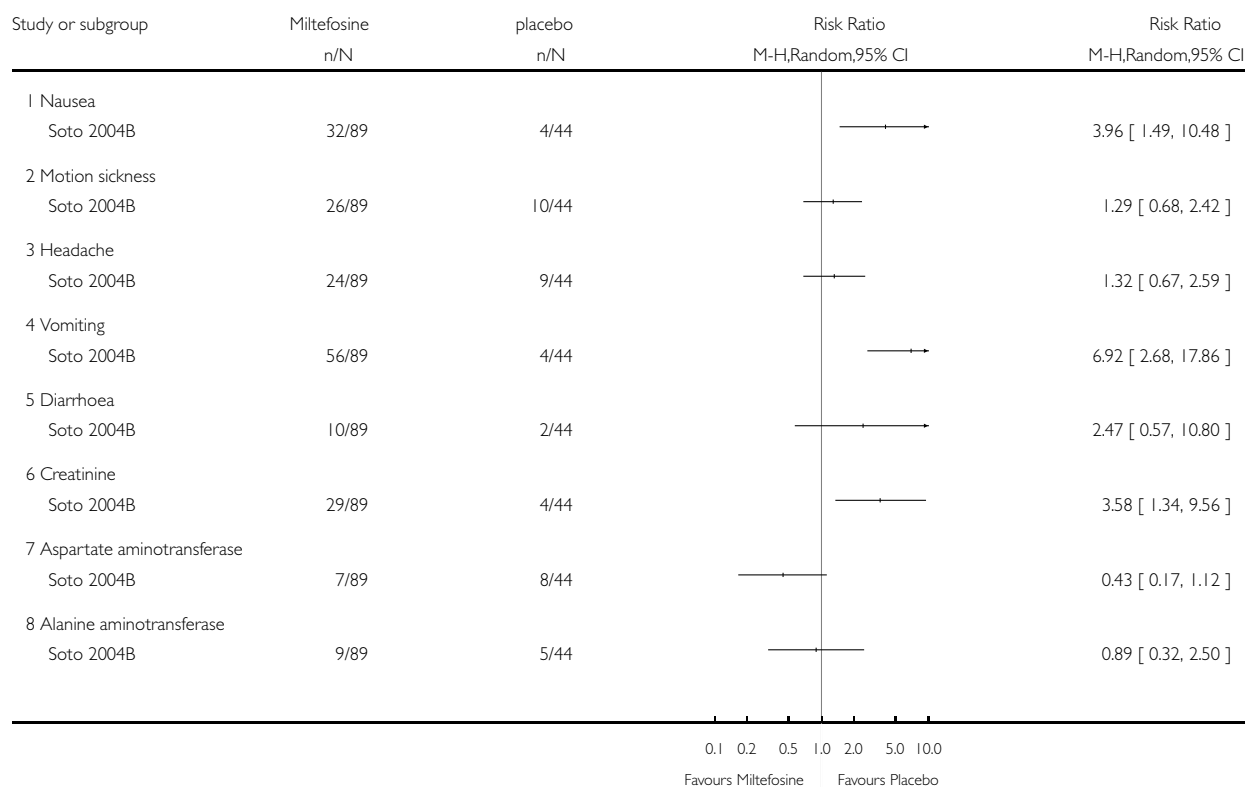


**Analysis 21.2. Comparison 21 Oral miltefosine 50 mg for 28 d vs. placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months, Outcome 2 Adverse effects.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 21 Oral miltefosine 50 mg for 28 d vs. placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

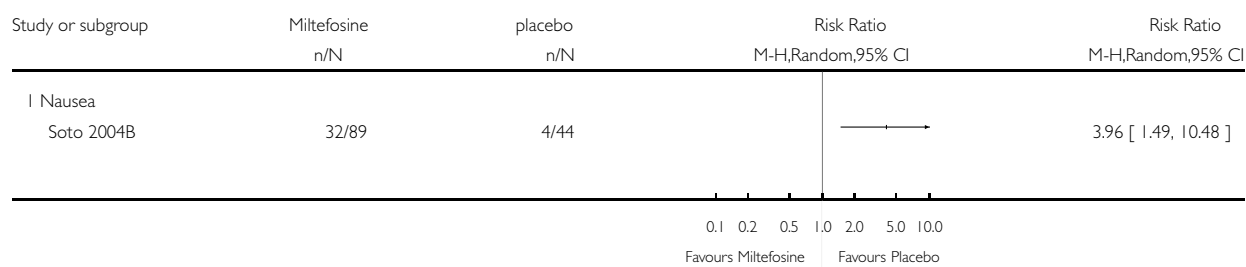
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 21 Oral miltefosine 50 mg for 28 d *vs.* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

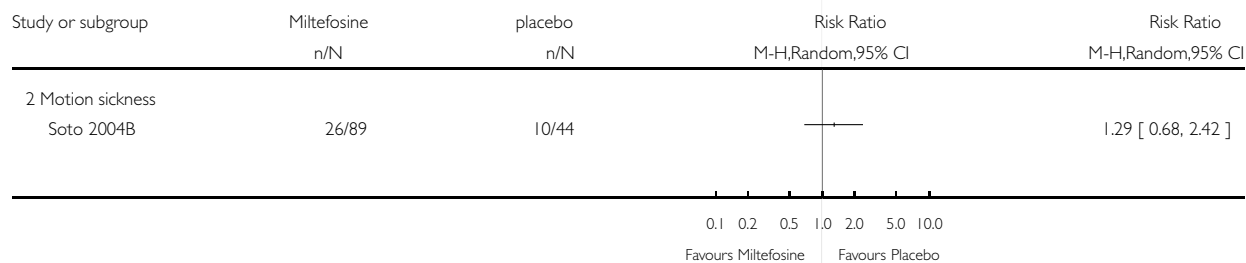
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 21 Oral miltefosine 50 mg for 28 d *vs.* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

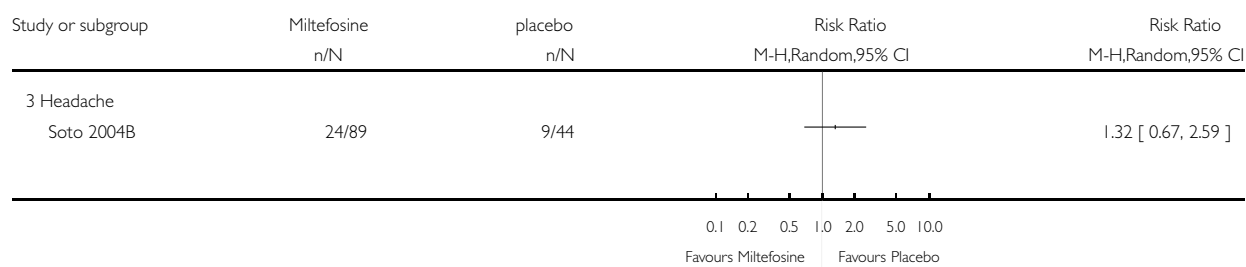
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 21 Oral miltefosine 50 mg for 28 d *vs.* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

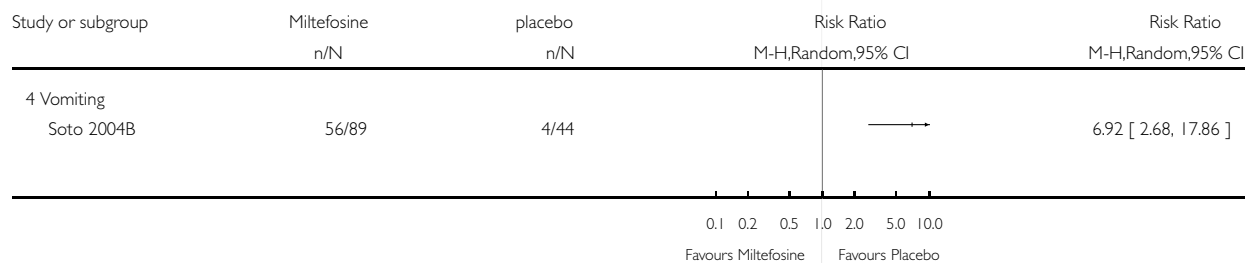
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 21 Oral miltefosine 50 mg for 28 d *vs.* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

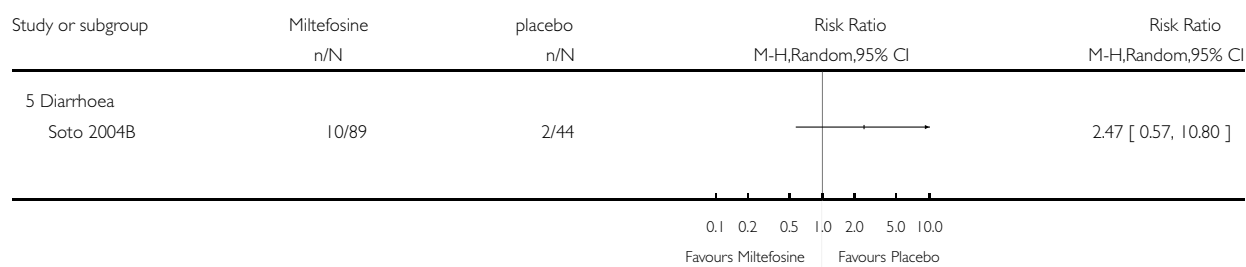
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 21 Oral miltefosine 50 mg for 28 d *vs.* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

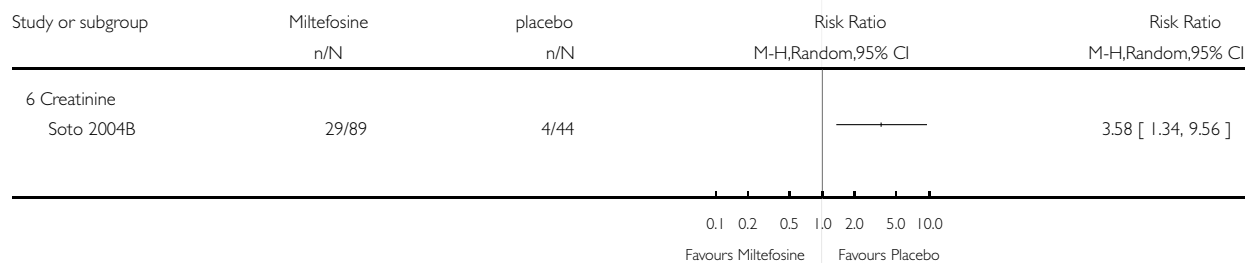
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 21 Oral miltefosine 50 mg for 28 d *vs.* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

