Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for American cutaneous and mucocutaneous leishmaniasis (Review)

Pinart M, Rueda JR, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, Reveiz L, Elias VM, Tweed JA

Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, Reveiz L, Elias VM, Tweed JA.
Interventions for American cutaneous and mucocutaneous leishmaniasis.
Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834.
DOI: 10.1002/14651858.CD004834.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Interventions for American cutaneous and mucocutaneous leishmaniasis

Mariona Pinart[1], José-Ramón Rueda[2], Gustavo AS Romero[3], Carlos Eduardo Pinzón-Flórez[4], Karime Osorio-Arango[5], Ana Nilce Silveira Maia-Elkhoury[6], Ludovic Reveiz[7], Vanessa M Elias[7], John A Tweed[8]

[1]Free time independent Cochrane reviewer, Berlin, Germany. [2]Department of Preventive Medicine and Public Health, University of the Basque Country, Leioa, Spain. [3]Center for Tropical Medicine, University of Brasilia, Brasilia, Brazil. [4]Research Centre for Insurance Medicine, Keralty, Bogotá, Colombia. [5]Dirección de Redes en Salud Pública, Instituto Nacional de Salud, Bogotá, Colombia. [6]Communicable Diseases and Environmental Determinants of Health (CDE), Neglected, Tropical and Vector Borne Diseases (VT), Pan American Health Organization/ World Health Organization (PAHO/WHO), Rio de Janeiro, Brazil. [7]Evidence and Intelligence for Action in Health Department, Pan American Health Organization (PAHO), Washington DC, USA. [8]c/o Cochrane Skin Group, The University of Nottingham, Nottingham, UK

Contact: Mariona Pinart, mariona.pinart@gmail.com.

Editorial group: Cochrane Skin Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 8, 2020.

Citation: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, Reveiz L, Elias VM, Tweed JA. Interventions for American cutaneous and mucocutaneous leishmaniasis. *Cochrane Database of Systematic Reviews* 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3.

ABSTRACT

Background

On the American continent, cutaneous and mucocutaneous leishmaniasis (CL and MCL) are diseases associated with infection by several species of *Leishmania* parasites. Pentavalent antimonials remain the first-choice treatment. There are alternative interventions, but reviewing their effectiveness and safety is important as availability is limited. This is an update of a Cochrane Review first published in 2009.

Objectives

To assess the effects of interventions for all immuno-competent people who have American cutaneous and mucocutaneous leishmaniasis (ACML).

Search methods

We updated our database searches of the Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, LILACS and CINAHL to August 2019. We searched five trials registers.

Selection criteria

Randomised controlled trials (RCTs) assessing either single or combination treatments for ACML in immuno-competent people, diagnosed by clinical presentation and *Leishmania* infection confirmed by smear, culture, histology, or polymerase chain reaction on a biopsy specimen. The comparators were either no treatment, placebo only, or another active compound.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Our key outcomes were the percentage of participants 'cured' at least three months after the end of treatment, adverse effects, and recurrence. We used GRADE to assess evidence certainty for each outcome.

Main results

We included 75 studies (37 were new), totalling 6533 randomised participants with ATL. The studies were mainly conducted in Central and South America at regional hospitals, local healthcare clinics, and research centres. More male participants were included (mean age: roughly 28.9 years (SD: 7.0)). The most common confirmed species were *L. braziliensis*, *L. panamensis*, and *L. mexicana*. The most assessed interventions and comparators were non-antimonial systemics (particularly oral miltefosine) and antimonials (particularly meglumine antimoniate (MA), which was also a common intervention), respectively.

Three studies included moderate-to-severe cases of mucosal leishmaniasis but none included cases with diffuse cutaneous or disseminated CL, considered the severe cutaneous form. Lesions were mainly ulcerative and located in the extremities and limbs. The follow-up (FU) period ranged from 28 days to 7 years. All studies had high or unclear risk of bias in at least one domain (especially performance bias). None of the studies reported the degree of functional or aesthetic impairment, scarring, or quality of life.

Compared to placebo, at one-year FU, intramuscular (IM) MA given for 20 days to treat *L. braziliensis* and *L. panamensis* infections in ACML may increase the likelihood of complete cure (risk ratio (RR) 4.23, 95% confidence interval (CI) 0.84 to 21.38; 2 RCTs, 157 participants; moderate-certainty evidence), but may also make little to no difference, since the 95% CI includes the possibility of both increased and reduced healing (cure rates), and IMMA probably increases severe adverse effects such as myalgias and arthralgias (RR 1.51, 95% CI 1.17 to 1.96; 1 RCT, 134 participants; moderate-certainty evidence). IMMA may make little to no difference to the recurrence risk, but the 95% CI includes the possibility of both increased and reduced risk (RR 1.79, 95% CI 0.17 to 19.26; 1 RCT, 127 participants; low-certainty evidence).

Compared to placebo, at six-month FU, oral miltefosine given for 28 days to treat *L. mexicana*, *L. panamensis* and *L. braziliensis* infections in American cutaneous leishmaniasis (ACL) probably improves the likelihood of complete cure (RR 2.25, 95% CI 1.42 to 3.38), and probably increases nausea rates (RR 3.96, 95% CI 1.49 to 10.48) and vomiting (RR 6.92, 95% CI 2.68 to 17.86) (moderate-certainty evidence). Oral miltefosine may make little to no difference to the recurrence risk (RR 2.97, 95% CI 0.37 to 23.89; low-certainty evidence), but the 95% CI includes the possibility of both increased and reduced risk (all based on 1 RCT, 133 participants).

Compared to IMMA, at 6 to 12 months FU, oral miltefosine given for 28 days to treat *L. braziliensis*, *L. panamensis*, *L. guyanensis* and *L. amazonensis* infections in ACML may make little to no difference to the likelihood of complete cure (RR 1.05, 95% CI 0.90 to 1.23; 7 RCTs, 676 participants; low-certainty evidence). Based on moderate-certainty evidence (3 RCTs, 464 participants), miltefosine probably increases nausea rates (RR 2.45, 95% CI 1.72 to 3.49) and vomiting (RR 4.76, 95% CI 1.82 to 12.46) compared to IMMA. Recurrence risk was not reported.

For the rest of the key comparisons, recurrence risk was not reported, and risk of adverse events could not be estimated.

Compared to IMMA, at 6 to 12 months FU, oral azithromycin given for 20 to 28 days to treat *L. braziliensis* infections in ACML probably reduces the likelihood of complete cure (RR 0.51, 95% CI 0.34 to 0.76; 2 RCTs, 93 participants; moderate-certainty evidence).

Compared to intravenous MA (IVMA) and placebo, at 12 month FU, adding topical imiquimod to IVMA, given for 20 days to treat *L. braziliensis*, *L. guyanensis* and *L. peruviana* infections in ACL probably makes little to no difference to the likelihood of complete cure (RR 1.30, 95% CI 0.95 to 1.80; 1 RCT, 80 participants; moderate-certainty evidence).

Compared to MA, at 6 months FU, one session of local thermotherapy to treat *L. panamensis* and *L. braziliensis* infections in ACL reduces the likelihood of complete cure (RR 0.80, 95% CI 0.68 to 0.95; 1 RCT, 292 participants; high-certainty evidence).

Compared to IMMA and placebo, at 26 weeks FU, adding oral pentoxifylline to IMMA to treat CL (species not stated) probably makes little to no difference to the likelihood of complete cure (RR 0.86, 95% CI 0.63 to 1.18; 1 RCT, 70 participants; moderate-certainty evidence).

Authors' conclusions

Evidence certainty was mostly moderate or low, due to methodological shortcomings, which precluded conclusive results. Overall, both IMMA and oral miltefosine probably result in an increase in cure rates, and nausea and vomiting are probably more common with miltefosine than with IMMA.

Future trials should investigate interventions for mucosal leishmaniasis and evaluate recurrence rates of cutaneous leishmaniasis and its progression to mucosal disease.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of different treatments for American (muco)cutaneous leishmaniasis (a parasitic disease of the skin and mucous membranes)?

Why this question is important

American (muco)cutaneous leishmaniasis (ACML) is a disfiguring disease that affects people in Central and South America. It is caused by parasites that are transmitted to humans by sandflies. Different forms of ACML have different symptoms. People with the cutaneous form develop skin sores that often heal within a few months without treatment, but can leave scars. In people with mucosal or mucocutaneous leishmaniasis, destructive sores develop in the protective lining (mucous membranes) of the nose, mouth and throat.

To compare the effectiveness and risks of the many treatments for ACML, we reviewed evidence from research studies (randomised controlled trials). We looked for information on the proportion of people whose sores had healed three months or more after treatment, unwanted effects, quality of life, re-appearance of sores, damage associated with the disease and prevention of scarring.

How we identified and assessed the evidence

First, we searched for all relevant studies. We then compared the results, summarised the evidence, and assessed the certainty of the evidence.

What we found

We found 75 studies on 6533 people (approximately 75% male; average age: 29 years).

- One study investigated children (2 to 12 years).
- Most studies (67) involved people with cutaneous leishmaniasis.
- Eight studies investigated people with mucosal or mucocutaneous leishmaniasis.
- The parasite *Leishmania braziliensis* caused the disease in 52 studies.
- Studies were conducted at regional hospitals, local clinics, and research centres.
- Studies lasted between 28 days and seven years.
- Most studies reported their funding source: the US army funded eight studies, industry funded 10, and institutional grants funded 33 (five of these also reported industry funding).

Treatments were mainly compared to a placebo (fake treatment) or meglumine antimoniate (an antimonial).

Here we report this review's main results. We were only able to report the risk of recurrence and side effects for the comparisons of meglumine antimoniate (MA) or miltefosine versus placebo and miltefosine versus MA.

Main results

Antimonials

Compared to placebo, MA may increase chances of complete healing of ACML, but treatment effects vary, so it is possible that it may make little to no difference. MA probably increases the likelihood of pain in the muscles or joints. There may be little to no difference in the risk of developing the disease again, but there is also a possibility of increased or reduced risk due to the wide range of effects seen.

Non-antimonials

Miltefosine probably improves chances of complete healing of American cutaneous leishmaniasis (ACL) compared to placebo, but there may be little to no difference compared to treatment with MA in ACML. Miltefosine may make little to no difference to the risk of developing ACL again when compared to placebo, but treatment effects on recurrence varied, so it may also increase or decrease the risk. Miltefosine probably increases the likelihood of vomiting or nausea when compared to either placebo or MA in ACML. We do not know the effect on recurrence of miltefosine compared to MA.

Azithromycin probably reduces chances of complete healing of ACML compared to MA.

Imiquimod in combination with MA probably makes little to no difference to the chance of complete healing of ACL compared to MA in combination with placebo.

Physical therapies

Thermotherapy lowers the chance of complete healing of ACL compared to MA.

Immuno-chemotherapy

Pentoxifylline plus MA probably makes little to no difference to chances of complete healing of ACML compared with MA plus placebo.

No study reported information about damage, prevention of scarring, or quality of life.

What this means

The main findings of this review suggest that:

- MA and miltefosine probably increase chances of complete healing; and
- vomiting or nausea are probably more common with miltefosine, and joint or muscle ache is probably more common with MA.

The evidence was mostly of moderate certainty, so the true results are likely close to what we found. Evidence was limited by the inclusion of very few people in some studies, and participants or investigators knowing which treatments they were receiving.

How-up-to date is this review?

The evidence in this Cochrane Review is current to August 2019.

Summary of findings 1. Meglumine antimoniate (IMMA) (20 mg/kg/d for 20 days) compared to placebo (3 tablets/4 times a day for 28 d) in L. *braziliensis* and L. *panamensis* for American cutaneous and mucocutaneous leishmaniasis

IMMA (20 mg/kg/d for 20 d) compared to placebo (3 tablets/4 times a day for 28 d) in *L. braziliensis* and *L. panamensis* for American cutaneous and mucocutaneous leishmaniasis

Patient or population: People with American cutaneous and mucocutaneous leishmaniasis
Setting: outpatients
Intervention: IMMA (20 mg/kg/d for 20 days)
Comparison: placebo (3 tablets/4 times a day for 28 d) in *L. braziliensis* and *L. panamensis*

Follow-up time: 1 year

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo (3 tablets/4 times a day for 28 d) in *L. braziliensis* and *L. panamensis*	Risk with IMMA (20 mg/kg/d for 20 d)				
Complete cure, at least 3 months after the end of treatment Follow-up: 1 year	Study population		RR 4.23 (0.84 to 21.38)	157 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	-
	239 per 1000	756 per 1000 (201 to 1000)				
Adverse effects (number of participants who had at least one adverse effect) Follow-up: 1 year	Study population		RR 1.51 (1.17 to 1.96)	134 (1 study)	⊕⊕⊕⊖ Moderate[a]	Adverse effects considered as relevant: myalgias, arthralgias, anorexia, nausea, and headache
	522 per 1000	789 per 1000 (611 to 1000)				
Recurrence Follow-up: 1 year	Study population		RR 1.79 (0.17 to 19.26)	127 (1 study)	⊕⊕⊖⊖ Low[b]	-
	17 per 1000	30 per 1000 (3 to 321)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk of the number of participants with the event in the control group of the analyses.

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due to imprecision: wide confidence interval.
[b]Downgraded two levels due to imprecision: very wide confidence interval, showing an appreciable benefit and harm, as well as no difference between groups.

Summary of findings 2. Oral miltefosine (50 mg for 28 days) compared to placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis* for American cutaneous leishmaniasis

Oral miltefosine 50 mg for 28 d compared to placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis* for American cutaneous leishmaniasis

Patient or population: People with American cutaneous and mucocutaneous leishmaniasis
Setting: outpatients
Intervention: Oral miltefosine 2.5 mg/kg/d for 28 days
Comparison: placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*

Follow-up time: 6 months

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with placebo (same regimen) in L. *mexicana*, L. *panamensis* and L. *braziliensis*	Risk with Oral miltefosine 50 mg for 28 d				
Complete cure, at least 3 months after the end of treatment Follow-up: 6 months		Study population		RR 2.25 (1.42 to 3.38)	133 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	-
		295 per 1000	644 per 1000 (378 to 1000)				
Adverse effects (number of participants who had the event) Follow-up: 6 months	Nausea	Study population		RR 3.96 (1.49 to 10.48)	133 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Also higher risk with miltefosine for increasing creatinine levels
		131 per 1000	518 per 1000 (195 to 1000)				

Vomiting	Study population		RR 6.92 (2.68 to 17.86)	133 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	-
	91 per 1000	629 per 1000 (244 to 1000)				
Recurrence Follow-up: 6 months	Study population		RR 2.97 (0.37 to 23.89)	133 (1 RCT)	⊕⊕⊖⊖ Low[b]	-
	23 per 1000	68 per 1000 (8 to 543)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). The assumed risk of the number of participants with the event in the control group of the analyses.

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due to imprecision: wide confidence interval.
[b]Downgraded two levels due to imprecision: very wide confidence interval, showing an appreciable benefit and harm, as well as no difference between groups.

Summary of findings 3. Oral miltefosine (1.2 to 3.3 mg/kg/d 28 days) compared to meglumine antimoniate (20 mg/kg 20 days) in L. *braziliensis*, *L. panamensis, L. guyanensis* and L. *amazonensis* for American cutaneous and mucocutaneous leishmaniasis

Oral miltefosine compared to meglumine antimoniate for American cutaneous and mucocutaneous leishmaniasis

Patient or population: People with American cutaneous and mucocutaneous leishmaniasis
Setting: outpatients
Intervention: Oral miltefosine
Comparison: meglumine antimoniate

Follow-up time: 6 - 12 months

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

		Risk with meglumine antimoniate	Risk with Oral miltefosine				
Complete cure, at least 3 months after the end of treatment Follow-up: 6 - 12 months		Study population		RR 1.05 (0.90 to 1.23)	676 (7 RCTs)	⊕⊕⊖⊖ Low[a]	No differences in results related with length of follow-up (up to 6 months or up to 12 months). No differences in results among compared treatments for people with only mucosal disease neither for people with only cutaneous disease. Studies in children between 2 and 12 years with cutaneous disease found no differences in results among compared treatments
		693 per 1000	741 per 1000 (616 to 893)				
Adverse effects (number of participants who had the event) Follow-up: 6 - 12 months	Nausea	Study population		RR 2.45 (1.72 to 3.49)	464 (3 RCTs)	⊕⊕⊕⊖ Moderate[b]	-
		147 per 1000	360 per 1000 (252 to 512)				
	Vomiting	Study population		RR 4.76 (1.82 to 12.46)	464 (3 RCTs)	⊕⊕⊕⊖ Moderate[b]	-
		87 per 1000	415 per 1000 (159 to 1000)				
Recurrence - not measured		Study population		Not estimable	-	See comment	No studies measured recurrence
		See comment	See comment				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). The assumed risk of the number of participants with the event in the control group of the analyses.

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded two levels, one due to study limitations (risk of bias) as outcome assessment was not blinded in some studies (detection bias), and another level for high heterogeneity: $I^2 > 50\%$.
[b]Downgraded one level due to study limitations (risk of bias) as outcome assessment was not blinded (detection bias).

Summary of findings 4. Azithromycin (500 mg 20 - 28 days) compared to meglumine antimoniate (15 - 20 mg/kg/d for 20 - 28 days) in *L. braziliensis* for American cutaneous and mucocutaneous leishmaniasis

Azithromycin compared to meglumine antimoniate for American cutaneous and mucocutaneous leishmaniasis

Patient or population: People with American cutaneous and mucocutaneous leishmaniasis
Setting: outpatients
Intervention: Azithromycin
Comparison: Meglumine antimoniate

Follow-up time: 6 months to 1 year

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Meglumine Antimoniate	Risk with Azithromycin				
Complete cure, at least 3 months after the end of treatment Follow-up: 6 months to 1 year	Study population		RR 0.51 (0.34 to 0.76)	93 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	-
	745 per 1000	410 per 1000 (253 to 670)				
Adverse effects Follow-up: 1 year	Study population		Not estimable	45 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	No serious events reported in any of the treatments. Statistical comparison was not possible, given that adverse effect types were different and related to the method of administration (*oral* azithromycin versus *intramuscular* meglumine antimoniate)
	Not estimable	Not estimable				
Recurrence - not measured	Study population		Not estimable	-	See comment	No studies measured recurrence
	See comment	See comment				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk of the number of participants with the event in the control group of the analyses.

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due to study limitations (risk of bias) as outcome assessment was not blinded (detection bias).

Summary of findings 5. Topical imiquimod 5% (3 times/week) + meglumine antimoniate (IVMA) (20 mg/kg/d for 20 days) compared to placebo + IVMA in L. *braziliensis*, L. *guyanensis* and L. *peruviana* for American cutaneous leishmaniasis

Topical imiquimod 5% + IVMA compared to placebo + IVMA in *L. braziliensis, L. guyanensis* and *L. peruviana* for American cutaneous leishmaniasis

Patient or population: People with American cutaneous leishmaniasis
Setting: outpatients
Intervention: Topical imiquimod 5% + IVMA
Comparison: placebo + IVMA in *L. braziliensis, L. guyanensis* and *L. peruviana*

Follow-up time: 1 year

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo + IVMA in *L. braziliensis*, *L. guyanensis* and *L. peruviana*	Risk with Topical imiquimod 5% + IVMA				
Complete cure, at least 3 months after the end of treatment Follow-up: 1 year	Study population		RR 1.30 (0.95 to 1.80)	80 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	All 80 participants had not been previously treated. Another study (n = 40) also assessed this outcome, but they only included participants with previous treatment failure and used IMMA.
	653 per 1000	750 per 1000 (435 to 975)				
Adverse effects (number of participants who had the event) Follow-up: 1 year	Study population		See comment	80 (1 RCT)	⊕⊕⊕⊕ High	Over the study period, only 1 topical adverse effect (rash) was recorded in the imiquimod arm
	See comment	See comment				

Recurrence - not measured	Study population		Not estimable	-	See comment	No studies measured recurrence
	See comment	See comment				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk of the number of participants with the event in the control group of the analyses.

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due to imprecision: wide confidence interval.

Summary of findings 6. Thermotherapy one session (at 50 ºC for 30 seconds) compared to meglumine antimoniate (20 mg Sb5/kg/day for 20 days) in *L. panamensis* and *L. braziliensis* for American cutaneous leishmaniasis

Thermotherapy compared to MA for American cutaneous leishmaniasis

Patient or population: People with American cutaneous leishmaniasis
Setting: outpatients
Intervention: Thermotherapy
Comparison: Meglumine antimoniate (MA)

Follow-up time: 6 months

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with MA	Risk difference with Thermotherapy				
Complete cure, at least 3 months after the end of treatment Follow-up: 6 months	Study population		RR 0.80 (0.68 to 0.95)	292 (1 RCT)	⊕⊕⊕⊕ High	-
	720 per 1000	576 fewer per 1000 (490 fewer to 684 fewer)				
Adverse effects	Study population		Not estimable	292 (1 RCT)	⊕⊕⊕⊕ High	No serious events reported in any of the treatments. Statistical comparison

Follow-up: 6 months	Not estimable	Not estimable				was not possible given that adverse effect types were different and related to method of administration
Recurrence - not measured	Study population		Not estimable	-	See comment	No studies measured recurrence
	See comment	See comment				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). The assumed risk of the number of participants with the event in the control group of the analyses.

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Summary of findings 7. Pentoxifylline (oral 400 mg thrice daily) plus meglumine antimoniate (IMMA) (20 mg/ kg /day for 20 days) compared to IMMA plus placebo for American cutaneous and mucocutaneous leishmaniasis

Pentoxifylline plus IMMA compared to IMMA plus placebo for American cutaneous and mucocutaneous leishmaniasis

Patient or population: People with American cutaneous leishmaniasis
Setting: outpatients
Intervention: Pentoxifylline plus IMMA
Comparison: IMMA plus placebo

Follow-up time: 26 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with IMMA plus placebo	Risk with Pentoxifylline plus IMMA				
Complete cure, at least 3 months after the end of treatment Follow-up: 26 weeks	Study population		RR 0.86 (0.63 to 1.18)	70 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	-
	750 per 1000	645 per 1000 (473 to 885)				

Adverse effects Follow-up: 26 weeks	Study population Not estimable	Not estimable	Not estimable	70 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Reported more topical adverse effects (none severe) for pentoxifylline plus IMMA, but necessary data for statistical analysis were not provided
Recurrence - not measured	Study population See comment	See comment	Not estimable	-	See comment	No studies measured recurrence

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). The assumed risk of the number of participants with the event in the control group of the analyses.

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due to imprecision: wide confidence interval.

BACKGROUND

Unfamiliar terms are described in the glossary in Table 1.

Description of the condition

Definition

On the American continent, human cutaneous and mucocutaneous leishmaniasis are zoonotic diseases associated with infection by several species of *Leishmania* parasites (Cupolillo 1994; Cupolillo 2001; Schonian 2010). The parasites are transmitted through the infected bites of sandflies belonging to *Lutzomyia* genus. Conditional on the immune status and species of *Leishmania*, American tegumentary leishmaniasis (ATL) clinical types vary from self-limiting cutaneous lesions to mucocutaneous lesion forms. Cutaneous leishmaniasis is defined as skin involvement characterised by the onset of one or more painless ulcerations heralded or accompanied by local lymph node enlargement. Mucocutaneous leishmaniasis is defined as the upper airway mucosal involvement, characterised by inflammatory and destructive lesions usually affecting the nose, palate, pharynx and rarely the larynx. Cutaneous disease precedes most of the mucosal-affected cases and is usually presented as a scar. In both diseases there is diversity in parasite, reservoirs and arthropod vector, heterogeneity of transmission cycles, wide variation of clinical presentations, and heterogeneous geographical distribution across the continent (Lainson 1994).

Epidemiology and impact

The leishmaniases are relevant public health problems, classified as neglected tropical diseases by the World Health Organization (WHO), for whom there are not enough preventive, diagnostic and therapeutic solutions. Estimating the disease burden attributable to leishmaniasis has been a challenging task (Bern 2008). However, recent approaches estimated annual cutaneous leishmaniasis incidence between 187,200 to 307,800 cases in the American continent (Alvar 2012). The improvement in surveillance activities, conducted by national control programmes supported by the Pan American Health Organization (PAHO) has been fruitful, and currently data on incident cases are available at subnational levels by most of the endemic countries. In the American continent, cutaneous leishmaniasis is endemic in 18 countries extending from Mexico to Argentina. Numbers of cutaneous and mucocutaneous leishmaniasis, reported to PAHO in 2014 by 16 out of 18 endemic countries, revealed 51,098 total cases and an incidence rate of 19.76 cases per 100,000 inhabitants. Seventy-five per cent of the cases were reported by Brazil, Colombia and Peru, but the higher incidence rates were observed in Nicaragua and Costa Rica (PAHO 2015). A report on the cutaneous leishmaniasis disease burden demonstrated that Andean Latin America had one of the highest Disability-Adjusted Life Year (DALYs) in the world, and Nicaragua appears among countries with the highest incidence among the male and female population (Karimkhani 2016).

In spite of the total number of cases and the possibility of underreporting, a huge population could be at risk of acquiring the disease. The heterogeneity of transmission cycles, determined by the behaviour of arthropod vectors and vertebrate reservoirs in their natural environment, plus anthropic interventions where the disease naturally occurs, also makes the scenario for implementing control measures extremely dynamic and challenging (Lainson 1994; Shaw 1988; Yadon 2003). Risk factors for human populations are related to a wide variety of situations such as work exposure, travelling, recreational activities and war operations (Alcais 1997; Alexander 2009; Beyrer 2007; Davies 1997; Davies 2000; Mansueto 2014; Monteiro 2009). Climate and environmental changes could play a role in the distribution of risk across the continent, mainly because of their impact on the vector populations (Perez-Florez 2016; Peterson 2003). Finally, although there is a general perception that most of the cases are observed among people with lower income living in rural areas, there are no specific studies exploring the association between poverty and the risk of cutaneous leishmaniasis in Latin America.

Aetiology and transmission

The main parasite species, given the burden of disease and the geographical dispersion in the American continent, are *Leishmania (Viannia) braziliensis, L. (V.) guyanensis* and *L.(V.) pananamensis*. Other species can be especially relevant for some regions such as *L. (Leishmania) mexicana* in the peninsula of Yucatán, *L.(V.) peruviana* in the Andean valleys of Peru, and *L. (L.) amazonensis* which is associated with the very severe diffuse form of the disease. Parasite diversity is very relevant because of its crucial influence on clinical manifestations and disease severity, the accuracy of diagnostic tests (Navin 1990; Romero 2001b; Romero 2005), and the response to therapeutic measures (Arevalo 2007; Fernandez 2014; Llanos-Cuentas 2008; Romero 2001a). Sympatric circulation of the parasite should be highlighted as an extra challenge when planning disease-control activities (Tojal da Silva 2006).

Vector diversity is less well explored for its influence on the human population. However, some data have emerged on the role of a vector's saliva as a potential immunogen or adjuvant for vaccine development (Abdeladhim 2014; Reed 2016), but also as a modulator of the parasite-host relationship, with impact on clinical findings (Carvalho 2015; Mondragon-Shem 2015).

Clinical manifestations

Clinical manifestations of cutaneous leishmaniasis offer a wide spectrum of lesions, from a few small non-ulcerated nodules observed in people in Central America due to *L.(L.) infantum* (De Lima 2009) to disseminated disease due to *L. (V.) braziliensis,* with hundreds of ulcerated and non-ulcerated lesions involving the entire body (Turetz 2002). However, the most common manifestation of cutaneous leishmaniasis is a single ulcerated lesion with elevated borders, usually painless, unless affected by superimposed bacterial infection, localised in one extremity and frequently heralded by satellite lymph node enlargement (Bomfim 2007). Arbitrarily, the term localised cutaneous leishmaniasis is used to denominate a clinical picture of six or fewer cutaneous lesions localised in one or more corporal contiguous segments, but there are no specific studies dedicated to establishing such a cut-off of six lesions, and the clinical appearance of lesions should be more useful to characterise the condition than simply the number of observed lesions (Costa 1986; Dantas 2014; Turetz 2002). Ampuero 2006 demonstrated that fewer than 5% of over 4000 cases of cutaneous leishmaniasis in Brazil had more than five cutaneous lesions. The diffuse clinical form of the diseases deserves special attention despite its rarity, because of the lack of response to specific treatments (Becker 1999; Hashiguchi 2016; Salaiza-Suazo 1999). Diffuse disease is almost always caused by *L. (L.) amazonensis* and rarely by other members of the same subgenus

(Hashiguchi 2016). It is characterised by multiple, progressive, non-ulcerated lesions (Barral 1995).

Mucosal or mucocutaneous disease is a relatively rare entity usually associated with infection by parasites belonging to the *Viannia* subgenus (Handler 2015). *L. (V.) braziliensis* is by far the most common agent isolated from patients with mucosal involvement (Marsden 1994), but *L. (V.) guyanensis* (Prestes 2015; Santrich 1990) and *L.(V.) panamensis* (Osorio 1998) have also been reported to cause this clinical form. Mucosal diseases are frequently observed in patients who have been affected by localised cutaneous leishmaniasis within the previous two years and more rarely in patients with active cutaneous ulcers or without any skin disease (Zajtchuk 1989). Patients affected by the disseminated cutaneous form of the disease should be screened carefully for mucosal involvement, because it is known that they have a higher probability of concomitant mucosal disease (Turetz 2002). Disease severity is variable and could depend in part on host characteristics, but mostly on the duration of the disease. In the past, it was common to observe patients with extremely advanced destructive lesions. Nowadays, in some endemic areas with improving access to health services, such destructive lesions are diminishing, and mild cases are detected through endoscopic evaluation of the upper airway (Lessa 2012). The mucosal involvement affects mainly the mucosal surfaces of the nose, with or without septal perforation, and oral surfaces as well. Larynx lesions are rare but represent a special challenge because of the possibility of airway obstruction and long-term sequela.

Diagnosis

Diagnosis of cutaneous and mucocutaneous leishmaniasis is based on parasitological conventional methods, including direct parasite examination in smears obtained from the lesions or histopathological sections and parasite culture (Boggild 2008; Boggild 2010; Navin 1990; Weigle 1987). There are currently no rapid tests commercially available for point-of-care diagnosis of either disease. Direct parasite examination looking for amastigotes could be a hard task in areas affected by *L. (V.) braziliensis,* in contrast with areas affected by *L. (V.) guyanensis* (Romero 2001b) or *L. (L.) mexicana* (Navin 1990), where the parasite is easily visible. Culture-proven cases are essential for surveillance and to accumulate data on the geographical distribution of each parasite species. Furthermore, the parasite species identification process is crucial in the formulation of treatment policies, taking into consideration the relationship between parasite species and the therapeutic response, as previously mentioned. However, in most of the scenarios where transmission occurs there is no access to parasitological diagnosis or parasite isolation. Molecular methods are very promising, including the possibility of parasite species identification (Fraga 2012; Gomes 2015; Graca 2012), but so far there is no point-of-care affordable diagnostic instrument to perform the detection of parasite DNA. The Montenegro (Leishmanin) skin test for detection of delayed cellular immune response is specific but does not distinguish between current or past infection (Weigle 1991). However, putting together the history of exposure to transmission area, the clinical findings, and the result of Montenegro skin test, it is possible to correctly classify more patients (Rojas 2002; Weigle 1993). Unfortunately, the leishmanin skin test is currently unavailable. All the available diagnostic tests generally had lower sensitivity in patients affected by mucosal disease (PAHO 2019b). Thus, all the tests should be applied concomitantly in those patients in order to improve sensitivity. Finally, there is no consensus on the use of antibody detection through serological tests for diagnosis of tegumentary leishmaniasis, and no stringent validation studies have been developed for this purpose.

Description of the intervention

Localised cutaneous leishmaniasis has been considered a self-healing disease. However, in contrast with the Old World scenario where no treatment has been an option, in the New World most of the cases receive specific treatment because of the prolonged period of the self-healing process, and consequent disfiguring scars. The risk of mucosal disease has also been historically considered as a justification for systemic treatment. The issue of self-healing in the American continent has recently been revised, concluding that there is an advantage in administering specific treatment to those suffering from cutaneous leishmaniasis and therefore avoiding the use of placebo in clinical trials (Cota 2016). Disseminated cutaneous leishmaniasis has an aggressive pattern with higher mucosal involvement, and is not considered a self-healing condition. Diffuse disease is also a progressive form which improves temporarily with specific treatment, with most of the patients remaining exposed to several drugs without full remission; when a clinical cure is achieved, it is not prolonged. Mucosal disease, on the other hand, is progressive and destructive, but heals with proper treatment, with few exceptions (Marsden 1998). Data on the impact of leishmaniasis on quality of life have been scarce in Latin America and it would be desirable in the near future to construct related quality-of-life endpoints for clinical trials (Toledo 2013).

The choice of treatments for leishmaniasis depends on many factors such as efficacy, treatment schedule, toxicity, costs, and cultural issues about acceptability for the target population. There is currently no effective and low-cost oral treatment available for American cutaneous or mucocutaneous leishmaniasis. The available treatments are characterised by their moderate efficacy, frequent adverse events, and relevant concerns for their safety during pregnancy and childbearing age. Most of them are also expensive drugs used in long-term schedules requiring special care for administration and monitoring. Antimonials, e.g. sodium stibogluconate and meglumine antimoniate, the oldest drugs available, were first used at the beginning of the 20th century and are still considered first-line treatments against most forms of leishmaniasis, and they have also been used as a reference to compare the efficacy of other potential treatments (Biagi 1953; Marsden 1979; PAHO 2015). Antimonials; amphotericin B; pentamidine isethionate (PI); and more recently, the oral drug miltefosine constitute the therapeutic armamentarium for systemic treatment of American tegumentary leishmaniasis. Neither oral agents such as ketoconazole, itraconazole, and fluconazole; the purine analogue allopurinol; nor the aminoglycoside aminosidine sulphate for systemic use have been extensively studied in the American continent or registered for treating leishmaniasis. The azalide azithromycin has been scarcely tested in people with CL. Topical formulations, such as the aminoglycoside paromomycin, amphotericin B cream, or imiquimod formulations, as well as local treatment modalities such as cryotherapy or thermotherapy, have also been tried for localised American cutaneous leishmaniasis, but again, none has been incorporated as part of the recommended treatments. Intralesional meglumine antimoniate (N-methylglucamine) was recently incorporated into

the armamentarium against CL in the American continent (PAHO 2018). Finally, vaccines, immunotherapy with antigenic compounds or with cytokines, as well as immunomodulatory drugs deserve attention, mainly as part of combined therapeutic schemes including antimonials or other antileishmanial drugs. Table 2 shows the profile of the currently-available interventions that reached at least the clinical phase of development, although not necessarily registered for use against leishmaniasis.

Based on the immunopathogenesis of leishmaniasis, treatment with antimonial drugs has been combined with cytokines and free radicals, such as interferon-gamma (IFN-γ) or granulocyte macrophage colony-stimulating factor (GM-CSF), and nitric oxide (NO) patch, respectively (Almeida 2005; Arana 1994; Lopez-Jaramillo 2010). The immunomodulatory agent pentoxifylline has also been used in combination with meglumine antimoniate, pursuing the reduction of the dysregulated inflammatory response in mucosal leishmaniasis patients (Machado 2007). No current recommendation for routine use has been made for such combinations. Finally, there is currently no licensed vaccine against human leishmaniasis. Vaccines for the prophylaxis of leishmaniasis are divided into first- and second-generation vaccines (Alvar 2013). The first-generation vaccines were composed of killed and attenuated *Leishmania* parasites. Vaccines with killed *Leishmania* and attempts to use killed parasites together with the BCG vaccine did not confer significant protection against human leishmaniasis (Sharifi 1998). Second-generation vaccines are based on the subunit/recombinant protein using a range of adjuvants to augment the immunogenicity of the selected antigens (Alexander 2009; Beaumier 2013; Duthie 2012; Llanos-Cuentas 2010). Another approach has been to use the antigenic salivary proteins of sandfly vector, which has delivered some promising results (Abdeladhim 2014; Reed 2016).

How the intervention might work

Once injected, pentavalent antimony (Sb^{+5}) is further reduced to trivalent antimony (Sb^{+3}) that will destroy the parasite. Both forms of antimonials (Sb^{+5} and Sb^{+3}) have been known to destroy *Leishmania* species by DNA fragmentation, which indicates a role in apoptosis (Lee 2002; Sereno 2001; Sudhandiran 2003). The antileishmanial activity of amphotericin B is attributed to the interaction with ergosterol in the cell membrane, which increases the cell permeability, causing cell death (Ramos 1996). Allopurinol was considered a promising candidate for treatment of leishmaniasis, since the inhibition of purine anabolism in *Leishmania* could inhibit its growth. Miltefosine could act as an antileishmanial drug through the modulation of different components of the cell, resulting in apoptosis (Verma 2004). Aminosidine sulphate (Paromomycin sulphate) causes interference in protein synthesis in bacterial species (Tracy 2001) and their antileishmanial effect could be related to the same mechanism (Sundar 2008). Fluconazole and itraconazole are fungistatic drugs, which inhibit the synthesis of ergosterol and have been shown to impede the growth of different in vitro species of *Leishmania* (Oliveira 2015). An in vitro study revealed that itraconazole induced the collapse of the *Leishmania* mitochondrial membrane potential, which was consistent with mitochondrial swelling and disorganisation and rupture of mitochondrial membranes (De Macedo-Silva 2013). Pentamidine has an effect on the parasite's genome by hindering reproduction and transcription at the mitochondrial level (Mishra 2007). Berman and Sacks demonstrated several pathogenic *Leishmania* species to be thermo-sensitive from 37 °C to 39 °C in vitro (Berman 1981; Sacks 1983). Photodynamic therapy is based on the principle of exposure to a relevant light source alongside oxygen, which leads to formation of reactive oxygen species followed by the destruction of the target cells. Also, the reaction caused by the photodynamic therapy may stimulate immune reactions, further enhancing the potential of the host against infections (Evangelou 2011). Pentoxifylline hinders the production of tumour necrosis factor-alpha and interferon-gamma (IFN-γ), while it prompts the creation of Th2-like (T-helper 2) cytokines, thereby stopping the Th1-mediated inflammatory and autoimmune responses (Brito 2014). Imiquimod is an immunomodulator that stimulates Toll-Like-Receptors (TLR) 7 and 8 on antigen-presenting cells to facilitate the creation of Th1 type cytokines, enhancing macrophage activity against *Leishmania* parasites. It has also been observed to have an antileishmanial effect which does not depend on the stimulation of TLR (Buates 1999). The interventions using combinations of IFN-γ and nitric oxide (NO) are based on the principle of enhancing the Th1 cytokine profile of the host immune response, which could improve the leishmanicidal activity of macrophages (Arana 1994; Lopez-Jaramillo 2010). The granulocyte macrophage colony-stimulating factor (GM-CSF) is a multipotential growth factor for marrow stem cells. In vitro, GM-CSF has stimulated macrophages to destroy *Leishmania* (Badaro 2001).

Why it is important to do this review

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 (Heras-Mosteiro 2017) and prevention measures (González 2015) for all types of cutaneous leishmaniasis have been addressed in separate Cochrane Reviews. This is an update of the review *Interventions for American cutaneous and mucocutaneous leishmaniasis* (González 2009).

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). In accordance with the priorities set by the WHO, we therefore 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.

Pentavalent antimonials remain the first-choice treatment for CL in most American countries, but most of the evidence for using either the first-choice or the alternative treatments is weak (Reveiz 2013; PAHO 2015). Since 2010, the debate on improving the quality of clinical trials in cutaneous leishmaniasis has been raised and specific recommendations have been published (González 2010; Olliaro 2013). Recent PAHO documents emphatically recommend the development of clinical trials for evaluation of alternatives currently in use in Latin America. (González 2010; PAHO 2015; Reveiz 2013; WHO 2010). However, the most neglected and challenging tegumentary and mucosal forms of leishmaniasis remain without any guideline for improving the methodology of clinical trials (Amato 2007). Alternative treatment regimens include

miltefosine, pentamidine isethionate, amphotericin B, antifungal agents, paromomycin, and local treatments. Other treatments such as immunotherapy and thermotherapy have also been tested. The limited number of available drugs, the high levels of side effects of most of them, the difficulties in administration and ongoing resistance highlight the need for reviewing the current evidence on efficacy and adverse effects of the available treatments for American cutaneous and mucocutaneous leishmaniasis. Given that a wide range of systemic and local treatments are currently being used or are under clinical development on a global scale, probably influenced by the increasing international travel trend, their effectiveness and safety needs to be well established.

OBJECTIVES

Main objective: To assess the effects of interventions for all immuno-competent people who have American cutaneous and mucocutaneous leishmaniasis (ACML).

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). We did not consider cross-over trials in this review because they are an inappropriate design for treatments which have the potential to cure an infectious disease.

Types of participants

All immuno-competent people who have American cutaneous leishmaniasis or mucocutaneous leishmaniasis, or both, diagnosed by clinical presentation, and *Leishmania* infection confirmed by smear, 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, placebo only, or another active compound.

1. Antimonials (intramuscularly, intravenously and intralesionally)

1.1 Meglumine antimoniate (Glucantime, SB N-methylglucamine)
1.2 Stibogluconate (Pentostam and others)

2. Non-antimonial systemic treatments

2.1 Antifungals
2.2 Allopurinol
2.3 Miltefosine
2.4 Aminosidine sulphate
2.5 Pentamidine isethionate
2.6 Azithromycin
2.7 Amphotericin B plus oral rehydration solution versus amphotericin B plus normal saline solution

3. Non-antimonial topical or intralesional therapies

3.1 Paromomycin (aminosidine)
3.2 Aminoglycosides
3.3 Amphotericin B
3.4 Nitric oxide patch (NOP)
3.5 Imiquimod

4. Physical therapies

4.1 Thermotherapy
4.2 Cryotherapy

5. Immuno-chemotherapy

5.1 Vaccines
5.2 Bacillus Calmette-Guerin (BCG)
5.3 Pentoxifylline
5.4 Granulocyte macrophage colony-stimulating factor (GM-CSF)
5.5 Interferon-gamma (IFN-γ)

Since this review aims to include only treatments for cutaneous leishmaniasis, we excluded studies where only vaccines were given (i.e. not in combination with other treatment), as these studies are likely to be aimed at preventing cutaneous leishmaniasis.

Types of outcome measures

We included studies that reported at least one of the outcomes listed below. Studies that did not report any of the outcomes of interest were therefore excluded.

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 epithelialisation has occurred in ulcerative lesions. Lesions were considered not to be healed if there was no re-epithelialised skin, or inflammatory signs remain after follow-up.

We reported all time points that addressed cure at three months after the end of treatment and beyond.

- Adverse effects

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 or prevention of scarring, or both.
- Quality of life.

Tertiary outcomes

- Speed of healing (i.e. average time from start of treatment to cure).

- 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. The definition assumes that the original susceptibility of the population is known, which is not always the case for *Leishmania*)" (Ponte-Sucre 2003)).
- Only microbiological or histopathological cure of skin lesions.
- Development of cell-mediated immunity (i.e. difference in the size of leishmanin skin test reaction (i.e. difference in the diameter of Montenegro skin test reaction before and after treatment).
- All-cause mortality.

To assess the results we primarily focused on end of follow-up time points.

Search methods for identification of studies

We aimed to identify all relevant RCTs, regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

For this update we revised all our search strategies in line with current Cochrane Skin practices. Details of the previous search strategies are available in González 2004 and González 2009. The Cochrane Skin Information Specialist searched the following databases up to 27 August 2019:

- the Cochrane Skin Group Specialised Register, using the search strategy in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL) 2019, Issue 8, in the Cochrane Library, using the strategy in Appendix 2;
- MEDLINE via Ovid (from 1946), using the strategy in Appendix 3;
- Embase via Ovid (from 1974), using the strategy in Appendix 4;
- LILACS (Latin American and Caribbean Health Science Information database, from 1982), using the strategy in Appendix 5;
- CINAHL via EBSCO (Cumulative Index to Nursing and Allied Health Literature, from 1981), using the strategy in Appendix 6.

MP searched the American College of Physicians (ACP) journal club from June 2007 to April 2008 for the previous review. Since May 2008, ACP Journal Club has been published as a monthly feature of Annals of Internal Medicine. For this update, MP searched the Annals of Internal Medicine from June 2007 to April 2016 using the search terms 'cutaneous and leishmaniasis'.

Trials registers

MP searched the following trials registers on 29 August 2019, using the terms 'leishmania' or 'leishmaniasis':

- the ISRCTN registry (www.controlled-trials.com);
- the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/);
- the EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

Searching other resources

References from published studies

We checked the bibliographies of included studies for further references to relevant trials and systematic reviews.

Adverse effects

The Cochrane Skin Information Specialist searched MEDLINE (Ovid) from 1950 to 23 October 2018 for adverse or side effects of interventions used for the treatment of cutaneous and mucocutaneous leishmaniasis (see strategy in Appendix 7). Although we recognise that searching one database with the terms in Appendix 7 does not constitute a comprehensive search for adverse effects (adverse-effects searching has moved on since this strategy was developed in 2007/8), we have used the same search terms as previously, as a pragmatic approach in terms of managing the workload around sifting and discussing adverse effects in relation to leishmaniasis.

Data collection and analysis

Some parts of the methods section of this review uses text that was originally published in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

At least two review authors (MP, LR) independently checked titles and abstracts identified from the searches, using the web-based software platform Covidence. If it was clear that the study did not refer to a RCT on American cutaneous and mucocutaneous leishmaniasis, we excluded it. If it was unclear, then we obtained the full-text study for independent assessment by two review authors (MP, LR). We decided which trials fitted the inclusion criteria, resolving any disagreements by discussion and consensus. 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 review authors (from VE, KO, MP, JRR) independently carried out the data extraction by using a predesigned data extraction form which was previously piloted. We extracted reported data pertaining to cure rates for all evaluated drugs, paying attention particularly to the doses and therapeutic frequencies. We extracted the following items:

- Study ID, country, study design, study setting, study period;
- Sample size, unit of randomisation, withdrawals, disease severity, baseline data;
- Type of interventions, duration of intervention, co-interventions;
- Outcome data;
- Ethical approval, informed consent, conflicts of interest and funding sources.

We resolved any disagreements by discussion or with referral to a third review author (LR). We obtained missing data from trial authors whenever possible.

Assessment of risk of bias in included studies

At least two of the review authors (from VE, KO, MP, JRR) independently assessed risks of bias using the Cochrane tool for assessing risk of bias as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or with referral to a third review author (LR).

We rated the following domains for each of the included studies to assess the degree to which:

- the allocation sequence was adequately generated ('sequence generation');
- the allocation was adequately concealed ('allocation concealment');
- knowledge of the allocated interventions was adequately prevented during the study ('blinding');
- incomplete outcome data were adequately addressed;
- study reports were free of suggestion of selective outcome reporting; and
- the study was apparently free of other sources of bias that could put it at high risk of bias. Other sources of bias included the calculation of the sample size, the reporting of the *Leishmania* species, and baseline comparability among intervention groups.

We also discussed the following issues under Description of studies in the Results section:

- 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;
- conflicts of interest;
- funding sources.

Each domain was allocated to one of three possible categories: low, high, and unclear risk of bias (where the risk of bias was uncertain or unknown). See Characteristics of included studies for more details.

Measures of treatment effect

We expressed the results as risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous outcomes. The percentage of lesions 'cured' at least three months after the end of treatment was the primary outcome measure if available.

For continuous outcomes we have calculated mean differences (MDs) and their 95% CIs.

Unit of analysis issues

We included clinical trials of parallel-group designs in which the individual participants were the allocation unit and the unit for assessing outcomes. The approach we followed for three-arm trials was to compare the arms in pairs (A vs B, B vs C, and A vs C), ensuring not to double count the number of participants from the intervention groups in the trials.

Dealing with missing data

For each study, we took all participants that were randomised into account when adding the data to our tables, and assumed that missing data were treatment failures for our efficacy outcomes. Where an intention-to-treat (ITT) approach was not stated, we used the numbers originally randomised to the groups to calculate the effect estimates.

Assessment of heterogeneity

We assessed clinical heterogeneity by examining the characteristics of the studies, the similarities between the types of participants, the interventions, the comparisons, and the outcomes, as specified in the criteria for included studies. We analysed statistical heterogeneity using a Chi^2 test (on one degree of freedom, with a significance level of 0.05) (Higgins 2003). To assess the consistency of the study results, we obtained the I^2 statistic, which measures the proportion of total variation across studies that is due to heterogeneity rather than to chance. I^2 values lie between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.

Assessment of reporting biases

In this review, the low number of studies evaluating similar interventions and comparisons did not permit an assessment of publication bias. In future updates, if a sufficient number of trials (10 or more) assessing similar effects are identified for inclusion in the review, we will assess publication bias according to the recommendations on testing for funnel plot asymmetry (Egger 1997), as described in section 13.3.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2019). If we detect asymmetry we will try to assess other possible causes and will explore them in the Discussion if appropriate.

Data synthesis

One review author (JRR) analysed the data in Review Manager 5 (RevMan) (Review Manager 2014) and reported them as specified in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2019). We carried out data synthesis of results from different studies only if we were able to identify at least two studies investigating similar treatments, a follow-up of at least three months after treatment cessation only for the primary outcome, and reporting data amenable to pooling. We considered that data on cure prior to three months after cessation of treatment showed only a short-term benefit, and although described, were excluded from statistical analysis. Such data were reported as a narrative summary, where appropriate. We used a random-effects model to combine the results of individual studies in this review.

Subgroup analysis and investigation of heterogeneity

In view of the limited number of included studies covering any one intervention, we did not conduct any of the subgroup analyses that we had originally planned: *Leishmania* species, location and severity of infection, geographical setting, diagnostic techniques, type of treatment (topical, systemic, or combination), and relapse or re-infection.

Following clinical recommendations we also considered age as a subgroup analysis, because therapeutic failure and relapses are frequent in children with cutaneous leishmaniasis, especially with pentavalent antimonials. This may be due to differences in

pharmacokinetics. Hence, with hindsight it is important to report results separately for children and adults, as this variable may influence the results. Where data permitted, we presented separate analyses for different age groups.

Sensitivity analysis

We planned to carry out a sensitivity analysis by excluding studies at high risk of bias, but we were unable to do this due to the limited number of studies we could pool. Furthermore, the reporting of the methodology of most of the studies was very poor, with registry information or study protocols unavailable. Most studies therefore had a high risk of bias in at least one domain.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to rate the certainty of the evidence (for each outcome) and strength of recommendations (Guyatt 2008). For better understanding of the review, we have highlighted the GRADE assessments in 'Summary of findings' tables of key comparisons and outcomes. The certainty of evidence can be high, moderate, low, or very low, based on the assessment of five domains: study limitations (risk of bias), imprecision, indirectness, inconsistency and publication bias. Each domain could be downgraded by one (for serious concerns) or by two levels (for very serious concerns).

We have created 'Summary of findings' tables for the following comparisons, which we believe are most relevant nowadays for clinicians:

- Intramuscular meglumine antimoniate (IMMA) vs placebo
- oral miltefosine vs placebo
- oral miltefosine vs meglumine antimoniate
- azithromycin vs meglumine antimoniate
- topical imiquimod + Intravenous (IV) meglumine antimoniate (MA) vs placebo + IVMA
- thermotherapy vs meglumine antimoniate
- pentoxifylline + IMMA vs IMMA + placebo.

We included our two primary outcomes (complete cure and adverse effects) as well as one secondary outcome (recurrence) in all tables.

RESULTS

Description of studies

Results of the search

For this update we ran searches to August 2019. As shown in our study flow diagram (Figure 1), we retrieved 1696 records from the Electronic searches (102 from Cochrane Skin Specialised Register, 331 from CENTRAL, 399 from MEDLINE, 589 from Embase, 119 CINAHL, and 156 from LILACS). We retrieved 106 trials from five trial registers. Ten records were identified through hand-searches, including two that were included in a previous non-Cochrane review (Reveiz 2013). We therefore had an overall total of 1812 records. After removal of duplicates, we had 522 records. We excluded 427 records based on titles and abstracts. We obtained the full text of the remaining 95 records, of which 29 were excluded (see Characteristics of excluded studies), 10 studies are awaiting classification (see Characteristics of studies awaiting classification), and 12 are ongoing trials (see Characteristics of ongoing studies). We included 37 new studies, along with 38 studies from the previous review, which brings the number of included studies in this update to 75 (6533 participants) (see Characteristics of included studies).

Figure 1. Study flow diagram.

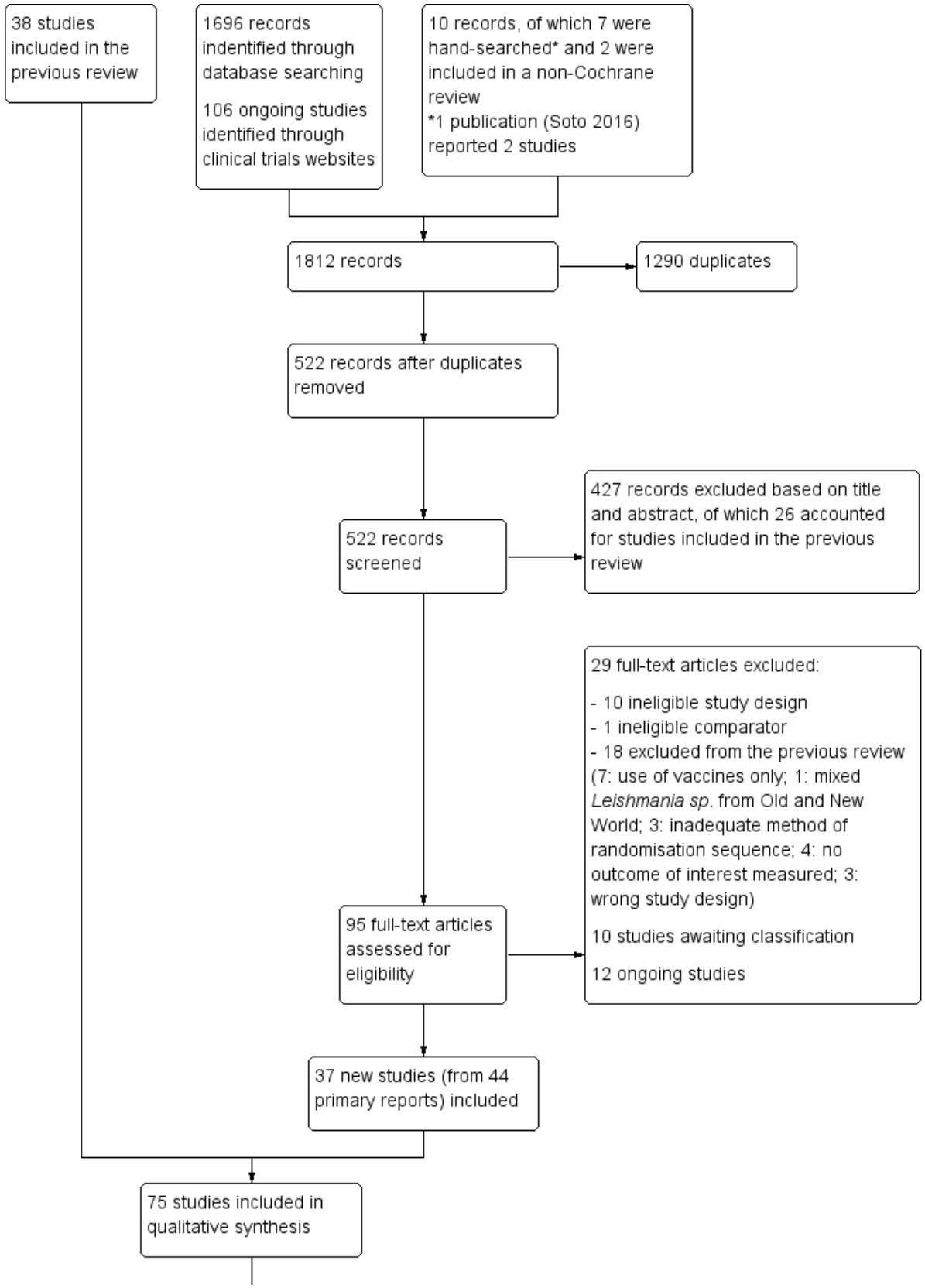
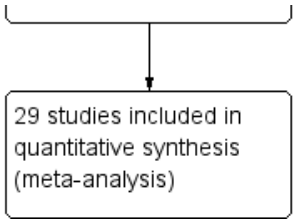


Figure 1. (Continued)



Two masters' theses (Lyra 2013; Saheki 2013), and two published articles (Lyra 2016; Ribeiro 2014) included the same study (registration number NCT01301924), and were grouped under the primary report (Saheki 2017). Two published articles (López 2012; López 2013) included the same study (registration number NCT00471705), and were grouped under the primary report (Vélez 2010). One trial published in clinicaltrials.gov with results (NCT01790659) was grouped under the primary report (Sosa 2019). Soto 2016 described two studies that we considered to be two separated studies (Soto 2016a; Soto 2016b). Of note, Soto 2013. as well as Soto 2016a and Soto 2016b, shared the same registration number NCT01300975 but were treated as separate studies after contact with the author of the studies, who claimed that the participants belonged to two different groups and were recruited at two different time points.

Included studies

Design

All of the studies were randomised clinical trials, of which four were pilot studies (Arévalo 2007; Brito 2014; Guzman-Rivero 2014; Soto 2002). Ten studies were phase II (Gadelha 2018; Garcia 2014; Llanos-Cuentas 1997; López 2018; Machado 2018; NCT01011309; Sosa 2013; Soto 2002; Soto 2016a; Soto 2016b), one was a phase II/III (Chrusciak-Talhari 2011), and six were phase III (Ferreira 2014; Saheki 2017; Sosa 2019; Soto 1998; Vélez 1997; Vélez 2010) (see Characteristics of included studies table).

Setting

Twenty-five studies were performed in Brazil, nine in Peru, six in Bolivia, five in Panama, four in Guatemala, three in Ecuador, two in Venezuela, two in Argentina, one in Honduras, and one in Suriname. We found 14 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), which recruited active-duty military personnel who had contracted leishmaniasis in endemic areas when deployed abroad (mainly in Panama, Belize and Brazil).

Of the 75 studies, 12 did not describe the setting, 17 recruited participants from health or medical care centres (mainly from Heath Post of Corte de Pedra, which is a reference centre for the management of American tegumentary leishmaniasis), nine recruited from centres or hospitals from the army, 11 from other outpatient clinics, seven from research institutes, 12 from hospitals (rural, urban or reference hospitals), and seven from clinics.

Sample sizes

The number of participants randomised in each study varied widely, from 19 to 437, with a median of 72 participants. Overall, 27 studies reported a sample size calculation, of which 21 were newly identified for the update, indicating that an increasing number of studies are performing sample size and power calculations and thus improving the quality of their research.

Participants

All of the studies reported their inclusion criteria, with the exception of three studies (Neva 1997; Ravis 2013; Souza 1998). The main criterion for inclusion was parasitological confirmation of cutaneous leishmaniasis or clinical diagnosis of leishmaniasis by various means, including scraping technique, delayed-type hypersensitivity skin test (also called 'the Montenegro skin test') to *Leishmania* antigen, parasite isolation or real-time polymerase chain reaction (PCR), smears (Giemsa staining), and histopathology (haematoxylin-eosin).

Most RCTs (n = 67) evaluated the cutaneous form of leishmaniasis. None of the studies included participants with diffuse or disseminated CL, which are both considered the severe forms of CL. We found only eight studies that included participants with mucosal leishmaniasis (ML) (Franke 1994; Garcia 2014; Machado 2007; Sampaio 2019) or mucocutaneous leishmaniasis (MCL) (Echevarria 2006; Ferreira 2014; Llanos-Cuentas 1997; Llanos-Cuentas 2007). Three studies included moderate or severe cases (Llanos-Cuentas 1997; Llanos-Cuentas 2007; Machado 2007). Severity of MCL was defined combining the criteria of mucosal lesion extension and severity of symptoms. Three studies included participants with a confirmed diagnosis of ML, irrespective of their degree of severity (Ferreira 2014; Franke 1994; Sampaio 2019). In contrast, one study included participants with suspected MCL presumably caused by *L. braziliensis* with attempts to microbiologically confirm the diagnosis (Echevarria 2006), and another study only stated that participants diagnosed with ML were included (Garcia 2014).

Cutaneous form

The mean age (SD) in the 67 studies assessing the CL form was 27.4 years (5.2) (age range in years: 2 to 87). The male:female ratio was 3.13:1 (3803/1214 - not all of the studies provided the sample size stratified by sex); eight studies included only male participants (Arana 1994; Balou 1987; Hepburn 1994; Navin 1990; Navin 1992; Saenz 1990; Soto 2002; Vélez 2010). Cutaneous lesions were mainly located in the extremities (arms and legs) and limbs, and to a lesser extent in the neck and trunk. The types of lesions were mainly proliferative, verrucose, nodular, papular, plaque, regional adenopathy, satellite lesion, oedematous or erythematous to a lesser extent.

Mucosal or mucocutaneous form

The mean age (SD) in the eight studies assessing the ML or MCL forms was 39.5 years (7.2) (age range in years: 22 to 77). The male:female ratio was 7.83:1 (274/35 - not all of the

studies provided the sample size stratified by sex), since four studies included males only (Echevarria 2006; Franke 1994; LLanos-Cuentas 1997; Llanos-Cuentas 2007). Mucosal lesions were more often located in the nose (septum, turbinates) or the oral cavity (palate-uvula-pharynx and larynx-epiglottis), and were mainly ulcerative or infiltrative.

Leishmania species involved

Five RCTs out of the 75 failed to mention the causative parasite (Armijos 2004; Cossio-Duque 2015; Figueiredo 1999; Ravis 2013; Souza 1998). Only 54 studies confirmed the type of causative organism, of which 28 confirmed the presence of a single species (*L. braziliensis* (21); *L. panamensis* (6); *L. peruviana* (1)); 15 RCTs, the presence of two species; 6 RCTs, the presence of three *Leishmania* species; 4 RCTs, confirmed the presence of four *Leishmania* species; and 1 RCT, the presence of five *Leishmania* species (see Characteristics of included studies and Table 3 for more details). The rest based their studies on endemic species or previous studies.

The confirmed species most commonly found were *L. braziliensis* (44), *L. panamensis* (19), and *L. mexicana* (10), whereas the least were *L. amazonensis* (4), *L. liansoni* (3), *L. chagasi* (3), *L. peruviana* (2), and *L. naiffi* (2), respectively.

The confirmed species from the eight RCTs assessing ML or MCL forms were: *L. braziliensis* alone (7 RCTs) or *L. braziliensis* with *L. amazonensis* (1 RCT). One RCT assessed participants with both forms of unknown species of leishmaniasis (Figueiredo 1999).

The geographic distribution of the species is described in Table 3.

Interventions

A wide range of interventions were evaluated. We grouped the trials into five categories of interventions:

- Antimonials: 24/75; of which eight were added in this update.
- Non-antimonial systemic treatments: 30/75; of which 17 were added in this update.
- Non-antimonial topical or intralesional therapies: 14/75; of which six were added in this update.
- Physical therapies: 4/75; of which two were added in this update.
- Immuno-chemotherapy: 11/75; of which four were added in this update.

The 75 studies covered 68 comparisons, of which 23 are newly added to this update.

Comparators

Fourteen studies were placebo-controlled, and 61 had active controls, of which 11 compared different doses of the same drug: intravenous meglumine antimoniate (5 studies), intravenous sodium stibogluconate (3), intramuscular pentamidine isethionate (1), intravenous aminosidine sulphate (1) and amphotericin (1). Of the 61 active comparators, 42 studies used meglumine antimoniate either intravenously (23) or intramuscularly (16) or both (3). Two studies administered meglumine antimoniate intralesionally (2). Ten studies used sodium stibogluconate intravenously, three studies used paromomycin, two used pentamidine isethionate administered intramuscularly (1) or intralesionally (1), one study used aminosidine sulphate intravenously, and one amphotericin.

Co-interventions and multi-arm studies

Fifty-three were two-arm studies. However, we found 20 multi-arm studies, of which 20 were three-arm studies (Arana 1994; Arévalo 2007; Armijos 2004; Correia 1996; Gadelha 2018; Guderian 1991; Machado 2018; Navin 1990; Navin 1992; NCT01011309; Neves 2011; Oster 1985; Saenz 1990; Soto 1994a; Soto 2013; Soto 2016a; Soto 2019; Souza 1998; Vélez 1997; Vélez 2010) and two were four-arm studies (Martínez 1992; Soto 1998). Of the three-arm studies, nine used active comparators such as antimonials (i.e. intravenous meglumine antimoniate (IVMA), IMMA, and intravenous sodium stibogluconate (IVSSG)), seven used placebo (Navin 1990; Navin 1992; Saenz 1990; Soto 2013; Soto 2019; Vélez 1997) or no treatment groups (Guderian 1991), and four assessed different regimens, i.e. IVMA with or without placebo or IFN-γ (Arana 1994), IVSSG (Oster 1985), aminosidine sulphate (Soto 1994a), and intramuscular pentamidine isethionate (Gadelha 2018). Of the four-arm studies, Martínez 1992 used an active comparator (IVMA) and group left untreated, whereas Soto 1998 compared two groups of topical 15% paromomycin sulphate/12% MBCL combined with IVMA. The other two groups were active comparators: 1) IVMA combined with topical placebo and 2) IVMA.

Eleven studies applied additional therapeutic interventions (so-called co-interventions) and 20 studies applied rescue therapies. Co-interventions used were mainly applied to avoid bacterial superinfections; for instance, they offered daily cleansing and antibiotic (orally, topically or systemically) prior to the start of study medication (Alves Noroes 2015; Arévalo 2007; Convit 1987; Convit 1989; Lobo 2006; Miranda-Verástegui 2005; Soto 2013; Vélez 2010), or oral antihelminthic based on parasitological assay results on the 60-day visit in the placebo (control) group (Newlove 2011). Other co-interventions applied were simultaneously-combined immunotherapy and chemotherapy in participants with intermediate or diffuse clinical forms of leishmaniasis (Convit 1989), intake of carbohydrate-rich food before receiving the pentamidine injection (Gadelha 2018), cortisone 1% cream for the treatment of pruritus, erythema or swelling or both, or paracetamol for pain treatment (Soto 2019).

Follow-up

The follow-up period ranged from 28 days (Lobo 2006) to seven years (Oliveira-Neto 1997), although the most common follow-up period was 12 months. The length of follow-up period was not reported in one study (Machado 2007).

Outcomes

Primary outcome measures were reported as:

- 'Percentage of participants cured at least three months after the end of treatment': this was reported in 22 studies in the previous review and in 40 studies in this update, totalling 62 studies. However, 72 RCTs reported the primary outcome as the percentage of participants cured, although the timing varied and included assessment prior to three months. One study reported the cure using both participants and lesions as the unit of analysis (Soto 2002). Three studies did not report the primary outcome (Guzman-Rivero 2014; Ferreira 2014; Ravis 2013). Overall the timings ranged from just at the end of treatment to four years after completion of treatment.

- Adverse effects were described in all but eight of the studies (D'Oliveira 1997; Echevarria 2006; Martínez 1992; Miranda-Verástegui 2009; Ravis 2013; Soto 1998; Soto 2008; Souza 1998).

Two studies did not report any of our primary outcomes (Echevarria 2006; Ravis 2013).

Secondary outcome measures were reported as:

- Recurrence: duration of remission and/or percentage of people with treated lesions that recur within six months, one, two and three years were reported in 34 studies (Andersen 2005; Arana 1994; Arana 2001; Armijos 2004; Brito 2014; Chrusciak-Talhari 2011; Convit 1989; D'Oliveira 1997; Ferreira 2014; Franke 1994; Garcia 2014; Hu 2015; Krolewiecki 2007; Llanos-Cuentas 1997; Lopez-Jaramillo 2010; Machado 2018; Machado-Pinto 2002; Martínez 1992; Martínez 1997; Navin 1992; Neva 1997; Rubiano 2012; Saenz 1987; Saheki 2017; Sosa 2013; Soto 2004b; Soto 2008; Soto 2013; Soto 2016a; Soto 2016b; Souza 1998; Toledo 2014; Vélez 1997; Vélez 2010);
- Degree of functional or aesthetic impairment (none of the studies measured this outcome);
- Prevention of scarring (none of the studies measured this outcome);
- Quality of life in (none of the studies measured this outcome).

Forty-one studies did not report any of our secondary outcomes.

Tertiary outcome measures were reported as:

- Speed of healing was reported in 14 studies (Almeida 1999; Alves Noroes 2015; Armijos 2004; Convit 1987; Convit 1989; López 2018; Machado 2007; Machado-Pinto 2002; Prates 2017; Saenz 1990; Santos 2004; Sosa 2019; Soto 2002; Soto 2008);
- Change in isolation or PCR of *Leishmania* and emergence of resistance (none of the studies measured this outcome);
- Microbiological or histopathological cure of skin lesions was reported in three studies (Navin 1990; Saenz 1987; Saenz 1990);
- Development of cell-mediated immunity (none of the studies measured this outcome);
- All-cause mortality (none of the studies measured this outcome), although one study (Saheki 2017) mentioned that one death occurred in the high-dose group but that no participant was lost to follow-up. Vélez 2010 mentioned that two participants were lost to follow-up because they were killed in combat.

Fifty-eight studies did not report any of our tertiary outcomes.

Conflicts of interest

Fifty-one studies declared no conflicts of interest, 15 did not mention a potential conflict of interest (Alves Noroes 2015; Arana 2001; Alves 2016; Ballou 1987; Cossio-Duque 2015; D'Oliveira 1997; Ferreira 2014; Hepburn 1994; Lopez-Jaramillo 2010; Machado 2018; Martínez 1992; Ravis 2013; Soto 2004a; Soto 2004b; Souza 1998); five declared that their views did not purport to reflect the views of the Department of Defense or the United States Army (Andersen 2005; Navin 1992; Oster 1985; Sosa 2013; Soto 2002); and four studies stated that an author was employed by a pharmaceutical company (Rubiano 2012; Soto 1994a; Soto 2008; Soto 2019).

Funding

One study reported that the authors did not receive specific funding for this work (Gadelha 2018). Fifty-one of the 75 included studies reported they had received funding, mainly from institutional (academic and/or governmental/WHO/PAHO) grants (n = 33), although five of these studies also received funding from pharmaceutical companies, i.e. Ingelheim Boehringer (Arana 1994), 3M Pharmaceuticals (Miranda-Verástegui 2005), AB Foundation and the US army (Soto 2002), Petroleros de Venezuela S.A (Convit 1987), and Camara Venezolana de la Industria de la Cerveza (Convit 1989).

Eight studies were exclusively funded by the US army (Andersen 2005; Franke 1994; Navin 1992; Neva 1997; Ravis 2013; Sosa 2013; Soto 2002; Sosa 2019), and 10 by industry, i.e. Farmitalia Carlo Erba (Soto 1994a), AB Foundation for Medical Research (Soto 1998; Soto 2004a; Soto 2008; Soto 2013; Soto 2016a; Soto 2016b; Soto 2019), Burroughs Wellcome Co. and Dember Foundation Inc (Chico 1995), and Zentaris (Soto 2004b).

Excluded studies

We excluded 29 RCTs: 10 were ineligible study designs; one had an ineligible comparator; and 18 had been excluded in the previous review. Reasons for exclusion were mainly ineligible study designs (non-randomised or randomised but using an inadequate method of randomisation), ineligible comparator (i.e. use of vaccines alone or non-comparative studies), or no outcomes of interest. One study mixed *Leishmania sp*. from the Old and the New World and did not report outcomes separately (see Characteristics of excluded studies).

Ongoing studies

We have found 12 registered ongoing RCTs which appear to meet the inclusion criteria (NCT00537953; NCT01301937; NCT02530697; NCT02687971; NCT03023111; NCT03084952; NCT03829917; NCT04072874; NTR2076; PER-007-16; RBR-5r93wn; RBR-6mk5n4). All of them are parallel, randomised trials of which eight were open-label, one was double-blind, one triple-blind (including outcome assessor) and one was quadruple-blind (including outcome assessor and care provider). One study did not report on blinding. Nine include the cutaneous form of leishmaniasis, two the mucosal form (RBR-5r93wn; NCT02530697), and one both mucosal and mucocutaneous forms (NCT01301937).

Two studies did not describe the method used to confirm parasite presence, and 10 detailed the method of confirmation (smear in skin biopsies, microscopic identification of amastigotes in stained lesion tissue, demonstration of Leishmania by PCR, positive culture for promastigotes). Seven studies assessed miltefosine alone (RBR-5r93wn) or combined with meglumine antimoniate (NCT00537953), pentoxifylline (NCT02530697), thermotherapy (NCT02687971; PER-007-16), GM-CSF (NCT03023111) or paromomycin (NCT03829917). Two studies assessed the effects of different doses (NCT01301937) or ways of administering meglumine antimoniate (RBR-6mk5n4). Three studies assessed different regimens of Curaleish lotion and cream combined (NCT04072874), different regimens of pentamidine isethionate (NTR2076) and 18-Methoxycoronaridine (NCT03084952). See Characteristics of ongoing studies for details.

Studies awaiting assessment

We have found 10 registered RCTs whose recruitment period is completed but that have not yet been published (NCT00004755; NCT00111514; NCT00111553; Silva 2006; NCT00317980; NCT00973128; NCT01380301; NCT01380314; NCT01464242; NCT03294161). All of them were parallel, randomised trials, of which five were double-blind, three single-blind and two were open-label. Stages were phase I (two studies), II (five studies), II/III (one study), III (one study), and IV (one study).

Nine included the cutaneous form of leishmaniasis and one the mucocutaneous form (NCT00111514). Four studies did not describe the method used to confirm parasite presence, and six detailed the method of confirmation (positive smear, in vitro culture, lesion biopsy or aspirate, positive Montenegro skin test or PCR test).

Treatments to be tested were: vaccines (NCT00111514; NCT00111553), miltefosine (NCT01380301; NCT01380314), oral allopurinol (NCT00004755), nitric oxide patches (Silva 2006), topical immucillin DI4G (NCT03294161), oral pentoxifylline in combination with IMMA (NCT01464242), different regimens of IVMA (NCT00317980), and Recombinant Human GM-CSF combined with IMMA (NCT00973128). See Studies awaiting classification for details.

Risk of bias in included studies

Figure 2 depicts the 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study, and Figure 3 depicts the 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' domain presented as percentages across all included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

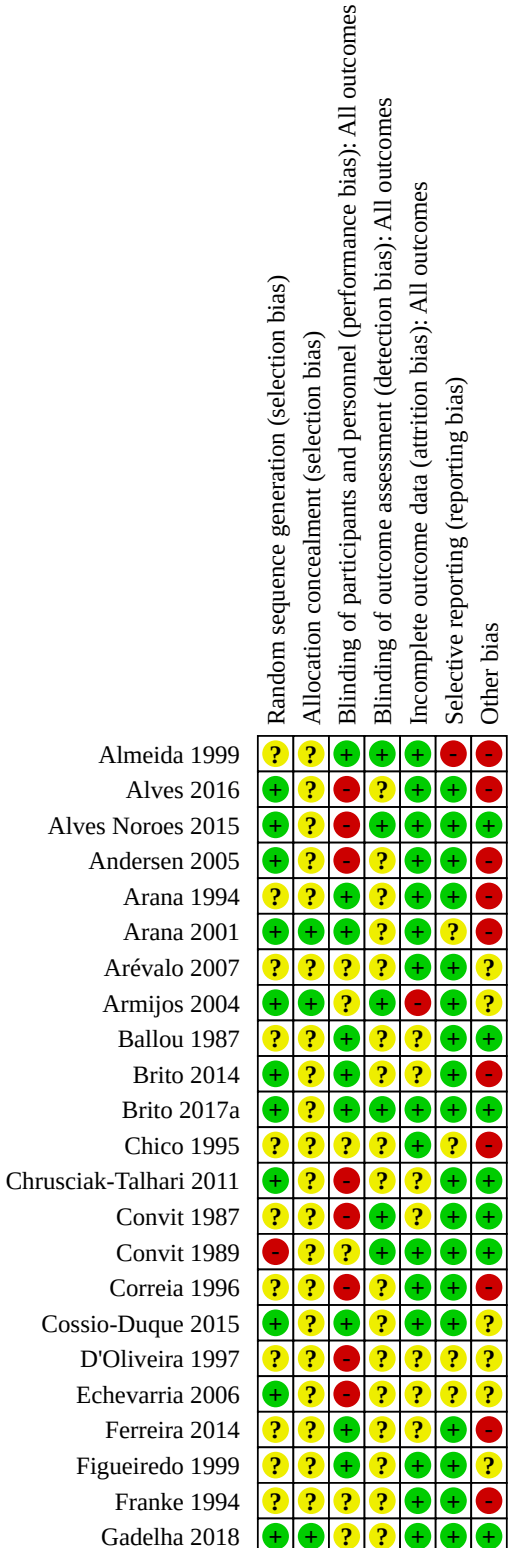


Figure 2. (Continued)

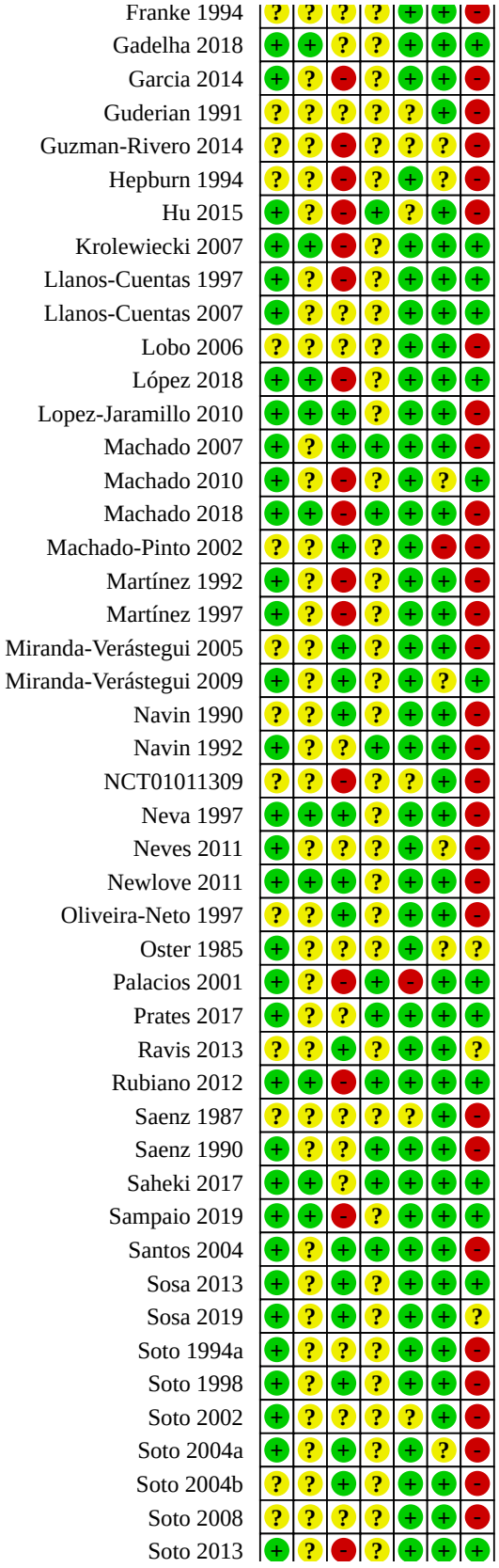


Figure 2. (Continued)

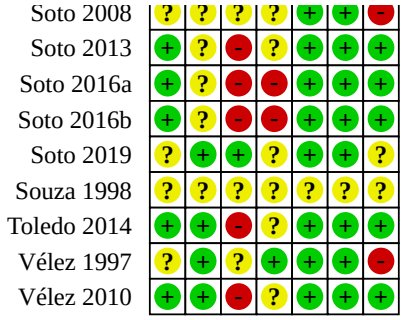
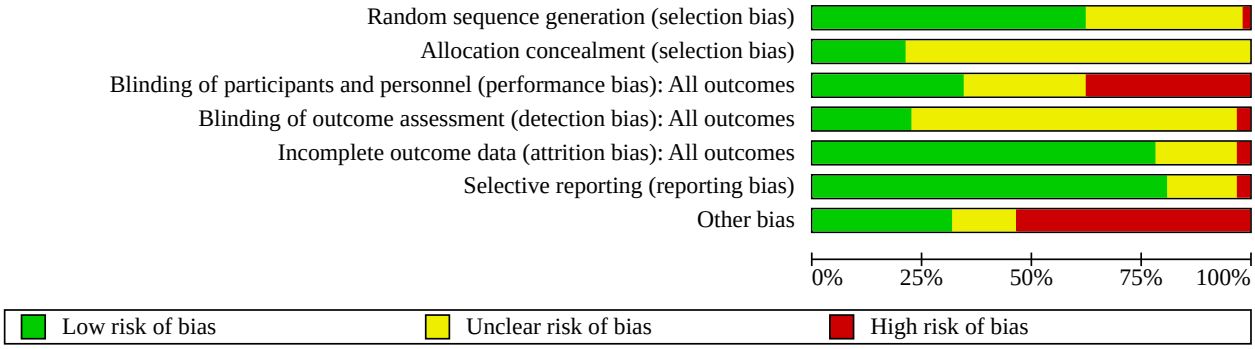


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

There were 47/75 (63%) studies where the method of generation of the randomisation sequence was clearly stated and therefore deemed to have low risk of bias, 27/75 (36%), had unclear risk of bias, and one study (Convit 1989) was classified as high risk because the number of participants assigned to the groups was uneven despite the use of serial numbers for randomisation (Characteristics of included studies; Figure 2; Figure 3).

Only 14/75 (19%) studies (Arana 2001; Armijos 2004; Gadelha 2018; Krolewiecki 2007; López 2018; Lopez-Jaramillo 2010; Machado 2018; Neva 1997; Newlove 2011; Rubiano 2012 ; Saheki 2017; Sampaio 2019; Toledo 2014; Vélez 2010) had both an adequate reporting of the method of allocation concealment and an adequate generation of randomisation sequence (see Characteristics of included studies for details). One study had a low risk of selection bias from allocation concealment but an unclear risk of selection bias from random sequence generation as it was not described (Vélez 1997). However, in most studies (59/75: 79%), the method used to conceal the allocation prior to assignment was unclear.

Blinding

Only four studies (5.3%) were at low risk for both performance and detection bias. Twenty-one studies were at low risk of performance bias but at unclear risk of detection bias, as it was not clear if outcome assessment was blinded.

Two studies were at high risk of both performance and detection bias because participants, study personnel and outcome assessors were not blinded to treatment allocation (Soto 2016a; Soto 2016b). Six studies (8%) were at high risk of performance bias because participants and study personnel were not blinded to treatment allocation but were judged as low risk of detection bias, as the outcomes were assessed under blinded conditions (Alves Noroes 2015; Convit 1987; Hu 2015; Machado 2018; Palacios 2001; Rubiano 2012). Twenty studies (27%) were also at high risk of performance bias but at unclear of detection bias as not enough information was provided to judge this risk. Seven studies were at unclear risk of performance bias because it was not clear if participants/study personnel were blinded to treatment group throughout the study, but we judged them as low risk of detection bias because outcome assessors were blinded (Armijos 2004; Convit 1989; Navin 1992; Prates 2017; Saenz 1990; Saheki 2017; Vélez 1997).

Fourteen studies were at unclear risk of bias for both domains.

See Characteristics of included studies for further details.

Incomplete outcome data

Of the 75 included studies, we rated 59 studies (79%) as having low risk, 14 studies (19%) unclear risk and two studies (3%) at high risk of bias. Armijos 2004 was considered at high risk of attrition bias because the dropout rates were moderate (21%) but no reasons were provided. Palacios 2001 had a high dropout rate of 40%,

with reasons including inadequate dose given, not adhering to treatment or missing follow-up appointments.

Dropouts

The overall number of participants lost to follow-up was 511, i.e. 7.8% of the total number of study participants included in the meta-analyses or single-study analyses. All the studies reported from which arm the losses occurred (Characteristics of included studies).

Intention-to-treat analyses

Losses to follow-up occurred in 49 studies, and the other 26 reported no dropouts. However, 31 of the 49 studies did not carry out an intention-to-treat analysis (ITT), but only assessed participants that completed treatment. Only 18 of the trials explicitly stated an ITT analysis. For each study, we have taken all randomised participants into account when entering the data into our tables, and have assumed that missing data were treatment failures.

Selective reporting

Of the 75 included studies, 61 (81.33%) reported all expected outcomes and were therefore rated at low risk of bias. Twelve studies (16%) were judged as having unclear risk of bias and two studies (2.67%) failed to report results for a key outcome that would be expected to have been reported, or reported them incompletely so that we cannot meta-analyse them, and were therefore rated at high risk of bias (Almeida 1999; Machado-Pinto 2002).

None of the older studies reported the clinical trial registration number, whereas 23 studies published between 2006 and 2018 were registered.

Other potential sources of bias

Other sources of bias that could put a study at high risk of bias included the calculation of the sample size, the reporting of the *Leishmania* species, and baseline comparability among intervention groups. If a study reported all three items correctly, it was classified as having a low risk of bias; if at least one of the items was not reported correctly it was classified as having an unclear risk of bias; and if none of the items were reported, the study was then classified as having a high risk of bias. Of the 75 included studies, 24 (32%), 11 (15%) and 40 (53%) were rated at low, unclear and high risk of bias, respectively. See Characteristics of included studies for further details.

Effects of interventions

See: **Summary of findings 1** Meglumine antimoniate (IMMA) (20 mg/kg/d for 20 days) compared to placebo (3 tablets/4 times a day for 28 d) in L. *braziliensis* and L. *panamensis* for American cutaneous and mucocutaneous leishmaniasis; **Summary of findings 2** Oral miltefosine (50 mg for 28 days) compared to placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis* for American cutaneous leishmaniasis; **Summary of findings 3** Oral miltefosine (1.2 to 3.3 mg/kg/d 28 days) compared to meglumine antimoniate (20 mg/kg 20 days) in L. *braziliensis*, *L. panamensis, L. guyanensis* and L. *amazonensis* for American cutaneous and mucocutaneous leishmaniasis; **Summary of findings 4** Azithromycin (500 mg 20 - 28 days) compared to meglumine antimoniate (15 - 20 mg/kg/d for 20 - 28 days) in *L. braziliensis* for American cutaneous and mucocutaneous leishmaniasis; **Summary of findings 5** Topical imiquimod 5% (3 times/week) + meglumine antimoniate (IVMA) (20 mg/kg/d for 20 days) compared to placebo + IVMA in L. *braziliensis*, L. *guyanensis* and L. *peruviana* for American cutaneous leishmaniasis; **Summary of findings 6** Thermotherapy one session (at 50 °C for 30 seconds) compared to meglumine antimoniate (20 mg Sb5/kg/day for 20 days) in *L. panamensis* and *L. braziliensis* for American cutaneous leishmaniasis; **Summary of findings 7** Pentoxifylline (oral 400 mg thrice daily) plus meglumine antimoniate (IMMA) (20 mg/ kg / day for 20 days) compared to IMMA plus placebo for American cutaneous and mucocutaneous leishmaniasis

The new studies identified for this update covered all five types of interventions, mainly addressing non-antimonial systemic treatments and to a lesser extent physical therapies or immuno-chemotherapies. Of note, the updated review assessed four new types of interventions: azithromycin, amphotericin B, nitric oxide patch, and cryotherapy.

We have created seven 'Summary of findings' tables that summarise the certainty of the body of evidence for those clinically-relevant comparisons.

We performed 68 comparisons, of which two presented in the previous review were updated with data from new studies (Analysis 36.1; Analysis 57.1). We were able to pool outcome data across studies for 12 interventions and comparisons; these investigated the effects of intramuscular or intravenous meglumine antimoniate, oral allopurinol, azithromycin, fluconazole, miltefosine, imiquimod, intramuscular or intralesional pentamidine isethionate (IM or ILPI), paromomycin plus gentamicin, vaccines, and pentoxifylline.

Table 4 shows which new comparisons were included in this update.

1. Antimonials

1.1 Meglumine antimoniate

Intramuscular meglumine antimoniate (IMMA) versus placebo

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

Two RCTs including 157 participants (Vélez 1997; Saenz 1990) compared IMMA for 20 days versus oral placebo in Colombia and Panama, respectively. One year and 3 months after treatment, the proportion of participants completely cured (cure rates) was higher in the IMMA group, which means that IMMA may increase the chance of complete healing in *L. braziliensis* and *L. panamensis* infections (risk ratio (RR) 4.23, 95% confidence interval (CI) 0.84 to 21.38; I^2 = 46%; Analysis 1.1) but may also make little or no difference, since the 95% CI includes the possibility of both increased healing (cure rates) and reduced healing. The statistical heterogeneity observed is likely to be due to zero events observed in the placebo group in one trial (Saenz 1990), which was a small study (only 30 participants).

Another RCT including 44 participants (Navin 1990) from Guatemala that compared IMMA for 15 days versus placebo, reported complete cure of participants in 16/22 (73%) and in 6/22 (27%) participants two months after treatment, respectively (short-term primary outcome, excluded from analysis).

Please see Summary of findings 1, where we assessed the certainty of evidence for this outcome as moderate, which means we are moderately certain about the difference in cure rates between IMMA and placebo. IMMA may increase the likelihood of complete cure.

Primary outcomes: Adverse effects

One RCT including 134 participants (Vélez 1997) reported that 79% (53/67) of participants in the IMMA group had moderate side effects and 52.2% (35/67) had severe adverse effects (myalgias, arthralgias, anorexia, nausea, and headache). Ten per cent (6/60) of the participants in the placebo group had moderate-to-severe side effects (RR 1.51, 95% CI 1.17 to 1.96; Analysis 1.2). IMMA probably increases severe adverse effects such as myalgias and arthralgias at 12-month follow-up, corresponding to 789 participants with these complaints per 1000 (95% CI 611 more to 1000 more). See Summary of findings 1, where there was moderate-certainty evidence for this outcome.

One RCT including 30 participants (Saenz 1990) recorded laboratory abnormalities in 47% (9/19) of participants in the IMMA 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 including 44 participants (Navin 1990) reported that no participant complained of symptoms related to treatment.

Secondary outcomes: Recurrence

One RCT including 127 participants (Vélez 1997) reported that relapse or mucocutaneous disease (1½ to 3 months after healing in the IMMA group and 12 months after healing in the placebo group) was seen in 3% (2/67) and 1.67% (1/60) in the IMMA and placebo groups respectively (RR 1.79, 95% CI 0.17 to 19.26; Analysis 1.3; low-certainty evidence). IMMA may make little to no difference to the risk of recurrence, as the 95% CI includes the possibility of both increased and reduced risk of recurrence, corresponding to 30 participants with recurrence of disease per 1000 (95% CI 3 more to 321 more); see Summary of findings 1.

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

One RCT including 136 participants (Palacios 2001) from Colombia compared IMMA for 10 days versus IMMA for 20 days.

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

One year after treatment, there was no significant difference in cure rates between 10-day and 20-day treatments with IMMA in *L. braziliensis* and *L. panamensis* infections (RR 1.17, 95% CI 0.76 to 1.79; Analysis 2.1).

The study authors performed separate analysis by age of participants and found no differences among treatments in cure rates for children, neither for those aged under five years (RR 0.44, 95% CI 0.05 to 4.02) nor for children aged between 5 and 15 years (RR 0.89, 95% CI: 0.59 to 1.34; Analysis 2.2), since the 95% CI includes the possibility of both increased and reduced cure rates.

Primary outcomes: Adverse effects

The most common adverse effects were anorexia (RR 1.00, 95% CI 0.52 to 1.94; Analysis 2.3) and myalgias (RR 1.08, 95% CI 0.55 to 2.12; Analysis 2.3) in the 10-day IMMA treatment group but with no differences between groups, since the 95% CI includes the possibilities of both increased and reduced numbers of participants with these complaints. Headache (RR 0.55, 95% CI 0.29 to 1.01; Analysis 2.3), malaise (RR 0.56, 95% CI 0.27 to 1.18; Analysis 2.3) and arthralgias (RR 0.36, 95% CI 0.14 to 0.94; Analysis 2.3) were mostly observed in the 20-day IMMA treatment group, but the 95% CI for headache and malaise included 1, showing that there might be little or no difference between groups.

Intravenous meglumine antimoniate (IVMA) versus no treatment

One RCT including 50 participants (Martínez 1992) from Colombia compared IVMA for 15 days versus no treatment.

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

One year after treatment, cure rates were higher in the IVMA group compared with no treatment, but the effect was not statistically significant in *L. panamensis* infections (RR 13.24, 95% CI 0.83 to 210.87; Analysis 3.1).

Secondary outcomes: Recurrence

One year after treatment, there was no statistically significant difference in relapse between the two groups (RR 1.55, 95% CI 0.35 to 6.85; Analysis 3.2), since the 95% CI includes the possibility of both increased and reduced recurrence rates.

7-day versus 20-day IV meglumine antimoniate

One RCT including 61 participants (Soto 1998) from Colombia compared IVMA for 20 days versus IVMA for 7 days.