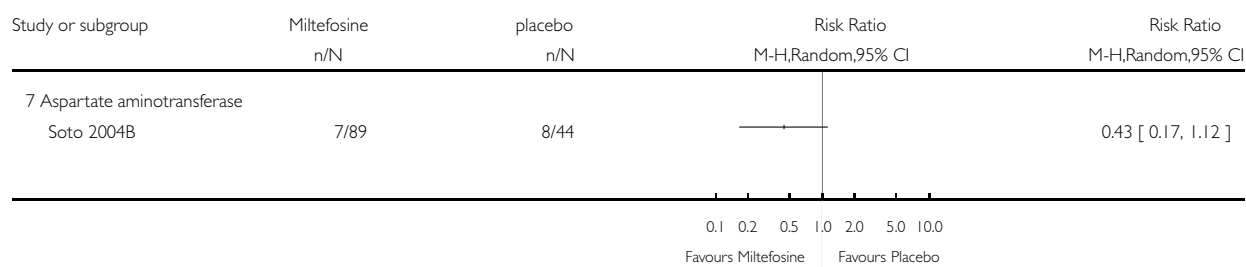
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 21 Oral miltefosine 50 mg for 28 d *vs.* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

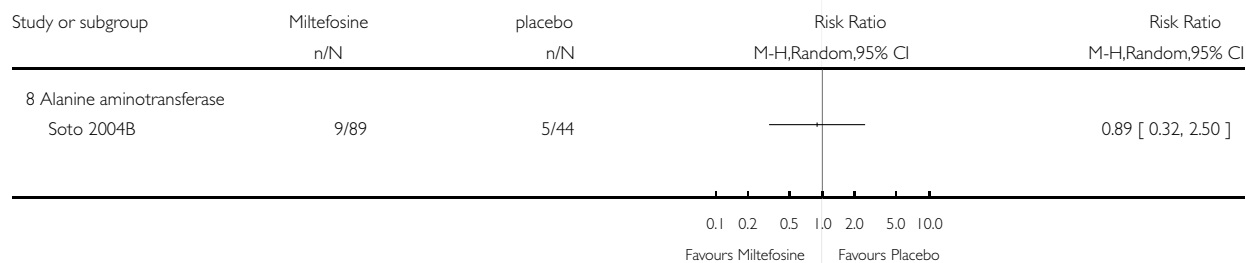
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 21 Oral miltefosine 50 mg for 28 d *vs.* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

Outcome: 2 Adverse effects

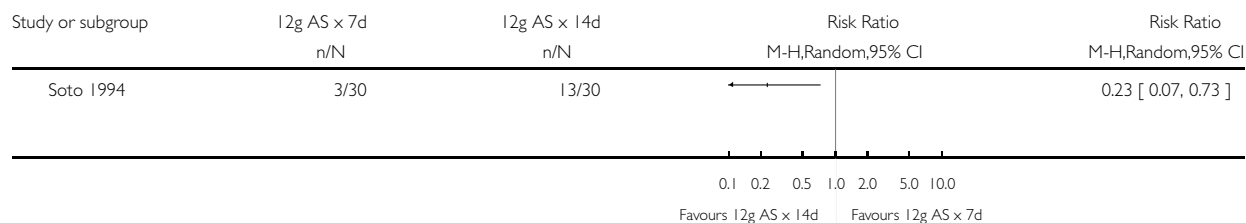


**Analysis 22.1. Comparison 22 Different regimens of IMAS in *L. panamensis*; FU: 1 year, Outcome 1 AS 12-g base x 7 days versus AS 12-g base x 14 days.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 22 Different regimens of IMAS in *L. panamensis*; FU: 1 year

Outcome: 1 AS 12-g base x 7 days versus AS 12-g base x 14 days



**Analysis 22.2. Comparison 22 Different regimens of IMAS in *L. panamensis*; FU: 1 year, Outcome 2 AS 12-g base x 7d versus AS 18-g base for 14 d.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 22 Different regimens of IMAS in *L. panamensis*; FU: 1 year

Outcome: 2 AS 12-g base x 7d versus AS 18-g base for 14 d



**Analysis 22.3. Comparison 22 Different regimens of IMAS in *L. panamensis*; FU: 1 year, Outcome 3 AS 12-g base x 14 d versus AS 18-g base x 14 d.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 22 Different regimens of IMAS in *L. panamensis*; FU: 1 year

Outcome: 3 AS 12-g base x 14 d versus AS 18-g base x 14 d

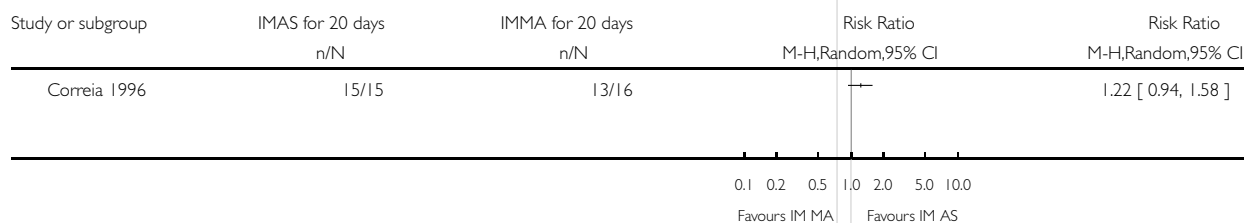


**Analysis 23.1. Comparison 23 IMAS for 20 days versus IMMA for 20 days in *L. braziliensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 23 IMAS for 20 days versus IMMA for 20 days in *L. braziliensis*; FU: 1 year

Outcome: 1 Complete cure

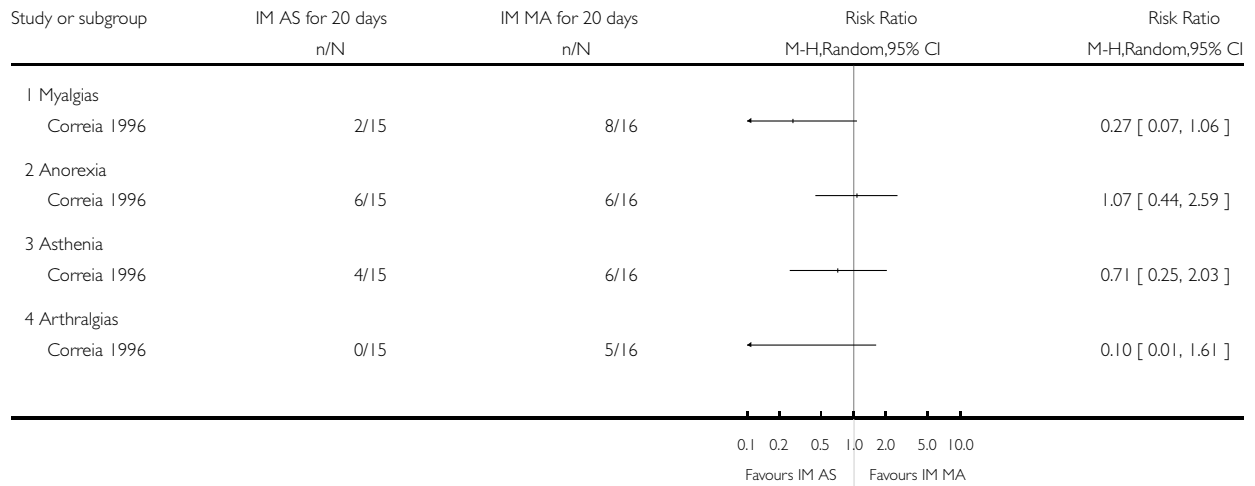


**Analysis 23.2. Comparison 23 IMAS for 20 days versus IMMA for 20 days in *L. braziliensis*; FU: 1 year, Outcome 2 Adverse effects.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 23 IMAS for 20 days versus IMMA for 20 days in *L. braziliensis*; FU: 1 year

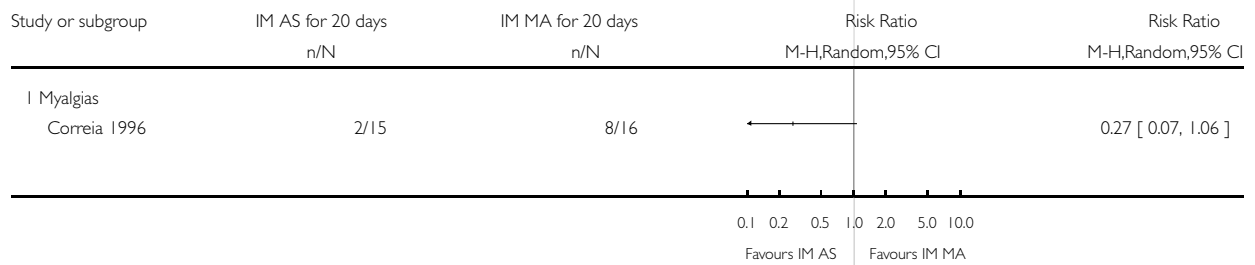
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 23 IMAS for 20 days versus IMMA for 20 days in *L. braziliensis*; FU: 1 year

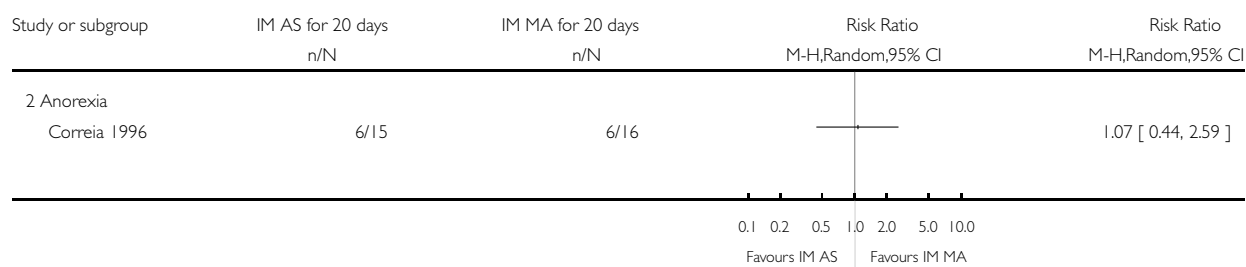
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 23 IMAS for 20 days *versus* IMMA for 20 days in *L. braziliensis*; FU: 1 year