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

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 to 0.92; Analysis 4.1).

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

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

One RCT including 43 participants (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) versus IVMA (28 mg/kg/day for 10 days). Two years after treatment, there was no statistically significant difference in cure rates between IVMA (14 mg/kg/day) and IVMA (28 mg/kg/day) (RR 0.67, 95% CI 0.39 to 1.14; Analysis 5.1) . When the clinical forms were analysed separately, there was no clear difference in either the cutaneous leishmaniasis form (RR 1.50, 95% CI 0.81 to 2.78; Analysis 5.2) or in the mucocutaneous form (RR 1.43, 95% CI 0.53 to 3.86; Analysis 5.3).

One RCT including 23 participants (Oliveira-Neto 1997) from Brazil compared a low-dose IVMA versus 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).

Two RCTs including 89 participants (Ferreira 2014; Saheki 2017) compared a low dose of MA 5 mg/kg/day versus a higher dose of MA (20-30 mg/kg/day) for 30 days. There was no significant difference in cure rates between the treatments (RR 1.10, 95% CI 0.77 to 1.58; I^2 = 37%; Analysis 6.1).

Primary outcomes: Adverse effects

One study including 23 participants (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 (i.e. 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. Considering all adverse effects together, higher doses may increase the risk of adverse effects but the 95% CI includes 1, showing that there may be little or no difference between groups (RR 3.27, 95% CI 0.83 to 12.95; Analysis 6.2).

One study including 72 participants (Saheki 2017) reported "more major adverse effects, a greater number of adverse effects and major adverse effects per participant, and more drug discontinuations in the high-dose antimony group (all P < 0.05)". Two participants in the high-dose group permanently stopped treatment due to AEs (drug eruption and arthralgia), but this did not happen in the low-dose group.

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

One RCT including 44 participants (Arana 1994) from Guatemala compared IVMA for 10 days versus IVMA for 20 days.

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

One year after treatment, there was no difference in cure rates between 10-day and 20-day IVMA (RR 0.95, 95% CI 0.73 to 1.23; Analysis 7.1).

Primary outcomes: Adverse effects

Twenty-three per cent of the participants (5/22) who received IVMA 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 IVMA for 10 days, only one episode of arthralgia was observed in one participant. Shorter duration of treatment may decrease arthralgia risk, but the results are very imprecise due to the wide confidence interval (RR 0.25, 95% CI 0.03 to 2.06; Analysis 7.2).

Secondary outcomes: Recurrence

Two of 22 participants (12.1%) receiving IVMA for 20 days did not respond to the treatment: 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 IVMA 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.

Intralesional antimony versus placebo

One RCT including 60 participants (Soto 2013) from Bolivia compared intralesional antimony (Sb) (1, 3 and 5 days) versus placebo.

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

Cure rates were higher for participants treated with IL Sb 60% versus 13% for placebo (RR 5.00, 95% CI 1.94 to 12.89; Analysis 8.1)

Primary outcomes: Adverse effects

None of the participants experienced severe side effects. IL Sb was more painful (P ≤ 0.001), but this application showed a tendency toward less irritation (P = 0.06) than cream application.

Meglumine antimoniate plus tamoxifen versus meglumine antimoniate alone

A phase II pilot RCT including 38 participants with localised cutaneous leishmaniasis from Brazil (Machado 2018) compared oral (40 mg/day for 20 days) or topical tamoxifen (0.1% tamoxifen citrate for 20 days) combined with meglumine antimoniate (20 mg SbV/kg/day for 20 days) versus the standard SbV protocol (20 mg/kg/day for 20 days).

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

The study found no significant differences in cure rates among the three options, either at three or at six months, since the 95% CI includes the possibility of both increased and reduced cure rates:

- MA plus oral tamoxifen versus MA alone: at three months follow-up cure rates accounted for 67% (8/12) and 53% (8/15), respectively (RR 1.25, 95% CI 0.67 to 2.32; Analysis 9.1); at six months follow-up cure rates accounted for 58% (7/12) and 40% (6/15), respectively (RR 1.46, 95% CI 0.67 to 3.19; Analysis 9.1).
- MA plus topical tamoxifen versus MA alone: at three months follow-up cure rates accounted for 45% (5/11) and 53% (8/15), respectively (RR 0.85, 95% CI 0.38 to 1.90; Analysis 10.1); at six months follow-up cure rates accounted for 36.4% (4/11) and 40% (6/15), respectively (RR 0.91, 95% CI 0.34 to 2.47; Analysis 10.1).

Primary outcomes: Adverse effects

In 87% of participants, a similar prevalence of AEs were reported in the three groups (87%, 82% and 92% for SbV, SbV plus topical and SbV plus oral tamoxifen). These AEs were mild in general; arthralgia and myalgia (frequently linked to SbV use) were most commonly reported. A grade 3 headache and palpitation caused one participant to drop out of SbV plus oral tamoxifen treatment on the second day of treatment. In the SbV plus topical tamoxifen group, after the second SbV application, angio-oedema led to one participant stopping therapy.

Secondary outcomes: Recurrence

The study found no significant differences in recurrence rates among the three options after six months, since the 95% CI includes the possibility of both increased and reduced recurrence rates:

- MA plus oral tamoxifen versus MA alone: 8% (1/12) and 13% (2/15) (RR 0.59, 95% CI 0.05 to 7.43; Analysis 9.2)
- MA plus topical tamoxifen versus MA alone: 9% (1/11) and 13% (2/15) (RR 0.68, 95% CI 0.07 to 6.61; Analysis 10.2)

Meglumine antimoniate plus zinc versus meglumine antimoniate plus placebo

One pilot RCT including 29 participants (Guzman-Rivero 2014) from Bolivia compared IMMA for 20 days plus 45 mg zinc daily for 60 days versus IMMA for 20 days plus placebo daily for 60 days.

Tertiary outcomes: Speed of healing

Authors reported that the time for reduction of lesion area did not differ significantly between placebo and zinc-supplemented groups, but did not provide detailed numbers.

Intravenous meglumine antimoniate (IVMA) plus antihelminthic treatment versus IVMA plus placebo

One RCT, Newlove 2011, including 90 participants, all co-infected with helminths and *Leishmania braziliensis*, from Brazil and all treated with intravenous Sbv (Glucantime) at 20 mg/kg/day for 20 days, compared adding oral placebo or antihelminthic treatment: albendazole (400 mg), ivermectin (200 µg/kg), and praziquantel (50 mg/kg) in an oral formulation at days 0 and 30 and day 60.

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

There was no difference in cure rates between those treated with IVMA and antihelminthics or IVMA placebo (RR 0.77, 95% CI 0.48 to 1.25; Analysis 11.1).

Primary outcomes: Adverse effects

Adverse events were reported in 60% of participants in the treatment group and 60% of participants in the control group, with no statistically significant difference in the type or grade of events reported. Only grade 1 and 2 events were observed. Muscle pain (26%), headache (16%), leg pain (14%), weakness (14%), fever (13%), joint pain (12%), and dizziness (12%) were the most frequently reported symptoms.

Tertiary outcomes: Speed of healing

The median time to cure was 88 days in the control group versus 98 days in the treatment group, but authors state that this result was not statistically significant.

1.2 Stibogluconate

IM sodium stibogluconate (IMSSG) versus no treatment

One RCT including 61 participants (Guderian 1991) from Ecuador compared IMSSG for 20 days versus no treatment. Complete cure occurred in 90% (27/30) and 60% (9/15) of participants in the respective groups 1½ months after treatment (short-term primary outcome, excluded from analysis).

IM sodium stibogluconate versus IM meglumine antimoniate

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

One RCT including 114 participants (Soto 2004a) from Bolivia and Colombia compared IMSSG (branded and generic) for 20 days versus IMMA for 20 days. Six months after treatment, there was no difference in cure rates between IMSSG and IMMA (RR 1.07, 95% CI 0.88 to 1.30; Analysis 12.1). Similarly, there was no difference in cure rates between branded and generic IMSSG (RR 1.11, 95% CI 0.82 to 1.51) in *L. panamensis* infections.

One RCT including 59 participants (Saenz 1987) from Panama compared IMSSG for 20 days versus 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).

Primary outcomes: Adverse effects

One RCT including 114 participants (Soto 2004a) reported myalgias in both SSG and MA groups respectively (RR 0.78, 95% CI 0.50 to 1.22; Analysis 12.3), but incidence of myalgia was higher for branded SSG compared to the generic SSG drug (RR 1.93, 95% CI 1.04 to 3.58; Analysis 13.2). There was no clear difference in headache between the SSG and MA groups (RR 0.68, 95% CI 0.37 to 1.26; Analysis 12.3) or between the branded and generic SSG groups (RR 1.67, 95% CI 0.65 to 4.25; Analysis 13.2). A metallic taste was observed more in the SSG than in the MA group (RR 0.49, 95% CI 0.27 to 0.92; Analysis 12.3) but the difference observed between the branded and generic SSG groups was less clear, as the result was very imprecise (RR 2.14, 95% CI 0.79 to 5.82; Analysis 13.2). There was also no clear difference in abdominal pain in the SSG and MA groups due to imprecision (RR 0.78, 95% CI 0.32 to 1.94; Analysis 12.3) but there may be more abdominal pain with branded compared to generic SSG (RR 3.00, 95% CI 0.85 to 10.63; Analysis 13.2).

One RCT including 59 participants (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 effects such as myalgias, arthralgias, headaches, pain at the site of injection, allergy and fever (RR 1.22, 95% CI 0.78 to 1.91; Analysis 12.2). There were no cases reporting hepatic, renal, haematologic or cardiac toxicity.

Secondary outcomes: Recurrence

One RCT including 59 participants (Saenz 1987) reported that 2% (13/59), 23.3% (7/30) and 20.7% (6/29) of cured participants had reactivation of lesions after 6 to 12 months of follow-up in the branded SSG, generic SSG and MA groups, respectively. Overall there was no clear difference in recurrence rates between SSG (branded and generic) and MA (RR 0.96, 95% CI 0.45 to 2.05; Analysis 12.4).

Tertiary outcomes: Microbiological or histopathological cure of skin lesions

One RCT including 59 participants (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, showing no difference between groups (RR 1.00, 95% CI 0.85 to 1.19; Analysis 12.5).

IV sodium stibogluconate versus placebo

One RCT including 40 participants (Navin 1992) from Guatemala compared IVSSG for 20 days versus placebo.

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

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).

Primary 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.

Secondary outcomes: Recurrence

In the SSG group, none of the participants (24/25: 96%) 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. None of the participants with *L. mexicana* had reactivations of their lesions between the 13- and 52-weeks follow-up examinations.

Different doses of IV sodium stibogluconate

One RCT including 40 participants (Ballou 1987) from the USA compared low-dose IVSSG for 20 days versus high-dose IVSSG for 20 days.

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

Complete cure occurred in 76% (16/21) and 100% (19/19) of participants in the respective groups 1½ months after treatment (short-term primary outcome, excluded from analysis).

Primary outcomes: Adverse effects

Mild-to-moderate muscle and joint stiffness were experienced by 62% (13/21) of participants in the low-dose group and by 58% (11/19) of participants in the high-dose group (RR 1.07, 95% CI 0.64 to 1.78; Analysis 14.1). Laboratory abnormalities were limited to increases in liver enzymes in 48% (10/21) and 53% (10/19), respectively (RR 0.90, 95% CI 0.49 to 1.68; Analysis 14.1); mild leucopenia in 9.5% (2/21) and 5.3% (1/19), respectively (RR 1.81, 95% CI 0.18 to 18.39; Analysis 14.1); and electrocardiographic abnormalities in 19% (4/21) and 21% (4/19), respectively (RR.0.90, 95% CI 0.26 to 3.12; Analysis 14.1).

Different regimens of IV sodium stibogluconate

One RCT including 40 participants (Franke 1994) from Peru compared IVSSG for 28 days versus IVSSG for 40 days.

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

One year after treatment, there was no clear difference in cure rates between 28 and 40 days of IVSSG (RR 0.83, 95% CI 0.47 to 1.47; Analysis 15.1) in *L. braziliensis* infections.

Primary outcomes: Adverse effects

None of the subjective complaints were severe enough to warrant cessation of treatment. Although more participants in 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

One RCT including 36 participants (Oster 1985) from the USA treated participants with IVSSG for 10 days at a dose of 600 mg a day by one of three 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 nine days; or a loading dose of 600 mg followed by 200 mg every eight hours for nine days.

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

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).

Primary 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.

Intralesional Stibogluconate (SB) versus Intralesional pentamidine (ILP)

Two RCTs in Bolivia by the same group (Soto 2016a; Soto 2016b), including a total of 120 participants, compared two topical intralesional treatments: ILSB (N-methylglucamine five injections) versus ILP (three injections).

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

No differences in cure rates for either treatment (RR 0.98, 95% CI 0.78 to 1.23, I^2 = 0%, 2 studies, 120 participants, Analysis 16.1).

Primary outcomes: Adverse effects.

There were no clear differences between treatments for frequency of adverse effects): myalgia (RR 3.93, 95% CI 0.45 to 35.54); local irritation (RR 1.19, 95% CI 0.55 to 2.58); or local pain (RR 1.74, 95% CI 0.79 to 3.83) (Analysis 16.2).

Secondary outcomes: Recurrence

Two participants out of 30 in the ILSB group had recurrence of the disease compared to none in the ILP group, but the results are very imprecise (RR 5.00, 95% CI 0.25 to 99.95; 1 study, 60 participants; Analysis 16.3).

2. Non-antimonial systemic treatments

2.1 Oral antifungals

Ketoconazole versus IM meglumine antimoniate

One RCT including 41 participants (Saenz 1990) from Panama compared oral ketoconazole for 28 days versus IMMA for 20 days.

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

Three months after treatment, there was no difference in cure rates between oral ketoconazole and 20 mg/kg/day IMMA for 20 days (RR 1.06, 95% CI 0.71 to 1.58; Analysis 17.1) in *L. panamensis* and *L. mexicana* infections.

Primary outcomes: Adverse effects

The laboratory abnormalities recorded in 27% (6/22) of ketoconazole-treated participants were mild elevations of liver transaminase values that normalised 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) of participants in the IMMA group (RR 0.58, 95% CI 0.25 to 1.32; Analysis 17.2), 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 IMMA 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

Fifty-six per cent of participants (9/16) in the oral ketoconazole group versus 54% of participants (7/13) in the IMMA group demonstrated complete re-epithelialisation of lesions by the end of approximately one month of therapy (RR 1.04, 95% CI 0.54 to 2.03; Analysis 17.3). In the ketoconazole group complete re-epithelisation occurred by three months after the end of therapy.

Tertiary outcomes: Microbiological or histopathological cure of skin lesions

For the 73% (16/22) of 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 IMMA group 69% (9/13) of the participants who were cured had a negative diagnostic test result for leishmanial organisms at the end of therapy (RR 0.81, 95% CI 0.46 to 1.43; Analysis 17.4).

Ketoconazole versus IV sodium stibogluconate

One RCT including 48 participants (Navin 1992) from Guatemala compared oral ketoconazole for 28 days versus IVSSG for 20 days. Complete cure occurred in 52% (12/23) and 96% (24/25) of participants in the respective groups two months after treatment (short-term primary outcome, excluded from analysis).

Primary 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.

Secondary outcomes: Recurrence

In the ketoconazole group, 17% (2/12) responders infected with *L. braziliensis* had reactivations of their lesions, one at 17 weeks and one 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. None of the participants with *L. mexicana* who had responded in all treatment groups had reactivations of their lesions at the 52-week follow-up examinations.

Ketoconazole versus placebo

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

One RCT including 41 participants (Saenz 1990) from Panama compared oral ketoconazole for 28 days versus 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 to 262.82; Analysis 18.1) in *L. panamensis* and *L. mexicana* infections, although results were very imprecise due to the wide confidence interval.

One RCT including 38 participants (Navin 1992) from Guatemala compared oral ketoconazole for 28 days versus 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).

Primary outcomes: Adverse effects

In one study including 41 participants (Saenz 1990) the laboratory abnormalities recorded in 27% (6/22) of ketoconazole-treated participants were mild elevations of liver transaminase values that normalised 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).

The other study, including 38 participants (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.

Secondary outcomes: Recurrence

In a study of 48 participants (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 and responded clinically had reactivations of their lesions, one at 14 weeks and the other at five months. All participants with *L. mexicana* who had responded in the two treatment groups had no reactivations of their lesions.

Fluconazole versus intravenous Glucantime

Two RCTs conducted in Brazil (Alves Noroes 2015; Prates 2017), including 173 participants in total, compared oral fluconazole versus intravenous Sbv (Glucantime).

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

Cure rates were lower with oral fluconazole (RR 0.60, 95% CI 0.37 to 0.96; $I^2 = 44\%$; 2 studies, 173 participants; Analysis 19.1), and the percentage of participants needing rescue therapy was higher for those treated with oral fluconazole (RR 2.20, 95% CI 1.09 to 4.46; 1 study, 53 participants; Analysis 19.3).

Primary outcomes: Adverse effects.

There was no clear difference between treatments in the percentage of participants who suffered adverse events (none severe) (RR 1.07, 95% CI 0.52 to 2.20; 1 study, 53 participants; Analysis 19.2).

Tertiary outcomes: Speed of healing

Average healing time (days) was much higher for those treated with oral fluconazole (mean difference (MD) 40.40 days, 95% CI 11.27 to 69.53; 1 study, 53 participants; Analysis 19.4).

2.2 Oral allopurinol

Oral allopurinol versus allopurinol combined with IM meglumine antimoniate

One RCT including 60 participants (Martínez 1992) from Colombia compared oral allopurinol for 15 days versus oral allopurinol plus IMMA in the same regimen.

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

One year after treatment, there was no difference in cure rates between oral allopurinol alone and oral allopurinol in combination with IMMA (RR 1.08, 95% CI 0.82 to 1.42; Analysis 20.1) in *L. panamensis* infections.

Secondary outcomes: Recurrence

When comparing the two groups, the difference after 12 months in relapse after cure was unclear, due to the highly imprecise results (RR 0.70, 95% CI 0.07 to 7.30; Analysis 20.2).

Oral allopurinol versus IV meglumine antimoniate

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

One RCT including 58 participants (Martínez 1992) from Colombia compared oral allopurinol for 15 days versus 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 to 3.60; Analysis 21.1).

One RCT including 34 participants (D'Oliveira 1997) from Brazil compared oral allopurinol versus 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, with antimonial 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).

Primary outcomes: Adverse effects

D'Oliveira 1997 reported that 11.1% (1/9) of participants developed mucocutaneous disease within three months, although the group is not stated.

Secondary outcomes: Recurrence

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, but the result was very imprecise due to the wide confidence interval (RR 0.66, 95% CI 0.06 to 6.88; Analysis 21.2).

Oral allopurinol combined with IV meglumine antimoniate versus IV meglumine antimoniate

One RCT including 60 participants (Martínez 1992) from Colombia compared oral allopurinol for 15 days combined with IVMA for 15 days versus IVMA monotherapy for 15 days.

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

One year after treatment, oral allopurinol had a significant synergistic effect with IVMA for 15 days compared to IVMA alone (RR 2.04, 95% CI 1.25 to 3.34; Analysis 22.1).

Secondary outcomes: Recurrence

Relapse after cure was similar between groups (RR 0.94, 95% CI 0.14 to 6.31; Analysis 20.2).

Oral allopurinol versus IM meglumine antimoniate

One RCT including 127 participants (Vélez 1997) from Colombia compared oral allopurinol for 28 days versus IMMA for 20 days. Another RCT including 75 participants (Chico 1995) from Ecuador compared allopurinol plus probenecid for 28 days versus IMMA for 20 days and versus no treatment, but the follow-up was short, only up to 70 days.

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

In the Vélez 1997 study, oral allopurinol showed lower cure rates compared with IMMA one year after treatment (RR 0.39, 95% CI 0.26 to 0.58; Analysis 23.1).

In the Chico 1995 study, cure rates were much lower for allopurinol plus probenecid (20%: 6/30) compared to IMMA (100%: 28/28) (short-term primary outcome, excluded from analysis).

Primary 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 IMMA group had moderate side effects and 52.2% (35/67) had severe adverse effects. Myalgias, arthralgias, anorexia, nausea, and headache were the common adverse effects.

Secondary outcomes: Recurrence

Relapse or mucocutaneous disease was seen in 5% (3/60) of the allopurinol group: one relapse occurred five months after healing and two mucocutaneous cases occurred at the end of treatment and 1½ months later. Similar relapse or mucocutaneous disease was seen 1½ to 3 months after healing in both groups (RR 1.68, 95% CI 0.29 to 9.69; Analysis 23.2).

Oral allopurinol combined with IV sodium stibogluconate versus IV sodium stibogluconate

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

One RCT including 100 participants (Martínez 1997) from Colombia compared oral allopurinol combined with IVSSG versus IVSSG alone, both for 15 days. One year after treatment, oral allopurinol had a significant synergistic effect with IVSSG compared to IVSSG alone (RR 1.82, 95% CI 1.23 to 2.70; Analysis 24.1).

When we pooled two RCTs including 168 participants (*L. braziliensis*) (Martínez 1992; Martínez 1997) where oral allopurinol combined with IV antimonials (20 mg/kg/day for 15 days) was compared to IV antimonials alone, the results showed that oral

allopurinol had a significant synergistic effect with IV antimonials (RR 1.90, 95% CI 1.40 to 2.59; I^2 = 0%; Analysis 24.2).

One RCT including 81 participants with MCL (Llanos-Cuentas 1997) from Peru compared oral allopurinol combined with IVSSG versus IVSSG alone, both for 28 days. One year after treatment, IVSSG alone presented similar cure rates (RR 0.62, 95% CI 0.38 to 1.03; Analysis 25.1).

Primary outcomes: Adverse effects

One RCT with 100 participants (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 seven days. The cause of this adverse effect 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 including 81 participants with MCL (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 (two in the allopurinol combined with SSG group and one in the SSG-alone group), and were treated with acyclovir, but one developed partial blindness as a consequence. The most frequent laboratory adverse effect was haematologic abnormality: the rate of thrombocytopenia was higher among the allopurinol-plus-SSG group.

Secondary outcomes: Recurrence

Two studies assessed recurrence (Llanos-Cuentas 1997; Martínez 1997); pooling their results, we found no differences in the recurrence rate between treatments (RR 1.16, 95% CI 0.73 to 1.85; 2 studies, 181 participants; I^2 = 0; Analysis 25.2).

Oral allopurinol ribonucleoside combined with probenecid versus IM sodium stibogluconate

One RCT including 61 participants (Guderian 1991) from Ecuador compared oral allopurinol ribonucleoside combined with probenecid for 28 days versus IMSSG for 20 days.

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

Complete cure occurred in 30% (9/30) and 60% (9/15) of participants in the respective groups 1½ months after treatment (short-term primary outcome, excluded from analysis). The authors also compared the experimental intervention versus no treatment, and reported complete cure of 30% (9/30) and 90% (27/30) of participants in the respective groups 1½ months after treatment.

Oral allopurinol versus no treatment

One RCT including 42 participants (Martínez 1992) from Colombia compared oral allopurinol for 15 days versus no treatment.

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

One year after treatment, oral allopurinol had significantly higher cure rates compared with no treatment, although results are very imprecise due to the wide confidence interval (RR 28.38, 95% CI 1.83 to 439.72; Analysis 26.1).

Secondary outcomes: Recurrence

Martínez 1992 reported that at 12 months 1/25 participants in the allopurinol group versus 2/17 in the no-treatment group had relapsed after cure (RR 0.34, 95% CI 0.03 to 3.46; Analysis 26.2).

Oral allopurinol versus placebo

One RCT including 61 participants (Vélez 1997) from Colombia compared oral allopurinol for 28 days versus placebo.

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

One year after treatment, there was no difference in cure rates between oral allopurinol and placebo (RR 1.06, 95% CI 0.61 to 1.85; Analysis 27.1).

Primary outcomes: Adverse effects

Moderate-to-severe side effects were observed in 25% (15/60) of the allopurinol group and in 10% (6/60) of the placebo group. The only side effects attributable to allopurinol were headache and epigastric pain.

Secondary outcomes: Recurrence

Relapse or mucocutaneous disease was seen in 5% (3/60) of the allopurinol group: one case of relapse was seen five months after healing and two mucocutaneous cases were seen at the end of treatment and 1½ months later. Relapse was seen in 1.67% (1/60) of the placebo group: this participant had developed mucocutaneous disease 12 months after healing. Results are very imprecise due to the wide confidence interval, and no differences were observed between treatment groups (RR 3.00, 95% CI 0.32 to 28.03; Analysis 27.2).

Oral allopurinol combined with IV meglumine antimoniate versus no treatment

One RCT including 52 participants (Martínez 1992) from Colombia compared oral allopurinol combined with IVMA for 15 days versus no treatment.

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

One year after treatment, oral allopurinol combined with IVMA had significantly higher cure rates than no treatment (RR 26.50, 95% CI 1.71 to 410.42; Analysis 28.1).

Secondary outcomes: Recurrence

Recurrence after cure at 12 months was higher in the no-treatment group, but the results are very imprecise due to the wide confidence interval (RR 0.49, 95% CI 0.07 to 3.16; Analysis 28.2).

2.3 Oral miltefosine

Oral miltefosine versus placebo

One RCT including 133 participants (Soto 2004b) from Colombia and Guatemala compared oral miltefosine for 28 days versus placebo in *L. braziliensis, L. panamensis* and *L. mexicana* infections.

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

Six months after treatment, oral miltefosine had significantly higher cure rates than placebo in the Colombian site (RR 2.18, 95% CI 1.28 to 3.71; Analysis 29.1) but the difference was not so strong for the Guatemalan site (RR 2.50, 95% CI 0.99 to 6.33; Analysis 29.1). There is moderate evidence about the difference in cure rate between oral miltefosine and placebo. Oral miltefosine probably improves the chance of healing, corresponding to 644 more participants completely cured per 1000 participants (95% CI 378 more to 1000 more) (RR 2.25, 95% CI 1.42 to 3.38) (Summary of findings 2).

Primary outcomes: Adverse effects

Nausea was observed more in the miltefosine group (RR 3.96, 95% CI 1.49 to 10.48; Analysis 29.2), and so was vomiting (RR 6.92, 95% CI 2.68 to 17.86; Analysis 29.2), but the difference in cases of diarrhoea was less clear across groups, due to imprecision (RR 2.47, 95% CI 0.57 to 10.80; Analysis 29.2), as well as motion sickness (RR 1.29, 95% CI 0.68 to 2.42; Analysis 29.2) and headache (RR 1.32, 95% CI 0.67 to 2.59; Analysis 29.2). The creatinine level increased towards the normal range in the miltefosine recipients (RR 3.58, 95% CI 1.34 to 9.56; Analysis 29.2). Aspartate aminotransferase levels were higher with placebo, but the 95% CI includes 1, showing there may be little or no difference (RR 0.43, 95% CI 0.17 to 1.12; Analysis 29.2). The difference between groups for alanine aminotransferase was less clear, due to imprecision (RR 0.89, 95% CI 0.32 to 2.50; Analysis 29.2). See Summary of findings 2.

Secondary outcomes: Recurrence

Recurrence occurred within six months in 4.1% (2/49) and 0% (0/24) of the respective treatment group in the Colombian site, and 10% (4/40) and 5% (1/20) of the respective treatment groups from the Guatemala site (RR 2.97, 95% CI 0.37 to 23.89; Analysis 29.3; Summary of findings 2).

Oral miltefosine versus meglumine antimoniate

Seven RCTs including 676 participants in total compared both treatments in participants with mucosal (Garcia 2014; Sampaio 2019) and cutaneous leishmaniasis (Chrusciak-Talhari 2011; Machado 2010; Rubiano 2012;

Soto 2008; Vélez 2010). Five of them followed the participants for six months after treatment cessation (Garcia 2014; Machado 2010; Rubiano 2012; Sampaio 2019; Vélez 2010) and two followed them up to 12 months (Chrusciak-Talhari 2011; Soto 2008).

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

There were no differences in cure rates among the treatments (RR 1.07, 95% CI 0.86 to 1.34; I^2 = 67%; Analysis 30.1) The relatively high heterogeneity is due to the studies reporting less favourable results for the miltefosine treatment (Soto 2008; Vélez 2010), but we could not identify any clinical or methodological differences between these studies and the other studies included in the meta-analysis.

A separate analysis of the two studies that included participants with mucosal leishmaniasis (Garcia 2014; Sampaio 2019) shows no differences in cure rates between the treatments (RR 1.04, 95% CI 0.81 to 1.34; 2 studies, 40 participants: I^2 = 0%), since the 95% CI includes the possibility of both increased and reduced cure rates.

Pooling the results of the studies that included only participants with cutaneous leishmaniasis (Chrusciak-Talhari 2011; Machado 2010; Rubiano 2012; Soto 2008; Vélez 2010) shows no differences in cure rates between the treatments (RR 1.06, 95% CI 0.87 to 1.29; 5 studies, 636 participants; I^2 = 72%).

After pooling the results of the RCT including 116 children aged between 2 and 12 years (Rubiano 2012) and the results for 28 children of the same age (Chrusciak-Talhari 2011), we found no relevant differences in cure rates between treatments (RR 1.19, 95% CI 0.98 to 1.46; I^2 = 0; Analysis 30.2).

Sampaio 2019, including 40 participants followed up to four years after treatment, found that both treatment groups had similar cure rates (16/20 versus 12/20: RR 0.66, 95% CI 0.33 to 1.32).

Please see Summary of findings 3, where we are not certain about differences in cure rate between oral miltefosine and meglumine antimoniate. Oral miltefosine may make little or no difference to the chance of healing, corresponding to 741 more participants with healing per 1000 participants (95% CI 616 to 893 more).

Primary outcomes: Adverse effects

Pooling the results from three RCTs including 464 participants with the cutaneous form (Machado 2010; Rubiano 2012; Vélez 2010) revealed that the risks of nausea (RR 2.45, 95% CI 1.72 to 3.49; I^2 = 0% Analysis 30.3) and vomiting (RR 4.76, 95% CI 1.82 to 12.46; I^2 = 48%; Analysis 30.3) were in both cases higher in the miltefosine group.

Please see Summary of findings 3, where we are moderately confident in the effect estimate. Oral miltefosine probably increases nausea and vomiting rates, corresponding to 360 more participants with nausea per 1000 (95% CI 252 more to 512 more) and 415 more participants with vomiting per 1000 (95% CI 159 more to 1000 more).

There were no reports of serious adverse effects in Chrusciak-Talhari 2011, which included 58 participants, and those adverse effects that were reported did not require participants to discontinue therapy. Clinical adverse events of the gastrointestinal tract were mostly reported in the miltefosine group, and they normally happened in the first week of treatment. The most common adverse effect was vomiting, which 48.3% (28/58) of participants reported, and 41% (7/17) with CTC grade 1 and 45.5% (5/11) with CTC grade 2 were children.

In the phase II RCT including 19 participants with ML (Garcia 2014) from Argentina, eight of the nine participants treated with miltefosine presented gastrointestinal symptoms (all of them of low severity). For the antimoniate group, six of the 10 participants presented with adverse effects that were treated with anti-inflammatory drugs in three of them (for asthenia, arthralgia and

headache); two participants presented pain in the injection area, fever and myalgia; and one suffered cutaneous rash.

In the RCT including 90 participants (Machado 2010), the incidence of adverse events was similar in the Sbv and miltefosine groups (76.7% versus 78.3%). Vomiting (41.7%), nausea (40%), and abdominal pain (23.3%) were significantly more frequent in the miltefosine group, while arthralgias (20.7%), myalgias (20.7%) and fever (23.3%) were significantly more frequent in the Sbv group.

In the RCT including 116 children all aged between 2 and 12 years, Rubiano 2012 found that 95% of clinical adverse effects were grade 1 ("mild symptoms that do not interfere with regular activities"). Children who were treated with meglumine antimoniate more commonly experienced increased levels of hepatic enzymes aspartate transaminase (AST) (16/57 versus 5/57; P = 0.01) and alanine transaminase (ALT) (10/57 versus 2/57; P = 0.01), compared with children receiving miltefosine. Children receiving miltefosine experienced gastrointestinal symptoms, nausea (9/57 versus 2/57; P = 0.02) and vomiting (15/57 versus 2/57; P < 0.001), more frequently than those receiving meglumine antimoniate.

Sampaio 2019, which included 40 participants, found that gastrointestinal effects (i.e. nausea, vomiting, and epigastric pain) were the only significant differences found between the two groups: participants in the miltefosine group most frequently reported these effects (RR 2.97, 95% CI 1.05 to 8.38).

Soto 2008, which included 58 participants, found that gastrointestinal symptoms were the main adverse effect for the miltefosine group during treatment: 61% of participants experienced these symptoms for a median of three days (range: 1 to 10 days). In the antimony group, 72% of participants reported arthralgias or local pain, or both, at the injection site, which lasted for a median of seven days (range: 5 to 14 days).

In the RCT including 288 participants, Vélez 2010 found that "with the exception of gastrointestinal problems, reports of adverse effects were generally more frequent and serious in the group treated with meglumine antimoniate; [the] frequency of adverse effects, such as fever, myalgia, arthralgia, and cephalea, was higher in the group that received meglumine antimoniate". See Summary of findings 3.

Tertiary outcomes: Speed of healing.

One RCT including 58 participants (Soto 2008) from Bolivia found that antimony cured more rapidly, with cure rates by one month after therapy higher for antimony-treated participants (RR 0.72, 95% CI 0.59 to 0.89; Analysis 30.4).

2.4 Aminosidine sulphate

Different regimens of aminosidine sulphate

One RCT including 60 participants (Soto 1994a) from Colombia compared aminosidine sulphate (AS) 12 mg/kg/day for seven days, and for 14 days, versus AS 18 mg/kg/day for 14 days.

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

One year after treatment, AS 12 mg/kg/day for seven days had significantly lower cure rates than AS 12 mg/Kg/day for 14 days (RR 0.23, 95% CI 0.07 to 0.73; Analysis 31.1), and 18 mg/Kg/day for 14 days (RR 0.20, 95% CI 0.06 to 0.62; Analysis 31.2). There was no clear difference between AS 12 mg/Kg/day and AS 18 mg/Kg/day, both for 14 days (RR 0.87, 95% CI 0.50 to 1.49; Analysis 31.3) in *L. panamensis* infections.

Primary outcomes: Adverse effects

The AST value was at 50% above the upper limit of normal in 3.3% (1/30) of participants in the AS 12 mg/kg/day for 14 days group. Of the participants in the AS 12 mg/kg/day for seven days group, 6.6% (2/30) had AST values between 100% and 200% above the upper limit, although no differences were seen between groups (RR 2.00, 95% CI 0.19 to 20.90; Analysis 31.4).

IV aminosidine sulphate versus IV sodium stibogluconate

One RCT including 34 participants (Hepburn 1994) conducted in British soldiers deployed in Belize compared IVAS versus IVSSG, both for 20 days.

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

Complete cure occurred in 59% (10/17) and 88% (15/17) of participants in the respective groups 1½ months after treatment (short-term primary outcome, excluded from analysis).

Primary outcomes: Adverse effects

SSG was not well tolerated, with all participants reporting aching muscles and joint stiffness which started after 12 - 17 days of treatment and persisted for two to four 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 two days after the course finished.

Intramuscular aminosidine sulphate (IMAS) versus IM meglumine antimoniate

One RCT including 31 participants (Correia 1996) from Brazil compared IMAS versus IMMA, both for 20 days.

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

One year after treatment, cure rates may be slightly higher with IMAS 20 mg/kg/day for 20 days compared with IMMA 10 mg/kg/day for 20 days in *L. braziliensis* infections (RR 1.22, 95% CI 0.94 to 1.58; Analysis 32.1).

Primary outcomes: Adverse effects

More participants reported myalgias in the IMMA group but the 95% confidence interval includes 1, showing that there might be no difference between groups (RR 0.27, 95% CI 0.07 to 1.06; Analysis 32.2). A similar finding was shown for arthralgias (RR 0.10, 95% CI 0.01 to 1.61; Analysis 32.2) but the difference between groups in asthenia is less clear (RR 0.71, 95% CI 0.25 to 2.03; Analysis 32.2), and also for anorexia (RR 1.07, 95% CI 0.44 to 2.59; Analysis 32.2).

IMAS versus Intramuscular pentamidine isethionate (IMPI)

One RCT including 30 participants (Correia 1996) from Brazil compared IMAS for 20 days versus IMPI for eight applications.

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

One year after treatment, there was no clear difference in cure rates between IMAS 20 mg/kg/day for 20 days and IMPI 4 mg/kg every two days for eight doses (RR 1.15, 95% CI 0.91 to 1.44; Analysis 33.1) in *L. braziliensis* infections.

Primary outcomes: Adverse effects

Fewer adverse effects were observed for myalgias (RR 0.33, 95% CI 0.08 to 1.39; Analysis 33.2), for anorexia (RR 0.86, 95% CI 0.38 to 1.95; Analysis 33.2), for asthenia (RR 0.80, 95% CI 0.27 to 2.41; Analysis 33.2), and for arthralgias (RR 0.20, 95% CI 0.01 to 3.85; Analysis 33.2) in the IMAS group, although results were imprecise due to the wide confidence interval (high uncertainty).

IM aminosidine sulphate versus IV meglumine antimoniate

One RCT including 38 participants with ML (Llanos-Cuentas 2007) from Peru compared IMAS for 21 days versus IVMA for 28 days.

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

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 to 0.78; Analysis 34.1).

Secondary outcomes: Adverse effects

Participants from the IVMA 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

Intravenous pentamidine isethionate (IVPI) versus IV meglumine antimoniate

One RCT including 80 participants (Andersen 2005) from Peru compared IVPI for seven doses versus IVMA for 20 days.

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

Six months after treatment, IVPI 2 mg/kg on alternate days for seven doses showed significantly lower cure rates than IVMA 20 mg/kg/ day for 20 days (RR 0.45, 95% CI 0.29 to 0.71; Analysis 35.1) in *L. braziliensis* infections.

Primary outcomes: Adverse effects

More gastrointestinal events were reported in the IVPI group (RR 1.44, 95% CI 0.90 to 2.29; Analysis 35.2). More participants reported musculoskeletal events with IVMA, but the result is imprecise, showing uncertainty (RR 0.80, 95% CI 0.49 to 1.31; Analysis 35.2). Headache was significantly higher in the IVMA group (RR 0.61, 95% CI 0.43 to 0.85; Analysis 35.2). Other minor side effects were lesion pain, paraesthesia, fever or chills, bad taste and cough.

Secondary outcomes: Recurrence

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

Tertiary outcomes: Microbiological or histopathological cure of skin lesions

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

IM pentamidine isethionate versus IM meglumine antimoniate

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

At one year of follow-up, pooled results from three RCTs including 226 participants (Alves 2016; Correia 1996; Neves 2011) show no difference in cure rates between IMPI and IMMA (RR 0.95, 95% CI 0.81 to 1.13; $I^2 = 0\%$; Analysis 36.1).

Primary outcomes: Adverse effects

Two RCTs including 156 participants (Correia 1996; Neves 2011) found statistically significant differences in adverse effects for arthralgias (RR 0.27, 95% CI 0.11 to 0.69; $I^2 = 0\%$; Analysis 36.2) with a smaller risk for pentamidine, but the difference was less clear for myalgias (RR 0.73, 95% CI 0.35 to 1.53; $I^2 = 0\%$; Analysis 36.2) and for asthenia or weakness (RR 0.77, 95% CI 0.34 to 1.76; $I^2 = 0\%$; Analysis 36.2).

One RCT including 31 participants (Correia 1996) from Brazil found no clear differences for anorexia (RR 1.24, 95% CI 0.54 to 2.86; Analysis 36.2).

One RCT including 125 participants (Neves 2011) found that mild or moderate adverse effects were reported by 74 (40%) participants, with a higher risk for pain (RR 53.84, 95% CI 3.35 to 864.51; Analysis 36.2) and induration at the site of injection (RR 17.27, 95% CI 1.02 to 292.90; Analysis 36.2) in the pentamidine group, although results were very imprecise (wide confidence intervals).

One RCT including 70 participants (Alves 2016) from Brazil reported non-significant differences in the percentage of participants with adverse effects among those treated with IMPI compared with IMMA (RR 1.06, 95% CI 0.60 to 1.88). The most common side effects in those treated with IMPI were pain at the injection site, paraesthesias in both legs and increase of CPK; and in the IMMA group were arthralgia, pain at the injection site, myalgia, increase of amylase, headache and ECG alterations.

Pentamidine isethionate 7 days versus pentamidine isethionate 4 days

One RCT including 163 participants (Hu 2015) from Suriname compared both treatment schedules.

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

At 12-week follow-up they found no significant differences in the proportion of participants clinically cured (RR 1.14, 95% CI 0.84 to 1.56; Analysis 37.1) among seven- and four-day treatments.

Primary outcomes: Adverse effects

At 12 weeks follow-up there was no serious toxicity in any group, and none of the reported side effects required discontinuation of treatment in any participant.

Pentamidine isethionate: single dose versus 2 doses versus 3 doses

One RCT including 159 participants with cutaneous leishmaniasis from Brazil (Gadelha 2018), 120 with *L. guyanensis,* compared a single dose, two or three doses of 7 mg/kg body weight, intramuscularly, with an interval of seven days between each dose.

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

At six months after the end of treatment, cure rates were lower in the single-dose group (45.3%: 24/53) than in the two-dose group (81.1%: 43/53; RR 0.56, 95% CI 0.40 to 0.77; Analysis 38.1), and lower than in the three-dose group (96.2%: 51/53; RR 0.47, 95% CI 0.35 to 0.64; Analysis 38.1).

Cure rates were lower in the two-dose group than in the three-dose group: RR 0.84, 95% CI 0.73 to 0.97; Analysis 38.1.

The results were analysed separately for 122 men and 37 women, finding no differences in the effect of the treatments between male and female participants.

Primary outcomes: Adverse effects

Quoted from Gadelha 2018: "No serious adverse events (SAE) occurred and none of the reported adverse events (AE) required discontinuation of therapy in any [participant. Some participants] presented erythema and swelling at the injection site. Asthenia, fever, malaise, and headache were also reported, [and] were more often reported by [participants] treated with three PI doses than by those treated with one or two doses. Pain was the most frequent AE, 128 participants experienced grade 1 and 8 participants grade 2. Twenty-three participants reported no AE. A 54-year-old male participant with a family history of diabetes developed type 2 diabetes mellitus one month after the treatment was concluded. This participant was treated with three PI doses with 1,764 mg PI.

Leukocytosis and discrete CPK, ALP, urea, and creatinine increase were observed one week after the treatment in all the participants. These values returned to normal one month after the treatment. The blood glucose level, measured 30 minutes before and after the injections, showed a significant reduction in groups treated with two and three PI doses."

2.6 Azithromycin versus meglumine antimoniate

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

One RCT including 45 participants (Krolewiecki 2007) from Argentina compared oral azithromycin, 500 mg/day versus intramuscular meglumine antimoniate, 10 mg Sb/kg/day, both for 28 days, with a second cycle of 15 days if necessary.

One RCT including 48 participants (Toledo 2014) from Brazil compared injectable meglumine antimoniate (15 mg/kg/day up to 1215 mg) versus oral azithromycin (AZ) (500 mg/day) during 20 consecutive days.

Pooling both studies, cure rates were lower for those treated with azithromycin (RR 0.51, 95% CI 0.34 to 0.76; I^2 = 0%; 2 studies, 93 participants; Analysis 39.1).

Please see Summary of findings 4, where we rate the certainty of the evidence for this outcome as moderate, which means we are moderately certain about the difference in cure rates between azithromycin and MA at six to 12 months' follow-up. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Primary outcomes: Adverse effects

Toledo 2014 found more adverse effects in the meglumine antimoniate group (49 events) than the azithromycin group (13 events), but there were no significant differences between the groups. The adverse effects were varied between the groups: in the meglumine antimoniate group, the most common were myalgia (22.4%), arthralgia (18.4%), and malaise (8.1%); in the azithromycin group, the most common were diarrhoea (30.8%) and abdominal pain (23.1%). When assessing by severity, most of the adverse effects (51/62; 82.5%) were deemed mild, nine were deemed moderate (14.5%), and two (3.2%) severe (e.g. malaise and vomiting).

Krolewiecki 2007 "found significant differences in tolerance between drugs, with 18 (78%) of 23 participants treated with MA reporting moderate or severe musculoskeletal symptoms (local and general myalgias, arthralgias or injection site pain, or both), with 11 participants (47.8%) requiring a change to the intravenous route to complete therapy." In participants treated with azithromycin, mild-to-moderate gastrointestinal issues were most common and occurred in six participants (27%). One participant experienced mild rash that resolved with oral antihistamines. See Summary of findings 4.

2.7 Amphotericin B plus oral rehydration solution versus amphotericin B plus normal saline solution (new comparison)

One RCT including 48 participants (Echevarria 2006) from Peru compared adding oral rehydration solution (ORS) versus adding an intravenous saline solution (SS) to treatment with intravenous amphotericin B, aiming to prevent nephrotoxicity.

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

Not assessed.

Primary outcomes: Adverse effects

They only assessed renal function, and found no difference in serum creatinine, creatinine clearance, serum urea, and serum sodium values during treatment, but serum potassium values were lower in the SS group than in the ORS group. Hypokalaemia was much less frequent in the group treated with oral rehydration solution (RR 0.39, 95% CI 0.18 to 0.85; Analysis 40.1).

3. Non-antimonial topical or intralesional therapies

3.1 Topical paromomycin (aminosidine)

Paromomycin versus placebo

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

One RCT including 76 participants (Arana 2001) from Guatemala compared topical 15% paromomycin in 12% MBCL ointment (PR-MBCL) for 20 days versus placebo. One year after treatment, topical paromomycin in MBCL had significantly higher cure rates than placebo (RR 2.38, 95% CI 1.50 to 3.80; Analysis 42.1) in *L. braziliensis* and *L. mexicana* infections.

One RCT including 53 participants, 48 of them under 18 years old, (Neva 1997) from Honduras compared topical 15% paromomycin in

10% urea ointment (PR-U) for four weeks versus placebo. Complete cure occurred in 4.3% (1/23) and 3.3% (1/30) of participants in the respective groups 2½ months (11 weeks) after treatment (short-term primary outcome, excluded from analysis).

Primary outcomes: Adverse effects

One study including 76 participants (Arana 2001) reported that of the 38 participants receiving PR-MBCL ointment, 57.9% (22) had 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 oedema 2.6% (1/38). All adverse effects disappeared within one week after finishing the treatment. In Neva 1997 (including 53 participants) no untoward effect of either the paromomycin or placebo ointment was reported or observed.