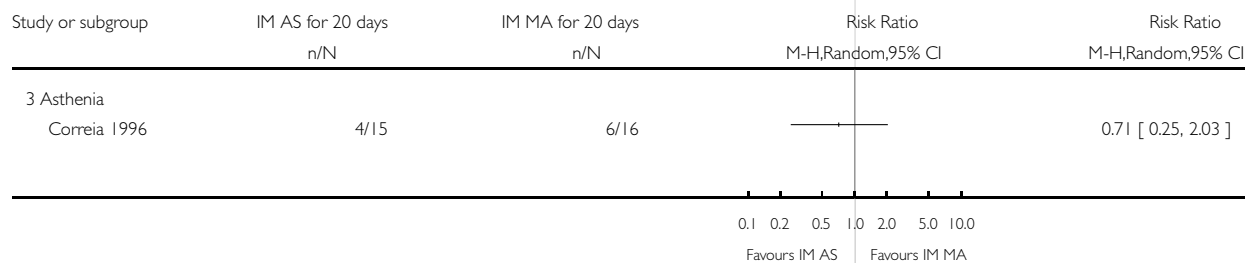
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 23 IMAS for 20 days *versus* IMMA for 20 days in *L. braziliensis*; FU: 1 year

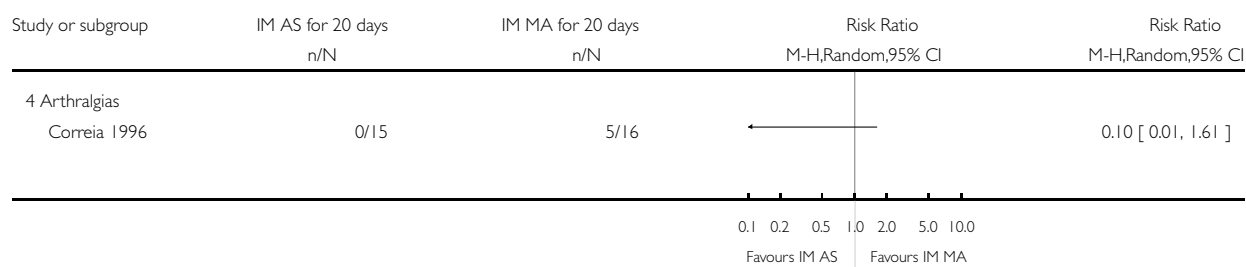
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 23 IMAS for 20 days *versus* IMMA for 20 days in *L. braziliensis*; FU: 1 year

Outcome: 2 Adverse effects

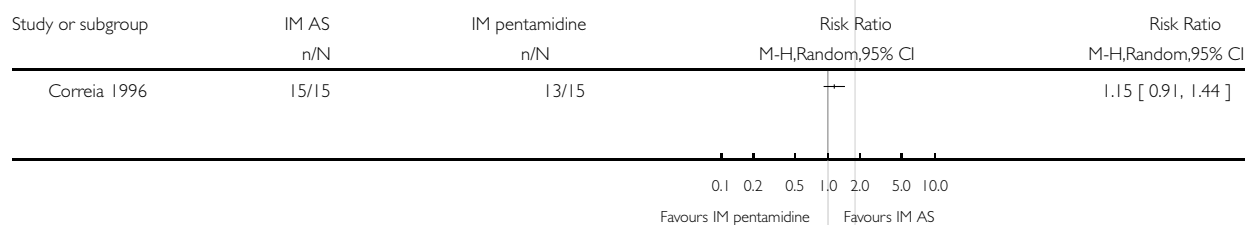


**Analysis 24.1. Comparison 24 IMAS for 20 days *versus* IMPI x 8 applications in *L. braziliensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 24 IMAS for 20 days *versus* IMPI x 8 applications in *L. braziliensis*; FU: 1 year

Outcome: 1 Complete cure

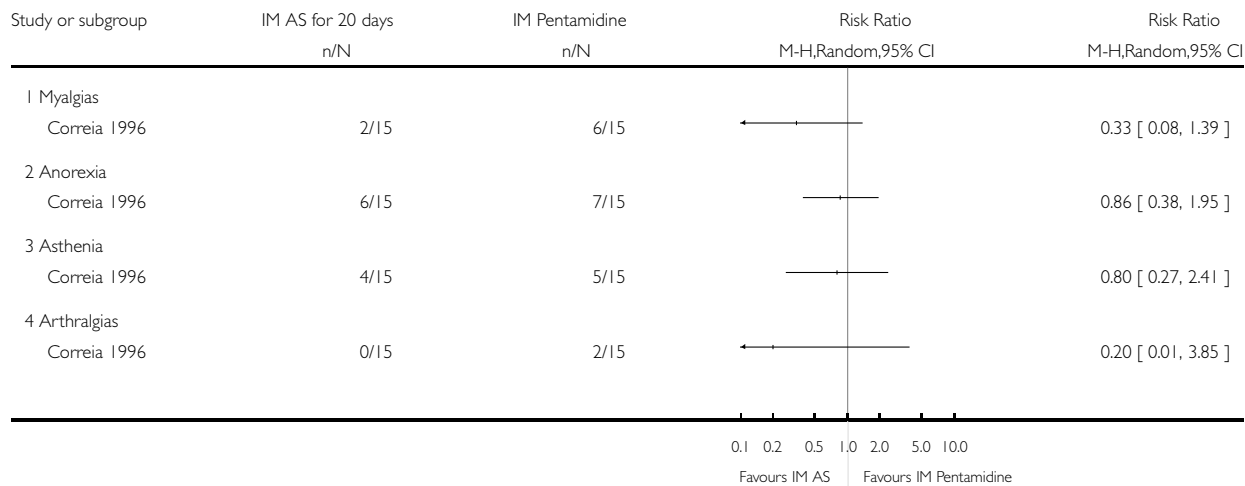


**Analysis 24.2. Comparison 24 IMAS for 20 days versus IMPI x 8 applications in *L. braziliensis*; FU: 1 year, Outcome 2 Adverse effects.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 24 IMAS for 20 days versus IMPI x 8 applications in *L. braziliensis*; FU: 1 year

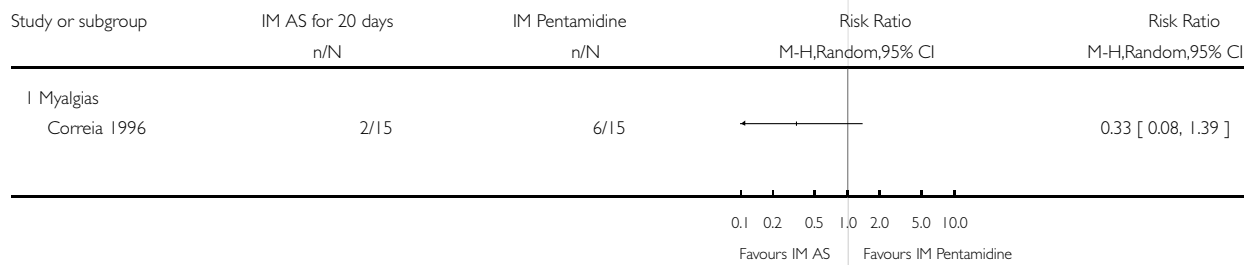
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 24 IMAS for 20 days versus IMPI x 8 applications in *L. braziliensis*; FU: 1 year

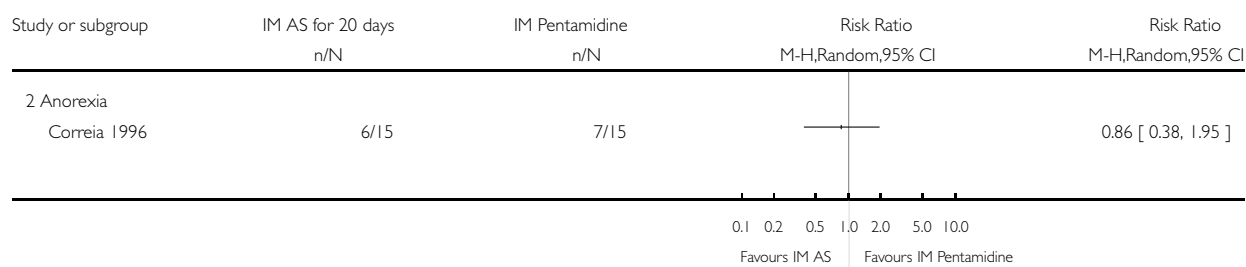
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 24 IMAS for 20 days *versus* IMPI x 8 applications in *L. braziliensis*; FU: 1 year

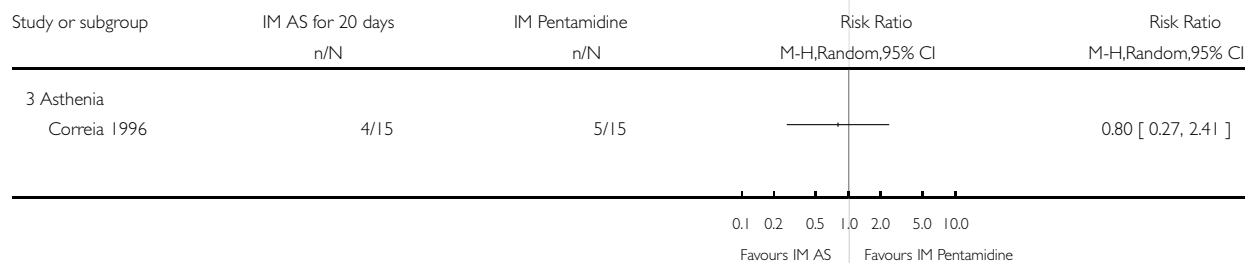
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 24 IMAS for 20 days *versus* IMPI x 8 applications in *L. braziliensis*; FU: 1 year