Secondary outcomes: Recurrence

One study including 76 participants (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; reactivation occurred in the one affected individual around 26 weeks.

In Neva 1997 (53 participants), 10 participants recruited to the trial had already had the condition for nine months. Their lesions persisted, regardless of whether they received drug or placebo, although there was no change in size.

Paromomycin plus gentamicin versus paromomycin alone

Two RCTs from Panama compared topical 15% paromomycin plus 0.5% gentamicin versus 15% paromomycin for 20 days. Sosa 2013 included only 30 participants, was a phase II exploratory study with a very small sample size designed to be a preliminary estimation of the initial clinical cure rate as a basis for calculating sample sizes for the other study, a phase III trial with 399 participants (Sosa 2019).

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

Paromomycin could result in higher rates of final clinical cure of all lesions, but the effects of paromomycin vary and it is possible that it worsens cure rates (RR 1.19, 95% CI 0.74 to 1.91; P = 0.45; I^2 = 72%; 2 studies, 429 participants; Analysis 41.1).

Sosa 2019 found no differences between treatments (RR 0.99, 95% CI 0.88 to 1.10; P = 0.94). Sosa 2013 found that paromomycin could result in higher rates of final clinical cure of all lesions, but the 95% confidence interval indicates that it may also make little or no difference (RR 1.63, 95% CI 0.97 to 2.72).

The high statistical heterogeneity found in this meta-analysis could be due to chance in the results of Sosa 2013, with a very small sample of only 15 participants in each compared group. Small changes in the number of participants cured in one group could result in large changes in the heterogeneity when combining the two studies.

Sosa 2019 performed separate analysis by age of participants and found no differences in cure rates, either in participants aged under 12 years (RR 0.86, 95% CI 0.74 to 1.01) nor in participants aged 12 to 17 years (RR 1.16, 95% CI 0.95 to 1.43; Analysis 41.2).

Primary outcomes: Adverse effects

Sosa 2013 found one severe adverse effect - migraine headache - in a participant treated with paromomycin plus 0,5% gentamicin and none in the paromomycin-alone group.

In Sosa 2019 two participants among those treated with paromomycin plus 0.5% gentamicin suffered severe adverse effects: one participant had a second-degree burn and the other an appendectomy; one participant in the paromomycin-alone group had an infection of the surgical site. Minor adverse effects were sustained by more participants in the combined therapy group: contact dermatitis (99/201), pruritus (60/201), application site injury (22/201), application site dermatitis (21/201), application site pain (14/201), application site pruritus (11/201). For the paromomycin-alone group: contact dermatitis (97/198), pruritus (53/198), application site injury (38/198), application site pain (16/198), application site dermatitis (13/198), and application site pruritus (8/198).

Tertiary outcomes: Speed of healing

In Sosa 2019 median times to initial clinical cure for index lesions were 36 days (95% CI 35 to 49) for paromomycin plus 0.5% gentamicin and 48 days (95% CI 36 to 49) for the paromomycin-alone group.

Paromomycin-MBCL versus IM meglumine antimoniate versus PR-U

One RCT including 120 participants (Armijos 2004) from Ecuador compared topical PR-MBCL for 30 days, topical PR-U for 30 days, versus IMMA for 10 days.

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

Complete cure occurred in 47.5% (19/40), 47.5% (19/40) and 70% (28/40) of participants in the respective groups two months after treatment (short-term primary outcome, excluded from analysis).

Primary 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. All three groups experienced a number of side effects, including local application-site reactions such as itch, burning, redness, heat and exudation, and systemic reactions including headache and weakness.

Secondary outcomes: Recurrence

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.

No differences were observed between PR-MBCL and MA groups (RR 0.80, 95% CI 0.23 to 2.76; Analysis 43.1) nor between PR-MCBL and PR-U (RR 2.00, 95% CI 0.39 to 10.31; Analysis 43.1).

Tertiary outcomes: Speed of healing

Speed of healing was longer for PR-MBCL compared to MA (MD 13.60, 95% CI 7.75 to 19.45; Analysis 43.2), but there were no differences between PR-MBCL and PR-U (MD −0.40, 95% CI −7.30 to 6.50; Analysis 43.2).

The days required for initial healing were 43.1 ± 14.4 (mean ± standard deviation (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 to PR-MBCL (P = 0.001) or to 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

One RCT including 89 participants (Soto 1998) from Colombia compared PR-MBCL for 10 days combined with a short course of IVMA for seven days versus PR-MBCL for 10 days combined with a short course of IVMA for three days.

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

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 to 6.09; Analysis 44.1) 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

In the same RCT including 89 participants (Soto 1998) from Colombia, PR-MBCL for 10 days combined with a short course of IVMA for seven days was compared to IVMA for seven days.

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

One year after treatment, there was no significant difference in cure rates between PR-MBCL plus IVMA for seven days and IVMA for seven days (RR 1.08, 95% CI 0.72 to 1.61; Analysis 45.1).

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

This RCT including 89 participants (Soto 1998) from Colombia also compared topical PR-MBCL for 10 days combined with a short course of IVMA for three days versus IVMA for seven days.

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

One year after treatment, PR-MBCL plus IVMA for three days had significantly lower cure rates than IVMA for seven days (RR 0.38, 95% CI 0.17 to 0.83; Analysis 46.1).

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

The same RCT including 89 participants (Soto 1998) from Colombia compared topical PR-MBCL for 10 days combined with a short course of IVMA for seven days, versus topical PR-MBCL for 10 days combined with a short course of IVMA for three days versus IVMA for 20 days.

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

One year after treatment, IVMA for 20 days had significantly higher cure rates than topical PR-MBCL plus IVMA for seven days (RR 0.69, 95% CI 0.53 to 0.90; 90 participants; Analysis 47.1) or topical PR-MBCL plus IVMA for three days (RR 0.24, 95% CI 0.11 to 0.50; 61 participants; Analysis 48.1) in *L. braziliensis* and *L. panamensis* infections.

Paromomycin in aquaphilic versus intralesional pentamidine

One RCT including 80 participants (Soto 2019) with cutaneous leishmaniasis, *L. braziliensis*, in Bolivia compared paromomycin-aquaphilic applied topically daily for 20 days, intralesional pentamidine administered on days 1, 3, and 5, and aquaphilic-vehicle, applied topically daily for 20 days.

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

Cure rates after six months of follow-up were similar for paromomycin-aquaphilic (77.5%: 31/40) and pentamidine (70%: 14/20) for intralesional pentamidine (RR 1.11, 95% CI 0.79 to 1.54; Analysis 49.1), since the confidence interval includes the possibilities of both increased and reduced cure rates.

Cure rates were higher for paromomycin-aquaphilic (77.5%: 31/40) than for aquaphilic vehicle (10%: 2/20), although results are very imprecise (RR 7.75, 95% CI 2.06 to 29.17; Analysis 49.1).

Primary outcomes: Adverse effects

Quote from Soto 2019: "There were several instances of erythema and pruritis in each group of participants, but all were grade 1. IL-pentamidine was less well tolerated, as expected of an intralesional injection. Although superficial necrosis was obviated by subcutaneous rather than intradermal administration, 40% of participants reported pain; 40% demonstrated erythema; and a lesser percentage had swelling, hard edema, and pruritis."

3.2 Topical aminoglycosides

Formulation of aminoglycosides (WR279396) versus placebo

One RCT including 45 participants (Soto 2002) from Colombia compared topical WR279396 for 20 days versus placebo.

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

Complete cure occurred in 51.5% (17/33) and 41.7% (5/12) of participants in the respective groups two months (70 days) after treatment (short-term primary outcome, excluded from analysis).

Primary outcomes: Adverse effects

No relevant differences between treatments were observed (RR 1.64, 95% CI 0.69 to 3.86; Analysis 50.1).

Tertiary outcomes: Speed of healing

The speed of healing was shorter for the WR279396 group (MD −21.00, 95% CI −38.39 to −3.61; Analysis 50.2).

3.3 Topical 3% amphotericin B cream twice a day versus three times a day

A phase II RCT including 80 participants from Colombia (López 2018) compared topical 3% amphotericin B cream twice a day versus three times a day for four weeks.

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

There were no differences in the rates of final clinical cure of all lesions between treatments, either at three months (RR 1.08, 95% CI 0.57 to 2.08; Analysis 51.1), or at six months (RR 1.12, 95% CI 0.60 to 2.08; Analysis 51.2).

Primary outcomes: Adverse effects

Only five participants, two in the twice-a-day group and three in the three-times-a-day group, reported adverse events related to the cream. The adverse events were all mild (burning sensation, itching and rash) and affected the area around the lesion where the cream was applied.

Tertiary outcomes: Speed of healing

Median time to cure was 57 days for the twice-a-day treatment and 62 days for the three-times-a-day regimen.

3.4 Nitric oxide patch

Nitric oxide patch (NOP) versus meglumine antimoniate

One RCT including 143 participants (Lopez-Jaramillo 2010) from Colombia compared a topical nanofiber NOP (≈ 3.5 µmol NO/cm^2/day for 20 days, NOP) with intramuscular meglumine antimoniate (Glucantime, 20 mg/kg/day for 20 days).

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

Complete cure percentages were much lower in participants treated with the NOP (38%) than in those treated with meglumine antimoniate (95%) (RR 0.40, 95% CI 0.29 to 0.55; Analysis 52.1).

Primary outcomes: Adverse effects

Participants treated with NOP had significantly less minor adverse effects, such as fever, headache, myalgia, and arthralgia. More participants had symptoms (itching or pain) at the site of the lesion in the NOP group compared with those treated with meglumine antimoniate.

3.5 Topical imiquimod

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

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

In an RCT of 14 participants (Arévalo 2007) from Peru, topical 7.5% imiquimod cream combined with IVMA was compared to IVMA, both for 20 days. Three months after treatment, there was no clear 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 to 3.15; Analysis 53.1) in *L. braziliensis*, *L. amazonensis*, *L. mexicana*, and *L. peruviana* infections.

One RCT from Peru (Miranda-Verástegui 2005), including 40 participants who had previously failed treatment with pentavalent antimony, compared topical 5% imiquimod cream combined with MA (IM in children and IV in older participants) to MA (IM in children and IV in older participants), 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 to 1.30; Analysis 54.1) in *L. peruviana* and *L. braziliensis* infections, since the confidence interval includes the possibilities of both increased and reduced cure rates.

One RCT from Peru (Miranda-Verástegui 2009) including 80 participants who had not been previously treated, compared topical imiquimod cream (125 - 250 mg per lesion three times a week) combined with IVMA 20 mg/kg/d IVMA for 20 days versus IVMA plus placebo. One year after treatment, there was no significant difference in cure rates (RR 1.30, 95% CI 0.95 to 1.80; Analysis 54.1), since the confidence interval includes the possibility of both increased and reduced cure rates. Over the study period, only one adverse effect (rash) was recorded, in the imiquimod arm.

Pooled results showed high statistical heterogeneity (I^2 = 58%), probably due to differences in the inclusion criteria for participants.

Adding topical imiquimod to IVMA probably makes little or no difference to the chance of healing in *L. braziliensis, L. guyanensis* and *L. peruviana* (see Summary of findings 5), corresponding to 750 more participants completely cured per 1000 participants (95% CI 435 to 975 more).

Primary outcomes: Adverse effects

In one study including 14 participants (Arévalo 2007), among participants treated with imiquimod, 77% (10/13) reported mild adverse effects (localised itch, erythema and oedema). 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, one participant voluntarily discontinued treatment with MA on day 15 of re-treatment because of flu-like symptoms, arthralgia, and myalgia.

In Miranda-Verástegui 2005 (40 participants), there was no clear difference in adverse effects between groups for oedema (RR 0.88, 95% CI 0.39 to 1.95; Analysis 54.2), itching (RR 0.67, 95% CI 0.12 to 3.57; Analysis 54.2) or burning (RR 3.00, 95% CI 0.34 to 26.45; Analysis 54.2), since the confidence intervals include the possibilities of both increased and reduced adverse effects. Local pain was reported with equal frequency by participants treated with imiquimod and those treated with the placebo cream. Only mild erythema was more common among participants in the imiquimod group and was evident during most of the 20-day treatment period, although results are very imprecise due to the wide confidence interval (RR 2.75, 95% CI 1.05 to 7.20; Analysis 54.2). In Miranda-Verástegui 2009, including 80 participants, they found no differences in adverse effects between imiquimod and placebo creams. See Summary of findings 5, where we found low-certainty evidence for these outcomes.

Imiquimod versus IV meglumine antimoniate

One RCT including 13 participants (Arévalo 2007) from Peru compared topical 7.5% imiquimod cream versus IVMA, both for 20 days.

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

Three months after treatment, cure rates were higher with 20 mg/kg/day IVMA (4/7 participants) versus topical 7.5% imiquimod (0/6 participants) for 20 days, but the results were very imprecise (RR

0.13, 95% CI 0.01 to 1.97; Analysis 55.1), since the confidence interval includes the possibility of both increased and reduced cure rates.

Primary 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 re-treatment because of flu-like symptoms, arthralgia, and myalgia.

4. Physical therapies

4.1 Thermotherapy

Thermotherapy versus placebo

One RCT including 44 participants (Navin 1990) from Guatemala applied three treatments of localised heat at 50 °C for 30 seconds, at seven-day intervals compared with placebo.

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

Complete cure occurred in 73% (16/22) and 27% (6/22) of participants in the respective groups two months after treatment (short-term primary outcome, excluded from analysis).

Primary 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 second-degree burns where the electrodes were applied.

Tertiary outcomes: Microbiological or histopathological cure of skin lesions

The rate of participants parasitologically-negative for *Leishmania* were higher for the thermotherapy group (RR 2.67, 95% CI 1.29 to 5.53; Analysis 56.1).

Thermotherapy versus IM meglumine antimoniate

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

One RCT including 44 participants (Navin 1990) from Guatemala applied three treatments of localised heat at 50 °C for 30 seconds, at seven-day intervals compared to IMMA for 15 days. Complete cure occurred in 59% (13/22) and 73% (16/22) of participants in the respective groups two months after treatment (short-term primary outcome, excluded from analysis).

One RCT including 292 participants (Vélez 2010) from Colombia compared a single thermotherapy session, which involved the application of 50 °C, via a device, at the centre and active edge of each lesion to IMMA given for 20 days. Complete cure occurred in 58% of those treated with thermotherapy and 72% of participants treated with IMMA (RR 0.80, 95% CI 0.68 to 0.95; Analysis 57.1). Thermotherapy reduced the chance of healing in *L. panamensis* and *L. braziliensis* at six-month follow-up, corresponding to 576 fewer participants completely cured per 1000 participants (95% CI 490 fewer to 684 fewer). See Summary of findings 6 where we found high-certainty evidence.

Primary outcomes: Adverse effects

In Navin 1990, 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 second-degree burns where the electrodes were applied.

In Vélez 2010 from Colombia, the only side effect of thermotherapy was pain at the area four days after the end of treatment.

Tertiary outcomes: Microbiological or histopathological cure of skin lesions

Navin 1990: 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 (RR 2.67, 95% CI 1.29 to 5.53; Analysis 57.2).

Thermotherapy versus miltefosine

One RCT including 294 participants (Vélez 2010) from Colombia compared a single thermotherapy session involving the application of 50 °C for 30 seconds over the lesion and surrounding area of each lesion to oral miltefosine given for 28 days.

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

There were no differences between treatments, with complete cure occurring in 58.5% of those treated with thermotherapy and 59.4% in participants treated with miltefosine (RR 0.98, 95% CI 0.81 to 1.20; Analysis 58.1), since the confidence interval includes the possibility of both increased and reduced cure rates.

Secondary outcomes: Adverse effects

Primarily pain at the lesion site after treatment for thermotherapy and gastrointestinal adverse effects for miltefosine, including one participant that developed haematemesis.

Thermotherapy combined with IV meglumine antimoniate versus IV meglumine antimoniate

One RCT including 37 participants (Lobo 2006) from Brazil compared heat therapy given in a single session combined with IVMA after day 28 versus IVMA, both for 20 consecutive days.

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

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).

Primary 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).

4.2 Cryotherapy

Cryotherapy versus placebo cream

One RCT including 50 participants (Soto 2013) from Bolivia compared two sessions of cryotherapy (days 1 and 14) with placebo cream (daily for 20 days).

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

There were no statistically significant differences between treatments; complete cure occurred in 20% of those treated with cryotherapy and in 17% of participants treated with placebo cream (RR 1.20, 95% CI 0.37 to 3.93; Analysis 59.1).

Primary outcomes: Adverse effects

No participants experienced severe side effects. Cryotherapy was more painful and created more irritation and more vesicles/bullae than topical cream.

Cryotherapy versus IL sodium stibogluconate (ILSB)

One RCT including 50 participants (Soto 2013) from Bolivia compared two sessions of cryotherapy (days 1 and 14) with ILSB (1, 3 and 5 days).

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

Cure rates were higher for participants treated with ILSB (70%) versus only 20% for cryotherapy (RR 0.29, 95% CI 0.12 to 0.71; Analysis 60.1).

Primary outcomes: Adverse effects

No participants experienced severe side effects. Cryotherapy was more painful and created more irritation and more vesicles/bullae than ILSB.

5. Immuno-chemotherapy

5.1 Vaccines

Vaccine versus IM meglumine antimoniate

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

Two RCTs from Venezuela including 277 participants (Convit 1987; Convit 1989) compared intradermal vaccine of the *L. mexicana amazonensis* strain combined with Bacille Calmette Guerin (BCG) versus IMMA. Six months after treatment, there was no difference in cure rates between the vaccine and IMMA (RR 0.96, 95% CI 0.90 to 1.04; I^2 = 0%; Analysis 61.1) in *L. braziliensis* infections.

Primary outcomes: Adverse effects

One study of 102 participants (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 IMMA 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 of 175 participants (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 IMMA 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.

Secondary outcomes: Recurrence

One study of 175 participants (Convit 1989) reported that no relapses were seen in the two treatment groups.

Tertiary outcomes: Speed of healing

Convit 1987 (102 participants) reported that the average time from start of treatment to cure was 18.3 weeks for the vaccine group and 16.1 weeks for the IMMA group (the original paper reported that the time to cure was not significant (P > 0.05) by the Students' t-test). In Convit 1989 (175 participants) the average time required for healing were 18.3 weeks in the vaccine group and 16.1 weeks in the IMMA group (the original paper reported that the difference was not statistically significant by variance analysis).

Tertiary outcomes: Development of cell-mediated immunity

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 IMMA group. In 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 IMMA group) but the differences between 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 plus placebo

In one RCT (Machado-Pinto 2002) from Brazil, subcutaneous vaccination of *L. amazonensis* strain combined with IMMA was compared to IMMA plus placebo, both for 10 days followed by 10 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).

Primary outcomes: Adverse effects

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

Secondary outcomes: Recurrence

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

Tertiary outcomes: Speed of healing

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

Intradermal vaccine of biological LEISH-F2 + MPL-SE versus sodium stibogluconate

One Phase II RCT from Chile (NCT01011309) compared an intradermal vaccine of biological LEISH-F2 + MPL-SE versus sodium stibogluconate and followed participants up to 336 days.

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

At 84 days follow-up clinical cure rates without rescue treatment at that time were smaller for the vaccine group (4/19; 21%) than for stibogluconate (15/16; 94%) (P = 0.00001).

Primary outcomes: Adverse effects

At 336 days follow-up they found one serious adverse effect in the 24 participants treated with vaccine (hospitalisation due to grade 3 cellulitis) and one in the 21 treated with stibogluconate (hospitalisation due to antimonial toxicity).

At 336 days follow-up, the rates of participants affected by non-serious adverse effects were similar in both groups (RR 0.96, 95% CI 0.86 to 1.08; Analysis 62.1): 23/24 for immunotherapy participants and 21/21 for chemotherapy participants. More frequent non-serious adverse effects for the immunotherapy participants were injection site problems (erythema or induration or pain, 102 events), increase in ALT (11/24 participants) and blood bilirubin increase (3/24 participants). More frequent non-serious adverse event for the chemotherapy participants were white blood cell (WBC) decrease (10/21 participants), increase in ALT (9/21 participants), blood haemoglobin decrease (7/21 participants), blood potasium decrease (4/21 participants) and blood bilirubin increase (3/21 participants).

5.2 Intradermal Bacillus Calmette-Guerin (BCG)

BCG versus IM meglumine antimoniate

One RCT including 93 participants (Convit 1989) from Venezuela compared three doses of intradermal BCG versus IMMA.

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

Six months after treatment, intradermal BCG had significantly lower cure rates than IMMA (RR 0.46, 95% CI 0.32 to 0.65; Analysis 63.1) in *L. braziliensis* infections.

Primary 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 IMMA, 48.9% (25/51) of the participants showed secondary effects, including bone and muscle pain, headache and fever. The serious 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.

Secondary outcomes: Recurrence

Only one relapse was observed in the BCG-alone group between three months and 2½ years. No relapses were seen in the other group.

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 IMMA group), but the differences between 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

In one RCT including 23 participants with mucosal leishmaniasis (Machado 2007) from Brazil oral pentoxifylline combined with IVSSG was compared to IVSSG, both for 30 days.

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

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 to 2.69; Analysis 64.1) in *L. braziliensis* infections.

Primary 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 shorter in the pentoxifylline combined with SSG group (MD −62.00, 95% CI −121.92 to −2.08; Analysis 64.2).

Pentoxifylline combined with IM meglumine antimoniate versus IM meglumine antimoniate plus placebo

One RCT including 70 participants with cutaneous leishmaniasis (Cossio-Duque 2015) from Colombia compared intramuscular MA (20 mg/ kg /day x 20 days) plus oral PTX 400 mg thrice daily versus IMMA plus placebo.

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

Cure rates were lower for added pentoxifylline (65% versus 75%), but the confidence interval indicated there might be little or no difference between groups (RR 0.86, 95% CI 0.63 to 1.18; Analysis 65.1).

Adding pentoxifylline to IMMA probably makes little or no difference to the chance of healing, corresponding to 645 more participants completely cured per 1000 participants (95% CI 473 more to 885 more). Please see Summary of findings 7.

Primary outcomes: Adverse effects

No differences between overall frequency and severity of adverse effects were found (Pentoxyfilline = 142 events versus placebo = 140 events). See Summary of findings 7.

Pentoxifylline combined with IM meglumine antimoniate versus IM meglumine antimoniate plus placebo

Two RCTs including 197 participants in total (Brito 2014; Brito 2017a) from Brazil compared pentavalent antimony given at a dose of 20 mg/kg a day plus oral pentoxifylline (400 mg) or placebo three times a day for 20 days.

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

There were no differences in complete cure rates among the treatments: 47% pentoxifylline group and 43% placebo group (RR 1.08, 95% CI 0.80 to 1.47; I^2 = 0%; Analysis 66.1).

Primary outcomes: Adverse effects

In one RCT including 164 participants (Brito 2017a) adverse effects were more common in the pentoxifylline group (37.8% of participants), versus 23% in the placebo group. However, serious AEs were more common in the placebo group (9 participants) compared to the pentoxifylline group (one participant). The most common side effects observed in the pentoxifylline group were myalgia (11), headache (9), nausea (7) and arthralgia (7). In the placebo group it was arthralgia (10) and myalgia (6). No cardiological AE was documented in either group.

In one RCT including 33 participants (Brito 2014), temporary, mild side effects, like arthralgia (four participants), headache (two participants), fever (two participants), and lack of appetite (two participants), were prevalent in the IMMA plus pentoxifylline group (five participants) as well as occurring in the IMMA plus placebo group. Neither group reported nausea, vomiting, or diarrhoea.

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

GM-CSF combined with IV meglumine antimoniate versus placebo

In one RCT including 22 participants (Santos 2004) from Brazil topical GM-CSF (for a total of nine applications over three weeks) combined with IVMA was compared to IVMA alone, both for 20 days.

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

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).

Primary outcomes: Adverse effects

No side effects were detected in participants in 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

One RCT including 20 participants (Almeida 1999) from Brazil compared intralesional GM-CSF combined with IVSSG versus 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 was shorter in the GM-CSF group (MD −61.00, 95% CI −104.25 to −17.75; Analysis 67.1).

5.5 Subcutaneous interferon-gamma (IFN-γ)

10-day IV meglumine antimoniate combined with subcutaneous IFN-γ versus 10-day and 20-day IV meglumine antimoniate

One RCT including 44 participants (Arana 1994) from Guatemala compared IVMA for 20 days, IVMA for 10 days versus IVMA for 10 days combined with 10 days of IFN-γ.

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

There may be little or no difference in cure rates between 10-day adjuvant subcutaneous IFN-γ to both 10-day IVMA therapy (RR 1.22, 95% CI 0.99 to 1.50; Analysis 68.1) and 20-day IVMA therapy (RR 1.15, 95% CI 0.96 to 1.39; Analysis 68.2).

Primary outcomes: Adverse effects

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

Results from the MEDLINE search for adverse effects

We conducted a MEDLINE search for adverse or side effects combined with therapeutic terms, which resulted in 204 hits. However, we could only find general papers reporting known adverse effects.

DISCUSSION

Summary of main results

The studies included in this review addressed varied clinical questions and were methodologically diverse in terms of settings, the range of interventions and comparators, included participants, *Leishmania* species involved in different geographical areas, and outcome measures.

The heterogeneity in study design, moderate-to-high risk of bias, missing standard deviations, and a mix of comparators and dosing regimens did not, in general, enable data to be pooled, permit the accurate and direct comparisons of a considerable number of interventions, or facilitate conclusions about comparative benefit. Nonetheless, this review documents the effectiveness of treatments of existing RCTs and relevant evidence that can be used for policy, practice and future research.

The 75 RCTs included in the review covered 68 comparisons, broadly categorised into five main groups (antimonials, non-antimonial systemic treatments, non-antimonial topical or intralesional therapies, physical therapies, immuno-chemotherapy). The most assessed class of treatment was non-antimonial systemics, followed by antimonials, of which meglumine antimoniate was the most-assessed intervention (15 studies). Non-antimonial topical or intralesional therapies or immuno-chemotherapy were assessed by similar numbers of studies, and of these, paromomycin, vaccines, pentoxifylline (in

combination with other treatments) were most often investigated. The following interventions were assessed by single studies only: amphotericin B, amphotericin B cream, nitric oxide patch, cryotherapy, Bacillus Calmette-Guerin (BCG), and IFN-y. None of the included studies tested lipid-based drugs, deoxycholate formulations, antimonial drugs combined with cytokines and free radicals, immunomodulatory therapy with cytokines, or itraconazole.

Our primary outcomes, percentage of participants cured at least three months after the end of treatment and adverse effects, were well measured. Forty-five per cent of the studies assessed recurrence, which we also deemed a key outcome. Just over half of the included studies did not report any of our secondary outcomes.

We created 'Summary of findings' tables for relevant comparisons that have been used in previous evidence-informed guidelines on the America continent (PAHO 2015). The most relevant findings in this updated systematic review are described below.

Compared to placebo:

- Intramuscular meglumine antimoniate (IMMA) may increase the likelihood of complete healing (moderate-certainty evidence), but may also make little to no difference, since the 95% confidence interval (CI) includes the possibilities of both increased and decreased healing (complete cure); IMMA probably increases severe adverse effects such as arthralgia and myalgia (moderate-certainty evidence), and may make little to no difference to the risk of recurrence, but the 95% CI includes the possibilities of both increased and decreased risk (low-certainty evidence). These results pertain to *L. braziliensis* and *L. panamensis* infections in American cutaneous and mucocutaneous leishmaniasis (ACML); participants were followed up for one year; Summary of findings 1.
- Oral miltefosine probably improves the likelihood of complete healing (moderate-certainty evidence); probably increases the risk of nausea and vomiting (moderate-certainty evidence); and may make little to no difference to recurrence rates (low-certainty evidence), but the 95% CI includes the possibilities of both increased and decreased risk. These results pertain to *L. mexicana*, *L. panamensis,* and *L. braziliensis* infections in American cutaneous leishmaniasis (ACL); participants were followed up for six months; Summary of findings 2.

Compared to meglumine antimoniate (MA) (active treatment):

- Oral miltefosine may make little to no difference to the likelihood of complete healing (low-certainty evidence). Oral miltefosine probably increases the risk of nausea and vomiting (moderate-certainty evidence). Recurrence was not reported. These results pertain to *L. braziliensis*, *L. panamensis*, *L. guyanensis* and *L. amazonensis* infections in ACML; participants were followed up for 6 to 12 months; Summary of findings 3.
- Oral azithromycin probably reduces the likelihood of complete healing (moderate-certainty evidence). Recurrence was not reported, and we could not calculate the risk of adverse effects. These results pertain to *L. braziliensis* infections in ACML; participants were followed up for 6 to 12 months; Summary of findings 4.
- Topical imiquimod and IVMA combined probably makes little to no difference to the likelihood of complete healing (moderate-certainty evidence). Risk of recurrence was not reported, and we could not calculate the risk of adverse effects. These results pertain to *L. braziliensis, L. guyanensis* and *L. peruviana* infections in ACL; participants were followed up for 1 year; Summary of findings 5.
- Local thermotherapy reduces the likelihood of complete healing (high-certainty evidence). Risk of recurrence was not reported, and we could not calculate the risk of adverse effects. These results pertain to *L. panamensis* and *L. braziliensis* infections in ACL; participants were followed up for six months; Summary of findings 6.
- Oral pentoxifylline and IMMA combined probably makes little to no difference to the likelihood of complete healing (moderate-certainty evidence). Risk of recurrence was not reported, and we could not calculate the risk of adverse effects. These results pertain to treatment of CL (the trial did not state the species); participants were followed up for 26 weeks; Summary of findings 7.

Some studies did report cure but were not statistically assessed because they did not report cure rates in our pre-specified time period for the primary outcome. Thus, there was insufficient RCT evidence to evaluate the efficacy of topical aminoglycosides, vaccine combined with IMMA, and topical or intralesional granulocyte macrophage colony-stimulating factor (GM-CSF).

The secondary objective of this review was to ascertain whether response to treatment is species-dependent or associated with their geographical distribution. Heterogeneity of treatments and regimens hindered our assessment of this objective. Nonetheless, we found no disparities of response to pentavalent antimonial drugs among the studied species, including *L. braziliensis*, *L. amazonensis*, and *L. guyanensis*, and neither did other species, such as *L. mexicana*, *L. chagasi*, *L. peruviana*, and *L. panamensis*, respond differently. However, they could not be analysed specifically because of the small numbers of studies. Moreover, some of the included studies did not identify the species responsible for the illness, precluding a detailed review of the benefits of each therapeutic option. Some other studies reported epidemiological information without any identification of the species causing the disease, which may be considered a methodological bias.

Overall completeness and applicability of evidence

This review was not able to fully address the main objective 'To assess the effects of interventions for all immuno-competent people who have American Cutaneous and Mucocutaneous Leishmaniasis (ACML)'. Key reasons for this included the scarcity of studies in the mucocutaneous form and the diversity of interventions and *Leishmania* species.

The review is applicable to immuno-competent participants. However, some studies did not require HIV-testing or other tests above and beyond clinically-evident diseases or chronic conditions referred by the research participants. Recent trials often performed HIV testing whereas older trials in general neither performed or mentioned it. Although most of the evidence came from trials conducted in Brazil, where HIV incidence is relevant, the Pan American Health Organization (PAHO) estimates that cutaneous leishmaniasis/HIV co-infection incidence is low. As an example, 209 co-infected cases from Latin America were reported in 2017, which represented a 27% increase compared with the 2016 figures. However, bearing in mind that almost 50,000 cases were reported

in Latin America in 2017, it seems reasonable to consider that the presence of co-infected participants in clinical trials is low (PAHO 2019a).

While most RCTs evaluated the cutaneous form (67 studies), the evidence for the treatment of the mucocutaneous form of leishmaniasis is limited, which hinders the conclusions we can make about the effectiveness and safety of interventions for this form of leishmaniasis. A better option for participants with mucosal leishmaniasis (ML) would be to refer them to a reference treatment centre where better management is possible, using e.g. nasal fibre-optic examination and molecular tests for improving diagnosis, more rigorous monitoring of toxicity to avoid lethality associated with treatment, and the possibility of offering combined treatments conducted by teams with expertise in treating participants with ML.

Several studies included some participants who tested negative for *Leishmania* parasite; whilst some might have been real cases (false negatives), others might have been affected by other diseases and therefore might have affected the results. Furthermore, almost a third of the studies either did not mention the causative parasite or made assumptions based on endemic species or previous studies. Of the 54 studies that identified the species, approximately half identified the presence of two or more species. This made it difficult for us to ascertain whether response to treatment is species-dependent or associated with their geographical distribution, which was our secondary objective. Parasite diversity has a crucial relevance for disease severity and duration, and for clinical manifestations. Supplementing with molecular studies carried out in the different areas of the countries could contribute to establishing the distribution of *Leishmania* species and strains in the region.

Not all the trials provided information about the primary, secondary and tertiary outcomes prespecified in our review. As previously discussed (González 2009), we consider that assessing the number of persons cured rather than the number of lesions healed is a stronger criterion because it gives a better idea of the real number of participants that achieved complete cure. Most of the studies assessed our primary outcomes, although the timing of the primary efficacy outcome was variable. Over half of the studies did not report any of our secondary outcomes.

A large number of outcomes were not addressed at all: no studies reported the degree of functional and aesthetic impairment, prevention of scarring, or quality of life. The only tertiary outcomes reported were speed of healing and microbiological or histopathological cure of skin lesions; no studies reported change in isolation or PCR of *Leishmania* and emergence of resistance; development of cell-mediated immunity; or all-cause mortality.

In this update, we identified new RCTs that evaluated healing therapies, topical amphotericin B and oral miltefosine treatments, but few or no studies assessing fluconazole, itraconazole, cryotherapy, alternative therapy, nitric oxide patch, photodynamic therapy or laser treatments. Overall, most interventions assessed in this review are likely to be used in regions where a low-cost treatment is needed. Finally, it was difficult to establish whether response to treatment is age-dependent, due to the lack of variation in the participant age range, with few participants being either very young or over 50.

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, we found no RCTs comparing lipid-based drugs and deoxycholate formulations. In fact, we found only one RCT (Neves 2011) comparing meglumine antimoniate, pentamidine and amphotericin B for the treatment of cutaneous leishmaniasis by *L. guyanensis*. One RCT (López 2018) compared different regimens of amphotericin B (twice versus three times a day) for four weeks for the treatment of CL by *L. panamensis* or *L. braziliensis*. Although the design of the study was not meant to determine differences in cure rates by *Leishmania* species and the number of participants in each group was small, cure rates were higher in participants infected by *L. panamensis* compared to those infected by *L. braziliensis.*

Although currently-available medications are not affordable by low-income populations, for most of the affected patients in most of the affected countries the medications are available without any direct charge from the national health authorities. Vaccine studies are far from a clinically-useful product.

Quality of the evidence

Most included trials were poorly designed and reported. Poor reporting is a major issue, since it may affect reliability. Sixty studies (80%) had at least one domain rated as high risk. An adequate randomisation method was reported in 63% (47/75) of the studies. Only 21% (16/75) had an adequate reporting of allocation concealment. Only four studies (5.3%) were at low risk of performance and detection bias. Attrition bias was low in 59 studies (79%). None of the studies were at low risk in all seven domains.

Other factors affecting the quality of the studies are related to attrition bias. Calculation of sample size was performed in 36% (27/75) of the studies, which may affect statistical power and may therefore add to imprecision. Although one study acknowledged a plan of 150 participants, owing to slow recruitment and insufficient evidence of efficacy in the immunotherapy group, enrolment was closed early (NCT01011309). Overall, few participants withdrew or were lost to follow-up. Most study authors stated that they had performed a compliance assessment but results were seldom shown in the assessed studies. In fact, only two studies reported an assessment of compliance (Sosa 2019; Soto 2004b).

We created 'Summary of findings' tables for seven of the comparisons, and conducted GRADE assessments on the certainty of evidence for the key outcomes. We considered the quality of the evidence as high in only one comparison (thermotherapy compared to MA in *L. panamensis* and *L. braziliensis*, Summary of findings 6), for complete cure and adverse effects.

We considered the outcomes measured by the other six comparisons to be based on moderate- or low-quality evidence. The main reasons we downgraded the quality of the evidence were imprecision (wide confidence interval of risk ratios), which occurred in four comparisons mainly for complete cure and adverse events (Summary of findings 1; Summary of findings 2; Summary of findings 5; Summary of findings 7), high heterogeneity in the results from different studies in one comparison for complete cure (Summary of findings 3), and risks of bias for the effect of unblinded evaluators in two comparisons for complete cure and adverse events (Summary of findings 3; Summary of findings 4).

We found many errors in the write-up of published study reports, and the quality of reporting was generally poor. It is therefore essential that submitted journal manuscripts undergo rigorous peer review. We agree with the updated systematic review on interventions in Old World Cutaneous Leishmaniasis (Heras-Mosteiro 2017), that there is a pressing need to prioritise and conduct well-designed clinical trials to minimise bias.

Potential biases in the review process

We conducted a thorough and comprehensive search with no language restriction to minimise selection bias. We searched for conference papers, theses and ongoing trials to minimise publication bias, and we also wrote to authors from endemic countries to identify further relevant trials. We decided to include only RCTs to further minimise selection bias, since they are designed in such a way that study groups are similar at baseline, allowing researchers the quantification of the effect of the intervention under study (minimising the risk of under- and overestimation of the effects of the intervention(s) under study). Selective reporting of dramatic effects from non-randomised trials without any control group is likely to be very misleading. However, we are aware that RCTs are not methodologically flawless and are therefore not exempt from bias either. Bias can occur throughout the steps of an RCT, i.e. from the allocation of participants to the intervention groups, through the delivery of interventions to the outcome measurement. Studies that report more positive effects have an increased chance of publication than those with less definitive results (Bigby 2003). It seems that the initial published study of an intervention has an increased likelihood of showing positive results.

We know that the search we used for identifying adverse effects of treatments for American cutaneous and mucocutaneous leishmaniasis was not comprehensive. Furthermore, we are aware that Embase would have been a better choice than MEDLINE, and that recommended practice would have been to leave out terms for the condition of interest, regardless of this increasing the number of results retrieved. However, we decided to be consistent with the original plan for the review by using the original adverse effects strategy, as this was a pragmatic approach for managing the workload around sifting and discussing adverse effects information in relation to leishmaniasis. Differences between the protocol and the updated review may have led to bias. For example, we did not contact research centres to identify unpublished literature, although we think it unlikely that missing unpublished literature may have changed the conclusions of our review. In the protocol, we had planned to explore reasons for heterogeneity using sensitivity or subgroup analyses, or both, but we did not do this because there were too few studies to perform these analyses. However, in the updated version we applied the GRADE tool to assess the strength of the evidence and explore magnitude and direction of the estimates, and we followed the Cochrane MECIR standards.

The authors of reviews may introduce bias by misinterpreting the results of a study. To minimise bias, at least two authors of this review assessed the eligibility of the studies and extracted data independently. However, we cannot rule out some bias due to the review authors' inability to resolve the information considered ambiguous or incomplete. At least two independent review authors assessed the quality of each of the included studies, to evaluate the direction and magnitude of bias relative to the effect of the interventions examined. Critical appraisal was examined by the seven-domain 'Risk of bias' tool in order to provide direct decision-makers with the best available evidence.

The fact that 10 studies are awaiting classification and have not yet been incorporated may be a potential source of bias.

Agreements and disagreements with other studies or reviews

Although leishmaniasis constitutes an important public health programme in Latin America, several reviews have found little reliable evidence on the effectiveness of new treatments for the diseases that go beyond the management of the disease with antimonial and several other treatments (Almeida 2011; Brito 2017b; Reveiz 2013). In a clinical practice guideline using the GRADE methodology, Aronson 2016 recommended initiating the systematic management of medication in people suffering from complex cutaneous leishmaniasis with options including amphotericin B deoxycholate, lipid formulations of amphotericin B, pentavalent antimonial (SbV) compounds, and pentamidine. They also suggested the use of miltefosine and antifungal compounds including ketoconazole as options for oral management. It is also important to note that the decision about which treatment and dosage regimen can be subjective for the health professional. Other guidelines consider the possibility of no treatment for uncomplicated CL caused by parasite species with low risk of ML development (Aronson 2016).

In a recent systematic review, the authors compared the use of antimony infiltration therapy versus its systematic use, finding similar efficacy; however, there is insufficient evidence about late mucosal complications and adverse effects. A systematic review that evaluated the effectiveness of thermotherapy through a meta-analysis of eight studies (Cardona-Arias 2015) found that the effectiveness of thermotherapy was similar to that of pentavalent antimonial drugs. The authors suggested that it should be used as the first treatment option in areas with low prevalence of mucocutaneous forms and in people with contra-indications for systemic treatment. The effectiveness of azole therapies (fluconazole, ketoconazole and itraconazole) was evaluated in 37 studies (not only randomised clinical trials) that included 1259 participants in the New World (13 studies) and in the Old World. The authors concluded that the effectiveness in the New World was 62% (95% CI 43 to 77%) and that there were no differences between azole therapy. In their conclusions, they suggested that there is no evidence for the exclusive treatment of azole therapy (Galvão 2017). A similar systematic review, which compared studies worldwide and meta-analysed eight RCTs (two from America) (López-Carvajal 2016), evaluated the effectiveness of cryotherapy compared with pentavalent antimonial; although there are no significant differences between the treatments, the cure rates were 63.6% and 74.7% per protocol respectively.

Our review provides additional evidence related to the use of miltefosine, topical treatments, local and combination therapies, and to the efficacy of several treatments (for example, azithromycin). It highlights the differences in the response to the different treatments according to the geographical areas and the diversity of parasite species, among other aspects. However, in contrast to Aronson 2016, which recommends the use of amphotericin B in the treatment of MCL or CL cases associated with increased risk for ML, our review found one study, (Neves

2011) which failed to assess the efficacy of amphotericin B due to high dropout rates (> 75%), and another study (López 2018) whose results do not support its use for the treatment of CL. Aronson 2016 included case/series reports and retrospective studies in their evidence summaries to support their recommendation. In agreement with Galvão 2017, Cardona-Arias 2015 and López-Carvajal 2016, we were not able to find significant evidence from RCTs to fully support or refute the use of azoles, nor the use of cryotherapy.

AUTHORS' CONCLUSIONS

Implications for practice

This updated review confirms the perception of the unfavourable therapeutic scenario faced by clinicians treating people with cutaneous or mucocutaneous leishmaniasis in Latin America. This is supported by the evident longevity of parenteral antimonials as the reference treatment, in spite of their unfavourable pharmacological and toxicity profile. This clearly reveals that American tegumentary leishmaniasis (ATL) remains a neglected disease, lacking modern therapeutic approaches which could overtake the antimonial era.

Importantly, the review demonstrates that the consolidation of antimonials as the reference treatment for ATL occurred during the 1980s and 1990s, and was based on small-sized clinical trials, which precluded definite conclusions on their efficacy compared with placebo.

The ATL treatment scenario has been slowly modified since the first RCT, exploring the efficacy of miltefosine, and the emerging interest in the development of local or topical treatments, overcoming systemic toxicity. The combination of systemic and local or topical treatment approaches has been revisited, including immunomodulatory drugs, new formulations of old drugs, and physical measures.

The evidence compiled herein is heterogeneous and mostly not suitable for meta-analysis, reflecting the influence of the response of each parasite species to treatments and probably to other unmeasured factors related to characteristics of human populations and environmental issues. Clinicians therefore need to be aware that evidence obtained in geographical regions with at least a different prevalent parasite species can not be directly applicable in all of the endemic regions.

The point estimate for systemic antimonial treatment in people with CL reveals that clinicians may expect a cure in up to 80% of cases. This is suboptimal, and a constant stimulus to producing new evidence with therapeutic alternatives. Data on systemic antimonials use in people with ML is scarce, with only two of the eight studies that included participants with ML or MCL assessing this class of treatment. The confidence intervals for effectiveness estimates from these study results were wide, precluding us from drawing any conclusions.

In *L. mexicana*, *L. panamensis,* and *L. braziliensis* infections in ACL compared to placebo, oral miltefosine probably improves the likelihood of complete cure and probably increases the risk of nausea and vomiting (moderate-certainty evidence). However, miltefosine may make little to no difference to recurrence rates (low-certainty evidence), but the 95% CI includes the possibility of both increased and decreased risk.

Based on low-certainty evidence, when compared to meglumine antimoniate (MA), oral miltefosine may make little to no difference to the likelihood of complete cure. We found moderate-certainty evidence that oral miltefosine probably increases the risk of nausea and vomiting. Recurrence was not reported. These results are based on *L. braziliensis*, *L. panamensis*, *L. guyanensis* and *L. amazonensis* infections in ACML.

We found moderate-certainty evidence that azithromycin, a candidate for oral treatment, probably reduces the likelihood of complete cure in *L. braziliensis* infections in ACML. Recurrence was not reported, and we could not calculate the risk of adverse effects.

The most notable feature of the current review is the phenomenon of emerging topical, local and combination therapies, some of them revisiting old modalities such as injected antimonials or thermotherapy, and newer therapies such as the association of pentoxifylline with antimonials.

Moderate-certainty evidence indicates that compared to MA, pentoxifylline combined with intramuscular meglumine antimoniate (IMMA) probably makes little to no difference to the likelihood of complete cure for CL. Risk of recurrence was not reported, and we could not calculate the risk of adverse effects.

Thermotherapy emerged as an alternative intervention, with the aim of avoiding systemic toxicity. We found high-certainty evidence that thermotherapy reduces the likelihood of complete cure *in L. panamensis* and L. *braziliensis* infections in ACL when compared with IMMA. Risk of recurrence was not reported, and we could not calculate the risk of adverse effects.

Evidence on the use of topical or locally-injected treatments for CL including: imiquimod, nitric oxide patch, intralesional GM-CSF and subcutaneous interferon gamma are scarce, precluding us from drawing any conclusions.

Intralesional infiltration of antimonials has been used for more than three decades across the continent, and has been included as an acceptable treatment modality, despite the lack of standardisation of the procedures for its application and therapeutic scheme.

Moderate-certainty evidence indicates that in *L. braziliensis* and *L. panamensis* infections in ACML, IMMA may increase the likelihood of complete cure, but may also make little to no difference, since the 95% CI includes the possibilities of both increased and decreased healing. IMMA probably leads to more severe adverse effects such as arthralgia and myalgia (moderate-certainty evidence), and may make little to no difference to the risk of recurrence, but the 95% CI includes the possibilities of both increased and decreased risk (low-certainty evidence).

In *L. braziliensis, L. guyanensis* and *L. peruviana* infections in ACL, topical imiquimod combined with intravenous meglumine antimoniate (IVMA) probably makes little to no difference to the likelihood of complete cure (moderate-certainty evidence). The studies in this comparison did not measure risk of recurrence, and we could not calculate the risk of adverse effects.