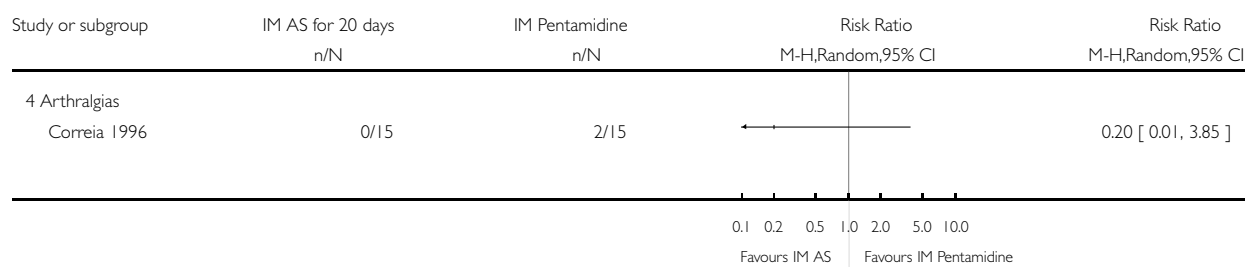
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 24 IMAS for 20 days *versus* IMPI x 8 applications in *L. braziliensis*; FU: 1 year

Outcome: 2 Adverse effects

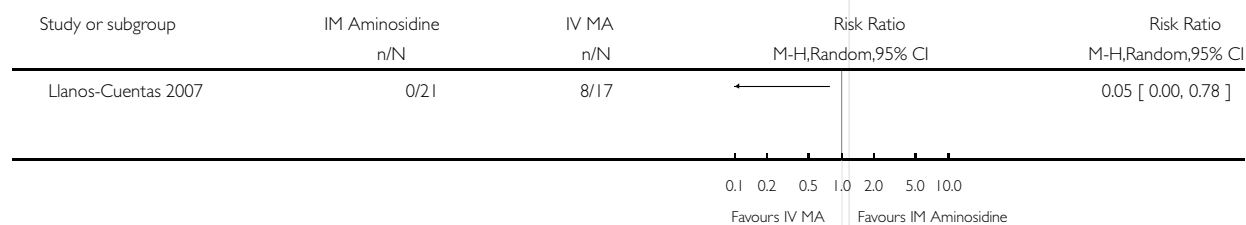


**Analysis 25.1. Comparison 25 IM Aminosidine 20 mg/kg/d for 28 d vs IVMA 20 mg/kg for 28 d; *L. braziliensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 25 IM Aminosidine 20 mg/kg/d for 28 d vs IVMA 20 mg/kg for 28 d; *L. braziliensis*; FU: 1 year

Outcome: 1 Complete cure

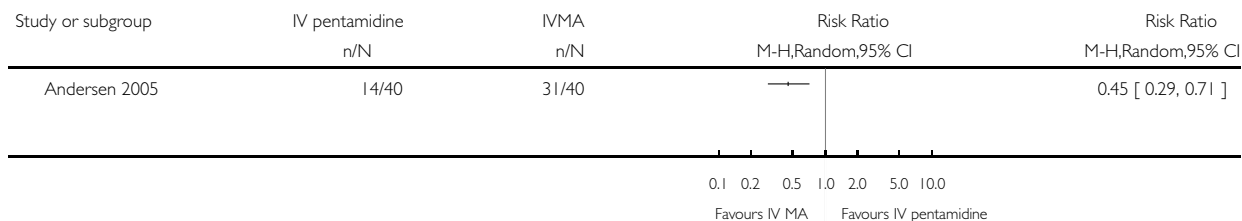


**Analysis 26.1. Comparison 26 IVPI for seven doses versus IVMA for 20 days in *L. braziliensis*; FU: 6 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 26 IVPI for seven doses versus IVMA for 20 days in *L. braziliensis*; FU: 6 months

Outcome: 1 Complete cure

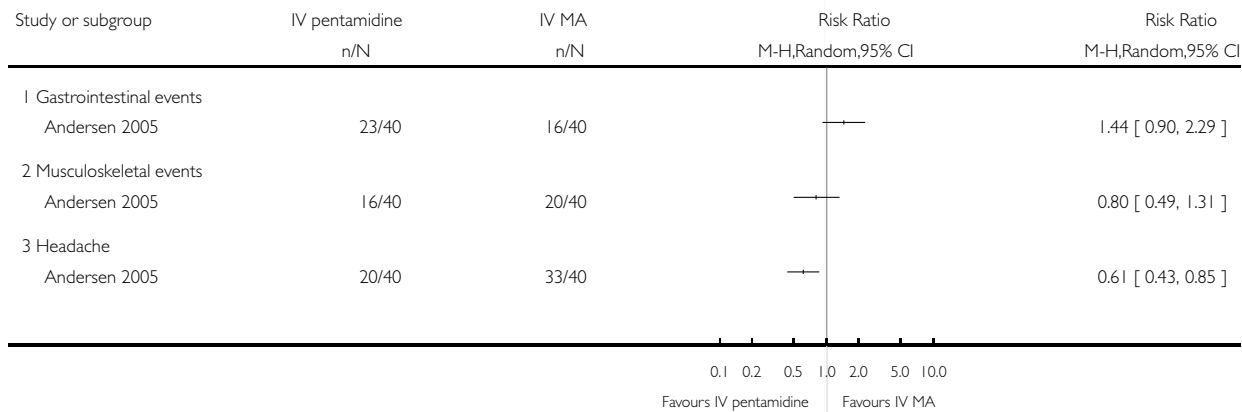


**Analysis 26.2. Comparison 26 IVPI for seven doses versus IVMA for 20 days in *L. braziliensis*; FU: 6 months, Outcome 2 Adverse effects.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 26 IVPI for seven doses versus IVMA for 20 days in *L. braziliensis*; FU: 6 months

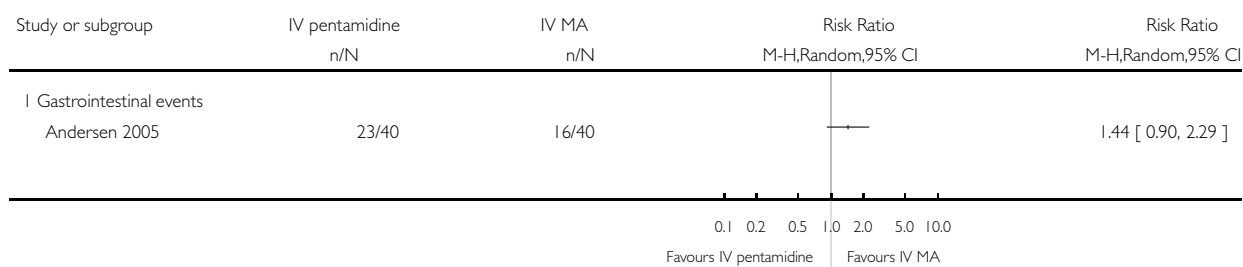
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 26 IVPI for seven doses *versus* IVMA for 20 days in *L. braziliensis*; FU: 6 months

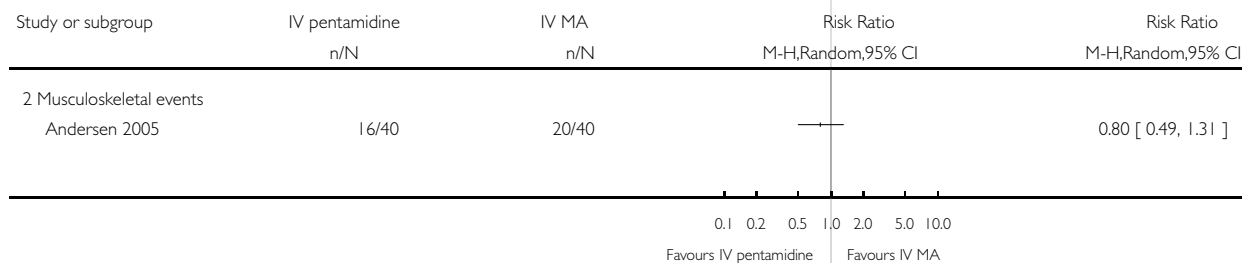
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 26 IVPI for seven doses *versus* IVMA for 20 days in *L. braziliensis*; FU: 6 months

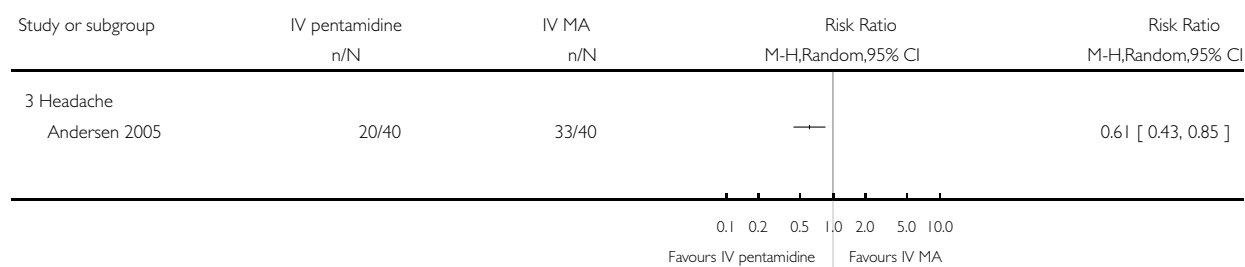
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 26 IVPI for seven doses *versus* IVMA for 20 days in *L. braziliensis*; FU: 6 months

Outcome: 2 Adverse effects



### Analysis 27.1. Comparison 27 IMPI *versus* IMMA for 20 days in *L. braziliensis*; FU: 1 year, Outcome 1 Complete cure.