The dearth of evidence on the treatment of the mucosal form of leishmaniasis precludes any conclusion on the comparative

efficacy/effectiveness of the available therapeutic modalities. The referral of people with mucosal leishmaniasis to a reference treatment centre would allow clinicians to take advantage of the centre's expertise in dealing with this rare clinical presentation. Our review highlights the need to explore prognosis in people with leishmaniasis because most of the studies, as is usual in RCTs, preclude the possibility of drawing conclusions applicable to younger children and the oldest adults, mainly those above 50 years. From the reviewed RCTs, there is no evidence of sex as a prognostic factor among people with CL or MCL.

The 10 studies in Studies awaiting classification, once assessed, may alter the conclusions of the review.

Implications for research

This review identifies an urgent need to improve the quality of future clinical trials to correct the lacunae identified in most of the current evidence. The main pitfalls are the lack of accurate and reliable diagnosis of parasite species affecting study participants, low-powered trials to prove efficacy/effectiveness, and lack of standardised endpoints measured at standardised follow-up periods.

Parasite species identification remains a crucial point to understand the large heterogeneity of efficacy estimations for the same treatments in different geographic areas. It seems that some progress has been made to improve the molecular diagnostic assays to achieve this goal, but the challenge of reaching consensus on what specific methodologies and targets should be the standard reference for clinical trials is still lacking. Development and implementation of feasible point-of-care molecular assays should be prioritised. A consensus is urgently needed on this issue to overcome this barrier.

Adequately-powered trials will be challenged by a growing understanding of the inappropriateness of using placebo in participants affected by American cutaneous leishmaniasis. The last Cochrane Review in this field concluded that "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." Since then, a systematic review on the controversial approach of using placebo as the comparator in clinical trials evaluating efficacy of treatments against American leishmaniasis concluded that the disease had "a low spontaneous cure rate following no-treatment or placebo use, confirming that this strategy for the control group in CL studies exposes patients to greater morbidity, especially for CL caused by L. braziliensis" (Cota 2016). Further developments will be impacted by the placebo issue, considering that trials conducted with the use of active comparators would require greater numbers of participants to prove efficacy/effectiveness, and longer follow-up to assess the risk of relapse or risk for mucosal disease. However, the evidence cited above constitutes a strong point to sustain a recommendation against the use of placebo.

Fortunately, the heterogeneity (due to the lack of standardised parameters for endpoint definition) and time-to-endpoint follow-up has recently been assessed, and a promising consensus has been achieved on cutaneous leishmaniasis (Olliaro 2018). Similar efforts should be prioritised for the more challenging mucosal disease presentation. It was clear that long-term follow-up looking at estimations of recurrence rate is currently absent. Although it is comprehensible that long-term follow-up means a huge financial and logistic investment for most researchers, precluding the likelihood of such endpoints, sponsors need to be receptive to such needs. Investments in better and effective surveillance systems co-operating with research centres could also be explored.

The scarring process could leave disfiguring sequelae. This could be extremely relevant for people with facial lesions, potentially affecting their quality of life. However, studies of this specific aspect of the disease are scarce, reflecting again its neglected character. Also, standardised instruments evaluating quality-of-life aspects in people with American cutaneous leishmaniasis are not yet fully validated (Galvão 2019). Endpoints for quality of life could therefore be included in future RCTs, at least in Brazil, where a promising instrument has recently been developed specifically for cutaneous leishmaniasis (Galvão 2018). Our review has not found RCTs on methods used in promoting wound-healing as a form of care of cutaneous leishmaniasis. The incorporation of evaluation tools such as the Burn Scar Index, often called the Vancouver Scar Scale (Baryza 1995), was not covered in the reported trials. The validation of those scales in the populations affected by leishmaniasis could allow their incorporation as effective tools for measuring long-term endpoints linked to quality of life in future RCTs.

A thorough discussion on the adequacy of using antimonials as the active comparator in RCTs for both cutaneous and mucosal diseases should be raised, because of their obvious inadequate pharmacological and toxicity profile**.** The current evidence on miltefosine and local therapies against cutaneous leishmaniasis seems to merit at least starting the appropriate debate on better comparators for future RCTs.

Treatment effectiveness evaluation through large-scale pragmatic trials should be considered as a medium-term goal for the more promising interventions. This is an essential and currently unmet step in the final development of those interventions. As stated above, the co-operation of researchers with other partners inside the health systems taking care of the affected populations could permit the conduct of that type of challenging trial. Those pragmatic trials would be extremely useful in producing real-world estimations of effectiveness, and an opportunity for adequate costing procedures, answering the critics of the piggy-back cost-effectiveness studies based on data from conventional RCTs.

All the effort invested in better trials producing more accurate and reliable efficacy/effectiveness estimations will be wasted if future trials are not considered as an essential but not a sufficient part of a complete development project which starts with a well-defined product target profile. This is a very challenging situation for the common scenario of drug re-purposing, looking for therapeutic alternatives for leishmaniasis, and a strong rationale should be used when the intervention includes such an approach (Jin 2014).

Prognosis and access issues are essential and should also be considered as research targets. Prognostic factors or at least prognostic markers are poorly understood in cutaneous and mucosal disease in Latin America. RCTs constitute an opportunity to identify prognostic factors, although exclusion criteria limit the external validity of such studies nested in RCTs. Future trials, ideally pragmatic ones, should offer the opportunity of identifying the main prognostic factors. Among these, parasite resistance

should also be explored. It is time for the establishment of an effective network for monitoring this phenomenon. Miltefosine and newer drugs should be properly monitored for the emergence of resistance. Finally, access deserves some dedicated research, in order to guarantee better options to make the therapies available to the affected population as soon as they are proved efficacious.

Last but not least, it is time to think about the development of safer alternatives for women of childbearing age, for those with co-morbid conditions, and in immuno-compromised patients. Pragmatic trials could bring the opportunity to increase knowledge about the effectiveness and safety profiles of the current therapeutic alternatives for these vulnerable populations, improving the equity of the research.

ACKNOWLEDGEMENTS

We would like to thank the people who co-authored the previous version of this systematic review.

The Cochrane Skin editorial base wishes to thank Urbà González who was the Key Editor for this updated review; Ching-Chi Chi who was the Methods Editor; Tarek Turk and Sandra Muvdi who were the clinical referees; Kate Cahill who copy-edited the review; and Nicole Pitcher who wrote the plain language summary, with support from Elizabeth Royle.

REFERENCES

References to studies included in this review

Almeida 1999 *{published data only}*

Almeida R, D'Oliveira A Jr, Machado P, Bacellar O, Ko AI, de Jesus AR, et al. Randomized, double-blind study of stibogluconate plus human granulocyte macrophage colony stimulating factor versus stibogluconate alone in the treatment of cutaneous leishmaniasis. *Journal of Infectious Diseases* 1999;**180**(5):1735-7. [CENTRAL: CN-00266553]

Alves 2016 *{published data only}*

Alves FHC, E Silva JSF, De Araujo Pereira LI, De Paula CDR, Ribeiro RN, Gomes CM, et al. The efficacy of pentamidine in comparison to pentavalent antimonial in American tegumentary leishmaniasis: an open label, randomized, controlled trial. *Journal of the American Academy of Dermatology* 2016;**74**(5 Suppl 1):AB155. [CENTRAL: CN-01160654]

Alves Noroes 2015 *{published data only}*

* Alves Norões IJ, Moraes MO, Silva Feitosa TT, Bonilha de Souza LS, Gonçalves Júnior J, Rolim-Neto ML, et al. Avaliation the therapeutic efficacy of fluconazol. *International Archives of Medicine* 2015;**8**(135):1-16. [DOI: 10.3823/1734]

Lima da Silva CG. Avaliaçao da eficácia terapêutica do fluconazol na leishmaniose tegumentar humana [Doctoral hesis]. Faculdade de Medicina, Fortaleza, Brazil: Universidade Federal do Ceará, 2012.

Andersen 2005 *{published data only}*

Andersen EM, Cruz-Saldarriaga M, Llanos-Cuentas A, Luz-Cjuno M, Echevarria J, Miranda-Verasategui C, et al. Comparison of meglumine and pentamidine for Peruvian cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2005;**72**(2):133-7. [CENTRAL: CN-00502527]

Arana 1994 *{published data only}*

Arana BA, Navin TR, Arana FE, Berman JD, Rosenkaimer F. Efficacy of a short course (10 days) of high-dose meglumine antimoniate with or without Interferon-gamma in treating cutaneous leishmaniasis in Guatemala. *Clinical Infectious Diseases* 1994;**18**(3):381-4. [CENTRAL: CN-00102358]

Arana 2001 *{published data only}*

Arana BA, Mendoza CE, Rizzo NR, Kroeger A. Randomized, controlled, double-blind trial of topical treatment of cutaneous leishmaniasis with the paromomycin plus methylbenzethonium chloride ointment in Guatemala. *American Journal of Tropical Medicine and Hygiene* 2001;**65**(5):466-70. [CENTRAL: CN-00375557]

Arévalo 2007 *{published data only}*

Arévalo I, Tulliano G, Quispe A, Spaeth G, Mathlashewski, Llanos-cuantas A, et al. Role of imiquimod and parenteral meglumine antimoniate in the intitial treatment of cutaneous lesihmaniasis. *Clinical Infectious Diseases* 2007;**44**(12):1549-54. [CENTRAL: CN-00589061]

Armijos 2004 *{published data only}*

Armijos RX, Weigel MM, Calvopiña M, Mancheno M, Rodriguez R. Comparison of the effectiveness of two topical paromomycin treatments versus meglumine antimoniate for New World cutaneous leishmaniasis. *Acta Tropica* 2004;**91**(2):153-60. [CENTRAL: CN-00480899]

Ballou 1987 *{published data only}*

Ballou WR, McClain JB, Gordon DM, Dhanks GD, Adujar J, Berman JD, et al. Safety and efficacy of high-dose sodium stibogluconate therapy of American cutaneous leishmaniasis. *Lancet* 1987;**4**(8549):13-6. [CENTRAL: CN-00048758]

Brito 2014 *{published data only}*

Brito G, Dourado M, Polari L, Celestino D, Carvalho LP, Queiroz A, et al. Clinical and immunological outcome in cutaneous leishmaniasis patients treated with pentoxifylline. *American Journal of Tropical Medicine and Hygiene* 2014;**90**(4):617-20. [CENTRAL: CN-00984312]

Brito 2017a *{published data only}*

Brito G, Dourado M, Guimaraes L, Meireles E, Schriefer A, Carvalho E, et al. Oral pentoxifylline associated with pentavalent antimony: a randomized trial for cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2017;**96**(5):1155-9. [CENTRAL: CN-01373250]

Chico 1995 *{published data only}*

Chico M, Armijos R, Racines J, Mancero T, Guderian RH. Evaluation of allopurinol-riboside therapy against Ecuadorian cutaneous leishmaniasis [Evaluación del ribósido de alpurinol contra la leishmaniasis cutánea ecuatoriana]. *Biomedica* 1995;**15**(3):116-22. [DOI: 10.7705/biomedica.v15i3.868]

Chrusciak-Talhari 2011 *{published data only}*

Chrusciak-Talhari A, Dietze R, Chrusciak Talhari C, Da Silva RM, Gadelha Yamashita EP, De Oliveira Penna G, et al. Randomized controlled clinical trial to access efficacy and safety of miltefosine in the treatment of cutaneous leishmaniasis caused by Leishmania (Viannia) guyanensis in Manaus, Brazil. *American Journal of Tropical Medicine and Hygiene* 2011;**84**(2):255-60. [CENTRAL: CN-00778313]

Convit 1987 *{published data only}*

Convit J, Castellanos PL, Rondon A, Pinardi ME, Ulrich M, Castes M, et al. Immunotherapy versus chemotherapy in localised cutaneous leishmaniasis. *Lancet* 1987;**21**(8530):401-5. [CENTRAL: CN-00046375]

Convit 1989 *{published data only}*

Convit J, Castellanos PL, Ulrich M, Castés M, Rondón A, Pinardi ME, et al. Immunotherapy of localized, intermediate, and diffuse forms of American cutaneous leishmaniasis. *Journal of Infectious Diseases* 1989;**160**(1):104-15. [CENTRAL: CN-00060507]

Correia 1996 *{published data only}*

Correia D, Macêdo VO, Carvalho EM, Barral A, Magalhães AV, De Abreu MV, et al. Comparative study of meglumine antimoniate,

pentamidine isothionate and aminosidine sulphate in the treatment of primary skin lesions caused by Leishmania (viannia) braziliensis. *Revista da Sociedade Brasilera de Medicina Tropical* 1996;**29**(5):447-53. [CENTRAL: CN-00132502]

Cossio-Duque 2015 *{published data only}*

Cossio-Duque A, Mar CM, Navas A, Valderrama L, Cuervo-Pardo L, Marquez R, et al. Effect of the addition of pentoxifylline on the therapeutic and inflammatory response in patients with cutaneous leishmaniasis: a randomized placebo controlled trial. *Frontiers* 2015;**93**(4 Suppl):536. [CENTRAL: CN-01249729]

D'Oliveira 1997 *{published data only}*

D'Oliveira A Jr, Machado PR, Carvalho EM. Evaluating the efficacy of allopurinol for treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 1997;**36**(12):938-40. [CENTRAL: CN-00147570]

Echevarria 2006 *{published data only}*

Echevarria J, Seas C, Cruz M, Chavez E, Campos M, Cieza J, et al. Oral rehydration solution to prevent nephrotoxicity of amphotericin B. *American Journal of Tropical Medicine and Hygiene* 2006;**75**(6):1108-12. [CENTRAL: CN-00577315]

Ferreira 2014 *{unpublished data only}*

Ferreira Terceiro BR. Comparação entre o esquema padrão e alternativo de antimoniato de meglumina no tratamento da leishmaniose mucocutânea ou mucosa [Comparison of the standard scheme and alternative meglumine antimoniate in the treatment of leishmaniasis mucocutaneous or mucosal] [Masters thesis]. Rio de Janeiro: Instituto Nacional de Infectologia Evandro Chagas, 2014. [lil-751645]

Figueiredo 1999 *{published data only}*

Figueiredo Kopke LF, Siviero do Vale EC, Grossi Araujo M, Araújo Magalhães P, Furtado T. Treatment of American cutaneous leishmaniasis by N-methyl-glucamine. Double-blind study with dosages of 14 mg/kg/day and 28 mg/kg/day of antimony [Tratamento da leishmaniose tegumentar americana pelo antimoniato de N-metil-glucamina: Estudo duplo-cego com doses de 14 mg/kg/dia e 28 mg/kg/dia de antimônio]. *Anais Brasileiros de Dermatologia* 1991;**66**(2):87-94. [CENTRAL: CN-00187782] [EMBASE: 21169232]

Franke 1994 *{published data only}*

Franke ED, Llanos-Cuentas A, Echevarria J, Cruz ME, Campos P, Tovar AA, et al. Efficacy of 28-day and 40-day regimens of sodium stibogluconate (pentostam) in the treatment of mucosal leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 1994;**51**(1):77-82. [CENTRAL: CN-00103648]

Gadelha 2018 *{published data only}*

Gadelha EP, Ramasawmy R, Da Costa Oliveira B, Morais Rocha N, De Oliveira Guerra JA, Allan Villa Rouco da Silva G, et al. An open label randomized clinical trial comparing the safety and effectiveness of one, two or three weekly pentamidine isethionate doses (seven milligrams per kilogram) in the treatment of cutaneous leishmaniasis in the Amazon Region. *PLOS Neglected Tropical Diseases* 2018;**12**(10):e0006850.

Garcia 2014 *{published data only}*

Garcia Bustos MF, Barrio A, Parodi C, Beckar J, Moreno S, Basombrio MA. Miltefosine versus meglumine antimoniate in the treatment of mucosal leishmaniasis. *Medicina* 2014;**74**(5):371-7. [CENTRAL: CN-01089869]

Guderian 1991 *{published data only}*

Guderian RH, Chico ME, Rogers MD, Pattishall KM, Grogl M, Berman JD. Placebo controlled treatment of Ecuadorian cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 1991;**45**(1):92-7. [CENTRAL: CN-00077349]

Guzman-Rivero 2014 *{published data only}*

Guzman-Rivero M, Rojas E, Verduguez-Orellana A, Pardo H, Torrico MC, Cloetens L, et al. Nutritional status in patients with cutaneous leishmaniasis and a study of the effects of zinc supplementation together with antimony treatment. *Food & Nutrition Research* 2014;**58**:23353. [CENTRAL: CN-01072233] [DOI: 10.3402/fnr.v58.23353]

Hepburn 1994 *{published data only}*

Hepburn NC, Tidman MJ, Hunter JA. Aminosidine (paromomycin) versus sodium stibogluconate for the treatment of American cutaneous leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994;**88**(6):700-3. [CENTRAL: CN-00111782]

Hu 2015 *{published data only}*

Hu RV, Straetemans M, Kent AD, Sabajo LO, De Vries HJ, Fat RF. Randomized single-blinded non-inferiority trial of 7 mg/kg pentamidine isethionate versus 4 mg/kg pentamidine isethionate for cutaneous leishmaniaisis in Suriname. *PLOS Neglected Tropical Diseases* 2015;**9**(3):e0003592. [CENTRAL: CN-01256791]

Krolewiecki 2007 *{published data only}*

Krolewiecki AJ, Romero HD, Cajal SP, Abraham D, Mimori T, Matsumoto T, et al. A randomized clinical trial comparing oral azithromycin and meglumine antimoniate for the treatment of American cutaneous leishmaniasis caused by Leishmania (Viannia) braziliensis. *American Journal of Tropical Medicine and Hygiene* 2007;**77**(4):640-6. [CENTRAL: CN-00620647]

Llanos-Cuentas 1997 *{published data only}*

Llanos-Cuentas A, Echevarria J, Cruz M, La Rosa A, Campos P, Campos M, et al. Efficacy of sodium stibogluconate alone and in combination with allopurinol for treatment of mucocutaneous leishmaniasis. *Clinical Infectious Diseases* 1997;**25**(3):677-84. [CENTRAL: CN-00143908]

Llanos-Cuentas 2007 *{published data only}*

Llanos-Cuentas A, Echevarria J, Seas C, Chang E, Cruz M, Alvarez E, et al. Parenteral aminosidine is not effective for peruvian mucocutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2007;**76**(6):1128-31. [CENTRAL: CN-00703926]

Lobo 2006 *{published data only}*

Lobo IM, Soares MB, Correia TM, De Freitas LA, Oliveira MI, Nakatani M, et al. Heat therapy for cutaneous leishmaniasis elicits a systemic cytokine response similar to that of antimonial

(Glucantime) therapy. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2006;**100**(7):642-9. [CENTRAL: CN-00561435]

López 2018 *{published data only}*

López L, Vélez I, Asela C, Cruz C, Alves F, Robledo S, et al. A phase II study to evaluate the safety and efficacy of topical 3% amphotericin B cream (Anfoleish) for the treatment of uncomplicated cutaneous leishmaniasis in Colombia. *PLOS Neglected Tropical Disiseases* 2018;**12**(7):e0006653.

Lopez-Jaramillo 2010 *{published data only}*

Lopez-Jaramillo P, Rincon MY, Garcia RG, Silva SY, Smith E, Kampeerapappun P, et al. A controlled, randomized-blinded clinical trial to assess the efficacy of a nitric oxide releasing patch in the treatment of cutaneous leishmaniasis by Leishmania (V.) panamensis. *American Journal of Tropical Medicine and Hygiene* 2010;**83**(1):97-101. [CENTRAL: CN-00749347]

Machado 2007 *{published data only}*

Machado PR, Lessa H, Lessa M, Guimaraes LH, Bang H, Ho JL, et al. Oral pentoxifylline combined with pentavalent antimony: a randomized trial for mucosal leishmaniasis. *Clinical Infectious Diseases* 2007;**44**(6):788-93. [CENTRAL: CN-00578520]

Machado 2010 *{published data only}*

Machado PR, Ampuero J, Guimaraes LH, Schriefer A, Carvalho EM, Talhari S, et al. Efficacy of miltefosine in the treatment of American cutaneous leishmaniasis caused by leishmania braziliensis in Brazil. *PLOS Neglected Tropical Diseases* 2010;**4**(12):e912. [DOI: 10.4269/ajtmh.2009.81.201]

Machado 2018 *{published data only}*

Machado PR, Ribeiro CS, França-Costa J, Dourado ME, Trinconi CT, Yokoyama-Yasunaka JK, et al. Tamoxifen and meglumine antimoniate combined therapy in cutaneous leishmaniasis patients: a randomised trial. *Tropical Medicine & International Health* 2018;**23**(9):936-42.

Machado-Pinto 2002 *{published data only}*

Machado-Pinto J, Pinto J, Da Costa CA, Genaro O, Marques MJ, Modabber F, et al. Immunochemotherapy for cutaneous leishmaniasis: a controlled trial using killed Leishmania (Leishmania) amazonensis vaccine plus antimonial. *International Journal of Dermatology* 2002;**41**(2):73-8. [CENTRAL: CN-00389013]

Martínez 1992 *{published data only}*

Martínez S, Marr J. Allopurinol in the treatment of American cutaneous leishmaniasis. *New England Journal of Medicine* 1992;**326**(11):741-4. [CENTRAL: CN-00081583]

Martínez 1997 *{published data only}*

Martínez S, Gonzalez M, Vernaza ME. Treatment of cutaneous leishmaniasis with allopurinol and stibogluconate. *Clinical Infectious Diseases* 1997;**24**(2):165-9. [CENTRAL: CN-00138905]

Miranda-Verástegui 2005 *{published data only}*

Miranda-Verástegui C, Llanos-Cuentas A, Arévalo I, Ward BJ, Matlashewski G. Randomized, double-blind clinical trial of topical imiquimod 5% with parenteral meglumine antimoniate in the treatment of cutaneous leishmaniasis in Peru. *Clinical Infectious Diseases* 2005;**40**(10):1395-403. [CENTRAL: CN-00560657]

Miranda-Verástegui 2009 *{published data only}*

Miranda-Verástegui C, Tulliano G, Gyorkos TW, Calderon W, Rahme E, Ward B, et al. First-line therapy for human cutaneous leishmaniasis in Peru using the TLR7 agonist imiquimod in combination with pentavalent antimony. *PLOS Neglected Tropical Diseases* 2009;**3**(7):e491. [CENTRAL: CN-00729032]

Navin 1990 *{published data only}*

Navin TR, Arana BA, Arana FE, De Mérida AM, Castillo AL, Pozuelos JL. Placebo-controlled clinical trial of meglumine antimoniate (glucantime) versus localized controlled heat in the treatment of cutaneous leishmaniasis in Guatemala. *American Journal of Tropical Medicine and Hygiene* 1990;**42**(1):43-50. [CENTRAL: CN-00065499]

Navin 1992 *{published data only}*

Navin TR, Aran BA, Arana FE, Berman JD, Chajón JF. Placebo-controlled clinical trial of sodium stibogluconate (pentostam) versus ketoconazole for treating cutaneous leishmaniasis in Guatemala. *Journal of Infectious Diseases* 1992;**165**(3):528-34. [CENTRAL: CN-00081938]

NCT01011309 *{published data only}*

NCT01011309. A study of the efficacy and safety of the LEISH-F2 + MPL-SE vaccine for treatment of cutaneous leishmaniasis [A phase 2, randomized, open-label, controlled study to evaluate the efficacy, safety, and immunogenicity of the LEISH-F2 + MPL-SE vaccine in the treatment of patients with cutaneous leishmaniasis]. clinicaltrials.gov/ct2/show/study/NCT01011309 (first received 11 November 2009).

Neva 1997 *{published data only}*

Neva FA, Ponce C, Ponce E, Kreutzer R, Modabber F, Olliaro P. Non-ulcerative cutaneous leishmaniasis in Honduras fails to respond to topical paromomycin. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1997;**91**(4):473-5. [CENTRAL: CN-00145412]

Neves 2011 *{published data only}*

Neves LO, Talhari AC, Gadelha EP, Silva Junior RM, Guerra JA, Ferreira LC, et al. A randomized clinical trial comparing meglumine antimoniate, pentamidine and amphotericin B for the treatment of cutaneous leishmaniasis by Leishmania guyanensis. *Anais Brasileiros de Dermatologia* 2011;**86**(6):1092-101. [CENTRAL: CN-00842795]

Newlove 2011 *{published data only}*

Newlove T, Guimaraes LH, Morgan DJ, Alcantara L, Glesby MJ, Carvalho EM, et al. Antihelminthic therapy and antimony in cutaneous leishmaniasis: a randomized, double-blind, placebo-controlled trial in patients co-infected with helminths and Leishmania braziliensis. *American Journal of Tropical Medicine and Hygiene* 2011;**84**(4):551-5. [CENTRAL: CN-00788444]

Oliveira-Neto 1997 *{published data only}*

Oliveira-Neto MP, Schubach A, Mattos M, Gonçalves-Costa SC, Pirmez C. Treatment of American cutaneous leishmaniasis: a comparison between low dosage (5mg/kg/day) and high dosage (20 mg/kg/day) antimony regimens [Traitement de la leishmanoise cutanee americaine: une comparison entre faible dose (5mg/kg/jour) et haute dose (20mg/kg/jour) d'antimoine]. *Pathologie-biologie* 1997;**45**(6):496-9. [CENTRAL: CN-00254046]

Oster 1985 *{published data only}*

Oster CN, Chulay JD, Hendricks LD, Pamplin CL III, Ballou WR, Berman JD, et al. American cutaneous leishmaniasis: a comparison of three sodium stibogluconate treatment schedules. *American Journal of Tropical Medicine and Hygiene* 1985;**34**(5):856-60. [CENTRAL: CN-00039556]

Palacios 2001 *{published data only}*

Palacios R, Osorio LE, Grajales LF, Ochoa MT. Treatment failure in children in a randomized clinical trial with 10 and 20 days of meglumine antimoniate for cutaneous leishmaniasis due to leishmania viannia species. *American Journal of Tropical Medicine and Hygiene* 2001;**64**(3-4):187-93. [CENTRAL: CN-00349275]

Prates 2017 *{published data only}*

Prates FV, Dourado ME, Silva SC, Schriefer A, Guimarães LH, Brito MD, et al. Fluconazole in the treatment of cutaneous leishmaniasis caused by Leishmania braziliensis: a randomized controlled trial. *Clinical Infectious Diseases* 2017;**64**(1):67-71. [CENTRAL: CN-01444134]

Ravis 2013 *{published data only}*

Ravis WR, Llanos-Cuentas A, Sosa N, Kreishman-Deitrick M, Kopydlowski KM, Nielsen C, et al. Pharmacokinetics and absorption of paromomycin and gentamicin from topical creams used to treat cutaneous leishmaniasis. *Antimicrobial Agents and Chemotherapy* 2013;**57**(10):4809-15. [CENTRAL: CN-00916363]

Rubiano 2012 *{published data only}*

Rubiano LC, Miranda MC, Muvdi Arenas S, Montero LM, Rodríguez-Barraquer I, Garcerant D, et al. Noninferiority of miltefosine versus meglumine antimoniate for cutaneous leishmaniasis in children. *Journal of Infectious Diseases* 2012;**205**(4):684-92. [CENTRAL: CN-00814449]

Saenz 1987 *{published data only}*

Saenz RE, Paz HM, Johnson CM, Narvaez E, De Vasquez AM. Evaluation of the effectiveness and toxicity of pentostam and glucantime in the treatment of cutaneous leishmaniasis [Evaluación de la effectividad y toxicidad del pentostam y del glucantime en el tratamiento de la leishmaniasis cutanea]. *Revista Médica de Panamá* 1987;**12**(3):148-57. [CENTRAL: CN-01139764]

Saenz 1990 *{published data only}*

Saenz RE, Paz H, Berman JD. Efficacy of ketoconazole against leishmania braziliensis panamensis cutaneous leishmaniasis. *American Journal of Medicine* 1990;**89**(2):147-55. [CENTRAL: CN-00069419]

Saheki 2017 *{published data only}*

Lyra MR. Phase III clinical trial for American cutaneous leishmaniasis. Equivalence between high and low dose schemes of meglumine antimoniate [Masters thesis] [Ensaio clínico fase iii para leishmaniose tegumentar americana forma cutânea. Equivalência entre esquemas de alta e baixa dose de antimoniato de meglumina]. www.arca.fiocruz.br/handle/icict/14378 (accessed prior to 1 February 2019).

Ribeiro MN, Pimentel MI, Schubach Ade O, Oliveira R de V, Teixeira JL, Leite MP, et al. Factors associated with adherence to different treatment schemes with meglumine antimoniate in a clinical trial for cutaneous leishmaniasis. *Revista do Instituto de Medicina Tropical de Sao Paulo* 2014;**56**(4):291-6.

* Saheki MN, Lyra MR, Bedoya-Pacheco SJ, Antonio LF, Pimentel MIF, Salgueiro MM, et al. Low versus high dose of antimony for American cutaneous leishmaniasis: a randomized controlled blind non-inferiority trial in Rio de Janeiro, Brazil. *PLOS One* 2017;**12**(5):e0178592. [CENTRAL: CN-01413190]

Saheki MN. A randomized, controlled, single blind, non-inferiority trial of low dose versus high dose meglumine antimoniate for American cutaneous leishmaniasis in Rio de Janeiro, Brazil [Masters thesis] [Ensaio clínico de não inferioridade, randomizado, controlado, cego,de antimoniato de meglumina em dose baixa versus dose alta paraleishmaniose cutânea americana no Rio de Janeiro, Brasil]. www.arca.fiocruz.br/handle/icict/12458 (accessed prior to 1 February 2019).

Sampaio 2019 *{published data only}*

Sampaio RN, Silva Jsfe, Paula CD, Porto C, Motta Jocd, Pereira LI, et al. A randomized, open-label clinical trial comparing the long-term effects of miltefosine and meglumine antimoniate for mucosal leishmaniasis. *Revista da Sociedade Brasileira de Medicina Tropical* 2019;**52**:e20180292.

Santos 2004 *{published data only}*

Santos JB, De Jesus AR, Machado PR, Magalhâes A, Salgado K, Carvalho EM, et al. Antimony plus recombinant human granulocyte-macrophage colony-stimulating factor applied topically in low doses enhances healing of cutaneous leishmaniasis ulcers: a randomized, double-blind, placebo-controlled study. *Journal of Infectious Diseases* 2004;**190**(10):1793-6. [CENTRAL: CN-00492355]

Sosa 2013 *{published data only}*

Sosa N, Capitan Z, Nieto J, Nieto M, Calzada J, Paz H, et al. Randomized, double-blinded, phase 2 trial of wr 279,396 (paromomycin and gentamicin) for cutaneous leishmaniasis in Panama. *American Journal of Tropical Medicine and Hygiene* 2013;**89**(3):557-63. [CENTRAL: CN-00876215]

Sosa 2019 *{published data only}*

NCT01790659. Phase 3 study of Walter Reed (WR) 279,396 and paromomycin alone for the treatment of cutaneous leishmaniasis in Panama [A randomized, double-blind, pivotal phase 3 study of WR 279,396 (paromomycin + gentamicin topical cream) and paromomycin alone topical cream for the treatment of cutaneous leishmaniasis in Panama].

clinicaltrials.gov/ct2/show/study/NCT01790659 (first received 13 February 2013).

* Sosa N, Pascale JM, Jimenez AI, Norwood JA, Kreishman-Detrick M, Weina PJ, et al. Topical paromomycin for New World cutaneous leishmaniasis. *PLOS Neglected Tropical Diseases* 2019;**13**(5):e0007253.

Soto 1994a *{published data only}*

Soto J, Grogl M, Berman J, Olliaro P. Limited efficacy of injectable aminosidine as single-agent therapy for Colombian cutaneous leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994;**88**(6):695-8. [CENTRAL: CN-00111780]

Soto 1998 *{published data only}*

Soto J, Fuya P, Herrera R, Berman J. Topical paromomycin/methylbenzethonium chloride plus parenteral meglumine antimoniate as treatment for American cutaneous leishmaniasis: controlled study. *Clinical Infectious Diseases* 1998;**26**(1):56-8. [CENTRAL: CN-00147306]

Soto 2002 *{published data only}*

Soto JM, Toledo JT, Gutierrez P, Arboleda M, Nicholls RS, Padilla JR, et al. Treatment of cutaneous leishmaniasis with a topical antileishmanial drug (WR279396): phase 2 pilot study. *American Journal of Tropical Medicine and Hygiene* 2002;**66**(2):147-51. [CENTRAL: CN-00390421]

Soto 2004a *{published data only}*

Soto J, Valda-Rodriguez L, Toledo J, Vera-Navarro L, Luz M, Monasterios-Torrico H, et al. Comparison of generic to branded pentavalent antimony for treatment of new world cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2004;**71**(5):577-81. [CENTRAL: CN-00504004]

Soto 2004b *{published data only}*

Soto J, Arana BA, Toledo J, Rizzo N, Vega JC, Diaz A, et al. Miltefosine for new world cutaneous leishmaniasis. *Clinical Infectious Diseases* 2004;**38**(9):1266-72. [CENTRAL: CN-00470183]

Soto 2008 *{published data only}*

Soto J, Rea J, Balderrama M, Toledo J, Soto P, Valda L, et al. Efficacy of miltefosine for Bolivian cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2008;**78**(2):210-1. [CENTRAL: CN-00629911]

Soto 2013 *{published data only}*

Soto J, Rojas E, Guzman M, Verduguez A, Nena W, Maldonado M, et al. Intralesional antimony for single lesions of Bolivian cutaneous leishmaniasis. *Clinical Infectious Diseases* 2013;**56**(9):1255-60. [CENTRAL: CN-00877427]

Soto 2016a *{published data only}*

Soto J, Paz D, Rivero D, Soto P, Quispe J, Toledo J, et al. Intralesional pentamidine: a novel therapy for single lesions of Bolivian cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2016;**94**(4):852-6. [CENTRAL: CN-01154109]

Soto 2016b *{published data only}*

Soto J, Paz D, Rivero D, Soto P, Quispe J, Toledo J, et al. Intralesional pentamidine: a novel therapy for single lesions of Bolivian cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2016;**94**(4):852-6. [CENTRAL: CN-01154109]

Soto 2019 *{published data only}*

Soto J, Soto P, Ajata A, Luque C, Tintaya C, Paz D, et al. Topical 15% paromomycin-aquaphilic for Bolivian leishmania braziliensis cutaneous leishmaniasis: a randomized, placebo-controlled trial. *Clinical Infectious Diseases* 2019;**68**(5):844-9.

Souza 1998 *{published data only}*

Souza e Souza I, Lima IC, Alecrim JF. American cutaneous leishmaniasis: therapeutic study of pentamidine isotionate versus N-metil-glucantime. *Journal of the European Academy of Dermatology and Venereology : JEADV* 1998;**11**(Suppl 2):S153.

Toledo 2014 *{published data only}*

Toledo Junior A, Daher AB, Amaral TA, Carvalho SF, Romero GA, Rabello A. Poor response to azithromycin in cutaneous leishmaniasis leading to a premature interruption of a multicentric phase III clinical trial in Brazil. *Revista Da Sociedade Brasileira de Medicina Tropical* 2014;**47**(6):756-62. [CENTRAL: CN-01048573]

Vélez 1997 *{published data only}*

Vélez I, Agudelo S, Hendrickx E, Puerta J, Grogl M, Modabber F, et al. Inefficacy of allopurinol as monotherapy for Colombian cutaneous leishmaniasis: a randomized, controlled trial. *Annals of Internal Medicine* 1997;**126**(3):232-6. [CENTRAL: CN-00135976]

Vélez 2010 *{published data only}*

López L, Cruz C, Godoy G, Robledo SM, Vélez ID. Thermotherapy effective and safer than miltefosine in the treatment of cutaneous leishmaniasis in Colombia. *Revista do Instituto de Medicina Tropical de Sao Paulo* 2013;**55**(3):S0036-46652013000300197.

López L, Robayo M, Vargas M, Vélez ID. Thermotherapy. An alternative for the treatment of American cutaneous leishmaniasis. *Trials* 2012;**13**:58.

* Vélez I, Lopez L, Sanchez X, Mestra L, Rojas C, Rodriguez E. Efficacy of miltefosine for the treatment of American cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2010;**83**(2):351-6. [CENTRAL: CN-00760206]

References to studies excluded from this review

Armijos 2004B *{published data only}*

Armijos RX, Weigel MM, Calvopina M, Hidalgo A, Cevallos W, Correa J. Safety, immunogeneicity, and efficacy of an autoclaved leishmania amazonensis vaccine plus BCG adjuvant against New World cutaneous leishmaniasis. *Vaccine* 2004;**22**(9-10):1320-6. [CENTRAL: CN-00471149]

De Luca 1999 *{published data only}*

De Luca PM, Mayrink W, Alves CR, Coutinho SG, Oliveira MP, Bertho AL, et al. Evaluation of the stability and immunogenicity

of autoclaved and nonautoclaved preparations of a vaccine against American tegumentary leishmaniasis. *Vaccine* 1999;**17**(9-10):1179-85. [CENTRAL: CN-00305330]

De Luca 2001 *{published data only}*

De Luca PM, Mayrink W, Pinto JA, Coutinho SG, Santiago MA, Toledo VP, et al. A randomized double-blind placebo-controlled trial to evaluate the immunogenicity of a candidate vaccine against American tegumentary leishmaniasis. *Acta Tropica* 2001;**80**(3):251-60. [CENTRAL: CN-00375249]

De Luca 2003 *{published data only}*

De Luca PM, Mayrink W, Santiago MA, Nogueira R, Conceição-Silva F, Mélo G, et al. Randomized, double-blind, placebo-controlled study on the immunogenicity of the leishmanin skin test. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2003;**97**(6):709-12. [CENTRAL: CN-00551996]

Deps 2000 *{published data only}*

Deps PD, Viana MC, Falqueto A, Dietze R. Evaluation of the efficacy and toxicity of N-methyl-glucamine vs BP88 Sodium Stibogluconate in the treatment of localized cutaneous leishmaniasis. *Revista da Sociedade Brasileira de Medicina Tropical* 2000;**33**(6):535-43. [CENTRAL: CN-00399871]

Fagundes 2007 *{published data only}*

Fagundes A, Marzochi MC, Perez M, Schubach A, Ferreira A, Silva JP, et al. Skin reactivity to thimerosal and phenol-preserved Montenegro antigen in Brazil. *Acta Tropica* 2007;**101**(1):25-30. [CENTRAL: CN-00577747]

Falquete 2002 *{published data only}*

Falquete A, Sessa AP. Leishmaniose tegumentar americana. In: Veronesi R, Focaccia R, editors(s). Tratado de infectologia. São Paulo: Atheneu, 2002:1241-53.

Gardlo 2003 *{published data only}*

Gardlo K, Horska Z, Enk CD, Rauch L, Megahed M, Ruzicka T, et al. Treatment of cutaneous leishmaniasis by photodynamic therapy. *Journal of the American Academy of Dermatology* 2003;**48**(6):893-6. [CENTRAL: CN-00466020]

Hendrickx 1998 *{published data only}*

Hendrickx EP, Agudelo SP, Munoz DL, Puerta JA, Velez Bernal ID. Lack of efficacy of mefloquine in the treatment of New World cutaneous leishmaniasis in Colombia. *American Journal of Tropical Medicine and Hygiene* 1998;**59**(6):889-92. [PMID: 9886195]

Hepburn 1993 *{published data only}*

Hepburn NC, Tidman MJ, Hunter JA. Cutaneous leishmaniasis in British troops from Belize. *British Journal of Dermatology* 1993;**128**(1):63-8. [PMID: 8381299]

Hepburn 1994b *{published data only}*

Hepburn NC, Siddique I, Howie AF, Beckett GJ, Hayes PC. Hepatotoxicity of sodium stibogluconate therapy for American cutaneous leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994;**88**(4):453-5. [CENTRAL: CN-00119186]

Herwaldt 1992 *{published data only}*

Herwaldt BL, Arana BA, Navin TR. The natural history of cutaneous leishmaniasis in Guatemala. *Journal of Infectious Diseases* 1992;**165**(3):518-27. [PMID: 1538157]

Krause 1999 *{published data only}*

Krause G, Kroeger A. Topical paromomycin/methylbenzethonium chloride plus parenteral meglumine antimonate as treatment of American cutaneous leishmaniasis: controlled study. *Clinical Infectious Diseases* 1999;**29**(2):466-7. [PMID: 10476776]

Laguna-Torres 1999 *{published data only}*

Laguna-Torres VA, Silva CA, Correia D, Carvalho EM, Magalhães AV, De Oliveira Macêdo V. Efficacy of mefloquine in the treatment of skin leishmaniasis in an endemic area of leishmania (viannia) braziliensis. *Revista da Sociedade Brasileira de Medicina Tropical* 1999;**32**(5):529-32. [CENTRAL: CN-00414710]

Llanos 1991 *{published data only}*

Llanos A, Cieza J, Bernardo J, Echevarria J, Biaggioni I, Sabra R, et al. Effect of salt supplementation on amphotericin B nephrotoxicity. *Kidney International* 1991;**40**(2):302-8. [CENTRAL: CN-00079305]

Llanos-Cuentas 2010 *{published data only}*

Llanos-Cuentas A, Calderon W, Cruz M, Ashman JA, Alves FP, Coler RN, et al. A clinical trial to evaluate the safety and immunogenicity of the LEISH-F1+MPL-SE vaccine when used in combination with sodium stibogluconate for the treatment of mucosal leishmaniasis. *Vaccine* 2010;**28**(46):7427-35. [CENTRAL: CN-00768896]

Monjour 1994 *{published data only}*

Monjour L, Neogy AB, Vouldoukis I, Silva OA, Boisnic S, Brito ME, et al. Exploitation of parasite derived antigen in therapeutic success of human cutaneous leishmaniasis in Brazil. *Memórias do Instituto Oswaldo Cruz* 1994;**89**(3):479-83. [CENTRAL: CN-00118323]

Motta 2012 *{published data only}*

Motta JO, Sampaio RN. A pilot study comparing low-dose liposomal amphotericin B with N-methyl glucamine for the treatment of American cutaneous leishmaniasis. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2012;**26**(3):331-5. [CENTRAL: CN-00882917]

Nascimento 1990 *{published data only}*

Nascimento E, Mayrink W, Da Costa CA, Michalick MS, Melo MN, Barros GC, et al. Vaccination of humans against cutaneous leishmaniasis: cellular and humoral inmune responses. *Infection and Immunity* 1990;**58**(7):2198-203. [CENTRAL: CN-00068740]

Oliveira-Neto 2000 *{published data only}*

Oliveira-Neto MP, Mattos M, Primez C, Fernandes O, Gonçalves-Costa SC, Souza CF, et al. Mucosal leishmaniasis ("espundia") responsive to low dose of N-methyl glucantime in Rio de Janeiro, Brazil. *Revista do Instituto de Medicina Tropical de São Paulo* 2000;**42**(6):321-5. [CENTRAL: CN-00372731]

Rodriguez 1995 *{published data only}*

Rodriguez LV, Dedet JP, Paredes V, Mendoza C, Cardenas F. A randomized trial of amphotericin B alone or in combination with itraconazole in the treatment of mucocutaneous leishmaniasis. *Memórias do Instituto Oswaldo Cruz* 1995;**90**(4):525-8. [CENTRAL: CN-00121054]

Saldanha 2000 *{published data only}*

Saldanha AC, Romero GA, Guerra C, Merchan-Hamann E, Macedo Vde O. Comparative study between sodium stibogluconate BP 88 and meglumine antimoniate in cutaneous leishmaniasis treatment. II. Biochemical and cardiac toxicity. *Revista da Sociedade Brasileira de Medicina Tropical* 2000;**33**(4):383-8. [PMID: 10936953]

Soto 1994b *{published data only}*

Soto J, Buffet P, Grogl M, Berman J. Successful treatment of Colombian cutaneous leishmaniasis with four injections of pentamidine. *American Journal of Tropical Medicine and Hygiene* 1994;**50**(1):107-11. [CENTRAL: CN-00098861]

Soto 1995 *{published data only}*

Soto J, Hernandez N, Mejia H, Grogl M, Berman J. Successful treatment of New World cutaneous leishmaniasis with a combination of topical paromomycin/methylbenzethonium chloride and injectable meglumine antimonate. *Clinical Infectious Diseases* 1995;**20**(1):47-51. [CENTRAL: CN-00113359]

Soto-Mancipe 1993 *{published data only}*

Soto-Mancipe J, Grogl M, Berman JD. Evaluation of pentamidine for the treatment of cutaneous leishmaniasis in Colombia. *Clinical Infectious Diseases* 1993;**16**(3):417-25. [CENTRAL: CN-00091785]

Urcuyo 1982 *{published data only}*

Urcuyo FG, Zaias N. Oral ketoconazole in the treatment of leishmaniasis. *International Journal of Dermatology* 1982;**21**(7):414-6. [PMID: 6290403]

Veiga 1985 *{published data only}*

Veiga JP, Rosa TT, Kimachi T, Wolff ER, Sampaio RN, Gagliardi AR, et al. [Renal function in patients with mucocutaneous leishmaniasis treated with pentavalent antimony compounds]. *Revista do Instituto de Medicina Tropical de Sao Paulo* 1985;**27**(6):298-302. [PMID: 3014634]

Vélez 2005 *{published data only}*

Vélez ID, Gilchrist K, Arbelaez MP, Rojas CA, Puerta JA, Antunes CM, et al. Failure of a killed Leishmania amazonensis vaccine against American cutaneous leishmaniasis in Colombia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2005;**99**(8):593-8. [CENTRAL: CN-00521907]

Wortmann 2002 *{published data only}*

Wortmann G, Scoot Miller R, Oster C, Jackson J, Aronson N. A randomized, double-blind study of the efficacy of a 10- or 20-day course of sodium stibogluconate for treatment of cutaneous leishmaniasis in United States military personnel. *Clinical Infectious Diseases* 2002;**35**(3):261-7. [PMID: 12115091]

References to studies awaiting assessment

NCT00004755 *{published data only}*

NCT00004755. Allopurinol, glucantime, or allopurinol/glucantime for cutaneous leishmaniasis in Brazil [Phase II randomized study of allopurinol versus glucantime versus allopurinol/glucantime for cutaneous leishmaniasis in Brazil]. clinicaltrials.gov/ct2/show/record/NCT00004755 (first received 25 February 2000).

NCT00111514 *{published data only}*

NCT00111514. Study to evaluate the Leish-111F + MPL-SE vaccine in the treatment of mucosal leishmaniasis [A phase 1, randomized, 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 mucosal leishmaniasis]. clinicaltrials.gov/ct2/show/study/NCT00111514 (first received 23 May 2005).

NCT00111553 *{published data only}*

NCT00111553. Study to evaluate the Leish-111F + MPL-SE vaccine in the treatment of cutaneous leishmaniasis [Randomized, 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]. clinicaltrials.gov/ct2/show/study/NCT00111553 (first received 24 May 2005).

NCT00317980 *{published data only}*

NCT00317980. Safety and efficacy of low-dose pentavalent antimony for treatment of cutaneous leishmaniasis (Lowdosesb) [Phase IV randomized 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 Leishmania (Viannia) braziliensis]. clinicaltrials.gov/ct2/show/study/NCT00317980 (first received 25 April 2006).

NCT00973128 *{published data only}*

NCT0973128. Reduced doses of antimony plus ranulocyte monocyte colony stimulating factor (GM-CSF) for cutaneous leishmaniasis (GMCSFSbv) [Reduced doses of antimony plus recombinant human GM-CSF compared with antimony in standard doses for cutaneous leishmaniasis: a randomized, single-blind, placebo-controlled, pilot study]. clinicaltrials.gov/ct2/show/study/NCT0973128 (first received 9 September 2009).

NCT01380301 *{published data only}*

NCT01380301. Treatment of cutaneous leishmaniasis with a combination of miltefosine and antimony [Treatment of Bolivian cutaneous leishmaniasis with a combination of short courses of miltefosine and antimony]. clinicaltrials.gov/ct2/show/study/NCT01380301 (first received 27 June 2011).

NCT01380314 *{published data only}*

NCT01380314. Oral miltefosine plus topical imiquimod to treat cutaneous leishmaniasis [Treatment of Bolivian cutaneous leishmaniasis with a combination of oral miltefosine plus

topical imiquimod 5%]. clinicaltrials.gov/ct2/show/record/NCT01380314 (first received 27 June 2011).

NCT01464242 *{published data only}*

NCT01464242. Add-on study of pentoxifylline in cutaneous leishmaniasis (GT) [Therapeutic gain of adding the immunomodulator pentoxifylline to the treatment of cutaneous leishmaniasis]. clinicaltrials.gov/ct2/show/record/NCT01464242 (first received 3 November 2011).

NCT03294161 *{published data only}*

NCT03294161. Fourth-generation immucillin derivative DI4G associated therapy in cutaneous leishmaniasis [Transition-state analog inhibitor of human purine nucleoside phosphorylase as an adjunct in cutaneous leishmaniasis therapy: a randomized and controlled trial]. clinicaltrials.gov/ct2/show/study/NCT03294161 (first received 26 September 2017).

Silva 2006 *{published data only}*

Silva SY, Rueda LC, Lopez M, Velez ID, Rueda-Clausen CF, Smith DJ, et al. Double blind, randomized controlled trial, to evaluate the effectiveness of a controlled nitric oxide releasing patch versus meglumine antimoniate in the treatment of cutaneous leishmaniasis [NCT00317629]. *Trials* 2006;**7**:14. [PMID: 16700912]

References to ongoing studies

NCT00537953 *{published data only}*

NCT00537953. Short course of miltefosine and antimony to treat cutaneous leishmaniasis in Bolivia [Efficacy and safety of a short course of the combination of miltefosine and antimony to treat cutaneous leishmaniasis in Bolivia]. clinicaltrials.gov/ct2/show/study/NCT00537953 (first received 2 October 2007).

NCT01301937 *{published data only}*

NCT01301937. Low antimonial dosage in American mucosal leishmaniasis [Phase III clinical trial for mucosal or mucocutaneous leishmaniasis. Comparison between the standard and alternative antimonial schemes]. clinicaltrials.gov/ct2/show/study/NCT01301937 (first received 23 February 2011).

NCT02530697 *{published data only}*

NCT02530697. The association of miltefosine and pentoxifylline to treat mucosal leishmaniasis: a clinical trial in Brazil. clinicaltrials.gov/ct2/show/study/NCT02530697 (first received 21 August 2015).

NCT02687971 *{published data only}*

NCT02687971. Thermotherapy + a short course of miltefosine for the treatment of uncomplicated cutaneous leishmaniasis in the New World. clinicaltrials.gov/ct2/show/study/NCT02687971 (first received 23 February 2016).

NCT03023111 *{published data only}*

NCT03023111. Miltefosine and GM-CSF in cutaneous leishmaniasis: a randomized and controlled trial. clinicaltrials.gov/ct2/show/NCT03023111 (first received 18 January 2017).

NCT03084952 *{published data only}*

NCT03084952. Phase 2 trial to evaluate 18-methoxycoronaridine efficacy, safety and tolerability in cutaneous leishmaniasis patients. clinicaltrials.gov/ct2/show/study/NCT03084952 (first received 21 March 2017).

NCT03829917 *{published data only}*

NCT03829917. Oral miltefosine plus topical paromomycin In American cutaneous leishmaniasis. clinicaltrials.gov/show/nct03829917 (first received 1 August 2019).

NCT04072874 *{published data only}*

NCT04072874. Evaluation of the safety and clinical activity of Curaleish lotion and cream in the topical treatment of cutaneous leishmaniasis in Colombia. clinicaltrials.gov/ct2/show/NCT04072874 (first received 4 September 2019).

NTR2076 *{published data only}*

NTR2076. Treatment of cutaneous leishmaniasis with pentamidine isethionate in Suriname; a comparison study between two treatment regimes, 3 days vs 7 days [Clinical, parasitological and pharmaco-economical evaluation of a 3 days versus 7 days pentamidine isethionate regimen for cutaneous leishmaniasis in Suriname]. www.trialregister.nl/trialreg/admin/rctview.asp?TC=2076 (first received 25 September 2009).

PER-007-16 *{published data only}*

PER-007-16. A randomized, open label multicenter study to determine the efficacy and safety of combining thermotherapy and a short course of miltefosine for the treatment of uncomplicated cutaneous leishmaniasis in the New World. www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevo.asp?ver=EN&numEc=007-16 (first received 5 July 2016).

RBR-5r93wn *{published data only}*

RBR-5r93wn. Comparison of the effect and toxicity between two options for the treatment of Mucosal Leishmaniasis: miltefosin and Liposomal Anfotericin B. apps.who.int/trialsearch/Trial2.aspx?TrialID=RBR-5r93wn (first received 15 January 2018).

RBR-6mk5n4 *{published data only}*

RBR-6mk5n4. Multicentre study evaluating the efficacy and safety of Intralesional administration of Meglumine Antimoniate compared to systemic treatment for cutaneous leishmaniasis. www.ensaiosclinicos.gov.br/rg/RBR-6mk5n4/ (first received 8 November 2017).

Additional references

Abdeladhim 2014

Abdeladhim M, Kamhawi S, Valenzuela JG. What's behind a sand fly bite? The profound effect of sand fly saliva on host hemostasis, inflammation and immunity. *Infection, Genetics and Evolution* 2014;**28**:691-703.

Alcais 1997

Alcais A, Abel L, David C, Torrez ME, Flandre P, Dedet JP. Risk factors for onset of cutaneous and mucocutaneous leishmaniasis in Bolivia. *American Journal of Tropical Medicine and Hygiene* 1997;**57**(1):79-84.

Alexander 2009

Alexander B, Agudelo LA, Navarro JF, Ruiz J F, Molina J, Aguilera G, et al. Relationship between coffee cultivation practices in Colombia and exposure to infection with Leishmania. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2009;**103**(12):1263-8.

Almeida 2005

Almeida RP, Brito J, Machado PL, De Jesus AR, Schriefer A, Guimaraes LH, et al. Successful treatment of refractory cutaneous leishmaniasis with GM-CSF and antimonials. *American Journal of Tropical Medicine and Hygiene* 2005;**73**(1):79-81.

Almeida 2011

Almeida OL, Santos JB. Advances in the treatment of cutaneous leishmaniasis in the new world in the last ten years: a systematic literature review. *Anais Brasileiros de Dermatologia* 2011;**86**(3):497-506.

Alvar 2012

Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, Cano J, et al. Leishmaniasis worldwide and global estimates of its incidence. *PLOS One* 2012;**7**(5):e35671.

Alvar 2013

Alvar J, Croft S L, Kaye P, Khamesipour A, Sundar S, Reed SG. Case study for a vaccine against leishmaniasis. *Vaccine* 2013;**31**(Suppl 2):B244-9.

Amato 2007

Amato VS, Tuon FF, Siqueira AM, Nicodemo AC, Neto VA. Treatment of mucosal leishmaniasis in Latin America: systematic review. *American Journal of Tropical Medicine and Hygiene* 2007;**77**(2):266-74.

Ampuero 2006

Ampuero J, Macedo V, Marsden P. Clinical findings of tegumentary leishmaniasis in children under five years of age in an endemic area of Leishmania (Viannia) braziliensis. *Revista da Sociedade Brasileira de Medicina Tropical* 2006;**39**(1):22-6.

Arevalo 2007

Arevalo I, Tulliano G, Quispe A, Spaeth G, Matlashewski G, Llanos-Cuentas A, et al. Role of imiquimod and parenteral meglumine antimoniate in the initial treatment of cutaneous leishmaniasis. *Clinical Infectious Diseases* 2007;**44**(12):1549-54.

Aronson 2016

Aronson N, Herwaldt BL, Libman M, Pearson R, Lopez-Velez R, Weina P, et al. Diagnosis and treatment of leishmaniasis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). *Clinical Infectious Diseases* 2016;**63**(12):e202-64.

Badaro 2001

Badaro R, Lobo I, Nakatani M, Muinos A, Netto EM, Coler RN, et al. Successful use of a defined antigen/GM-CSF adjuvant vaccine to treat mucosal Leishmaniasis refractory to antimony: a case report. *Brazilian Journal of Infectious Diseases* 2001;**5**(4):223-32.

Barral 1995

Barral A, Costa JM, Bittencourt AL, Barral-Netto M, Carvalho EM. Polar and subpolar diffuse cutaneous leishmaniasis in Brazil: clinical and immunopathologic aspects. *International Journal of Dermatolology* 1995;**34**(7):474-9.

Baryza 1995

Baryza MJ, Baryza GA. The Vancouver Scar Scale: an administration tool and its interrater reliability. *Journal of Burn Care & Rehabilitation* 1995;**16**(5):535-38.

Beaumier 2013

Beaumier CM, Gillespie PM, Hotez PJ, Bottazzi ME. New vaccines for neglected parasitic diseases and dengue. *Translational Research* 2013;**162**(3):144-55.

Becker 1999

Becker I, Volkow P, Velasco-Castrejon O, Salaiza-Suazo N, Berzunza-Cruz M, Dominguez JS, et al. The efficacy of pentamidine combined with allopurinol and immunotherapy for the treatment of patients with diffuse cutaneous leishmaniasis. *Parasitology Research* 1999;**85**(3):165-70.

Berman 1981

Berman JD, Neva FA. Effect of temperature on multiplication of Leishmania amastigotes within monocyte-derived macrophages *in vitro*. *American Journal of Tropical Medicine and Hygiene* 1981;**30**:318-21.

Bern 2008

Bern C, Maguire JH, Alvar J. Complexities of assessing the disease burden attributable to leishmaniasis. *PLoS Neglected Tropical Diseases* 2008;**2**(10):e313.

Beyrer 2007

Beyrer C, Villar JC, Suwanvanichkij V, Singh S, Baral SD, Mills EJ. Neglected diseases, civil conflicts, and the right to health. *Lancet* 2007;**370**(9587):619-27.

Biagi 1953

Biagi F. Synthesis of 70 case histories of cutaneous leishmaniasis of Mexico (ulcer of the chicle gatherers). *Medicina (Mex)* 1953;**33**(682):385-96.

Bigby 2003

Bigby M, Williams H. Appraising systematic reviews and meta-analyses. *Archives of Dermatology* 2003;**139**(6):795-8.

Boggild 2008

Boggild AK, Miranda-Verastegui C, Espinosa D, Arevalo J, Martinez-Medina D, Llanos-Cuentas A, et al. Optimization of microculture and evaluation of miniculture for the isolation of Leishmania parasites from cutaneous lesions in Peru. *American Journal of Tropical Medicine and Hygiene* 2008;**79**(6):847-52.

Boggild 2010

Boggild AK, Ramos AP, Espinosa D, Valencia BM, Veland N, Miranda-Verastegui C, et al. Clinical and demographic stratification of test performance: a pooled analysis of five laboratory diagnostic methods for American cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2010;**83**(2):345-50.

Bomfim 2007

Bomfim G, Andrade BB, Santos S, Clarencio J, Barral-Netto M, Barral A. Cellular analysis of cutaneous leishmaniasis lymphadenopathy: insights into the early phases of human disease. *American Journal of Tropical Medicine and Hygiene* 2007;**77**(5):854-9.

Brito 2017b

Brito NC, Rabello A, Cota GF. Efficacy of pentavalent antimoniate intralesional infiltration therapy for cutaneous leishmaniasis: A systematic review. *PLoS One* 2017;**12**(9):e0184777.

Buates 1999

Buates S, Matlashewski G. Treatment of experimental leishmaniasis with the immunomodulators imiquimod and S-28463: efficacy and mode of action. *Journal of Infectious Diseases* 1999;**179**(6):1485-94.

Cardona-Arias 2015

Cardona-Arias JA, Vélez ID, Lopez-Carvajal L. Efficacy of thermotherapy to treat cutaneous leishmaniasis: a meta-analysis of controlled clinical trials. *PLOS One* 2015;**10**(5):e0122569.

Carvalho 2015

Carvalho AM, Cristal JR, Muniz AC, Carvalho LP, Gomes R, Miranda JC, et al. Interleukin 10-dominant immune response and increased risk of cutaneous leishmaniasis after natural exposure to lutzomyia intermedia sand flies. *Journal of Infectious Diseases* 2015;**212**(1):157-65.

Consigli 2006

Consigli J, Danielo C, Gallerano V, Papa M, Guidi A. Cutaneous leishmaniasis: successful treatment with itraconazole. *International Journal of Dermatolology* 2006;**45**(1):46-9.

Costa 1986

Costa JM, Marsden PD, Llanos-Cuentas EA, Netto EM, Carvalho EM, Barral A, et al. Disseminated cutaneous leishmaniasis in a field clinic in Bahia, Brazil: a report of eight cases. *Journal of Tropical and Medicine Hygiene* 1986;**89**(6):319-23.

Cota 2016

Cota GF, De Sousa MR, Fereguetti TO, Saleme PS, Alvarisa TK, Rabello A. The cure rate after placebo or no therapy in American cutaneous leishmaniasis: a systematic review and meta-analysis. *PLOS One* 2016;**11**(2):e0149697.

Covidence [Computer program]

Veritas Health Innovation Covidence. Melbourne, Australia: Veritas Health Innovation, accessed prior to 9 April 2019. Available at covidence.org.

Cummings 1997

Cummings AM, Hedge JL, Laskey J. Ketoconazole impairs early pregnancy and the decidual cell response via alterations in ovarian function. *Fundamental and Applied Toxicology* 1997;**40**(2):238-46.

Cupolillo 1994

Cupolillo E, Grimaldi G Jr, Momen H. A general classification of New World Leishmania using numerical zymotaxonomy. *American Journal of Tropical Medicine and Hygiene* 1994;**50**(3):296-311.

Cupolillo 2001

Cupolillo E, Aguiar Alves F, Brahim LR, Naiff MF, Pereira LO, Oliveira-Neto MP, et al. Recent advances in the taxonomy of the New World leishmanial parasites. *Medical Microbiology and Immunology* 2001;**190**(1-2):57-60.

Dantas 2014

Dantas ML, Oliveira JM, Carvalho L, Passos ST, Queiroz A, Guimaraes LH, et al. Comparative analysis of the tissue inflammatory response in human cutaneous and disseminated leishmaniasis. *Memórias do Instituto Oswaldo Cruz* 2014;**109**(2):202-9.

Davies 1997

Davies CR, Llanos-Cuentas EA, Campos P, Monge J, Villaseca P, Dye C. Cutaneous leishmaniasis in the Peruvian Andes: risk factors identified from a village cohort study. *American Journal of Tropical Medicine and Hygiene* 1997;**56**(1):85-95.

Davies 2000

Davies CR, Reithinger R, Campbell-Lendrum D, Feliciangeli D, Borges R, Rodriguez N. The epidemiology and control of leishmaniasis in Andean countries. *Cadernos de Saude Publica / Ministerio da Saude, Fundacao Oswaldo Cruz, Escola Nacional de Saude Publica* 2000;**16**(4):925-50.

De Lima 2009

De Lima H, Rodriguez N, Feliciangeli MD, Barrios MA, Sosa A, Agrela I, et al. Cutaneous leishmaniasis due to Leishmania chagasi/Le. infantum in an endemic area of Guarico State, Venezuela. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2009;**103**(7):721-6.

De Macedo-Silva 2013

De Macedo-Silva ST, Urbina JA, De Souza W, Rodrigues JC. In vitro activity of the antifungal azoles itraconazole and posaconazole against Leishmania amazonensis. *PLOS One* 2013;**8**(12):e83247.

Deeks 2019

Deeks JJ, Higgins JP, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions version

6.0 (updated July 2019). The Cochrane Collaboration, 2019. Available from www.training.cochrane.org/handbook.

Duthie 2012

Duthie MS, Raman VS, Piazza FM, Reed SG. The development and clinical evaluation of second-generation leishmaniasis vaccines. *Vaccine* 2012;**30**(2):134-41.

Edwards 2000

Edwards L. Imiquimod in clinical practice. *Journal of the American Academy of Dermatology* 2000;**43**(1 Pt 2):S12-7.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.

Enk 2015

Enk CD, Nasereddin A, Alper R, Dan-Goor M, Jaffe CL, Wulf HC. Cutaneous leishmaniasis responds to daylight-activated photodynamic therapy: proof of concept for a novel self-administered therapeutic modality. *British Journal of Dermatology* 2015;**172**(5):1364-70.

Evangelou 2011

Evangelou G, Krasagakis K, Giannikaki E, Kruger-Krasagakis S, Tosca A. Successful treatment of cutaneous leishmaniasis with intralesional aminolevulinic acid photodynamic therapy. *Photodermatology, Photoimmunology and Photomedicine* 2011;**27**(5):254-6.

FDA 2011

Food And Drug Administration Drug Safety Communication. Use of long-term, high-dose Diflucan (fluconazole) during pregnancy may be associated with birth defects in infants. www.fda.gov/Drugs/DrugSafety/ucm266030.htm (accessed prior to 23 January 2019).

FDA 2013

Food And Drug Administration Drug Safety Communication. Nizoral (ketoconazole) oral tablets: Potentially fatal liver injury, risk of drug interactions and adrenal gland problems. www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-limits-usage-nizoral-ketoconazole-oral-tablets-due-potentially (accessed 09 August 2020).

FDA 2014

Food And Drug Administration Drug Safety Communication. Sporanox (itraconazole) Oral Solution - Detailed view: Safety labeling changes approved by FDA Center for Drug Evaluation and Research (CDER). www.accessdata.fda.gov/drugsatfda_docs/label/2012/020657s027lbl.pdf (accessed prior to 23 January 2019).

FDA 2016

Food And Drug Administration Drug Safety Communication. FDA evaluating study examining use of oral fluconazole (Diflucan) in pregnancy. www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-study-examining-use-oral-fluconazole-diflucan-pregnancy (accessed prior to 23 January 2019).

Fernandez 2014

Fernandez OL, Diaz-Toro Y, Ovalle C, Valderrama L, Muvdi S, Rodriguez I, et al. Miltefosine and antimonial drug susceptibility of Leishmania Viannia species and populations in regions of high transmission in Colombia. *PLOS Neglected Tropical Diseases* 2014;**8**(5):e2871.

Fontenele e Silva 2013

Fontenele e Silva JS, Galvao TF, Pereira MG, Silva MT. Treatment of American tegumentary leishmaniasis in special populations: a summary of evidence. *Revista da Sociedade Brasileira de Medicina Tropical* 2013;**46**(6):669-77.

Fraga 2012

Fraga J, Veland N, Montalvo AM, Praet N, Boggild AK, Valencia BM, et al. Accurate and rapid species typing from cutaneous and mucocutaneous leishmaniasis lesions of the New World. *Diagnostic Microbiology and Infectious Disease* 2012;**74**(2):142-50.

Gallis 1990

Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. *Revews of Infectious Diseases* 1990;**12**(2):308-29.

Galvão 2017

Galvão EL, Rabello A, Cota GF. Efficacy of azole therapy for tegumentary leishmaniasis: a systematic review and meta-analysis. *PLOS One* 2017;**12**(10):e0186117.

Galvão 2018

Galvão EL, Pedras MJ, Cota GF, Simões TC, Rabello A. Development and initial validation of a cutaneous leishmaniasis impact questionnaire. PLOS One 2018;**13**(8):e0203378.

Galvão 2019

Galvão EL, Pedras MJ, Cota GF, Rabello A, Simões TC. How cutaneous leishmaniasis and treatment impacts in the patients' lives: a cross-sectional study. *PLOS One* 2019;**14**(1):e0211374.

Gomes 2015

Gomes CM, Mazin SC, Santos ER, Cesetti MV, Bachtold GA, Cordeiro JH, et al. Accuracy of mucocutaneous leishmaniasis diagnosis using polymerase chain reaction: systematic literature review and meta-analysis. *Memórias do Instituto Oswaldo Cruz* 2015;**110**(2):157-65.

González 2010

González U, Pinart M, Reveiz L, Rengifo-Pardo M, Tweed J, Macaya A, et al. Designing and reporting clinical trials on treatments for cutaneous leishmaniasis. *Clinical Infectious Diseases* 2010;**51**(4):409-19.

González 2015

González U, Pinart M, Sinclair D, Firooz A, Enk C, Vélez ID, et al. Vector and reservoir control for preventing leishmaniasis. *Cochrane Database of Systematic Reviews* 2015, Issue 8. Art. No: CD008736. [DOI: 10.1002/14651858.CD008736.pub2]

Graca 2012

Graca GC, Volpini AC, Romero GA, Oliveira Neto MP, Hueb M, Porrozzi R, et al. Development and validation of PCR-based assays for diagnosis of American cutaneous leishmaniasis and identification of the parasite species. *Memórias do Instituto Oswaldo Cruz* 2012;**107**(5):664-74.

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6.

Handler 2015

Handler MZ, Patel PA, Kapila R, Al-Qubati Y, Schwartz RA. Cutaneous and mucocutaneous leishmaniasis: clinical perspectives. *Journal of the American Academy of Dermatology* 2015;**73**(6):897-908; quiz 909-10.

Hashiguchi 2016

Hashiguchi Y, Gomez EL, Kato H, Martini LR, Velez LN, Uezato H. Diffuse and disseminated cutaneous leishmaniasis: clinical cases experienced in Ecuador and a brief review. *Tropical Medicine and Health* 2016;**44**:2.

Heras-Mosteiro 2017

Heras-Mosteiro J, Monge-Maillo B, Pinart M, Lopez Pereira P, Reveiz L, Garcia-Carrasco E, et al. Interventions for Old World cutaneous leishmaniasis. *Cochrane Database of Systematic Reviews* 2017, Issue 12. Art. No: CD005067. [DOI: 10.1002/14651858.CD005067.pub5]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hoeltzenbein 2013

Hoeltzenbein M, Stieler K, Panse M, Wacker E, Schaefer C. Allopurinol use during pregnancy - outcome of 31 prospectively ascertained cases and a phenotype possibly indicative for teratogenicity. *PLOS One* 2013;**8**(6):e66637.

Jin 2014

Jin G, Wong ST. Toward better drug repositioning: prioritizing and integrating existing methods into efficient pipelines. Drug Discovery Today 2014;**19**(5):637-44.

Karimkhani 2016

Karimkhani C, Wanga V, Coffeng LE, Naghavi P, Dellavalle RP, Naghavi M. Global burden of cutaneous leishmaniasis: a cross-sectional analysis from the Global Burden of Disease Study 2013. *Lancet Infectious Diseases* 2016;**16**(5):584-91.

Kim 2009

Kim DH, Chung HJ, Bleys J, Ghohestani RF. Is paromomycin an effective and safe treatment against cutaneous leishmaniasis? A meta-analysis of 14 randomized controlled trials. *PLOS Neglected Tropical Diseases* 2009;**3**(2):e381.

Lainson 1994

Lainson R, Shaw JJ, Silveira FT, De Souza AA, Braga RR, Ishikawa EA. The dermal leishmaniases of Brazil, with special reference to the eco-epidemiology of the disease in Amazonia. *Memórias do Instituto Oswaldo Cruz* 1994;**89**(3):435-43.

Lee 2002

Lee N, Bertholet S, Debrabant A, Muller J, Duncan R, Nakhasi HL. Programmed cell death in the unicellular protozoan parasite Leishmania. *Cell Death Differentiation* 2002;**9**(1):53-64.

Lessa 2012

Lessa HA, Lessa MM, Guimaraes LH, Lima CM, Arruda S, Machado PR, et al. A proposed new clinical staging system for patients with mucosal leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2012;**106**(6):376-81.

Llanos-Cuentas 2008

Llanos-Cuentas A, Tulliano G, Araujo-Castillo R, Miranda-Verastegui C, Santamaria-Castrellon G, Ramirez L, et al. Clinical and parasite species risk factors for pentavalent antimonial treatment failure in cutaneous leishmaniasis in Peru. *Clinical Infectious Diseases* 2008;**46**(2):223-31.

Lopez 2012

Lopez L, Robayo M, Vargas M, Vélez ID. Thermotherapy. An alternative for the treatment of American cutaneous leishmaniasis. *Trials* 2012;**13**:58.

López-Carvajal 2016

López-Carvajal L, Cardona-Arias JA, Zapata-Cardona MI, Sánchez-Giraldo V, Vélez ID. Efficacy of cryotherapy for the treatment of cutaneous leishmaniasis: meta-analyses of clinical trials. *BMC Infectous Diseases* 2016;**16**:360. [DOI: 10.1186/s12879-016-1663-3]

Machado 2015

Machado PR, Rosa ME, Guimaraes LH, Prates FV, Queiroz A, Schriefer A, et al. Treatment of disseminated leishmaniasis with liposomal amphotericin B. *Clinical Infectious Diseases* 2015;**61**(6):945-9.

Mansueto 2014

Mansueto P, Seidita A, Vitale G, Cascio A. Leishmaniasis in travelers: a literature review. *Travel Medicine and Infectious Disease* 2014;**12**(6 Pt A):563-81.

Marsden 1979

Marsden PD. Current concepts in parasitology. Leishmaniasis. *New England Journal of Medicine* 1979;**300**(7):350-2.

Marsden 1994

Marsden PD. Mucosal leishmaniasis due to Leishmania (Viannia) braziliensis L(V)b in Tres Bracos, Bahia-Brazil. *Revista da Sociedade Brasileira de Medicina Tropical* 1994;**27**(2):93-101.

Marsden 1998

Marsden PD, Lessa HA, Oliveira MR, Romero GA, Marotti JG, Sampaio RN, et al. Clinical observations of unresponsive mucosal leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 1998;**59**(4):543-5.

Mishra 2007

Mishra J, Saxena A, Singh S. Chemotherapy of leishmaniasis: past, present and future. *Current Medicinal Chemistry* 2007;**14**(10):1153-69.

Modabber 2007

Modabber F, Buffet PA, Torreele E, Milon G, Croft SL. Consultative meeting to develop a strategy for treatment of cutaneous leishmaniasis. Institute Pasteur, Paris. 13-15 June, 2006. *Kinetoplastid Biology and Disease* 2006;**6**:3.

Mondragon-Shem 2015

Mondragon-Shem K, Al-Salem WS, Kelly-Hope L, Abdeladhim M, Al-Zahrani MH, Valenzuela JG, et al. Correction: Severity of Old World cutaneous leishmaniasis Is influenced by previous exposure to sandfly bites in Saudi Arabia. *PLoS Neglected Tropical Diseases* 2015;**9**(12):e0004294.

Monteiro 2009

Monteiro WM, Neitzke-Abreu HC, Ferreira ME, Melo GC, Barbosa Md, Lonardoni MV, et al. Population mobility and production of American tegumentary leishmaniasis in the State of Parana, southern Brazil. *Revista da Sociedade Brasileira de Medicina Tropical* 2009;**42**(5):509-14.

Neto 2006

Neto VL, Véras MM. American tegumentary leishmaniasis: fluconazole therapy. *Revista Brasileira de Medicina de Família e Comunidade* 2006;**2**(7):228-34.

Oliveira 2011

Oliveira LF, Schubach AO, Martins MM, Passos SL, Oliveira RV, Marzochi MC, et al. Systematic review of the adverse effects of cutaneous leishmaniasis treatment in the New World. *Acta Tropica* 2011;**118**(2):87-96.

Oliveira 2015

Oliveira MB, Calixto G, Graminha M, Cerecetto H, Gonzalez M, Chorilli M. Development, characterization, and in vitro biological performance of fluconazole-loaded microemulsions for the topical treatment of cutaneous leishmaniasis. *BioMed Research International* 2015;**2015**:396894.

Olliaro 2013

Olliaro P, Vaillant M, Arana B, Grogl M, Modabber F, Magill A, et al. Methodology of clinical trials aimed at assessing interventions for cutaneous leishmaniasis. *PLOS Neglected Tropical Diseases* 2013;**7**(3):e2130.

Olliaro 2018

Olliaro P, Grogl M, Boni M, Carvalho EM, Chebli H, Cisse M, et al. Harmonized clinical trial methodologies for localized cutaneous leishmaniasis and potential for extensive network with capacities for clinical evaluation. PLOS Neglected Tropical Diseases 2018;**12**(1):e0006141.

Osorio 1998

Osorio LE, Castillo CM, Ochoa MT. Mucosal leishmaniasis due to Leishmania (Viannia) panamensis in Colombia: clinical characteristics. *American Journal of Tropical Medicine and Hygiene* 1998;**59**(1):49-52.

Page 2019

Page MJ, Higgins JP, Sterne JA. Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). The Cochrane Collaboration, 2019. Available from www.training.cochrane.org/handbook.

PAHO 2015

Pan American Health Organization. Leishmaniasis in the Americas: Treatment recommendations [Leishmaniasis en las Américas. recomendaciones para el tratamiento]. www.paho.org/hq/index.php?option=com_topics&view=rdmore&cid=6123&item=leishmaniasis&cat=scie (accessed prior to 23 January 2019). [ISBN: 978-92-75-11752-1]

PAHO 2018

Pan American Health Organization. Leishmaniasis in the Americas: Treatment recommendations. www.paho.org/hq/index.php?option=com_topics&view=rdmore&cid=6123&item=leishmaniasis&cat=scie (accessed prior to 14 July 2020).

PAHO 2019a

Pan American Health Organization. Leishmaniasis: Epidemiological Report in the Americas. iris.paho.org/xmlui/bitstream/handle/123456789/50505/Leishreport2019_eng.pdf (accessed prior to 25 February 2020).

PAHO 2019b

Pan American Health Organization. Manual of Procedures for Leishmaniases Surveillance and Control in the Americas. Washington, D.C: PAHO, 2019. [ISBN: 9789275120637]

Perez-Florez 2016

Perez-Florez M, Ocampo CB, Valderrama-Ardila C, Alexander N. Spatial modeling of cutaneous leishmaniasis in the Andean region of Colombia. *Memórias do Instituto Oswaldo Cruz* 2016;**111**(7):433-42. [DOI: 10.1590/0074-02760160074]

Peterson 2003

Peterson AT, Shaw J. Lutzomyia vectors for cutaneous leishmaniasis in Southern Brazil: ecological niche models, predicted geographic distributions, and climate change effects. *International Journal of Parasitology* 2003;**33**(9):919-31.

Ponte-Sucre 2003

Ponte-Sucre A. Physiological consequences of drug resistance in Leishmania and their relevance for chemotherapy. *Kinetoplastid Biology and Disease* 2003;**2**(1):14.

Prestes 2015

Prestes SR, Guerra JA, Romero GA, Magalhaes LK, Santana RA, Maciel MG, et al. Polymerase chain reaction-based method for the identification of Leishmania (Viannia) braziliensis and

Leishmania (Viannia) guyanensis in mucosal tissues conserved in paraffin. *Revista da Sociedade Brasileira de Medicina Tropical* 2015;**48**(5):555-9.

Ramos 1996

Ramos H, Valdivieso E, Gamargo M, Dagger F, Cohen BE. Amphotericin B kills unicellular leishmanias by forming aqueous pores permeable to small cations and anions. *Journal of Membrane Biology* 1996;**152**(1):65-75.

Reed 2016

Reed SG, Coler RN, Mondal D, Kamhawi S, Valenzuela JG. Leishmania vaccine development: exploiting the host-vector-parasite interface. *Expert Review of Vaccines* 2016;**15**(1):81-90.

Reveiz 2013

Reveiz L, Maia-Elkhoury AN, Nicholls RS, Romero GA, Yadon ZE. Interventions for American cutaneous and mucocutaneous leishmaniasis: a systematic review update. *PLOS One* 2013;**8**(4):e61843.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rojas 2002

Rojas CA, Weigle KA, Barrera L, Collazos C. Surveillance and screening of American cutaneous leishmaniasis by Colombian primary health care workers using a clinical prediction rule. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2002;**96**(4):405-10.

Romero 2001a

Romero GA, Guerra MV, Paes MG, Macedo VO. Comparison of cutaneous leishmaniasis due to Leishmania (Viannia) braziliensis and L. (V.) guyanensis in Brazil: therapeutic response to meglumine antimoniate. *American Journal of Tropical Medicine and Hygiene* 2001;**65**(5):456-65.

Romero 2001b

Romero GA, Vinitius De Farias Guerra M, Gomes Paes M, De Oliveira Macedo V. Comparison of cutaneous leishmaniasis due to Leishmania (Viannia) braziliensis and L. (V.) guyanensis in Brazil: clinical findings and diagnostic approach. *Clinical Infectious Diseases* 2001;**32**(9):1304-12.

Romero 2005

Romero GA, De la Gloria Orge M, De Farias Guerra MV, Paes MG, De Oliveira Macedo V, De Carvalho EM. Antibody response in patients with cutaneous leishmaniasis infected by Leishmania (Viannia) braziliensis or Leishmania (Viannia) guyanensis in Brazil. *Acta Tropica* 2005;**93**(1):49-56.

Sacks 1983

Sacks DL, Barral A, Neva F. Thermosensitivity patterns of Old vs. New World cutaneous strains of Leishmania growing within mouse peritoneal macrophages in vitro. *American Journal of Tropical Medicine and Hygiene* 1983;**32**(2):300-4.

Salaiza-Suazo 1999

Salaiza-Suazo N, Volkow P, Tamayo R, Moll H, Gillitzer R, Perez-Torres A, et al. Treatment of two patients with diffuse cutaneous leishmaniasis caused by Leishmania mexicana modifies the immunohistological profile but not the disease outcome. *Tropical Medicine and International Health* 1999;**4**(12):801-11.

Sands 1985

Sands M, Kron MA, Brown RB. Pentamidine: a review. *Reviews of Infectious Diseases* 1985;**7**(5):625-34.

Santrich 1990

Santrich C, Segura I, Arias AL, Saravia NG. Mucosal disease caused by Leishmania braziliensis guyanensis. *American Journal of Tropical Medicine and Hygiene* 1990;**42**(1):51-5.

Savioli 2006

Savioli L, Engels D, Daumerie D, Jannin J, Alvar J, Asiedu K, et al. Response from Savioli and colleagues from the Department of Neglected Tropical Diseases, World Health Organization. *PLOS Medicine* 2006;**3**(6):e283.

Schonian 2010

Schonian G, Mauricio I, Cupolillo E. Is it time to revise the nomenclature of Leishmania? *Trends in Parasitology* 2010;**26**(10):466-9.

Sereno 2001

Sereno D, Holzmuller P, Mangot I, Cuny G, Ouaissi A, Lemesre JL. Antimonial-mediated DNA fragmentation in Leishmania infantum amastigotes. *Antimicrobial Agents and Chemotherapy* 2001;**45**(7):2064-9.

Sharifi 1998

Sharifi I, FeKri AR, Aflatonian MR, Khamesipour A, Nadim A, Mousavi MR, et al. Randomised vaccine trial of single dose of killed Leishmania major plus BCG against anthroponotic cutaneous leishmaniasis in Bam, Iran. *Lancet* 1998;**351**(9115):1540-3.

Shaw 1988

Shaw JJ. Animal reservoirs of Leishmania in different ecological situations and their importance in the epidemiology of the disease. *Memórias do Instituto Oswaldo Cruz* 1988;**83**(Suppl 1):486-90.

Sousa 2011

Sousa AQ, Frutuoso MS, Moraes EA, Pearson RD, Pompeu MM. High-dose oral fluconazole therapy effective for cutaneous leishmaniasis due to Leishmania (Vianna) braziliensis. *Clinical Infectious Diseases* 2011;**53**(7):693-5.

Sudhandiran 2003

Sudhandiran G, Shaha C. Antimonial-induced increase in intracellular Ca2+ through non-selective cation channels in the host and the parasite is responsible for apoptosis of intracellular Leishmania donovani amastigotes. *Journal of Biological Chemistry* 2003;**278**(27):25120-32.

Sundar 2006

Sundar S, Chatterjee M. Visceral leishmaniasis-current therapeutic modalities. *Indian Journal of Medicine Research* 2006;**123**(3):345-52.

Sundar 2008

Sundar S, Chakravarty J. Paromomycin in the treatment of leishmaniasis. *Expert Opinion on Investigational Drugs* 2008;**17**(5):787-94.

Tojal da Silva 2006

Tojal da Silva AC, Cupolillo E, Volpini AC, Almeida R, Romero GA. Species diversity causing human cutaneous leishmaniasis in Rio Branco, state of Acre, Brazil. *Tropical Medicine & International Health* 2006;**11**(9):1388-98.

Toledo 2013

Toledo AC Jr, Da Silva RE, Carmo RF, Amaral TA, Luz ZM, Rabello A. Assessment of the quality of life of patients with cutaneous leishmaniasis in Belo Horizonte, Brazil, 2009-2010. A pilot study. *Transactions of the Royal Society of Tropical Medicine* 2013;**107**(5):335-6.

Tracy 2001

Tracy JW, Webster LT Jr. Drugs used in the chemotherapy of protozoal infections. In: Hardman JG, Limbird LE, Gilman AG, editors(s). The Pharmacological Basis of Therapeutics. 10th edition. New York: McGraw-Hill, 2001.

Turetz 2002

Turetz ML, Machado PR, Ko AI, Alves F, Bittencourt A, Almeida RP, et al. Disseminated leishmaniasis: a new and emerging form of leishmaniasis observed in northeastern Brazil. *Journal of Infectious Diseases* 2002;**186**(12):1829-34.

Verma 2004

Verma NK, Dey CS. Possible mechanism of miltefosine-mediated death of Leishmania donovani. *Antimicrobial Agents and Chemotherapy* 2004;**48**(8):3010-5.

Weigle 1987

Weigle KA, De Davalos M, Heredia P, Molineros R, Saravia NG, D'Alessandro A. Diagnosis of cutaneous and mucocutaneous leishmaniasis in Colombia: a comparison of seven methods. *American Journal of Tropical Medicine and Hygiene* 1987;**36**(3):489-96.

Weigle 1991

Weigle KA, Valderrama L, Arias AL, Santrich C, Saravia NG. Leishmanin skin test standardization and evaluation of safety, dose, storage, longevity of reaction and sensitization. *American Journal of Tropical Medicine and Hygiene* 1991;**44**(3):260-71.

Weigle 1993

Weigle KA, Escobar M, Arias AL, Martinez F, Rojas C. A clinical prediction rule for American cutaneous leishmaniasis in Colombia. *International Journal of Epidemiology* 1993;**22**(3):548-58.

WHO 2010

World Health Organization. Control of the leishmaniasis: report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22-26 March 2010. apps.who.int/iris/handle/10665/44412 (accessed prior to 23 January 2019).

Wortmann 2010

Wortmann G, Zapor M, Ressner R, Fraser S, Hartzell J, Pierson J, et al. Lipsosomal amphotericin B for treatment of cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2010;**83**(5):1028-33.

Yadon 2003

Yadon ZE, Rodrigues LC, Davies CR, Quigley MA. Indoor and peridomestic transmission of American cutaneous leishmaniasis in northwestern Argentina: a retrospective case-control study. *American Journal of Tropical Medicine and Hygiene* 2003;**68**(5):519-26.

Yang 2012

Yang YG, Zou XB, Zhao H, Zhang YJ, Li HJ. Photodynamic therapy of condyloma acuminata in pregnant women. *Chinese Medical Journal (Engl)* 2012;**125**(16):2925-8.

Zajtchuk 1989

Zajtchuk JT, Casler JD, Netto EM, Grogl M, Neafie RC, Hessel CR, et al. Mucosal leishmaniasis in Brazil. *Laryngoscope* 1989;**99**(9):925-39.