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 27 IMPI *versus* IMMA for 20 days in *L. braziliensis*; FU: 1 year

Outcome: 1 Complete cure

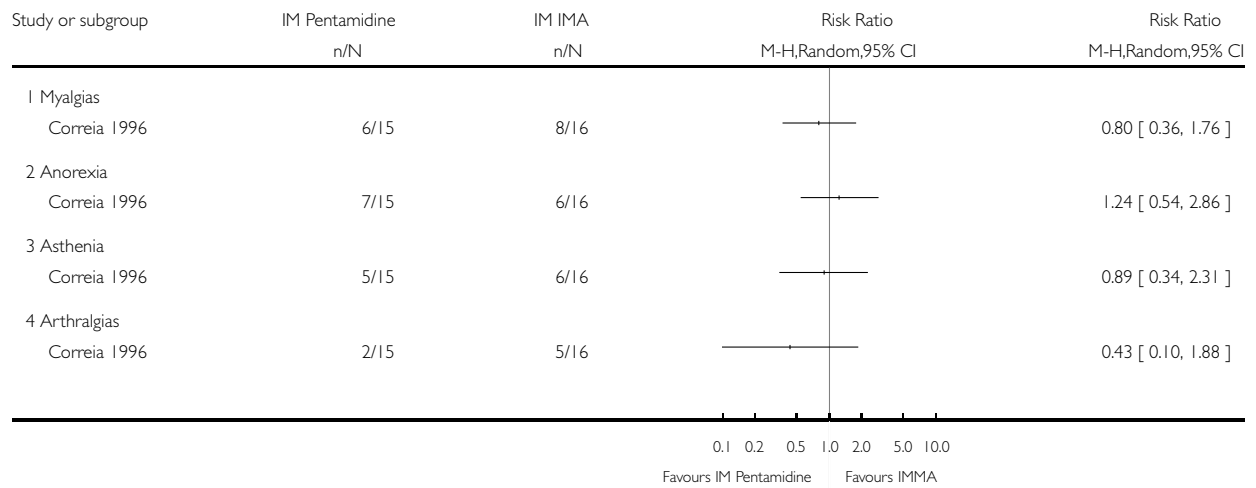


**Analysis 27.2. Comparison 27 IMPI versus IMMA for 20 days in *L. braziliensis*; FU: 1 year, Outcome 2 Adverse effects.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 27 IMPI versus IMMA for 20 days in *L. braziliensis*; FU: 1 year

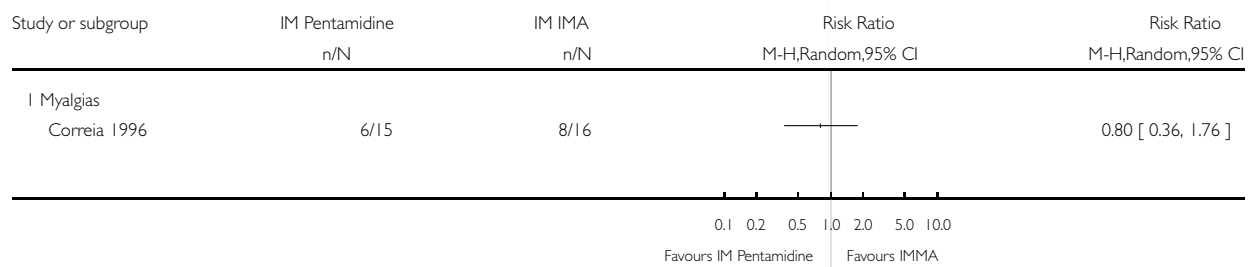
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 27 IMPI versus IMMA for 20 days in *L. braziliensis*; FU: 1 year

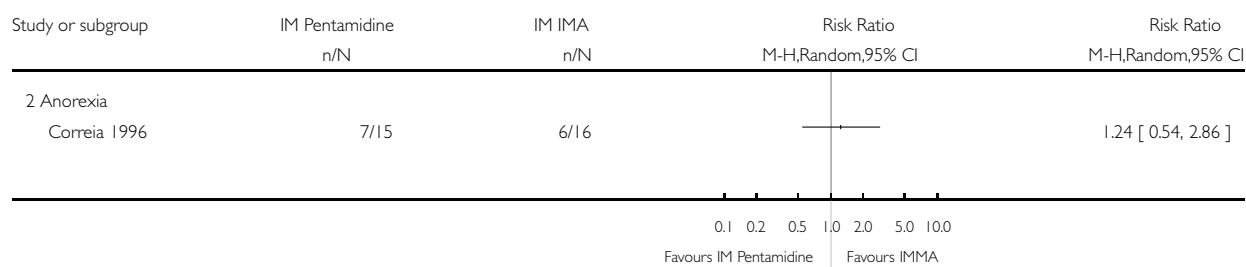
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 27 IMPI *versus* IMMA for 20 days in *L. braziliensis*; FU: 1 year

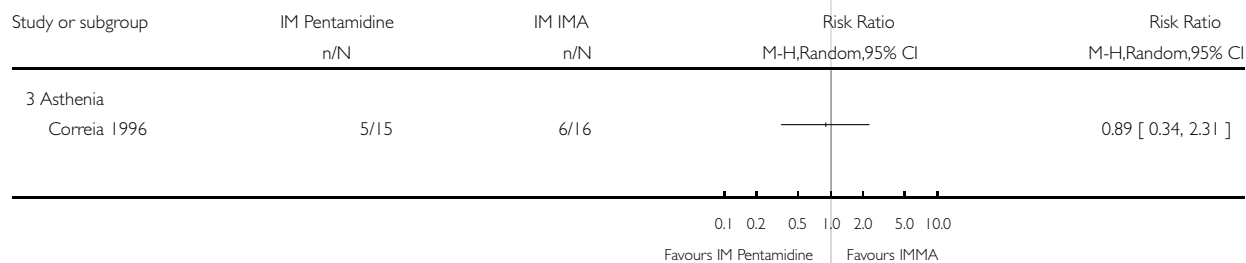
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 27 IMPI *versus* IMMA for 20 days in *L. braziliensis*; FU: 1 year

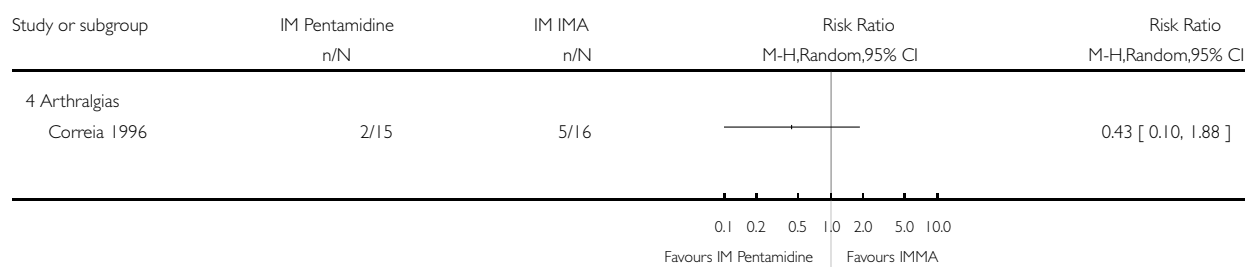
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 27 IMPI *versus* IMMA for 20 days in *L. braziliensis*; FU: 1 year

Outcome: 2 Adverse effects

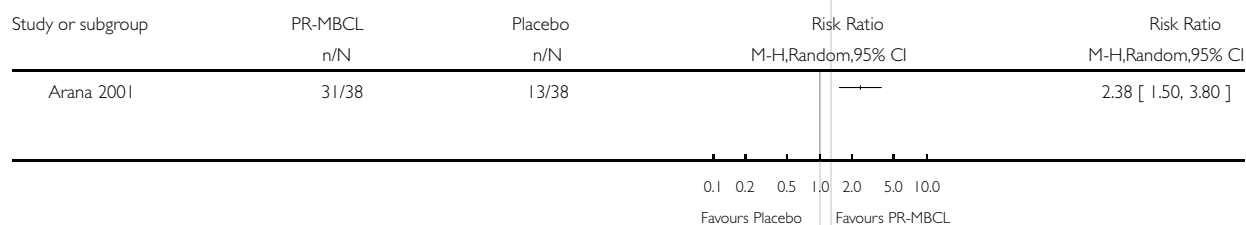


**Analysis 28.1. Comparison 28 Topical PR-MBCL TD for 20d *vs* placebo TD for 20d in *L. panamensis* and *L. mexicana*; FU: 12 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 28 Topical PR-MBCL TD for 20d *vs* placebo TD for 20d in *L. panamensis* and *L. mexicana*; FU: 12 months

Outcome: 1 Complete cure



**Analysis 29.I. Comparison 29 Topical PR-MBCL (TD x 10d) + IVMA x 7 d vs Placebo + IVMA x 7 d in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 29 Topical PR-MBCL (TD x 10d) + IVMA x 7 d vs Placebo + IVMA x 7 d in *L. braziliensis* and *L. panamensis*; FU: 1 year

Outcome: 1 Complete cure

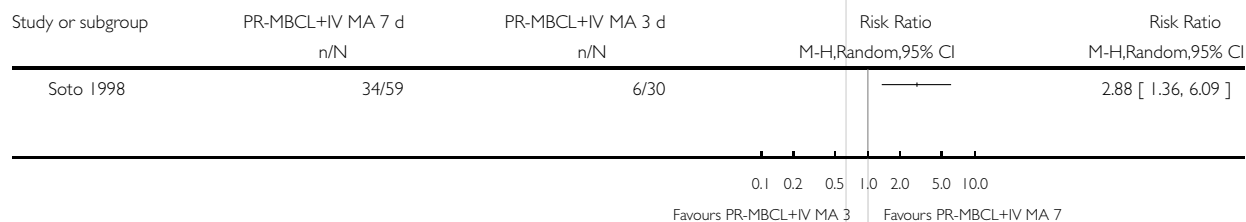


**Analysis 30.I. Comparison 30 Topical PR-MBCL (TD x 10d) + IVMA x 7 d vs PR-MBCL + IVMA x 3 d in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 30 Topical PR-MBCL (TD x 10d) + IVMA x 7 d vs PR-MBCL + IVMA x 3 d in *L. braziliensis* and *L. panamensis*; FU: 1 year

Outcome: 1 Complete cure

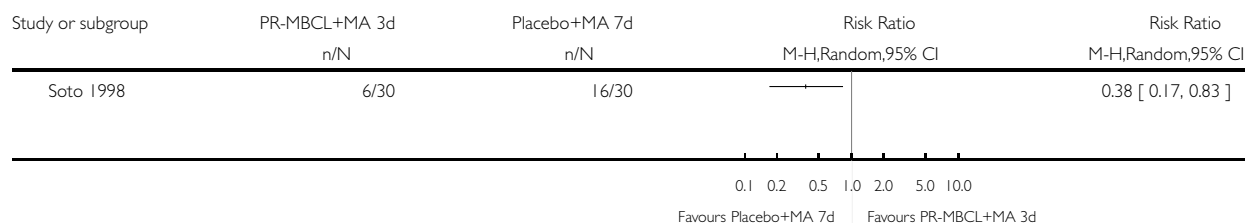


**Analysis 31.1. Comparison 31 Topical PR-MBCL (TD x 10d) + IVMA x 3 d vs Placebo + IVMA x 7 d in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 31 Topical PR-MBCL (TD x 10d) + IVMA x 3 d vs Placebo + IVMA x 7 d in *L. braziliensis* and *L. panamensis*; FU: 1 year

Outcome: 1 Complete cure



**Analysis 32.1. Comparison 32 Topical PR-MBCL (TD x 10d) + IVMA x 7 d vs IVMA for 20 d in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 32 Topical PR-MBCL (TD x 10d) + IVMA x 7 d vs IVMA for 20 d in *L. braziliensis* and *L. panamensis*; FU: 1 year

Outcome: 1 Complete cure

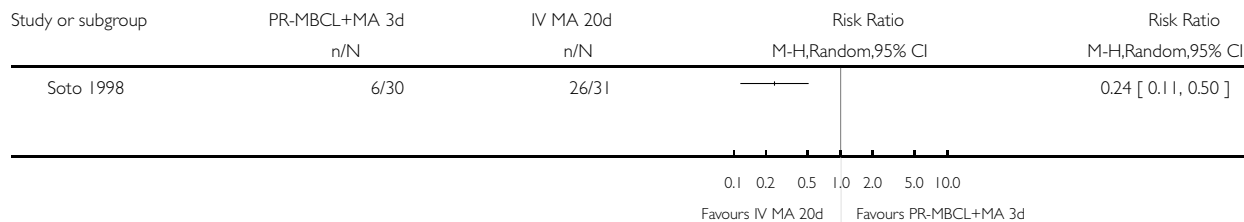


**Analysis 33.1. Comparison 33 Topical PR-MBCL (TD x 10d) + IVMA x 3 d vs IVMA for 20 d in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 33 Topical PR-MBCL (TD x 10d) + IVMA x 3 d vs IVMA for 20 d in *L. braziliensis* and *L. panamensis*; FU: 1 year

Outcome: 1 Complete cure

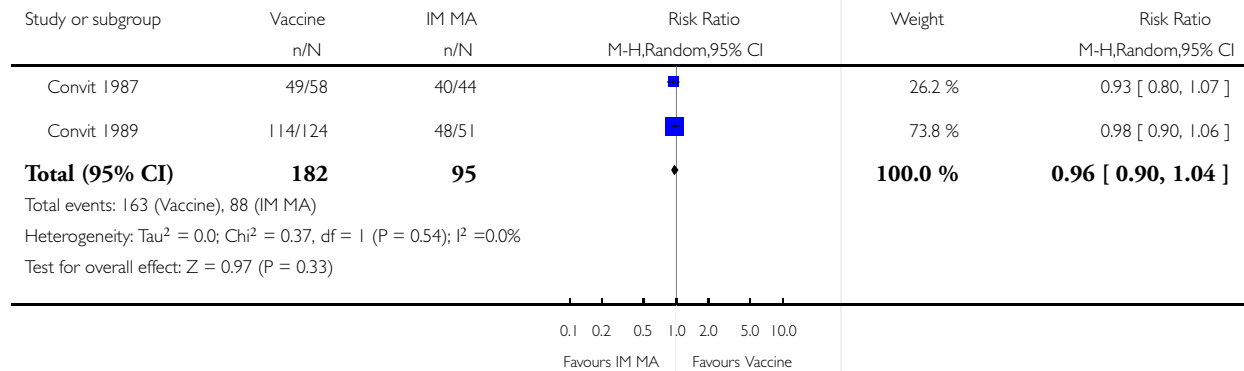


**Analysis 34.1. Comparison 34 Vaccine vs IMMA (50 mg/kg in 2-3 series of 20 daily injections) in *L. braziliensis*; FU: 6 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 34 Vaccine vs IMMA (50 mg/kg in 2-3 series of 20 daily injections) in *L. braziliensis*; FU: 6 months

Outcome: 1 Complete cure

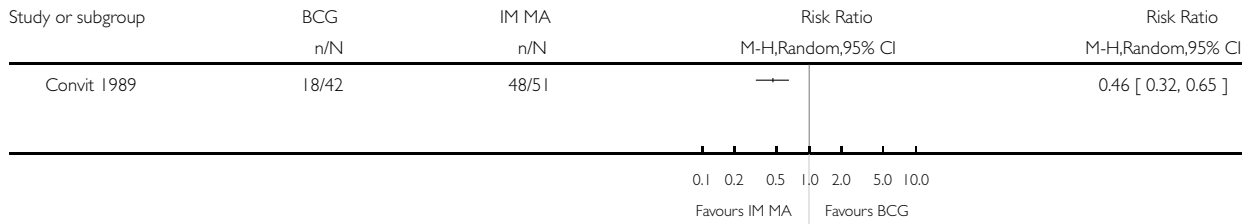


**Analysis 35.1. Comparison 35 BCG vs. IMMA in *L. braziliensis*; FU: 6 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 35 BCG vs. IMMA in *L. braziliensis*; FU: 6 months

Outcome: 1 Complete cure

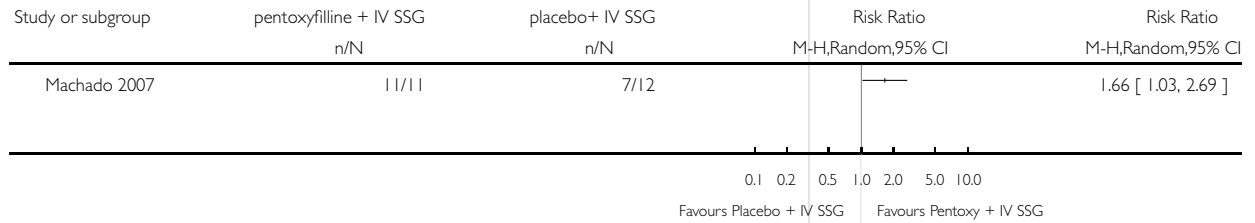


**Analysis 36.1. Comparison 36 Oral pentoxifylline 400 mg 3 times daily for 30d + IVSSG 20 mg/kg /d vs. placebo + IVSSG in *L. braziliensis*; FU: 4 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 36 Oral pentoxifylline 400 mg 3 times daily for 30d + IVSSG 20 mg/kg /d vs. placebo + IVSSG in *L. braziliensis*; FU: 4 months

Outcome: 1 Complete cure

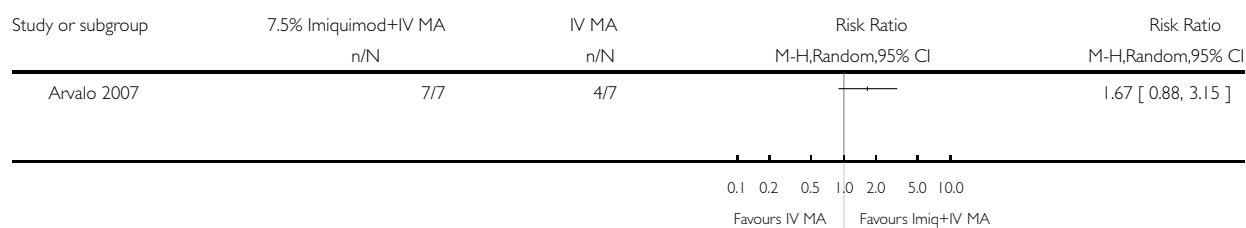


**Analysis 37.1. Comparison 37 7.5% imiquimod cream x 20 days plus IVMA for 20 days versus IVMA x 20 days in *L. braziliensis*, *L. peruviana*, *L. mexicana* and *L. amazonensis*; FU: 3 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 37 7.5% imiquimod cream x 20 days plus IVMA for 20 days versus IVMA x 20 days in *L. braziliensis*, *L. peruviana*, *L. mexicana* and *L. amazonensis*; FU: 3 months

Outcome: 1 Complete cure

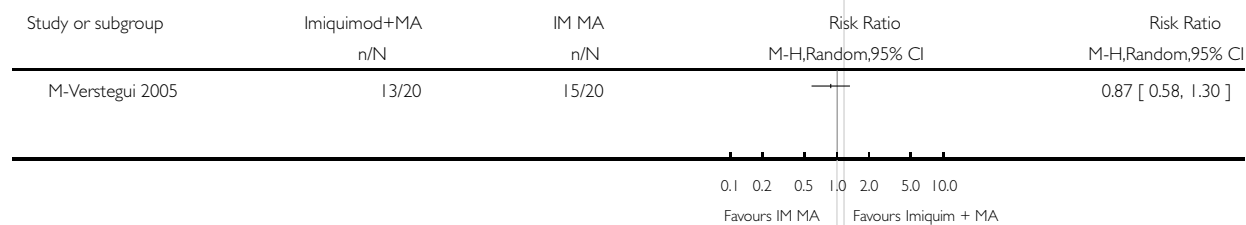


**Analysis 38.1. Comparison 38 Topical imiquimod 5% + IVMA vs placebo + IM/IVMA in *L. braziliensis* and *L. peruviana*; FU: 1 year, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 38 Topical imiquimod 5% + IVMA vs placebo + IM/IVMA in *L. braziliensis* and *L. peruviana*; FU: 1 year