References to other published versions of this review

González 2004

González U, Pinart M, Rengifo-Pardo M, Macaya A, Alvar J. Interventions for mucocutaneous leishmaniasis. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No: CD004834. [DOI: 10.1002/14651858.CD004834]

González 2009

González U, Pinart M, Rengifo-Pardo M, Macaya A, Alvar J, Tweed JA. Interventions for American cutaneous and mucocutaneous leishmaniasis. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No: CD004834. [DOI: 10.1002/14651858.CD004834.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Almeida 1999

Study characteristics

Almeida 1999 *(Continued)*

Methods	**Study design:** randomised, double-blind, placebo-controlled clinical trial **Setting/location:** Ambulatory clinic in an endemic region in Brazil **Period of study:** not stated **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** Previous studies have showed *L. braziliensis* to be the aetiologic agent in this area **Inclusion criteria:** 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 Leishmania antigen **Exclusion criteria:** pregnancy, other associated acute or chronic illnesses, and history of allergy to GM-CSF and/or antimonial. **Randomized:** 20 **Withdrawals:** 0 **Patients assessed:** GM-CSF + antimony group: 10, placebo + antimony group: 10 **Age (years):** GM-CSF + antimony group: 31.80 ± 12.48, placebo + antimony group: 27.70 ± 12.94 **Sex:** M/F: 13/7: GM-CSF + antimony group: M/F: 8/2; Placebo + antimony group: M/F: 5/5 **Baseline imbalances:** no **Severity Illness:** Mean size of the lesions before treatment in the group treated with GM-CSF 1 antimony was 18.80 ± 5.75 mm and the range was 13 - 30 mm. Mean size in the group treated with placebo + antimony was 17.90 ± 4.86 mm and the range was 13 - 29 mm
Interventions	**Type of interventions:** Topical miltefosine and glucantime intralesional injection • **Intervention group:** The GM-CSF group of participants received 2 local injections of 200 mg of hr–GMCSF at entry and 1 week later (designated as GM-CSF group) • **Control group:** received saline (designated as placebo group) All participants received intravenous pentavalent antimonial, at 20 mg per kg of body weight, daily for 20 days **Duration of intervention:** 20 days **Co-interventions:** None **Rescue Therapy:** All participants who had evidence of an active ulcer at 90 days after initiating the first treatment were defined as treatment failures and received an additional course of pentavalent antimonial treatment (20 mg/kg 21/day21 IV for 20 days)
Outcomes	**Definition:** • ***Clinical cure:*** A cure was defined as a participant whose previous ulcer (crater and border) had undergone complete re-epithelialisation **Time points reported:** The participants were evaluated minimally on days 30, 60, 90, 120, and 180 after treatment onset

Almeida 1999 *(Continued)*

	Adverse effects: Participants were questioned about expected adverse effects for 3 days (Days 5 – 7) following administration of the doses. These were considered drug-related if they were not reported at presentation
Notes	**Ethical approval needed/obtained for study**: The study was approved by the ethics committee at Hospital Universitário Prof. Edgard Santos **Informed consent obtained:** Written consent was obtained from all participants older than 18 years and from the parents of younger participants **Study funding sources:** This work was supported by National Institutes of Health grant AI-30639 and by Financiadora de Estudos e Projetos, Centro de Apoio ao Desenvolvimento da Ciência e Tecnologia, and Programa de Apoio aos Núcleos de Excelência. **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The selected patients were randomized into 2 study groups." Method of generation of randomization sequence was not reported.
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The research team was blinded to the administered drug." Comment: study is refered to as double-blind so assume participants were also blinded as it was placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To maintain the double-blind nature of the experiment, questions on possible side effects of the treatment were deferred to a third medical doctor who was conversant with the known side reactions of GM-CSF, such as general malaise and muscle ache." Comment: assessment of side effects was blinded, which is likely to be affected by unblinded assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	High risk	Side effects were claimed to have been assessed but were not reported in the Results section
Other bias	High risk	Leishmania sp was not confirmed and sample size calculation was not adequately reported

Alves 2016

Study characteristics

Methods	**Study design:** randomised, open-label, controlled trial **Setting/location:** Faculty of Medicine of Ribeirao Preto - University of Sao Paulo, Ribeirao Preto - SP, Brazil

Alves 2016 *(Continued)*

	Period of study: not reported **Sample size calculation:** not reported
Participants	**Type of Leishmania:** In the PCR exams, *Leishmania (Viannia) braziliensis* was identified in 15/15 (100%) participants of the intervention group and in 14/14 (100%) participants of the control group **Inclusion criteria:** Patients suffering from American tegumentary leishmaniasis. The diagnosis was constituted by clinical history, epidemiological and physical examination compatible with ATL, and it has been confirmed by positive results of the following diagnostic methods: MST, histopathology and smear (with presence of amastigotes forms) and culture, indirect IFT and PCR **Exclusion criteria:** any previous treatment **Randomised:** 70 (intervention group (N = 34) and control (N = 36)) **Withdrawals:** 0 **Patients assessed:** 70 **Age (years) and sex:** not reported **Baseline data:** MST was positive in 31 (91.2%) patients in the intervention group, and in 33 (91.7%) in the control group. IFI, smear, culture, histopathology and PCR were positive in 7/10 (70.0%), 5/15 (33.3%), 7/15 (46.6%), 8/19 (42.1%) and 15/15 (100%) participants in the intervention group; and 15/15 (100%), 3/11 (27.2%), 3/12 (25%), 7/20 (35%) and 14/14 (100%) in the control group, respectively.
Interventions	**Type of interventions:** • **Intervention:** IM use of 3 pentamidine doses, 4 mg/kg/per day each 3 days • **Control:** IV N-Methyl-glucamine 20 mg SbV/kg/per day for 20 days **Duration of intervention:** 20 days **Co-interventions:** not reported **Duration of follow-up:** not reported
Outcomes	**Definition:** • ***Clinical cure:*** complete ulcer healing without any sign of inflammation **Adverse effects:** not described in Methods but reported in Results: “Side effects were observed in 14/34 (41.1%) patients in group I and in 14/36 (38.8%) in group II (P ¼.42). The most common side effects observed in the intervention group were pain in the injection site, paraesthesias in both legs and increase of CPK. In the control group, arthralgia, pain the local application, myalgia, increase of amylase, headache and ECG alterations". **Time points reported:** Clinical cure was assessed 180 days after the end of each treatment. Clinical assessments for secondary endpoints were carried out 1, 2, 3, 6, and 12 months after treatment
Notes	**Ethical approval needed/obtained for study**: NR **Informed consent obtained:** NR **Baseline imbalances:** “The statistical analysis has demonstrated homogeneity between groups regarding gender, age, number of lesions, location of all lesions and evolution time”. **Study funding sources:** not reported, although no commercial support was identified **Possible conflicts of interest:** NR
Risk of bias	

Alves 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation was made following a random assignment in fixed block sizes of 4 patients." Comment: randomisation sequence considered adequate
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	Study protocol not available, but all outcomes described in the Methods section were reported in the Results
Other bias	High risk	Sample size calculation was not adequately reported

Alves Noroes 2015

Study characteristics	
Methods	**Study design:** parallel, randomised clinical trial **Setting/location:** Brazil. Patients proceeded from Tropical Pathology Clinic of the Medical School of the Federal University of Ceará, in Barbalha. The Clinic is part of the health structure of the Department of Health of Barbalha, South Municipality of Ceará, located in the metropolitan region of Cariri, on the banks of Araripe. **Period of study:** from July 2009 to December 2011 **Sample size calculation:** The calculation of the sample (n) was based on the Central Limit Theorem, which advocates samples from more than 30 observations for continuous variables; the distribution of mean is Gaussian - normal.
Participants	**Type of Leishmania:** *Leishmania (V.) braziliensis* confirmed by identification of the parasite in at least 1 of 3 parasitological methods used and the Montenegro intradermal reaction. **Inclusion criteria:** men or women aged above 18 years, presenting lesion with parasitological confirmation for leishmaniasis and without prior treatment to agree to participate in the study by signing the Instrument of Consent **Exclusion criteria:** men or women under 18, pregnant or breastfeeding, patients with heart disease, liver disease (or only increases in enzymes, SGOT, SGPT), kidney disease, HIV carriers; and patients who had already developed a mucosal form of LTA and did not agree to participate **Randomised:** 120 (Fluconazole (N = 60) and Glucantime (N = 60))

Alves Noroes 2015 *(Continued)*

Withdrawals: 0

Patients assessed: 120

Age (years) and sex: M/F: 56/64, average age between 30 and 40 years (Intervention group, mean of 41 years; Control group, mean 33.7 years)

- Intervention (M/F): 26/34
- Control (M/F): 30/30

Baseline data:

Fluconazole group:

Size of lesions: ranged from a minimum of 8.2 mm and a maximum of 113.5 mm

Lower limb 21 (35.0%)

Top member 21 (35.0%)

Head 05 (8.3%)

Joint 09 (15.0%)

Trunk 04 (6.7%)

Mixed 40 (66.7%)

Glucantime group:

Size of lesions: ranged from a minimum of 8.0 mm and a maximum of 190.6 mm

Lower limb 19 (31.7%)

Top member 22 (36.6%)

Head 06 (10.0%)

Joint 06 (10.0%)

Trunk 07 (11.7%)

Mixed 45 (75.0%)

Interventions	**Type of interventions:** • **Intervention:** Participants received capsules of 126 or 168 Fluconazol ® at a concentration of 150 mg/capsule, respectively, having to eat 2 or 3 capsules at once in the morning • **Control:** intravenous Glucantime® at a dose of 20mg/kg/day **Duration of intervention:** 20 consecutive days (control) and 42 consecutive days (intervention) **Co-interventions:** Lesions with secondary infections were treated with topical antibiotics or, when necessary, a systemic antibiotic (azithromycin) **Duration of follow-up:** after 20, 40, 60 and 90 days
Outcomes	**Definition:** • ***Cure:*** defined by re-epithelialisation of ulcerated lesions, total regression of the infiltration and erythema **Speed of healing:** not reported **Adverse effects:** The observed side effects were recorded at each visit

Alves Noroes 2015 *(Continued)*

	Time points reported: at 90 days
Notes	**Ethical approval needed/obtained for study**: **Informed consent obtained:** The original project was submitted and approved (Protocol 4/2008) to the Ethics Committee of Hospital São José of Infectious Diseases - HSJ/Health Secretary of the State of Ceará and appreciated by the Ethics Committee of the Medical Program of Research in Barbalha, the Federal University of Ceará (UFC) **Baseline imbalances:** There were more women in the intervention group. **Study funding sources:** not reported **Possible conflicts of interest:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Was performed exchanged randomization in blocks. In a box, were deposited 20 records; each half of the records had different color. The blue color was defined as Group I and the red as Group II. Each patient who met the inclusion criteria withdrew, randomly, a record to define in which group it would be included". Comment: randomisation method considered adequate
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	One treatment intravenous and the other oral capsules. Placebo drugs not used Comment: it is unlikely that participants/personnel were blind to the treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients were evaluated by the principal researcher for the clinical follow-up, using the protocol itself and by a blinded observer (clinical doctor's clinic), which recorded the clinical outcome and side effects in the conventional patient record." Comment: assessment blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	Protocol not available. Study not included in a RCT public registry. However, all outcomes described in the Methods section were reported in the Results
Other bias	Low risk	All information was provided

Andersen 2005

Study characteristics

Methods	**Study design:** Open-label, randomised study **Setting/location:** Cuzco, Peru

Andersen 2005 *(Continued)*

	Period of study: 01 March 2001 to 17 June 2002 **Sample size calculation:** not described
Participants	**Type of Leishmania:** Cutaneous leishmaniasis (CL) caused by *L. braziliensis* **Inclusion criteria:** age between 18 and 60 years; a parasitologic diagnosis of cutaneous leishmaniasis from a lesion; no evidence of mucosal involvement of the 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 **Exclusion criteria:** being pregnant or nursing **Randomised:** 80 **Withdrawals:** 0 **Patients assessed:** 40 participants administered glucantime and 40 participants administered pentamidine **Age (years) and sex:** - Glucantime: age 28 (8.5), 34 men, 6 women - Pentamidine: age 31 (10), 31 men, 9 women **Baseline data:** - Glucantime: weight 56 kg (7.5), number of lesions 2.1 (1.7), 35% on arms, 46% on legs, duration of lesions 137 days (133) - Pentamidine: weight 57 kg (5.1), number of lesions 2.3 (1.8), 34% on arms, 52% on legs, duration of lesions 119 days (163)
Interventions	**Type of interventions:** • **Intervention 1:** 20 mg of antimony Sb/kg/day intravenously for 20 days • **Intervention 2:** 2 mg/kg pentamidine every other day for 7 injections intravenously **Duration of intervention:** 7 - 20 days **Co-interventions:** not described **Duration of follow-up:** 6 months follow-up
Outcomes	***- Complete clinical response:*** was defined as 100% re-epithelialisation of the lesion ***- Clinical improvement:*** was defined as 75 − 99% re-epithelialisation of the lesion compared with the previous measurement ***- Clinical failure:*** was defined as > 50% enlargement of the lesion at any time in comparison to the previous measurement ***- Clinical relapse:*** was an enlargement of a previously clinically-responsive or clinically-improved lesion, a new lesion at the original site, or a new lesion along the lymphatic drainage of the original lesion ***- Parasitologic cure:*** was defined as the inability to culture or stain parasites from the lesion and parasitologic failure was the presence of culturable or stainable parasites Definitions of lesion cure and failure were based on both clinical and parasitologic criteria - Failure: was defined as lesions that demonstrated clinical failure, clinical improvement with parasitologic failure, clinical relapse, or the lack of complete clinical response at 6 months

Andersen 2005 *(Continued)*

- Cure was the opposite of failure. Any lesion that did not meet the definition of failure prior to the 6-month follow-up and was completely re-epithelialised by that time was considered to be cured. For a participant to be considered cured, all lesions had to be evaluated as cured

- Adverse effects

Time points reported: 2 weeks, 3 months, and 6 months

Notes	**Ethical approval needed/obtained for study**: The trial was reviewed and approved by the ethical committees of the Ministry of Health, Peru, and the University of Peru Cayetano Heredia. In addition, the study protocol was reviewed and approved by the Naval Medical Research Center Institutional Review Board (Protocol no. Naval Medical Research Center Detachmen2001.0012 (Department of Defense 31525) in compliance with all Federal regulations governing the protection of human subjects **Informed consent obtained:** NR **Baseline imbalances:** not described **Study funding sources:** This work was supported by United States Navy Work Unit Number no. 100401 000 9MPE B0018 **Possible conflicts of interest:** "The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Volunteers were randomized to receive pentamidine isethionate (Pentam; Fujisawa, Deerfield IL) or meglumine antimoniate (Glucantime; Rhone Poulenc Rorer, Paris, France) in a 1:1 allocation." Comment: randomisation done
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote:"This study was an open-label, randomized comparison of meglumine antimoniate (Glucantime) to pentamidine isethionate (pentamidine) in 80 patients with Peruvian cutaneous leishmaniasis"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further information about blinding of outcome assessment was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing results data
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	High risk	Sample size calculation was not adequately reported

Arana 1994

Study characteristics	
Methods	**Study design:** Randomised, prospective, double-blind trial **Setting/location:** Guatemala **Period of study:** not stated **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** *Leishmania braziliensis, Leishmania mexicana* **Inclusion criteria:** male Guatemalan soldiers with parasitologically-proven cutaneous Leishmaniasis **Exclusion criteria:** not stated **Randomized:** 66 **Withdrawals:** 3. 2 participants, who had both received meglumine for 10 days, were lost to follow-up after their 26-week examinations. The other participant, who had received meglumine for 20 days, was lost to follow-up after his 13-week examination. In all cases, the participants were free of disease at their last examination **Patients assessed:** meglumine for 20 days: 22; meglumine for 10 days: 22; and meglumine for 10 days plus IFN-γ: 22 **Age (years), (mean, range):** meglumine for 20 days: 20.1 ± 0.5; meglumine for 10 days: 18.9 ± 0.5; and meglumine for 10 days plus IFN-γ: 19.6 ± 0.5 **Sex:** All men **Baseline imbalances:** no **Severity Illness:** The mean area of ulcers was: meglumine for 20 days: 1.0 ± 0.2 cm^2; meglumine for 10 days: 0.8 ± 0.1 cm^2; and meglumine for 10 days plus IFN-γ: 1.4 ± 0.4 cm^2
Interventions	**Type of interventions:** • **Meglumine for 20 days:** Participants randomised received 20 days of meglumine • **Meglumine for 10 days:** Participants randomized to receive I0 days of meglumine were then treated with 10 days of a saline infusion • **Meglumine for 10 days + IFN-γ:** 1 mL solution containing 0.2 mg of recombinant **IFN-γ**/mL given subcutaneously in the forearm every other day for 5 doses In each case, meglumine, at a dose of 20 mg of pentavalent antimony/(kg of body weight/d), was given as an intravenous infusion over ~ 15 minutes **Duration of intervention:** 10 - 20 days **Co-interventions:** None **Rescue therapy:** Participants whose lesions were not completely re-epithelialised by the 13-week examination were removed from the study and treated with additional meglumine
Outcomes	**Definition:** • **Clinical cure:** A complete response was defined as complete re-epithelialisation of all lesions with no residual erythema, test-of-cure cultures at the end of therapy and at the 9-week follow-up examination that were negative for Leishmania and no reactivations of lesions during 12 months of follow-up

Arana 1994 *(Continued)*

	• **Adverse effects** **Time points reported:** Participants were examined for adverse effects and response to treatment at the following times after beginning treatment: 10 and 20 days and 6, 9, 13, 26, and 52 weeks.
Notes	**Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** Informed consent was obtained from the participants **Study funding sources:** The investigation was supported by the United Nations Development Programme/World Bank/WHO Special Programme for Research and Training in Tropical Diseases and by Boehringer Ingelheim **Possible conflicts of interest:** none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"Treatments were given in a double-blinded fashion." Comment: participants and personnel probably blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/60 (5%) losses to follow-up: Group 1 (MA 20 days): 1 participant was lost to follow-up after his 13-week examination Group 2 (MA 10 days): 2 participants were lost to follow-up after their 26-week examination Group 3 (MA 10 days + IFN-γ): 0
Selective reporting (reporting bias)	Low risk	All outcomes were reported in Results
Other bias	High risk	Sample size calculation was not adequately reported

Arana 2001

Study characteristics

Methods	**Study design:** Double-blind, randomised trial **Setting/location:** Guatemala **Period of study:** not described

Arana 2001 *(Continued)*

	Sample size calculation: not described
Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL). *L. braziliensis* and *L. mexicana* reported in previous studies **Inclusion criteria:** either male or female, aged 10 – 60 years, and parasitologically confirmed CL **Exclusion criteria:** > 4 lesions or an active lesion measuring > 5 cm in diameter; previous use of antimony-containing drugs; serious concomitant medical problems; and evidence of mucosal involvement of leishmaniasis **Randomised:** 76 **Withdrawals:** All participants except 4 received their treatment without interruption. The 4 participants who did not finish their treatment, and 4 more participants who were lost after their 21-day clinical evaluation were not included in the final analysis. Out of the 68 who completed their evaluation at the 13-week examination, 35 belonged to the treatment group (PR-MBCL ointment) and 33 to the placebo group **Patients assessed:** The treatment group included 35 participants, and the placebo group 33 participants **Age (years) and sex:** • Paromomycin and methylbenzethonium chloride group: mean age 22.3 years (1.8) • Placebo group: mean age 20.3 years (0.8) **Baseline data:** • Paromomycin and methylbenzethonium chloride group: No. of lesion per participant 1.1 (0.05), mean area of ulcers 1.1cm^2 (0.3), mean duration of lesions 101.2 days (19.9) • Placebo group: No. of lesion per participant 1.3 (0.1), mean area of ulcers 1.3cm^2 (0.3), mean duration of lesions 105.1 days (13.8)
Interventions	**Type of interventions:** • **Intervention 1:** 15% paromomycin applied twice a day for 20 days • **Intervention 2:** 12% methylbenzethonium chloride applied twice a day for 20 days The ointment was applied topically twice a day for 20 days across the lesions in 2 different directions at 90 ° to each other. Participants were instructed to wash their lesions with soap and water before applying the ointment. After the applications, the lesion was left uncovered. The amount of ointment used during each application varied depending on the lesion size, but a 14-g tube per participant was enough to treat all the participants **Duration of intervention:** 20 days **Co-interventions:** not described **Duration of follow-up:** 12 months
Outcomes	**Definition:** • ***Initial clinical response:*** a participant whose lesions had completely re-epithelialised and who had no evidence of inflammation or indurations by the 13-week follow-up examination • ***Final clinical response:*** a participant who had an initial clinical response and had no disease reactivation during the follow-up period between 13 and 52 weeks • ***Reactivation:*** the appearance of a lesion within or at the border of a previously-healed lesion • ***Treatment failure:*** an increase in lesion size of > 100% compared with the size at the first day of treatment; lack of a clinical response by the 13-week follow-up examination; or reactivation of a lesion. Participants who experienced treatment failure were removed from the study and treated with meg-

Arana 2001 *(Continued)*

lumine antimonate (20 mg antimony per kilogram of body weight per day, administered intravenously, for 20 days)

- **Adverse effects**

Time points reported: All participants were evaluated at the end of weeks 1, 2, 3, 4, 6, 9, 13, 26, and 52 after therapy

Notes

Baseline imbalances: Sex not reported

Ethical approval needed/obtained for study: The Ethical Review Committee of the Universidad del Valle de Guatemala approved the study.

Informed consent obtained: Informed consent was obtained from all adult participants and from parents or legal guardians of minors

Study funding sources: This investigation received financial support from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)

Possible conflicts of interest: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: The PR ointment, paromomycin sulphate 15% plus MBCL 12%, and the placebo ointment tubes, which contained only soft paraffin, were prepared and randomly numbered by Teva Pharmaceutical Industries, Petach Tikva, Israel." Comment: randomisation method was described
Allocation concealment (selection bias)	Low risk	Quote: "The codes identifying the contents of each tube were kept in Geneva by the TDR/WHO representative (F. M.) until the study was completed." Comment: likely that allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither the researchers nor the patients knew if the active substance or the placebo were in the tube. The codes identifying the contents of each tube were kept in Geneva by the TDR/WHO representative (F. M.) until the study was completed." Comment: blinding achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further information about blinding of outcome assessment was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results for sex are missing
Selective reporting (reporting bias)	Unclear risk	Relevant outcomes were reported
Other bias	High risk	Leishmania sp was not confirmed and sample size calculation was not adequately reported

Armijos 2004

Study characteristics	
Methods	**Study design:** Randomised, controlled, double-blinded study **Setting/location:** The study sample was recruited from a pool of patients with parasitologically-confirmed CL infection who attended the National Leishmaniasis Reference Laboratory clinic located in the Central University of Ecuador School of Medicine (Quito, Ecuador) **Period of study:** 24-month period (February 1998 – January 2000). **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** All but 10% of participants were found to be infected with the subgenus Vianna; the remainder belonged to the subgenus Leishmania **Inclusion criteria:** Patients with the Leishmania parasite in their ulcerated lesions; with lesion evolution time ≥ 4 months prior to enrolment in the study; they had 1 – 3 CL lesions; age between 5 and 60 years, and gave their informed written consent **Exclusion criteria:** pregnant or lactating, had ≥ 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 (e.g. hypertension, diabetes) or immunosuppression (e.g. AIDS), had prior CL infection, were being treated with steroid or other immunosuppressant drugs, and had acute malnutrition **Randomised:** 120 participants to paromomycin plus methylbenzonium chloride (PR–MBCL); paromomycin plus urea (PR–U); meglumine antimoniate (MA) **Withdrawals:** 4 participants in the MA control group, 11 in the PR-MBCL group and 10 in the PR-U group. The failure to complete treatment was due to non-compliance in all but 1 participant belonging to the PR–MBCL group who migrated to Spain to seek employment **Patients assessed:** PR–MBCL group: 40; PR–U group: 40 and MA control group: 40 **Age (years):** mean age PR–MBCL group: 20.6 ± 15.3; PR–U group: 18.0 ± 11.7; and MA control group: 21.3 ± 11.0 **Sex:** not stated **Baseline imbalances:** no **Severity Illness:** Mean lesion number: PR–MBCL group (1.5 ± 0.74); PR–U group (1.8 ± 1.1) and MA control group (1.7 ± 0.85). Mean lesion duration (mos): PR–MBCL group (3.0 ± 2.5); PR–U group (3.2 ± 2.6) and MA control group (2.7 ± 1.6). Mean lesion size (mm2): PR–MBCL group (259 ± 351); PR–U group (308 ± 529) and MA control group (418 ± 391)

Interventions	**Type of interventions:** paromomycin plus methylbenzonium chloride (PR–MBCL); paromomycin plus urea (PR–U); meglumine antimoniate (MA).
	
	• **Intervention group:**
	  • Group 1: the participants were treated twice daily for 30 days with the topical PR–MBCL ointment which was dissolved in a soft, white paraffin base
	  • Group 2: the participants were treated in an identical fashion twice daily for 30 days with the topical PR–U formulation which was dissolved in the same soft, white parafin base
	• **Control group:** meglumine antimoniate (Glucantime, Specia Laboratories, France), administered IM at a dosage of 20 mg of Sb/kg/day for 10 days

Armijos 2004 *(Continued)*

Duration of intervention: 30-day and 10-day treatment periods, respectively, for the paromomycin and MA groups

Co-interventions: None

Rescue therapy: Prior to each application in the intervention group, the clinicians cleaned lesions with hydrogen peroxide. They then placed a cross of ointment over each lesion and rubbed it in gently. Treated lesions were protected by a new gauze and adhesive tape dressing

Outcomes

Definition:

- ***Clinical cure:*** The complete healing of all lesions by week 12 after the start of treatment with no relapse observed during the 52-week follow-up period
- ***Treatment failure:*** Cases where the lesions failed to completely heal (100% re-epithelialisation) by 12 weeks after the start of treatment. Was also considered to have failed in cases where the lesions initially healed but later reappeared on the surface or periphery of the original lesion site anytime during the 52-week follow-up observation period, i.e. relapse

Time points reported: The lesions were evaluated every 15 days during the first 3 months after the start of treatment. Thereafter, they were re-examined once every 4 weeks during study weeks 16 – 24, and once again at weeks 36 and 52

Adverse effects: Potential treatment-related toxicity was evaluated during the initial treatment period, on every fourth day, by physical examination, a symptom questionnaire, laboratory examination of blood and urine, and an electrocardiogram

Notes

Ethical approval needed/obtained for study: The study protocol and informed consent form were approved by the Universidad Central (UCE) del Ecuador Medical Research Committee

Informed consent obtained: The participants were enrolled in the study after signing written informed consent forms

Study funding sources: The study was funded by PAHO (HDP/HDR/RG/ECU/1218)

Possible conflicts of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “The 120 subjects were randomized to one of three experimental groups using a computer-generated random numbers table.” Comment: randomisation method described
Allocation concealment (selection bias)	Low risk	Quote: “The study codes for the three subject groups were unknown to clinicians, laboratory technologists, and other study personnel involved in selection, treatment and follow-up. These were kept secured in a locked file cabinet until data analysis." Comment: allocation was concealed throughout the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: “Subjects in the two paromomycin treatment groups and the clinicians treating them were blinded with respect to the identity of the topical treatment received. However, it was not possible to blind the control subjects who received intramuscular (IM) meglumine antimoniate treatment.” Comment: 2 treatment groups blinded, but not control group
Blinding of outcome assessment (detection bias)	Low risk	Comment: Clinicians treating participants were blinded and were likely to also assess the outcomes

Armijos 2004 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up reported (25/120 = 20.83%) but reason was not provided: MA group: 4/40 (10%) P-MBCL: 11/40 (27.5%) P-U: 10/40 (25%)
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	Unclear risk	There was insufficient information to evaluate bias

Arévalo 2007

Study characteristics	
Methods	**Study design:** Randomised 3-arm pilot study **Setting/location:** This study was carried out at Cayetano Heredia Hospital in Lima, Peru **Period of study:** from August 2005 to October 2005 **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** 20 participants with cutaneous leishmaniasis (CL) where *L. braziliensis*, *L. peruviana*, *L. mexicana*, and *L. amazonensis* were endemic **Inclusion criteria:** Adults (> 18 years of age) with a confirmed diagnosis of CL and who had been newly referred to the outpatient Leishmania clinic. The patients were from cities in Peru where CL is endemic **Exclusion criteria:** Patients with mucosal involvement, other known diseases (e.g., AIDS, tuberculosis, bartonellosis, leprosy, or sporotrichosis), immunodeficiency, lesions 125 cm^2 in area, and those with a history of previous treatment for leishmaniasis were excluded, as were women who were breast-feeding or pregnant **Randomised:** 20 **Withdrawals:** 0 **Patients assessed:** meglumine antimonite group: 7; imiquimod cream group: 6; and meglumine antimoniate and imiquimod cream group: 7 **Age (years):** mean 34.9 ± 15.9 and median 32 (18 – 87) **Sex:** 11 (55%) male and 9 (45%) female **Baseline imbalances:** no **Severity Illness:** lesion area (cm^2): meglumine antimonite group: mean 7.1 ± 8.7 and median 1.5 (0.18–25.5); imiquimod cream group: mean 4.2 ± 2.07 and median 2.7 (0.4 – 12.5; meglumine antimoniate and imiquimod cream group: mean 8.1 ± 10.4 and median 5.0 (0.9 – 33)
Interventions	**Type of interventions:**

Arévalo 2007 *(Continued)*

- **Meglumine antimonite group:** administered daily at a dosage of 20 mg/kg by slow intravenous infusion over a 10-min period
- **Imiquimod cream group:** Imiquimod was applied every other day as a 7.5% topical cream directly to the lesion(s). Imiquimod was provided in a syringe that contained a total of 10 doses. Each dose contained 125 mg of imiquimod. The amount of drug dispensed was based on the surface area of the lesion: if the lesion was ≤ 3 cm in length, 1 dose of imiquimod was applied; if the lesion was > 3 cm in length, 2 doses of imiquimod were applied. After application of the cream, each individual lesion was covered with an occlusive dressing (tegaderm patch (3M)) that was maintained for 6 h to ensure adequate exposure to the medication. Participants were instructed to remove the patch after 6 h and to wash the lesions with soap and water
- **Meglumine antimoniate and imiquimod cream group:** 2 treatments as described

Duration of intervention: 20 days

Co-interventions: If bacterial superinfection of a lesion was observed, the participant was administered a regimen of daily cleansing and an oral antibiotic prior to the start of study medication. At the termination of the treatment period or during follow-up visits, participants for whom therapy had failed were offered outpatient treatment with a second course of intravenous meglumine antimoniate, according to the established guidelines of the Peruvian Ministry of Health

Outcomes

Definition:

- ***Clinical cure:*** was defined as complete re-epithelialisation without signs of inflammation
- ***Clinical improvement:*** was defined as a reduction in lesion size and inflammation but without full re-epithelialisation
- ***Treatment failure:*** was defined as no improvement, with the lesion either unchanged or larger than at the start of treatment
- ***Relapse:*** was defined as signs of activity, such as oedema, erythema, or an open ulcer of a lesion that was considered to be clinically cured at the end of treatment

Time points reported: The clinical outcome was recorded on days 0, 10, and 20 of active treatment and at each follow-up visit

Adverse effects: The following scale for evaluating adverse effects was used: mild, defined as causing no significant interference with daily activities; moderate, defined as causing mild interference with daily activities but not requiring treatment; and severe, defined as moderate or severe interference with daily activities, requiring treatment or intervention

Notes

Ethical approval needed/obtained for study: This study was approved by the Institutional Review Board of New York University School of Medicine (New York, New York) and the Ethical Committee of the Universidad Peruana Cayetano Heredia (Lima, Peru)

Informed consent obtained: the participants were enrolled in the study after signing written informed consent forms.

Study funding sources: This study was funded, in part, by a grant from the American Society of Tropical Medicine and Hygiene-Burroughs Wellcome Fund and by the Division of Pediatric Infectious Diseases, New York University School of Medicine. Imiquimod 7.5% was provided without cost by Dutriec SRL (Lima, Peru). I.A. is the recipient of the American Society of Tropical Medicine and Hygiene-Burroughs Wellcome Funds

Possible conflicts of interest: All authors: no conflicts declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were recruited and assigned randomly to 1 of the following 3 treatment groups"

Arévalo 2007 *(Continued)*

		Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes were reported in Results section
Other bias	Unclear risk	There was insufficient information to evaluate bias

Ballou 1987

Study characteristics	
Methods	**Study design:** Double-blind, randomised controlled trial **Setting/location:** Walter Reed Army Medical Center, USA **Period of study:** between November 1984 and June 1986. **Sample size calculation:** The study was designed to enrol patients until either a statistically significant difference between the efficacies of the 2 treatment arms was identified or a total of 100 participants had been recruited
Participants	**Type of Leishmania:** American cutaneous leishmaniasis caused by *L. panamensis* and *L. chagasi* **Inclusion criteria:** diagnosis established by culture of promastigotes from lesion aspirates or biopsy specimens (26 patients), by identification of amastigotes and granulomatous inflammation in biopsy material (26 patients, including 13 with positive cultures), or by identification of granulomatous inflammation in biopsy material without demonstrable parasites but with a serum IFA titre > 1:8 (1 1 patient); no evidence of underlying cardiac, hepatic, or renal diseases; no previous treatment with pentavalent antimonials; at least 18 years of age; and informed consent to participation in the trial **Exclusion criteria:** not described **Randomised:** 40 participants meeting these criteria were randomly assigned to group P20 or group P10 **Withdrawals:** not described **Patients assessed:** 21 participants were randomly assigned to 10 mg Sb/kg daily (group P10) and 19 participants to 20 mg Sb/kg daily (group P20) **Age (years) and sex:** All participants were men

Ballou 1987 *(Continued)*

	- Group P10: mean age 27.9 - Group P20: mean age 28.5 **Baseline data:** - Group P10: mean weight 72.9 kg; mean number of lesions 2.9; mean duration 10.8 week; location extremity 31, head and neck 18, trunk 10 - Group P20: mean weight 77.8 kg; mean number of lesions 2.7; mean duration 9.7 week; location extremity 38, head and neck 12, trunk 3
Interventions	**Type of interventions:** • **Intervention 1:** sodium stibogluconate at a dose of either 20 mg Sb/kg (P20) • **Intervention 2:** sodium stibogluconate at a dose of either 10 mg Sb/kg (P10) Once daily for 20 consecutive days **Duration of intervention:** 10 or 20 days **Co-interventions:** not described **Duration of follow-up:** 12 months after completion of treatment
Outcomes	**Definition:** • ***Efficacy:*** was determined by both clinical and parasitological criteria • ***Failures:*** were identified 9 weeks after the start of treatment and were defined as either persistence of ulceration or persistence of subcutaneous nodules or lymphadenopathy, plus a culture or biopsy specimen positive for Leishmania • ***Relapse:*** was defined as ulceration or positive cultures developing in a lesion that had previously healed • ***Adverse reactions*** **Time points reported:** 3, 6, and 12 months after completion of treatment.
Notes	**Baseline imbalances**: not stated **Ethical approval needed/obtained for study**: The study (work unit 1908) was approved by an institutional review board **Informed consent obtained:** yes **Study funding sources:** not stated **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A double-blind, randomised study was conducted at the Walter Reed Army Medical Center between November, 1984 and June, 1986. The study was designed to enrol patients until either a statistically significant difference between the efficacies of the two treatment arms was identified or a total of 100 patients had been recruited". Comment: insufficient detail was reported about the method used to generate the allocation sequence

Ballou 1987 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A double-blind, randomised study was conducted…" Comment: participants and personnel were probably blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	Low risk	All information was provided

Brito 2014

Study characteristics	
Methods	**Study design:** Single-centre, pilot randomised and double-blind clinical trial **Setting/location:** Health Post of Corte de Pedra, Bahia, Brazil **Period of study:** Not provided **Sample size calculation:** Not calculated
Participants	**Type of Leishmania:** *L. braziliensis* **Inclusion criteria:** Presented 1 - 3 cutaneous ulcers, had a duration of illness between 1 and 3 months, and had documentation of *L. braziliensis* infection by parasite isolation or real-time PCR **Exclusion criteria:** None stated. **Randomized:** 36 **Withdrawals:** 3 **Patients assessed:** 33 **Age (years) and sex:** age 34 years ± 10 (SD) placebo group; 29 years ± 5 (SD) pentoxifylline group;M/F: 23/10 **Baseline data:** Number of lesions: 1 ± 0 SD placebo group; 1.7 ± 0.5 SD pentoxifylline group Size of lesions: 25 x 22 placebo group; 25 x 19 pentoxifylline group
Interventions	**Type of interventions:** • ***Intervention group:*** pentavalent antimony (Sbv) given at a dose of 20 mg/kg per day associated with oral pentoxifylline (400 mg)

Brito 2014 *(Continued)*

	• ***Control group:*** pentavalent antimony (Sbv) given at a dose of 20 mg/kg per day associated with oral placebo three times per day). **Duration of intervention:** 20 days **Co-interventions:** not stated **Duration of follow-up:** 90 days
Outcomes	**Definition:** • ***Cure or failure*** was determined on day 90. Cure was defined by complete healing of the lesions with re-epithelisation of the skin • ***Failure*** was defined as persistence of ulceration or infiltrated borders • Adverse effects **Time points reported:** 90 days
Notes	**Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** not stated **Baseline imbalances:** "There was no difference between the two groups regarding age, sex, or number and size of the lesions." **Study funding sources:** INCT-DT 573839/2008-5 and ICIDR grant AI088650 **Possible conflicts of interest:** Nothing declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote page 617: "Patients were assigned to receive Sbv plus pentoxifylline (study group) or Sbv plus placebo (control group) by a randomization table obtained at www.randomization.com."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote page 617: "Double-blind pilot trial" Comment: participants and personnel were probably blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote page 617: "Double-blind pilot trial". Unclear whether evaluators were the same doctors (personnel)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT analyses were performed. Losses to follow-up: 3/36 (8.3%). Quote page 617: "Three patients were excluded because of loss to follow-up or absence for the second immunological evaluation." Comment: No detailed information on treatment group or reason
Selective reporting (reporting bias)	Low risk	Study protocol not available but main relevant outcomes reported (cure rates and secondary effects) No clinical trial identifier provided

Brito 2014 *(Continued)*

Other bias	High risk	Sample size calculation was not adequately reported

Brito 2017a

Study characteristics	
Methods	**Study design:** Randomised, double-blind and placebo-controlled trial **Setting/location:** Health post of Corte de Pedra, Bahia, Brazil **Period of study:** December 2010 to October 2013 **Sample size calculation:** For this superiority trial, the sample size was calculated assuming an expected 25% difference between groups with α = 0.05 and a power of 80%
Participants	**Type of Leishmania:** PCR identified *L. braziliensis* in most participants (62%) **Inclusion criteria:** presence of 1 - 3 ulcerated lesions measuring 1 - 5 cm diameter with < 90 days, in a patient of 18 – 50 years **Exclusion criteria:** evidence of severe underlying disease (cardiac, renal, hepatic, or pulmonary), including serious infection other than CL; immunodeficiency or antibody to HIV; pregnancy or lactation **Randomised:** 164 (IVMA plus oral pentoxifylline group (N = 82) and IVMA plus oral placebo (N = 82)) **Withdrawals:** 0 **Patients assessed:** 164 **Age (years) and sex:** age range 18 to 62 years (MA+placebo: 33.4 ± 11.2; MA + pentoxifylline: 33.4 ± 10.4); MA+placebo (M/F): 59/23; MA + pentoxifylline (M/F): 51/31 **Baseline data:** *MA+placebo group:* • Number of lesions (Md; R)*: 1; 1 - 3 • Area of lesions (mm^2) (M ± SD): 132 ± 227 • Lesions in inferior limbs (%) 82 *MA + pentoxifylline group:* • Number of lesions (Md; R)*: 1; 1 - 4 • Area of lesions (mm^2) (M ± SD): 132 ± 248 • Lesions in inferior limbs (%) 73.2
Interventions	**Type of interventions:** • **Intervention:** IVMA 20 mg Sbv/Kg/day for 20 consecutive days (maximum daily dose of 1215 mg) and simultaneously pentoxifylline (400 mg) 3 times daily for 20 days • **Control:** IVMA 20 mg Sbv/Kg/day (maximum daily dose of 1,215 mg) day during 20 days and inert pills (3 times daily for 20 days) **Duration of intervention:** 20 days **Co-interventions:** not reported **Duration of follow-up:** 2 weeks, 1, 2, 3 and 6 months post-therapy

Brito 2017a *(Continued)*

Outcomes	**Definition:** • ***Cure:*** Only lesions with complete re-epithelialisation, without raised borders or infiltrations were considered cured • ***Cure without relapse*** at six months after completion of treatment • ***Cure at 2 months*** after completion of treatment **Adverse effects:** were graded according to the Common Terminology Criteria for Adverse Event v3.0 (CTCAE) of the National Cancer Institute (ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). **Speed of healing**: not reported **Time points reported:** Clinical cure was assessed 2 and 6 months after the end of each treatment
Notes	**Ethical approval needed/obtained for study**: Ethics Committee of the Federal University of Bahia, Salvador, Brazil(CEP/MCO/UFBA-Par/Res 078/2009) **Informed consent obtained:** consent was obtained from all participats before enrolment **Baseline imbalances:** predominance of male sex in the groups **Study funding sources:** INCT-DT 573839/2008-5 and ICIDR grant AI088650 **Possible conflicts of interest:** The authors declare that they have no conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to receive Sbv plus pentoxifylline (study group) or Sb^{v} plus placebo (control group) by a randomization table obtained at www.randomization.com." Comment: randomisation method described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind, with placebo and pentoxifylline looking identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	2 physicians who were unaware of the group assignment independently examined the participants at all visits
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analyses were performed No losses to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes were reported and the protocol was available (trial registered)
Other bias	Low risk	All information was provided

Chico 1995

Study characteristics	
Methods	**Study design:** random study **Setting/location:** Ecuador **Period of study:** not reported **Sample size calculation:** convenience, not described.
Participants	**Type of Leishmania:** 75 Ecuadorian patients with cutaneous leishmaniasis, complexes *braziliensis, mexicana, panamensis, guyanensis, amazonensis* **Inclusion criteria:** laboratory diagnosis of leishmania in lesions by: smears (Giemsa staining), histopathology (haematoxylin-eosin), direct immunofluorescence with specific monoclonal antibodies (DIFMATB) **Exclusion criteria:** mucocutaneous lesions, severe concomitant diseases, abnormalities in laboratory tests (CBC, ESR, glucose, urea, creatinine, uric acid, total bilirubin, direct and indirect, SGOT, SGPT, phosphatase alkaline, Na, K, CI, EMO), or X-ray and ECG were performed before inclusion **Randomised:** Group 1: 30 participants, treated with allopurinol riboside (1500 mg/6 h, 4 times per day) plus probenecid (500 mg/6 h, 4 times per day) for 28 days; Group 2: 30 participants, positive control, treated with pentostam (Sb) (20 mg/kg/day IM for 20 days); Group 3: 15 participants, untreated control group **Withdrawals:** only 62 completed the protocol with 365 days of follow-up (22 of 30 participants treated with allopurinol riboside (RA); 28 of 30 participants treated with pentostam (Sb) and 12 of 15 patients untreated) **Patients assessed:** 75. Allopurinol riboside group: 30, pentostam group: 30, control group: 15 **Age (years) and sex:** average age allopurinol riboside: 28, pentostam: 29, untreated: 34; male/female ratio allopurinol riboside: 17/13, pentostam: 16/14, untreated: 8/7. **Baseline data:** allopurinol riboside: 1 lesion: 18, 2 lesions: 9, 3 lesions: 3; < 3 months of evolution: 15, 3 - 6 months of evolution: 14, > 6 months of evolution: 1; in head: 6, in torso: 3, in extremities: 18, mixed: 3; average lesion diameter: 4,4 cm. Pentostam: 1 lesion: 16, two lesions: 7, three lesions: 7; < 3 months of evolution: 15, 3 -6 months of evolution: 10, > 6 months of evolution: 5; in head: 8, torso: 0, in extremities: 18, mixed: 4; average lesion diameter: 3,8 cm. Untreated: 1 lesion: 11, 2 lesions: 2, 3 lesions: 2; < 3 months of evolution: 6, 3 - 6 months of evolution: 7, > 6 months of evolution: 2; in head: 2, torso: 2, in extremities: 11, mixed: 0; average lesion diameter: 1.3 cm
Interventions	**Type of interventions:** • Group 1: Intervention group: allopurinol riboside (1500 mg/6 h, 4 times per day) plus probenecid (500 mg/6 h, 4 times per day) for 28 days • Group 2: Positive control: pentostam (Sb) (20 mg/kg/day IM for 20 days) • Group 3: Untreated control group **Duration of intervention:** G1: 28 days and G2: 30 days **Co-interventions:** None **Rescue therapy:** All failed cases were subsequently successfully treated with pentostam **Duration of follow-up:** 1 year post-treatment
Outcomes	**Definition:** • ***Cure* :** having a complete re-epithelialisation without relapse

Chico 1995 *(Continued)*

	• ***Adverse effects***
	Time points reported: days 7, 14, 70, 90, 180 and 365
Notes	**Ethical approval needed/obtained for study**: not stated
	Informed consent obtained: Included after previous consent
	Baseline imbalances: average diameter of lesions was lower in the untreated control group compared to others
	Study funding sources: Suported by Burroughs Wellcome Co. and Dember Foundation, Inc
	Possible conflicts of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 6/75 (8%). Reasons not provided
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	High risk	Sample size calculation was not adequately reported

Chrusciak-Talhari 2011

Study characteristics

Methods	**Study design:** Single-centre phase II/III randomised clinical trial
	Setting/location: dermatology outpatient clinic at the Fundação de Medicina Tropical—Amazonas, Manaus, AM, Brazil
	Period of study: February 2007 to December 2008
	Sample size calculation: "The sample size was calculated assuming an expected 30% difference between groups (effectiveness of at least 50% for meglumine and 80% for miltefosine), 95% confidence interval (CI) and a power of 80%."

Chrusciak-Talhari 2011 *(Continued)*

Participants	**Type of Leishmania:** 86 *L.* (*V.*) *guyanensis; 3 L.* (*V.*) *braziliensis; 1 L.* (*V.*) *lainsoni* **Inclusion criteria:** 1) clinical diagnosis of CL with 1 – 5 lesions with at least 1 ulcerated lesion with a diameter of 1 – 5 cm; 2) illness duration of < 3 months; 3) visualisation of Leishmania amastigotes on Giemsa Diff-Quick, Dade Behring, Newark, EUA stained imprint from lesion biopsies; 4) no previous leishmania treatment **Exclusion criteria:** 1) evidence of immunodeficiency or antibodies to HIV; 2) pregnancy or patients not willing or unable to use contraceptives during and 3 months after the end of therapy; 3) ALT, AST ≥ 3× normal reference values, Billirubin ≥ 2× reference values, and creatinine and blood urea nitrogen (BUN) ≥ 1.5× normal reference values; 4) any evidence of serious underlying disease (cardiac, renal, hepatic, or pulmonary) including serious infection other than CL **Randomised:** 90 (60 Miltefosine, 30 Glucantime) **Withdrawals: "**Only three patients were lost in follow-up: two in the miltefosine group (second- and fourth-month visits) and one in the antimonial group (fourth-month visit)". Caution: In Table 2 it appears that the 3 withdrawals occurred in the miltefosine group **Patients assessed:** 84. **"**Six patients were not included in the intention to treat efficacy analysis: two patients in each treatment group were excluded because of different leishmania species and another two in the miltefosine group were excluded in the first week of treatment: one because of emigration and the other because of concomitant *Plasmodium falciparum* malaria. Therefore, only 84 patients were considered for drug efficacy analysis. Study compliance was very good" **Age (years) and sex: "**Subjects enrolled were from both genders, with ages ranging from 4 to 62 years of age." **Baseline data:** N of lesions (Miltefosine/Glucantime): 1 lesion (32/15), 2 lesions (9/6), 3 lesions (9/4), 4 lesions (8/3), 5 lesions (2/2). Parasitology (Miltefosine/Glucantime): L. (V.) *guyanensis* (58/28), L. (V.) *braziliensis* (1/2), L. (V.) *lainsoni* (1/0).

Interventions	**Type of interventions:**
	
	• ***Intervention group:*** Miltefosine was supplied in blister packs with 7 capsules each, containing 10 mg or 50 mg. Miltefosine was administered orally at the total target daily dosage of 2.5 mg/kg of body weight (maximum daily dose of 150 mg) for 28 consecutive days. Treatment was equally divided into 2 or 3 doses and was always given with meals according to the following weight scale:
	  • Participants at ≤ 14 kg – total dose of 30 mg/day
	  • Participants at ≥ 15 kg and ≤ 29 kg – total dose of 50 mg/day
	  • Participants at ≥ 30 kg and ≤ 45 kg – total dose of 100 mg/day
	  • Participants at ≥ 46 kg – total dose of 150 mg/day
	• ***Control group:*** Glucantime was supplied in vials of 5 mL containing 81 mg/Sb $^{+5}$ /mL. Glucantime was administered intravenously at a dose of 20 mg Sb $^{+5}$ /kg/day (age group 13 – 65 y/o) and 15 mg Sb $^{+5}$ / kg/ day (age group 2 – 12 y/o) for 20 consecutive days (maximum daily dose of 3 ampoules), according to the Ministry of Health guidelines.
	