Outcome: 1 Complete cure

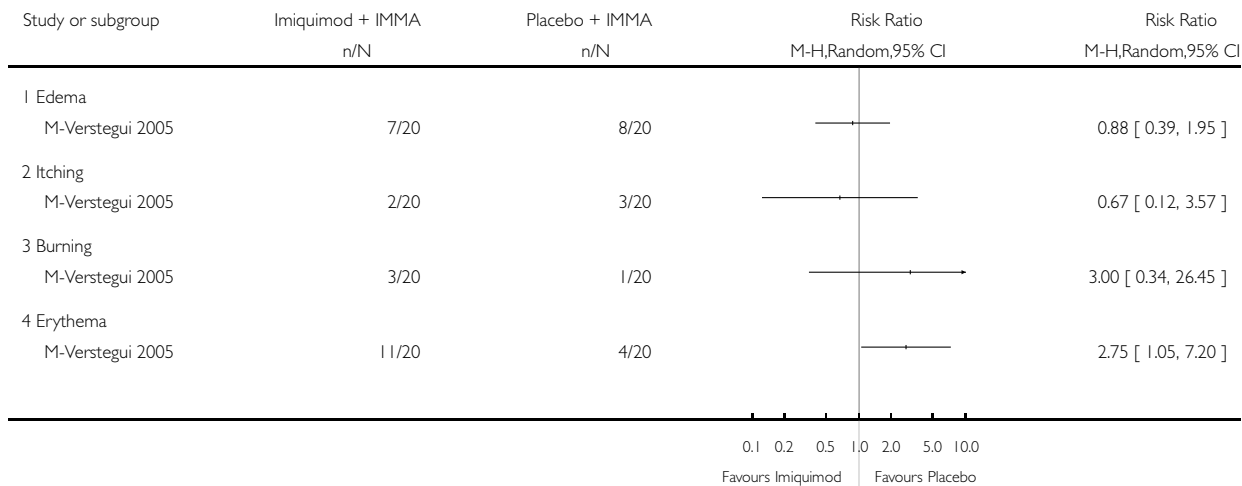


**Analysis 38.2. Comparison 38 Topical imiquimod 5% + IVMA vs placebo + IM/IVMA in *L. braziliensis* and *L. peruviana*; FU: 1 year, Outcome 2 Adverse effects.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 38 Topical imiquimod 5% + IVMA vs placebo + IM/IVMA in *L. braziliensis* and *L. peruviana*. FU: 1 year

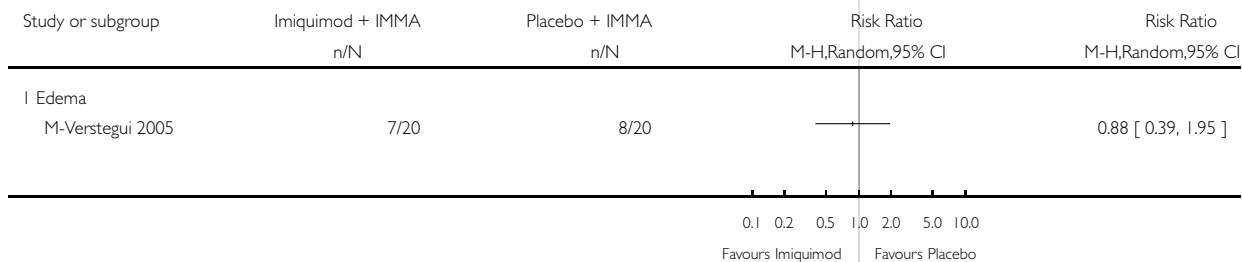
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 38 Topical imiquimod 5% + IVMA vs placebo + IM/IVMA in *L. braziliensis* and *L. peruviana*. FU: 1 year

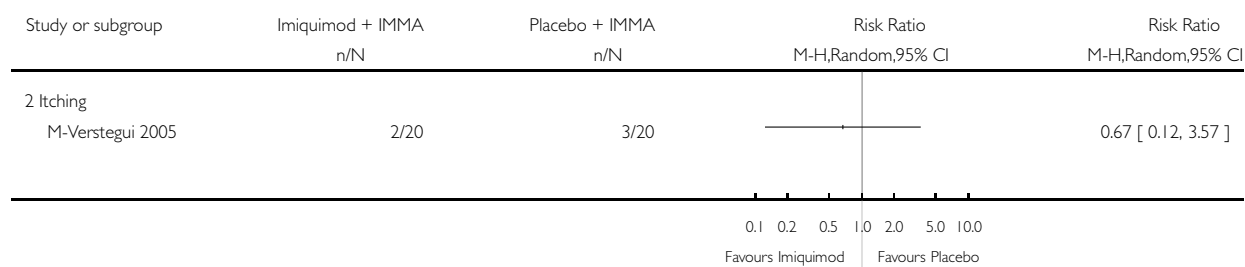
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 38 Topical imiquimod 5% + IVMA *vs* placebo + IM/IVMA in *L. braziliensis* and *L. peruviana*, FU: 1 year

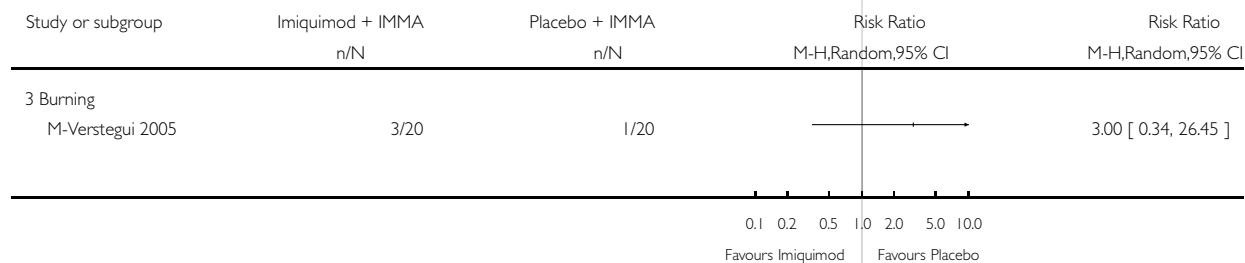
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 38 Topical imiquimod 5% + IVMA *vs* placebo + IM/IVMA in *L. braziliensis* and *L. peruviana*, FU: 1 year

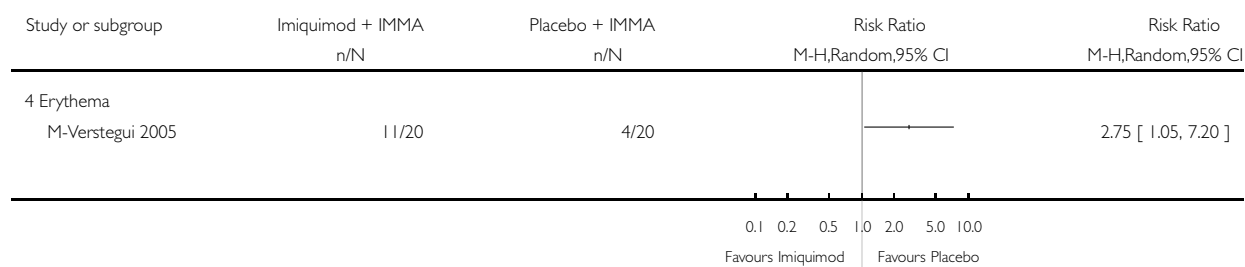
Outcome: 2 Adverse effects



Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 38 Topical imiquimod 5% + IVMA *vs* placebo + IM/IVMA in *L. braziliensis* and *L. peruviana*; FU: 1 year

Outcome: 2 Adverse effects

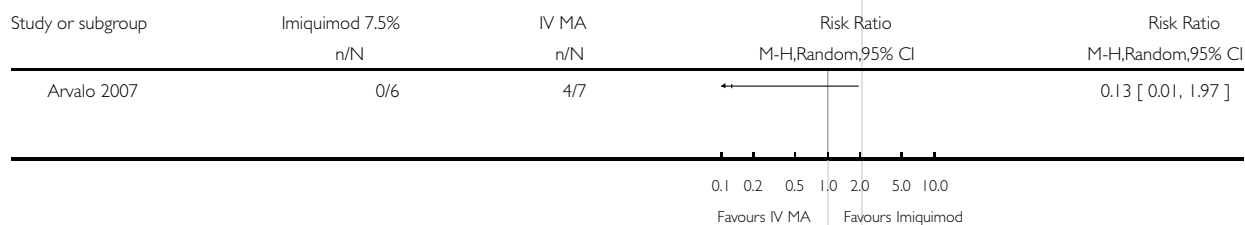


**Analysis 39.1. Comparison 39 7.5% imiquimod cream x 20 days *versus* IVMA x 20 days in *L. braziliensis*, *L. peruviana*, *L. mexicana* and *L. amazonensis*; FU: 3 months, Outcome 1 Complete cure.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 39 7.5% imiquimod cream x 20 days *versus* IVMA x 20 days in *L. braziliensis*, *L. peruviana*, *L. mexicana* and *L. amazonensis*; FU: 3 months

Outcome: 1 Complete cure

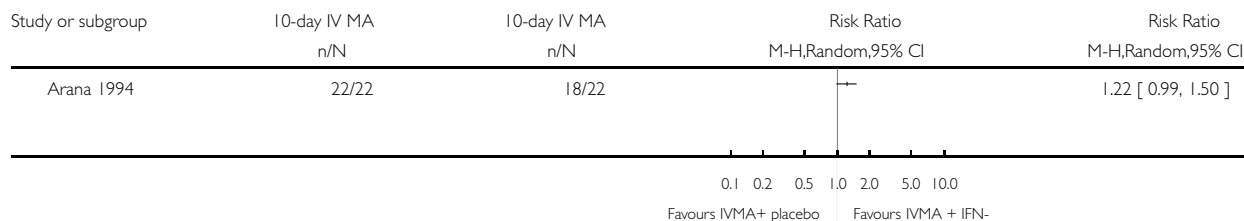


**Analysis 40.1. Comparison 40 IVMA combined or in different regimens in *L. braziliensis* and *L. mexicana*; FU: 1 year, Outcome 1 10-day IV MA+10-day IFN- $\gamma$  versus 10-day IV MA+10-day placebo.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 40 IVMA combined or in different regimens in *L. braziliensis* and *L. mexicana*; FU: 1 year

Outcome: 1 10-day IV MA+10-day IFN- versus 10-day IV MA+10-day placebo

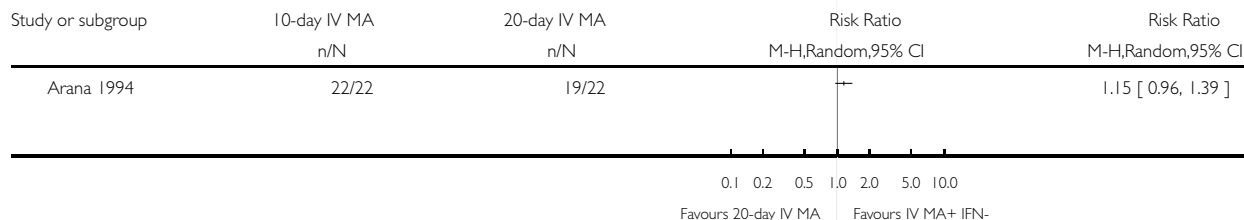


**Analysis 40.2. Comparison 40 IVMA combined or in different regimens in *L. braziliensis* and *L. mexicana*; FU: 1 year, Outcome 2 10-day IV MA+ 10-day IFN- $\gamma$  versus 20-day IV MA.**

Review: Interventions for American cutaneous and mucocutaneous leishmaniasis

Comparison: 40 IVMA combined or in different regimens in *L. braziliensis* and *L. mexicana*; FU: 1 year

Outcome: 2 10-day IV MA+ 10-day IFN- versus 20-day IV MA



## APPENDICES

### Appendix 1. Cochrane Search strategy

#1(leish\*)  
#2MeSH descriptor Leishmaniasis, Mucocutaneous explode all trees  
#3(mucocutan\* or mucos\* or nose or nas\* or pharynx or larynx or palat\* or cartila\* or ear)  
#4(#1 AND #3)  
#5espundia  
#6(#2 OR #4 OR #5)  
#7nariz or faring\* or laring\* or paladar or cartila\* or oreja  
#8(#1 AND #7)  
#9(#6 OR #8)  
#10(cutaneous leishmania\*):ti,ab,kw  
#11MeSH descriptor Leishmaniasis, Cutaneous, this term only  
#12(#10 OR #11)  
#13(solitary or limited or localised or (old and world)):ti,ab,kw  
#14(#12 AND #13)  
#15(#9 OR #14)

### Appendix 2. MEDLINE (OVID) Search Strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (animals not (human and animals)).sh.
10. 8 not 9
11. exp Leishmaniasis, Cutaneous/
12. (solitary or limited or old world or localised).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
13. 11 and 12
14. mucocutaneous leishmaniasis.mp. or exp Leishmaniasis, Mucocutaneous/
15. (mucocutan\$ or mucos\$ or nose or naziz or pharyn\$ or faring\$ or laring\$ or laryn\$ or paladar or palat\$ or cartila\$ or naso\$ or ear or oreja or tegument\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16. espundia.mp.
17. leish\$.mp.
18. 15 and 17
19. 13 or 14 or 16 or 18
20. 19 and 10

### Appendix 3. EMBASE (OVID) Search Strategy

1. random\$.mp.
2. factorial\$.mp.
3. crossover\$.mp.
4. placebo\$.mp. or PLACEBO/
5. (doubl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. assign\$.mp.
8. volunteer\$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. \*Leishmaniasis/ or \*Skin Leishmaniasis/ or mucocutaneous leishmaniasis.mp.
15. (mucocutan\$ or mucos\$ or nose or naziz or pharyn\$ or faring\$ or laring\$ or laryn\$ or paladar or palat\$ or cartila\$ or naso\$ or ear or tegument\$ or oreja).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
16. cutaneous leishmaniasis.mp.
17. (solitary or limited or old world or localised).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
18. espundia.mp.
19. 14 and 15
20. 16 and 17
21. 18 or 19 or 20
22. 13 and 21

### Appendix 4. CINAHL (OVID) Search Strategy

1. exp clinical trials/
2. Clinical trial.pt.
3. (clinic\$ adj trial\$1).tw.
4. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
5. Randomi?ed control\$ trial\$.tw.
6. Random assignment/
7. Random\$ allocat\$.tw.
8. Placebo\$.tw.
9. Placebos/
10. Quantitative studies/
11. Allocat\$ random\$.tw.
12. leishmaniasis.mp. or exp LEISHMANIASIS/
13. (mucocutan\$ or mucos\$ or nose or naziz or pharyn\$ or faring\$ or laring\$ or laryn\$ or paladar or palat\$ or cartila\$ or naso\$ or ear or tegument\$ or oreja).mp. [mp=title, subject heading word, abstract, instrumentation]
14. 12 and 13
15. espundia.mp. [mp=title, subject heading word, abstract, instrumentation]
16. cutaneous leishmaniasis.mp. [mp=title, subject heading word, abstract, instrumentation]
17. (solitary or limited or old world or localised).mp. [mp=title, subject heading word, abstract, instrumentation]
18. 12 or 16
19. 18 and 17
20. 14 or 15 or 19

21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
22. 20 and 21
23. from 22 keep 1

## Appendix 5. LILACS Search Strategy

((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control\$ or tw aleat\$ or tw random\$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic\$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Palavras] and (((cutaneous or mucocutaneous) and leishmaniasis) or ((cutanea or mucocutaneo or mucos\$ or nose or naziz or pharyn\$ or faring\$ or laring\$ or laryn\$ or paladar or palat\$ or cartila\$ or naso\$ or ear or tegument\$ or oreja or solitary or unico or limite\$ or (old and world) or localised) and leishmaniosis)) or espundia [Palavras]

## Appendix 6. Adverse effects search

1. exp product surveillance, postmarketing/ or exp adverse drug reaction reporting systems/ or exp clinical trials, phase iv/
2. adverse events.mp.
3. adverse effects.mp.
4. exp hypersensitivity/ or exp drug hypersensitivity/ or exp drug eruptions/ or exp hypersensitivity, delayed/ or exp hypersensitivity, immediate/
5. exp hypersensitivity, immediate/ or exp anaphylaxis/ or exp conjunctivitis, allergic/ or exp dermatitis, atopic/ or exp food hypersensitivity/ or exp respiratory hypersensitivity/ or exp urticaria/
6. side effect\$.mp.
7. exp Poisoning/
8. exp Substance-Related Disorders/
9. exp Drug Toxicity/
10. exp Abnormalities, Drug-Induced/
11. exp Teratogens/
12. exp Mutagens/
13. exp Carcinogens/
14. exp dermatitis, contact/ or exp dermatitis, allergic contact/ or exp dermatitis, irritant/ or exp dermatitis, phototoxic/
15. photoallergic reactions.mp.
16. exp dermatitis, allergic contact/ or exp dermatitis, photoallergic/
17. sensitization.mp.
18. fetal abnormalities.mp.
19. exp Drug Monitoring/
20. harm\$ effects.mp.
21. (toxic effects or drug effects).mp.
22. undesirable effect\$.mp.
23. (safe or safety).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
24. toxicity.mp.
25. noxious.mp.
26. serious reaction\$.mp.
27. complication\$.mp.
28. tolerability.mp.
29. (adverse adj3 (effect\$ or reaction\$ or event\$ or outcome\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
30. Tachyphylaxis/ci, de [Chemically Induced, Drug Effects]
31. \*Itraconazole/

32. \*Ketoconazole/
33. \*Paromomycin/
34. \*Allopurinol/
35. \*Amphotericin B/
36. aminosidine sulphate.mp.
37. pentamidine isethionate.mp. or \*Pentamidine/
38. \*Aminoglycosides/
39. miltefosine.mp.
40. thermotherapy.mp.
41. \*Granulocyte-Macrophage Colony-Stimulating Factor/
42. \*Mefloquine/
43. \*Immunotherapy/
44. \*BCG Vaccine/ or bacillus calmette guerin.mp.
45. \*Meglumine/
46. sodium stibogluconate.mp.
47. meglumine antimoniate.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
48. imiquimod.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
49. IFN-gamma.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
50. new world.mp.
51. American.mp.
52. cutaneous leishmaniasis.mp. or exp Leishmaniasis, Cutaneous/
53. mucocutaneous leishmaniasis.mp. or exp Leishmaniasis, Mucocutaneous/
54. 50 or 51
55. 52 and 54
56. 53 or 55
57. or/1-30
58. or/31-49
59. 56 and 57 and 58

## HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 2, 2009

30 April 2008	Amended	Converted to new review format.
14 February 2007	New citation required and conclusions have changed	Substantive amendment

## CONTRIBUTIONS OF AUTHORS

Link with editorial base and co-ordinate contributions from co-authors (UG, MP)

Searching for trials (includes developing a search strategy, obtaining papers, contacting authors, investigators or drug companies) (UG, MP)

Selecting which trials to include and extracting data from trials (UG, AM, MP, MR, JT)

Enter data into RevMan (MP)

Carry out analysis (UG, MP)

Interpret data (UG, MP)

Draft final review (contribution from all)

The expert representative (JA) focused on relevance and applicability of the review

The Cochrane Skin Group editorial base would like to thank the referees Simon Croft, Valdir Amato and Borja Mila.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- Spanish Society of Dermato-epidemiology and Evidence-Based Dermatology, Spain.
- Hospital Plató, c/ Plató 21 08006 Barcelona, Spain.

### External sources

- Office of Control of Neglected Tropical Diseases (WHO/CDS/NTD/IDM), Communicable Disease Cluster, World Health Organization, Not specified.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol of this review was called “Interventions for mucocutaneous leishmaniasis”. However, for the review the title has been amended to “Interventions for American cutaneous and mucocutaneous leishmaniasis”. This change was made because mucocutaneous leishmaniasis affects mainly endemic areas of Central and South America. In this area cutaneous leishmaniasis differs from the form affecting the Old World and can lead to the chronic mucocutaneous form.

Because of these changes the background and objectives have been modified considerably. The objectives in particular have been altered to focus on American cutaneous and mucocutaneous leishmaniasis rather than the mucocutaneous form only as in the original protocol.

In the Methods section, under “Type of interventions” we added a list of interventions to ease the readability and in line with the Results section.

Also in the Methods section under “Type of outcome measures”, the original primary outcome was the assessment of the percentage of lesions “cured” at three months after the end of treatment. With the exception of one study that reported the percentage in terms of participants but also lesions, in the rest of the included RCTs, participants was the “unit of analysis” used.

Lesions cured do not provide a reliable approach to how many participants are completely cured or rather have all their lesions healed. In addition, in terms of clinical appraisal, it may be more relevant to know whether a participant is completely or partially cured

irrespective of how many lesions are fully healed by the tested drug. Furthermore, authors assessed the outcome before the above mentioned time period. Despite all this, only the RCTs collecting data over a period of three months, either in participants or lesions, were considered suitable for primary outcome assessment.

According to the Key Editor's comments, we have changed one secondary outcome "Duration of remission and percentage of people with treated lesions that recur within six months, one, two and three years" as remission and recurrence are two different things for "Recurrence: duration of remission and/or percentage of people with treated lesions that recur within six months, one, two and three years".

Finally, we added a phrase to define emergence of resistance under "Tertiary outcomes" on advice of external referees.