	Compliance to treatments was determined as follows:
	
	Glucantime was administered at local primary health clinics and injection records kept in clinics were checked weekly by the study physician Participants receiving miltefosine had to return the empty blister packs to receive the subsequent weekly dose
	
	Both drugs were delivered weekly to the study site
	
	Duration of intervention: Each participant received enough drugs for 7 days at a time
	
	Co-interventions: None
	
	Duration of follow-up: 6 months after the end of treatment

Chrusciak-Talhari 2011 *(Continued)*

Outcomes	**Definition:** • ***Partial cure:*** Incomplete epithelialisation or incomplete regression of inflammatory induration of 1 or more lesions, and no appearance of new lesions • ***Apparent cure:*** Complete epithelialisation of all ulcers and regression ≥ 70% of inflammatory indurations from all lesions • ***Definite cure:*** Complete epithelialisation of all ulcers and complete disappearance of inflammatory induration from all lesions at 6-month follow-up visit • ***Clinical failure:*** Any of the following was classified as clinical failure: residual lesions with presence of parasites in Giemsa Diff-Quick stained imprint, or appearance of any new lesions, or ≥ 20% enlargement or no improvement of previously documented lesions. If a patient fulfilled the criteria for partial cure 2 months after the end of treatment, he was classified as clinical failure and rescue treatment with antimonials or pentamidine (3 doses of 4 mg/kg IM with a maximum daily dose of 300 mg, every 48 h). The same procedure was adopted if a participant fulfilled the criteria for clinical failure at any time after the end of treatment • ***Toxicity:*** Clinical and laboratory adverse effects were graded according to the Common Toxicity Criteria (CTC) of the National Cancer Institute. Primary study endpoints were calculated at 6 months follow-up visits (definitive cures) or when criteria defined previously were fulfilled for clinical failure **Time points reported:** 1, 2, 4, and 6 months post-therapy
Notes	**Ethical approval needed/obtained for study**: The study protocol was reviewed and approved by the Institutional Review Board of the Fundação de Medicina Tropical - Amazonas and by the Brazilian National Council of Ethics on Research (CONEP) **Informed consent obtained:** Informed consent was obtained from all study participants and/or guardians before enrolment **Baseline imbalances: "**There was no difference between treatment arms regarding gender, age, duration of illness, and number of lesions". **Study funding sources:** FINEP/Brazil (project no. 3726/05) **Possible conflicts of interest: "**None of the authors of this manuscript have an association with a commercial or other entity that may pose a conflict of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote page 256: ""Random numbers in a 2:1 allocation for miltefosine were obtained using StataCorp LP 9 (College Station, TX)." "Patients who met the entry criteria were randomly allocated (2:1) to oral miltefosine for 28 days or parenteral antimony for 20 days. In addition, patients were stratified according to age groups: 2–12 y/o and 13–65 y/o." Comment: randomisation method described
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This phase II/III prospective open label active-control trial was designed to evaluate the efficacy and safety of miltefosine" Comment: not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	No information provided

Chrusciak-Talhari 2011 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In Table 2 it appears that at 6-month follow-up 2 withdrawals occurred in the miltefosine group and 1 in the control group. Caution: It depends on the time points of assessment
Selective reporting (reporting bias)	Low risk	The article presents all relevant primary and secondary outcomes stated in the study protocol, available at ClinicalTrials.gov. ClinicalTrials.gov identifier NCT0060054
Other bias	Low risk	All information was provided

Convit 1987

Study characteristics	
Methods	**Study design:** Randomised observer-blind study **Setting/location:** Venezuela **Period of study:** 12-month period (1985 to 1986) **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** they assumed a minimum sample of 34 for 2 independent groups with 95% cure for the group with chemotherapy and with groups large enough to render 15% differences as significant, with an alpha error of 0.05 and beta error of 0.50
Participants	**Type of Leishmania:** *L. braziliensis* **Inclusion criteria:** All participants were selected from the same endemic area, over 12 years of age, localised clinical form of leishmaniasis < 1 year in evolution, written agreement to participate in the trial, and no contraindication to either chemotherapy or immunotherapy **Exclusion criteria:** not stated **Randomised:** 113 **Withdrawals:** Of the 113 participants initially selected, 11 were excluded because the diagnosis could not be confirmed by parasitology or because of previous ill effects from chemotherapy. Then, 6 participants had to be eliminated from the chemotherapy group and 2 from the immunotherapy group because they did not keep appointments or because they did not comply with the treatment regimens **Patients assessed:** 94; Immunotherapy: 52, and chemotherapy: 42 **Age (years):** Immunotherapy: 12 - 19 y (26.92%), 20 - 39 y (36.55%), 40 - 59 y (15.38%), ≥ 60 y (21.15%); chemotherapy: 12 - 19 y (28.57%), 20 - 39 y (40.48%), 40 - 59 y (21.43%), ≥ 60 y (9.52%) **Sex:** M/F: 61/33; Immunotherapy: female 36.54%, male 63.46%; chemotherapy: female 33.33% male 66.67% **Baseline imbalances:** no **Severity Illness:** Location of lesions: immunotherapy (lower limbs 55.77%, upper limbs 28.85%, ears 5.77%, others 11.31%), chemotherapy (lower limbs 50.00%, upper limbs 40.48%, ears 7.14%, others 14.29%). Mean size MNT (mm): immunotherapy 21.8 ± 9.14, and chemotherapy: 20.50 ± 8.02

Convit 1987 *(Continued)*

Interventions	**Type of interventions:** • **Immunotherapy:** Promastigotes of a strain of *L Mexicana* isolated from a DCL patient (strain MEL) and adapted to high-yield growth in vitro were cultured in liquid antibiotic medium 3 (Difco) supplemented with 20% fetal bovine serum. After 8 - 10 days, cultured parasites were centrifuged, washed twice in sterile phosphate-buffered saline (PBS), counted by a technique developed by Shepard, standardised at a concentration of 6.4 x 10^8 promastigotes in 0.4 ml of PBS per dose, and heat-killed by autoclaving. BCG was lot 1220-1 from Connaught Laboratories, Canada. The amount used in the first dose depended on the response to a previous tuberculin skin test, read at 48 h. When the diameter of induration was < 10 mm we used 0.2 mg BCG; when it was between 10 and 20 mm, we used 0.02 mg; and when it was > 20 mm we used 0.01 mg. In later doses we used 0.1 g. The mixture was prepared immediately before use and the vaccine was injected intradermally, half in each deltoid region (0.25 ml in each of 2 sites). A second dose was given 6 - 8 weeks after the first, in a proportion of participants, a third dose 12 - 18 weeks after the second • **Chemotherapy:** All participants received intramuscular meglumine antimonate ('Glucantime' Specia, Paris, lot 110) 50 mg/kg in series of 20 daily injections, with a maximum of 3 and a minimum of 2 series, and with 15 days between series All participants were injected with a Leishmania antigen prepared with *L mexicana* promastigotes cultured in minimal essential medium (GIBCO) supplemented with fetal calf serum and vitamins and nucleotides. After culture, the parasites were concentrated, washed with PBS, standardised to a concentration of 6.25 x 10^6 promastigotes/ml, and heat-killed by autoclaving. This antigen was injected in 0.1 ml doses intradermally on the volar surface of the left forearm and read 48 h later in mm of induration (ball-point-pen technique) **Duration of intervention:** 27 weeks **Co-interventions:** When there was no improvement of the infectious process after 15 days, systemic antibiotics were given according to bacterial sensitivities
Outcomes	**Definition:** • ***Clinical cure:*** Participants were judged clinically cured when ulcerated lesions healed completely and infiltration had totally disappeared leaving no signs in any part of the healed surface or borders. Scabs or desquamation of borders should also have disappeared and the skin around the lesion should show no signs of inflammation, nor should there be any clinical evidence of lymphangitis, lymph-node abnormality, or suspicious lesions in the skin or mucous membranes **Time points reported:** All participants were evaluated every 2 weeks. Once clinical cure was established, all participants were re-evaluated clinically (1 - 3 months later) and by MNT, lymphocyte transformation tests, and ELISA. At present, the observation period for individual participants varies between 3 and 12 months after cure • **Adverse effects:** a specialist (not blinded) recorded side-effects and made decisions about treatment.
Notes	**Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** not stated **Study funding sources:** This work was partly financed by the Pan American Health Organization (PAHOjWHO); Petroleos de Venezuela, S.A.; Ministerio de Sanidad y Asistencia Social; and Universidad Central de Venezuela **Possible conflicts of interest:** none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Of the 113 patients initially selected, 11 were excluded because the diagnosis could not be confirmed by parasitology or because of previous ill-ef-

Convit 1987 *(Continued)*

		fects from chemotherapy. The remainder were assigned at random to the two therapy groups, when the preliminary studies were completed." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Observer-blind study Quote:"Both groups were examined every two weeks and classified, as cured or not, by an experienced dermatologist who did not know to which group they belonged. For this examination the patients 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."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 19/113 (16.81%) Reasons were provided but no ITT analysis was carried out
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	Low risk	All information was provided

Convit 1989

Study characteristics	
Methods	**Study design:** Randomised clinical trial **Setting/location:** Miranda State, Venezuela **Period of study:** not reported **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** The minimum number of participants per group that would reveal a 20% difference in response at a 95% confidence level was 35
Participants	**Type of Leishmania:** localised cutaneous leishmaniasis (LCL). All isolates of parasites from these patients were identified as *L. braziliensis* **Inclusion criteria:** clinical disease classified as LCL with < 1 y of evolution, no contraindications for the use of immunotherapy or chemotherapy, age > 12 y, and informed written consent of the patient or a legal representative **Exclusion criteria:** existence of cardiovascular, renal, or hepatic lesions. Hyperreactivity to PPD (purified protein derivative of tuberculin), defined as reactions > 30 mm at 48 h, and the use of steroids or other immunosuppressant were contraindications for immunotherapy. Pregnant women and people

Convit 1989 *(Continued)*

	suffering from malnutrition or other diseases affecting the general state of health were not included in the study **Randomised:** 217 **Withdrawals:** 0 **Patients assessed:** Immunotherapy: 124, BCG: 42, and chemotherapy: 51 **Age (years):** Immunotherapy: 12 - 19 y (28.0%), 20 - 39 y (40.2%), 40 - 59 y (22.0%), ≥ 60 y (9.8%); BCG: 12 - 19 y (23.3%), 20 - 39 y (51.1%), 40 - 59 y (23.3%), ≥ 60 y (2.3%); chemotherapy: 12 - 19 y (31.1%), 20 - 39 y (40.0%), 40 - 59 y (20.0%), ≥ 60 y (8.9%) **Sex:** M/F:147/70; Immunotherapy: female 29.9%, male 70.1%; BCG: female 32.6%, male 67.4%; chemotherapy: female 37.8% male 62.2%, **Baseline imbalances:** no **Severity Illness:** Mean size (mm) of the lesions before treatment in the group treated with immunotherapy: 21.6 ± 10.1, BCG: 18.6 ± 6.6 and chemotherapy: 20.4 ± 7.9
Interventions	**Type of interventions:** Topical miltefosine and glucantime intralesional injection • **Immunotherapy:** Combined immunotherapy was carried out by the intradermal injection of a mixture of 6.4 x 108 heat-killed promastigotes of *L. mexicana amazonensis*, strain MHOM/VE/84/MEL, isolated from a case of diffuse cutaneous leishmaniasis and variable amounts of BCG (Statens Seruminstitut, Denmark) in a volume of 0.5 ml. The promastigotes were cultivated in Antibiotic Medium Three (Difco) supplemented with 20% fetal calf serum. After 8 - 10 d, the protozoa were washed with phosphate-buffered saline, pH 7.2, counted by the method of Shepard and McRae and autoclaved at 121 °C for 15 mins after appropriate dilution. The amount of BCG admixed with the suspension of heat-killed promastigotes just prior to inoculation was based on each participant's reactivity to 2 units of PPD in the first dose; 0.2 mg of BCG was used if the reaction to PPD was < 10 mm in diameter, 0.02 mg was used in participants with reactions of 10 - 20 mm, and 0.01 mg was used if the reaction was > 20 mm. In successive doses, 0.01 mg of BCG was used in all participants. The mixture was injected intradermally in 2 sites in the deltoid regions; 3 doses were applied at 6- to 8-week intervals • **Chemotherapy:** consisted of the intramuscular injection of meglumine antimoniate (Glucantime; Specia, Paris), 50 mg/kg body weight per 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 • **BCG alone:** administered in the third group using the same quantities, number of doses, and time intervals described above All participants received intravenous pentavalent antimonial, at 20 mg per kg of body weight, daily for 20 days **Duration of intervention:** 20 days **Co-interventions:** All participants in the 3 groups were instructed in local treatment of their lesions with soapy water, removal of scabs, and application of antiseptics 3 times a day. Local antiseptics included Alibour solution (250 mg of $CUS0_4$, 875 mg of $ZnS0_4$ and 25 mg of boric acid in 200 ml of H_20) or iodinepolyvinylpyrollidone. Systemic antibiotics were administered on the basis of antibiograms if infectious foci did not respond to local treatment within 15 d Some participants with intermediate and all with 10 diffuse clinical forms of leishmaniasis were treated simultaneously with combined immunotherapy and chemotherapy, on the protocols described above
Outcomes	**Definition:** • ***Clinical cure:*** complete healing of the initial lesion and absence of peripheral infiltration or inflammation, satellite lesions, adenopathy, lymphangitis, or new lesions • ***Intermediate forms:*** characterised by single or multiple lesions accompanied by extraordinary hypersensitivity in in vivo and in vitro tests, verrucous or vegetative development, and plaques consisting of innumerable small ulcers

Convit 1989 *(Continued)*

	Time points reported: The participants were evaluated at 2-week intervals by a clinician who was unaware of their group assignment. Follow-up consists of observations at 6-month intervals to detect relapses, reinfection, or the appearance of mucosal lesions • **Adverse effects:** Side effects during treatment were evaluated as slight, moderate, or severe as described previously
Notes	**Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** Written consent was obtained from all participants **Study funding sources:** Funded by the Petróleos de Venezuela, Ministry of Health, Central University of Venezuela, Cámara Venezolana de la Indústria de Cerveza, the US National Institutes of Health, and the Pan American Health Organization **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "The 217 patients who met the criteria for entry into the trial were given serial numbers and were assigned randomly to one of the three study groups. Because the minimum number of participants per group that would reveal a 20% difference in response at a 95% confidence level was 35, slightly more than that (42 and 51) were assigned to the 2 control groups (BCG only and chemotherapy only, respectively). The rest (124) were assigned to the experimental group (combined immunotherapy) to increase the likelihood that differences would be detected" Comment: Number of participants assigned to the groups was uneven
Allocation concealment (selection bias)	Unclear risk	It was not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The patients were evaluated at 2-w intervals by a clinician who was unaware of their group assignment. This was ensured by covering the vaccination site with a plaster bandage before examination." Comment: outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	Low risk	All information was provided

Correia 1996

Study characteristics

Correia 1996 *(Continued)*

Methods	**Study design:** Randomised, prospective, open-label study **Setting/location:** Corte de Pedra-Bahía, Brazil **Period of study:** October 1992 - January 1993 **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** American Cutaneous Leishmaniasis (ACL) caused by *L. braziliensis* **Inclusion criteria:** primary cutaneous lesions compatible with ACL, aged 12 to 60, maximum of 5 ulcers and < 6 months **Exclusion criteria:** not stated **Randomised:** 46 patients were dynamically allocated into 3 groups, 2 of 15 (pentamidina and aminosidime) and a 16 (glucantime). **Withdrawals:** 0. **Patients assessed:** Pentamidine: 15 (32.6%), aminosidime: 15 (32.6%), and glucantime: 15 (35.0%) **Age (years):** mean age**:** Pentamidine 23.2 ± 8.3, aminosidime 29.8 ± 13.2 and glucantime 24.8 ± 12.5 **Sex:** Pentamidine: 12 male, 3 female; aminosidime: 9 male, 6 female; glucantime: 9 male, 7 female. **Baseline imbalances:** no **Severity Illness:** number of lesions: 1 lesion (pentamidine 12 (80%), aminosidime 10 (66.7%), glucantime 14 (87.5%)); 2 lesions (pentamidine 3 (20%), aminosidime 5 (33.3%), glucantime 2 (12.5%)). Location of lesions: lower limbs (pentamidine 12 (80%), aminosidime 11 (73.3%), glucantime 10 (62.5%)); others (pentamidine 3 (20%), aminosidime 4 (26.7%), glucantime 6 (37.5%))
Interventions	**Type of interventions:** • **Pentamidine:** received pentamidine at a dose of 4 mg/kg/day, IM in varying locations on alternate days for a total of 8 applications • **Aminosidime:** received aminosidine 20 mg/kg/day, IM, at various sites, for 20 days • **Glucantime:** meglumine dose of 10 mg/kg/day, IM in different locations, for 20 days **Duration of intervention:** 20 days **Co-interventions:** None
Outcomes	**Definition:** • ***Clinical cure:*** A cure was defined to be a participant whose previous ulcer (crater and border) had undergone complete re-epithelialisation. **Time points reported:** before and after treatment and every 3 months for 1 year **Adverse effects:** They were not detected
Notes	**Ethical approval needed/obtained for study**: The protocol was approved by the ethics committee of the Universidade de Brasília and Universidade Federal da Bahia **Informed consent obtained:** the consent was obtained in writing, from participants or their guardians, or both

Correia 1996 *(Continued)*

Study funding sources: Núcleo de Medicina Tropical e Nutrição. Convênio FUB/OMS-28100121; NIH Grant: Al-30639 e PCDEN/Ministério da Saúde do Brasil

Possible conflicts of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...a field study was conducted on randomized treatment of patients with primary cutaneous leishmaniasis" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote:"Realizou-se um estudo prospectivo, aberto, em face à toxicidade dos compostos..." Translated quote: Prospective, open-label study was carried out to assess the toxicity of the compounds Comment: Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section.
Other bias	High risk	Sample size calculation was not adequately reported

Cossio-Duque 2015

Study characteristics

Methods	**Study design:** Randomised, double-blind, "Add on" placebo-controlled trial **Setting/location:** In 2 centres in Colombia **Period of study:** not reported **Sample size calculation:** not reported
Participants	**Type of Leishmania:** cutaneous leishmaniasis **Inclusion criteria:** Age 18 - 65 years; lesion > 1 month evolution; multiple lesions or single lesion ≥ 3 cm **Exclusion criteria:** not reported **Randomised:** 75 (but 73 assigned to intramuscular Meglumine antimoniate (MA) + pentoxifylline (N = 36) and intramuscular MA + placebo (N = 37)) .

Cossio-Duque 2015 *(Continued)*

	Withdrawals: 2 (unknown group) **Patients assessed:** 70 participants were assessed by ITT analysis (intramuscular MA + pentoxifylline (N = 2/36) and intramuscular MA + placebo (N = 1/37) lost), and 48 per protocol (PP) **Age (years) and sex:** 18 - 65 years but sex unknown **Baseline data:** not reported
Interventions	**Type of interventions:** • **Intervention:** intramuscular MA (20 mg/ kg /day x 20 days) plus oral PTX 400 mg thrice daily • **Control:** MA plus placebo. **Duration of intervention:** 20 days **Co-interventions:** not reported **Duration of follow-up:** 26 weeks
Outcomes	**Definition:** • ***Clinical cure:*** not reported. Treatment failure was assessed **Adverse effects:** not defined. **Time points reported:** end of treatment 5, 7, 13 and 26 weeks
Notes	**Baseline imbalances:** not reported **Ethical approval needed/obtained for study**: The protocol was approved and monitored by the institutional ethical committee **Informed consent obtained:** not stated **Study funding sources:** The study was financed by COLCIENCIAS Contracts 253 - 2010 **Possible conflicts of interest:** Not reported Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Seventy-five parasitologically diagnosed patients were randomly allocated by computer” Comment: randomisation method was probably adequate
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided

Cossio-Duque 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Analyses were reported by ITT and by protocol. Reasons for dropouts were not provided MA+ pentoxifylline group: 2 participants were not analysed. MA +placebo group: 1 participant was not analysed
Selective reporting (reporting bias)	Low risk	Study protocol not available but all outcomes described in the Methods section were reported in the Results.
Other bias	Unclear risk	There was insufficient information to evaluate the risk of bias

D'Oliveira 1997

Study characteristics	
Methods	**Study design:** Open controlled trial **Setting/location:** Corte de Pedra, Salvador Bahia, Brasil **Period of study:** Not described **Sample size calculation:** Not described
Participants	**Type of Leishmania:** cutaneous leishmaniasis caused by *L. braziliensis* **Inclusion criteria:** aged 12 to 45 years, with leishmania-positive skin test and a maximum of 3 ulcerated lesions (with a minimum lesion diameter of 10 mm and a maximum diameter of 50 mm) who had received no previous treatment **Exclusion criteria:** chronic disease, use of other drugs, history of allergy to allopurinol, pregnancy, breast feeding, or forms of leishmaniasis other than cutaneous **Randomized:** 34: 18 in the allopurinol group and 16 in the antimonial group **Withdrawals:** 8 (50%) of the 16 participants in the antimonial group had completely healed ulcers after the 90-day follow-up period. In contrast, when the results for the first 9 participants in the allopurinol group were analysed, none of the participants had completely healed lesions within 3 months. One of these 9 participants had progressed to develop mucosal disease. The other 9 participants in the allopurinol group were not included in the evaluation because the protocol was broken and antimonial was administered before 90 days of treatment **Patients assessed:** 25 **Age (years) and sex:** Allopurinol group: age 24.8 years Antimonial group: age 27.7 years **Baseline data:** Allopurinol group: Disease duration prior to treatment 38.0 days; site of the lesion: above diaphragm 4, below diaphragm 18; number of lesions per participant: 15 had 1, 2 had 2, 1 had 3; lesion area prior to treatment 371.8 mm^2 Antimonial group: Disease duration prior to treatment 31.9 days; site of the lesion: above diaphragm 12, below diaphragm 11; number of lesions per participant: 10 had 1, 5 had 2, 1 had 3; lesion area prior to treatment 341.4 mm^2

D'Oliveira 1997 *(Continued)*

Interventions	**Type of interventions:** 20 mg/kg of allopurinol orally, 3 times a day, or 10 mg/kg of intravenous antimoniate of meglumine, once a day. Both groups used the drugs for a period of 20 days **Duration of intervention:** 20 days **Co-interventions:** Not described. **Duration of follow-up:** 1 year
Outcomes	**Definition:** • ***Therapeutic failure*** included incomplete use of treatment protocol, use of a treatment different from the protocol, lesions not healed 3 months after the beginning of treatment, or relapse or development of new cutaneous or mucosal lesions caused by leishmaniasis within 1 year of treatment **Adverse reactions:** Not described. **Time points reported:** Participants were re-examined on days 10 and 20 and at monthly intervals for 1 year following the beginning of treatment
Notes	**Baseline imbalances:** not stated **Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** Informed consent was obtained from all participants after the nature of the procedures had been fully explained to them **Study funding sources:** The Financiadora de Pesquisas (FINEP) and NIH Grant A.I. 30639 provided financial support **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomly selected patients received 20 mg/kg of allopurinoi orally, or 10 mg/kg of intravenous antimoniate of meglumine." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This open controlled trial included 34 patients..." Comment: Open controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open controlled trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: “The study protocol was stopped prematurely because of the clear difference in cure rates observed between the two patient groups after 90 days of follow-up, and the development of mucosal disease in two (11%) of the 18 patients (mucosal leishmaniasis was only documented in 3% of patients with a previous history of cutaneous ulcer treated with antimonials”

D'Oliveira 1997 *(Continued)*

		Comment: study ended early so information on attrition bias for whole length of study not known
Selective reporting (reporting bias)	Unclear risk	Not described.
Other bias	Unclear risk	There was insufficient information to evaluate the risk of bias

Echevarria 2006

Study characteristics	
Methods	**Study design:** Open and randomised trial **Setting/location:** Cuzco, Peru **Period of study:** April 1994 to January 1995 **Sample size calculation:** The sample size was estimated in 48 participants, 24 participants in each study group, to detect a difference in the incidence of hypokalaemia of 40% between study groups with an alpha error of 0.05 and a beta error of 0.2
Participants	**Type of Leishmania:** *Leishmania braziliensis* **Inclusion criteria:** Eligible patients were adults between 18 and 60 years of age with clinically-suspected muco-cutaneous leishmaniasis presumably caused by *Leishmania braziliensis* v. *braziliensis* with indication to receive amphotericin B deoxycholate (AB), either because they had failed conventional treatment with 2 regimens of pentavalent antimonials, or because they had extensive muco-cutaneous disease with laryngeal involvement. Attempts to microbiologically confirm the diagnosis were made using a Giemsa stain of an aspirate from a mucosal site, culture of an aspirate or tissue obtained by biopsy, or by a specific PCR applied to a tissue sample **Exclusion criteria:** People with history of allergy to AB or who had received AB in the week before recruitment were excluded, as well as pregnant or nursing women, people with severe underlying medical conditions including renal disease, cardiac disease, chronic liver disease, alcohol abuse, tuberculosis, and HIV infection. Patients receiving other nephrotoxic drugs, such as amino glycosides, antivirals, nonsteroidal anti-inflammatory drugs, and cyclosporine were also excluded. We also excluded patients who had baseline creatinine values above 1.5 mg/dl, haemoglobin levels below 10 gr/dl, and serum albumin concentration below 3 gr/dl **Randomized:** 48 patients were included (ORS: 25, SS: 23) **Withdrawals:** 0 **Patients assessed:** 48 patients were included in the study, 23 in the SS group and 25 in the ORS group. **Age (years) and sex:** All patients were male. Age in years, mean ± SD: SS group: 35.8 ± 11.4 ORS group: 38.8 ± 10.6 **Baseline data:** Weight in kg, mean ± SD: SS group 53.1 ± 7.0, ORS group 53.7 ± 3.2. Duration in months of mucosal involvement, mean ± SD: SS group 78.4 ± 65.2, ORS group 67.5 ± 49.0. Previous treatment with pentavalent antimonials, n (%): SS group 18 (78), ORS group 17 (68). Laryngeal involvement, n (%): SS group 22 (96), ORS group 22 (88). Parasitological confirmation, n (%): SS group 22 (96), ORS group 22 (88). Haemoglobin, g/dl, mean ± SD: SS group 15.6 ± 1.4, ORS group 15.4 ± 1.4. White blood cells, cells/l, mean ± SD: SS group 7.7 ± 1.1, ORS group 7.6 ± 1.5. creatinine, mg/dl, mean ± SD: SS group 0.7 ± 0.2, ORS group 0.7 ± 0.1. Blood urea, mg/dl, mean ± SD: SS group 25.2 ± 6.7, ORS group 22.2 ± 7.3. creatinine clearance, mil/min, mean ± SD: SS group 73.6 ± 14.0, ORS group 73.0 ± 19.5. Serum sodium, mEq/

Echevarria 2006 *(Continued)*

	L, mean ± SD: SS group 140.0 ± 14.5, ORS group 136.1 ± 13.8. Serum potassium, mEq/L, mean ± SD: SS group 5.6 ± 1.7, ORS group 6.1 ± 1.7
Interventions	**Type of interventions:** • Intravenous normal saline solution (SS group): received 1 L of the solution 60 minutes before starting the infusion of AB (sodium 153 mEq/l, chloride 153 mEq/L, osmolarity 306 mosm/L) • Oral rehydration solution (Laboratorios Luza, Lima, Peru) (ORS group): received 1 L of a solution containing: 90 mEq/L of sodium, 104 mEq/L of chloride, 22 mEq/L of bicarbonate, and 12 mEq/L of potassium, osmolarity 290 mosm/L, 60 minutes before starting the infusion of AB, and 2 L throughout the rest of the day, for a total of 3 L per day **Duration of intervention:** 7 months **Co-interventions:** Patients in both groups received AB (Fungizone, Bristol Myers Squibb, Bedfordview, NJ) for the treatment of leishmaniasis, at a daily dose of 0.6 mg/kg until attaining a cumulative dose of 25.2 mg/kg **Duration of follow-up:** 42 days
Outcomes	**Definition:** The primary outcome of the study was the effect of the 2 interventions on renal function while receiving AB therapy. Renal function was evaluated with periodic measurements of serum creatinine, urea, creatinine clearance (collecting 24-hour urine), and electrolytes, including serum sodium and potassium at baseline, and on treatment days 8,16, 24, 32, and 42 **Time points reported:** days 8,16, 24, 32, and 42
Notes	**Ethical approval needed/obtained for study**: Ethical approval from Universidad Peruana Cayetano Heredia's Institutional Review Board was obtained **Informed consent obtained:** Participants gave written consent to participate in the study **Baseline imbalances:** All participants were male. Baseline values for serum potassium were unexpectedly high but comparable in both treatment groups **Study funding sources:** Instituto de Medicina Tropical Alexander von Humboldt **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomly allocated to the two study groups using a computer generated random table." Comment: randomisation sequence method described.
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "it was conducted in a randomized but open fashion. Double masking the two interventions was not possible to achieve." Comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided

Echevarria 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Insufficient reporting of attrition/exclusions to permit judgement of Low risk or High risk (e.g. number randomised not stated), no reasons for missing data provided
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	There was insufficient information to evaluate the risk of bias

Ferreira 2014

Study characteristics	
Methods	**Study design:** Controlled clinical trial randomised, double-blind and phase III **Setting/location:** Rio de Janeiro, Brasil **Period of study:** 2008 - 2013 **Sample size calculation:** not stated
Participants	**Type of Leishmania:** *Leishmania (Viannia) braziliensis*. **Inclusion criteria:** people with mucocutaneous leishmaniasis (MCL) **Exclusion criteria:** pregnant women, people on immunosuppressive therapy, presence of severe basal clinical alteration similar to adverse effect (AE) grade ≥ 3 (G3); laboratory anomaly grade ≥ 2 (G2) or corrected basal QT interval ≥ 0.46 seconds, equivalent to grade 3 (G3) **Randomised:** 20 participants with MCL (High dose n = 10; Low dose n = 10) **Withdrawals:** Of the 20 eligible patients, 3 were excluded for breach of the treatment protocol and 5 did not finish treatment due to adverse affects **Patients assessed:** 17 studied participants and 12 completed treatment **Age (years) and sex:** 35 to 77 years, 80% were male (M/F: 16/4) **Baseline data:** 94.1% acquired infection in the Southeast, The mucosal lesion location was in decreasing order, 82.4% in the nasal cavity, 58.8% in the oropharyngeal cavity and 17.6% in the larynx. The nasal cavity was the only structure affected in 41.2% cases. Nasal obstruction was reported by 11 participants; crust, bleeding and rhinorrhoea by 10; odynophagia and dysphagia by 6 and cough and dysphonia by 4 participants. The distribution of the social-demographic and clinical characteristics was homogeneous between the 2 treatment groups.
Interventions	**Type of interventions:** • High-dose group: 20 mg Sb5 +/kg/day for 30 continuous days • Low-dose group: Sb5 + 5 mg/kg/day continued until cured, with a limit of 120 days of treatment **Duration of intervention:** high dose for 30 days, low dose for maximum 120 days **Co-interventions:** not reported **Duration of follow-up:** 1 year
Outcomes	**Definition:** • ***Immediate clinical healing*** was characterised by mucosal lesion epithelialisation and scarring within 120 days after beginning treatment

Ferreira 2014 *(Continued)*

- ***Delayed clinical healing*** was characterised by the maintenance of the mucosal lesions scars within one year after the end of treatment
- ***Treatment failure*** was characterised by the absence of response to a treatment scheme within 120 days after beginning treatment
- ***Recurrence*** was characterised by reappearance of the lesion after clinical healing
- ***Adverse effects***

Time points reported: every 10 days during treatment and 1, 3, 6, 9 and 12 months after the end of treatment

Notes	**Ethical approval needed/obtained for study**: This study was approved by the Ethics Committee on Research /IPEC under the number -005.0.009.000-07) **Informed consent obtained:** All participants signed an informed consent form **Baseline imbalances:** 80% of participants were male **Study funding sources:** FIOCRUZ **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomly divided into groups of “high dose” and “low dose"" Comment: Does not describe the process of randomisation
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Randomized controlled trial, double-blind” Comment: assume participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: “Randomized controlled trial, double-blind” Quote: “To keep the blind quality of the test in relation to treatment efficiency, an otolaryngologist of the team evaluated patients before beginning treatment” Comment: not clear if all outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	60% of participants completed treatment
Selective reporting (reporting bias)	Low risk	All of the study’s prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way
Other bias	High risk	Leishmania sp was not confirmed and sample size was not adequately reported

Figueiredo 1999

Study characteristics	
Methods	**Study design:** Randomised, double-blind **Setting/location:** Brazil. The treatment of cutaneous form was performed in a medical post in Caritinga, located in the Vale do Rio Doce; most participants were located at a maximum of 100 kilometres from the city. The treatment of the mucocutaneous form was performed at the Hospital Santa Casa de Misericordia de Belo Horizonte or the Hospital das Clinicas UFMG; patients came from various regions of the state of Minas Gerais and three other states. **Period of study:** August 1981 to March 1986 **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** cutaneous and mucocutaneous leishmaniasis (sp unknown) **Inclusion criteria:** aged between 15 and 60 years, without specific treatment, considered healthy **Exclusion criteria:** kidney, liver, heart and central nervous system diseases, has MNT reaction negative, pregnant women **Randomised:** 26 participants with cutaneous leishmaniasis and 17 mucocutaneous leishmaniasis were randomised into 2 groups with different therapeutic dose for 14 and 28 mg/kg/day **Withdrawals:** 0 **Patients assessed:** 43 participants: 26 cutaneous form and 17 mucocutaneous form **Age (years):** not stated **Sex:** not stated **Baseline imbalances:** no **Severity Illness:** NR
Interventions	**Type of interventions:** • **Group 1:** corresponding to 14 mg/kg/day dose. The drug was applied to 15% on alternating days with placebo, in 2 series of 20 days, separated by intervals of 15 days for cutaneous form. For mucocutaneous form of 3 series it was applied for 30 days at intervals of 15 days • **Group 2:** corresponding to 28 mg/kg/day dose. The drug was applied to 30% applied daily in the first half of the series and placebo in the remaining days, in 2 series of 20 days, separated by intervals of 15 days for the cutaneous form. The mucocutaneous form 3 series received 30-day intervals separated by 15 days **Duration of intervention:** 2 series of 20 days for cutaneous leishmaniasis and 3 series of 20 days to mucocutaneous leishmaniasis **Co-interventions:** not reported **Rescue therapy:** Healed lesions of the cutaneous form were subjected to histopathological examination control 2 months after treatment and mucosal lesions healed after 6 months
Outcomes	**Definition:** • ***Clinical cure:*** the cure was defined as lesion healing **Time points reported:** Participants were observed for at least 2 years after treatment

Figueiredo 1999 *(Continued)*

	Adverse effects: the drug toxicity was evaluated in the cutaneous form before the start of treatment on day 8 of the series 1, day 11 interval and then after finishing the second set. Patients in the mucocutaneous form were subjected to the same tests before treatment and at the beginning and end of each series
Notes	**Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** not stated **Study funding sources:** UNDP/World Bank/WHO Special Program for Research and Training for Tropical Diseases **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated, but it was stated that after 2 years the random generated sequence was revealed (“Ao término dos dos anos de acompanhamento, aberto o segredo do studio, verificou-se….”)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "Double-blinded", and the drugs were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	Unclear risk	There was insufficient information to evaluate the risk of bias

Franke 1994

Study characteristics

Methods	**Study design:** Randomised clinical trial **Setting/location:** Villages of Oncongate and Sicuani in the Department of Cuzco, Peru **Period of study:** not stated **Unit of randomisation:** participaent **Unit of analysis:** participant **Sample size calculation:** not stated

Franke 1994 *(Continued)*

Participants	**Type of Leishmania:** mucosal leishmaniasis caused by *L. braziliensis* **Inclusion criteria:** if cultures prepared by inoculating aspirates from mucosal lesions into Senekji´s blood agar medium were positive for *Leishmania* **Exclusion criteria:** patients who received antimonials for treatment of leishmaniasis in the previous 12 months, had significant concomitant disease of any organ, or had abnormalities on subsequent baseline test (complete blood count; serum levels of glucose, glutamate-pyruvate transaminase, bilirubin, urea nitrogen, and creatinine: electro-cardiogram; chest radiograph) **Randomised:** 40 were randomised to receive either the (P28)- or (P40)-day regimen of Pentostam **Withdrawals:** treatment was prematurely terminated due to thrombocytopenia in 3 participants, and 2 participants did not complete 6 months of follow-up **Patients assessed:** P28: 20; P40: 20 **Age (years):** P28 mean age 33.7 ± 7.3 (24 - 47); P40 mean age 30.7 ± 6.3 (22 - 42) **Sex:** All participants were male, because it is more common for men to work in the jungles **Baseline imbalances:** no **Severity Illness:** duration in years of the mucosal disease: P28 mean 2.9 ± 2.1 (0.3 - 8.5); P40 mean 2.9 ± 2.6 (0.2 - 10)
Interventions	**Type of interventions:** Receive either 28 days (P28) or 40 days (P40) of sodium stibogluconate (Pentostam) • **Intervention 1:** Pentostam 20 mg of Sb/kg of body weight/day with no upper limit of the daily dose for 28 days • **Intervention 2:** Pentostam 20 mg of Sb/kg of body weight/day with no upper limit of the daily dose for 40 days. The daily dose of Pentostam was administered in 50 ml of 5% dextrose in water by intravenous infusion over a 30 - 45-min period **Duration of intervention:** 28 or 40 days **Co-interventions:** not stated
Outcomes	**Definition:** • ***Clinical cure:*** the ulcerated or infiltrated lesions were defined as healed if they re-epithelialised or became uninfiltrated, respectively, during the 12-month follow-up period. Lesions that were oedematous or erythematous after treatment were considered healed if they did not became infiltrated or ulcerated during the follow-up period • ***Nonhealed lesion:*** was one that had not re-epithelialised or had not lost its infiltrate • ***Failure:*** a participant was defined as having failed therapy if any lesion did not heal, or relapsed or if a new lesion appeared during the follow-up period **Time points reported:** the nasal, oral, pharyngeal and laryngeal areas were examined at the end of therapy and the lesions were re-cultured at this time. The participants were re-examined at 1, 3, 6, 9, and 12 months after the end of therapy, at which times cultures were taken when clinically indicated **Adverse effects:** Patients were asked daily during treatment for symptomatic complaints including headache, dizziness, insomnia, nervousness, palpitation, abdominal pain, nausea, vomiting, diarrhoea, anorexia, itching, backache, arthralgias and myalgias
Notes	**Ethical approval needed/obtained for study**: The protocol for this study was approved by the Peruvian Ministry of Health by the scientific and ethical review committees of the U.S. Naval Medical Research Institute Detachment and by the U.S: Food and Drug Administration

Franke 1994 *(Continued)*

Informed consent obtained: Each participant gave informed consent

Study funding sources: This work was supported in part by the U.S. Naval Medical Research and Development Command, Department of the Navy work unit no. M1620A80AN521, and the U.S Army Medica. Research and Development Command Project no. 89PP9920

Possible conflicts of interest: "none declared"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized to receive either the 28- or 40-day regimen of Pentostam." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment was described
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 participants dropped out: 4 in P28 and 1 in P40. Reasons were reported: 3 participants (P28: 2 and P40: 1) had thrombocytopenia and 2 participants (P28 group) did not appear for the 6 - 12 months follow-ups.
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	High risk	Sample size was not adequately reported

Gadelha 2018

Study characteristics

Methods	**Study design:** an open-label, randomised, and controlled phase-II clinical trial **Setting/location:** at the outpatient clinic of the Service of Dermatology at FMT-HVD in Manaus, Amazonas, Brazil **Period of study:** From November 2013 to December 2015 **Sample size calculation:** The sample size was calculated by using the difference between proportions test by considering the alpha and beta errors. To achieve statistical significance, 53 individuals were sufficient for each group. The cure rate estimated for the group treated with three PI doses was 80%, and for the group treated with a single PI dose it was 58.1% at a power of 80% and a confidence level of 95%

Gadelha 2018 *(Continued)*

Participants	**Type of Leishmania:** The aetiologic agent was identified in 120 cases and distributed as follows: *L. guyanensis* (114 participants), *L. naifi* (4 participants), and *L. braziliensis* (2 participants). The diagnosis of the 39 remaining participants was confirmed through positive skin smear without species identification PCR was performed to amplify a fragment of the Hsp 70 gene and of miniexon of Leishmania sp **Inclusion criteria:** Individuals aged 16 – 64 years; 1 - 6 lesions; confirmed CL based on amastigotes visualisation in direct examination of Giemsa stained of dermal scraping from the border of the lesion; no previous treatment for CL; no abnormal values for liver enzymes: amylase, creatine phosphokinase (CPK), ALP, ALT, AST, creatinine, and glucose **Exclusion criteria:** People with history of diabetes, cardiac, renal, and hepatic disease; Inability to attend one of the study visits; Pregnancy or lactation; people with CL treated in the previous 3 months; protein–calorie malnutrition **Randomised:** 159: Group 1: 53; Group 2: 53; Group 3: 53 **Withdrawals:** 0 **Patients assessed:** 159 **Age (years) and sex:** M/F: 122 /37 **Age:** The average age was 32 years old. Number of participants per age group: < 18: Group 1: 1 (1.9), Group 2: 1 (1.9), Group 3: 2 (3.8); 18 – 36: Group 1: 30 (56.6), Group 2: 21 (50.9), Group 3: 29 (54.7); 36 – 54: Group 1: 20 (37.7), Group 2: 17 (37.7), Group 3: 20 (37.7); > 54: Group 1: 2 (3.8), Group 2: 4 (9.4), Group 3: 2 (3.8). Children accounted for 4/159 (2.5%) **Baseline data:** 84 participants had a single lesion, 34 had 2 lesions, 22 had 3 lesions, 10 had 4 lesions, 5 had 5 lesions, and 4 had 6 lesions. Most of the lesions were located in the upper limbs No. of lesions (%): 1: Group 1: 33 (62.3), Group 2: 26 (49.1), Group 3: 25 (47.2); 2: Group 1: 11 (20.8), Group 2: 10 (18.9), Group 3: 13 (24.5); 3: Group 1: 8 (15.1), Group 2: 6 (11.3), Group 3: 8 (15.1); 4: Group 1: 1 (1.9), Group 2: 8 (15.1), Group 3: 1 (1.9); 5: Group 2: 3 (5.7), Group 3: 2 (3.8); 6: Group 3: 4 (7.5)
Interventions	**Type of interventions:** • **Intervention 1:** single intramuscular injection of 7 mg/kg pentamidine isethionate (PI) salt • **Intervention 2:** 2 intramuscular injections of 7 mg/kg within a 7-day interval • **Intervention 3:** 3 intramuscular injections of 7 mg/kg with a 7-day interval between each dose **Duration of intervention:** single dose, 2 and 3 weeks **Co-interventions:** not reported **Rescue therapy:** All participants were instructed to eat carbohydrate-rich food before receiving the PI injection. Rescue therapy for clinical failure was the administration of 20 mg/Sb (meglumine antimoniate)/kg body weight per day for 20 days according to the BMH recommendation **Duration of follow-up:** Clinical evaluation was conducted at enrolment, during the treatment visits, and during the follow-up visits 1, 4, 8, and 24 weeks after treatment
Outcomes	**Definition:** *Primary outcome* Number of participants with complete healing in the diameters of the ulcers and lesions skin six months after the end of the treatment Clinical and laboratory adverse effects were graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 5.0) of the National Cancer Institute (ctep.cancer.gov/reporting/ctc.html). CTCAE consider grade 1: asymptomatic or mild; grade 2: moderate, non-invasive medical

Gadelha 2018 *(Continued)*

	intervention indicated; grade 3: severe or medically significant but not immediately life-threatening; grade 4: life-threatening; grade 5: death *Secondary outcomes* A 50% reduction in lesion diameters 2 months after the end of the treatment ***Clinical failure*** was defined as the emergence of new lesions or a 50% increase in previously-documented lesions 8 weeks after the treatment was concluded **Time points reported:** 6 months after the end of the treatment
Notes	**Ethical approval needed/obtained for study**: "The study was approved by the Research and Ethics Committee of the FMT-HVD." **Informed consent obtained:** "Written informed consent was obtained from the patients enrolled in the study. For patients under 18 years old, written informed consent was obtained from parents or legal guardians." **Baseline imbalances:** More men than women although no imbalances were seen between groups **Study funding sources**: "The author(s) received no specific funding for this work" **Possible conflicts of interest:** "The authors have declared that no competing interests exist"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by a statistician with no clinical involvement in the trial using a random allocation sequence generated by the open software available at www.randomization.com."
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence was concealed in sequentially numbered, sealed envelopes until interventions were assigned. Patients chose one envelope and accordingly [was] assigned to one of the group." Comment: We believe that envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Injections were administered by a nurse aware of the intervention allocation. Treatment assignment could not be masked to subjects due to the intramuscular injections." Comment: there is no reason to believe that participants or nurse professionals would behave differently in a way that could bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the study protocol registered at ClinicalTrials.gov (NCT02919605).
Other bias	Low risk	All information was provided

Garcia 2014

Study characteristics	
Methods	**Study design:** Randomised clinical trial, phase II **Setting/location:** Institute of Experimental Pathology (IPE) / Salta province, Argentina **Period of study:** February 2010 to December 2012 **Sample size calculation:** no information provided.
Participants	**Type of Leishmania:** Only available for 3 participants (two L. *braziliensis* and one L. *amazonensis*) **Inclusion criteria:** patients affected by mucosal Leishmaniasis, older than 12 years, with at least the previous 3 months without treatment for leishmaniasis **Exclusion criteria:** expected lack of adherence to treatment or for follow-up; contraindications for miltefosine or meglumine antimoniate; concomitant diseases **Randomised:** 19 **Withdrawals:** 1 participant abandoned the study for personal reasons **Patients assessed:** 18 **Age (years) and sex:** Mean (SD): MF group: 38 y (20); MA group: 54 y (12); M/F: 14/5 **Baseline data:** Severity score, mean (SD); MF: 17 (14), MA: 20 (3); time of evolution of disease in years, mean (SD): MF: 10.9 (14), MA: 22.7 (10.4); number of sites affected, mean (SD): MF: 3.3 (1.2), MA: 3.7 (0.7)
Interventions	**Type of interventions:** • ***Intervention group:*** oral miltefosine, 2.5 to 3.3 mg/kg/day (maximum dose 150 mg/day) • ***Control group:*** intramuscular meglumine antimoniate, 10 to 20 mg/kg/day (maximum dose 850 mg/day) **Duration of intervention:** from 28 to 35 days **Co-interventions:** not reported **Duration of follow-up:** 15 days after treatment, at 2, 6, 9 and 12 months
Outcomes	**Definition:** • ***Clinical Cure:*** > 90% decrease in the score* compared to pretreatment; • ***Clinical improvement:*** score decrease between 50% and 90%; • ***No changes:*** changes between 49% decrease to < 25% increase; • ***Clinical worsening:*** > 25% increase or recurrence. **Adverse effects:** *mucosal lesions severity score based on clinical symptoms (presence and intensity of erythema, oedema, infiltration and/or erosion; score 0 = no symptoms; 1 = light symptoms; 2 = moderate; 3 = serious) **Time points reported:** 12 months after treatment
Notes	**Ethical approval needed/obtained for study**: Yes (Ministerio de Salud Pública de Salta) **Informed consent obtained:** Yes **Baseline imbalances:** none relevant

Garcia 2014 *(Continued)*

Study funding sources: Consejo Nacional de Investigaciones Científicas y Técnicas, Fundación Bunge y Born, Agencia Nacional de Promoción Científica y Tecnológica

Possible conflicts of interest: "None declared"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random number table (GraphPad software)" Comment: method given
Allocation concealment (selection bias)	Unclear risk	Quote p 373: "Random sequence unknown for researchers" Comment: They stated that allocation on the randomisation list was unknown to the investigators but the method of concealment is not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Referred to as "Un-blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Referred to as "Un-blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT was not performed but losses to follow-up were < 20% (1/19 = 5.3%). 1 participant in the miltefosine group dropped out due to personal reasons and was not included in the 12 month- post-treatment analysis
Selective reporting (reporting bias)	Low risk	No, but protocol not available. They report side effects Clinical Registration Number: none.
Other bias	High risk	Sample size was not adequately reported

Guderian 1991

Study characteristics

Methods	**Study design:** randomized, clinical trial **Setting/location:** Ecuador **Period of study:** April to August 1998 **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL) caused by *L. panamensis, L. guyanensis, L. braziliensis*, and *L. mexicana*. The clinical diagnosis was parasitologically confirmed by culture, histopathologic analysis, Giemsa stain, and a direct immunofluorescent monoclonal antibody stain (DIFMA) **Inclusion criteria:** Participants were initially examined between April and August 1988 and were included in the study if Leishmania parasites were identified

Guderian 1991 *(Continued)*

	Exclusion criteria: Participants were excluded if they had facial or mucosal lesions, significant concomitant disease of any organ, or abnormalities on subsequent baseline laboratory tests **Randomised:** patients were randomised into 3 groups: standard therapy with Pentostam, allopurinol ribonucleoside plus probenecid (AR), and untreated controls. Because it was anticipated that few untreated patients would be cured, all participants were randomised in a ratio of 2:2:1 **Withdrawals:** 75 persons were eligible for the study; 61 of these completed treatment and at least 6 months of follow-up, and were evaluated for this report. 2 of the 30 Pentostam participants, 9 of the 30 AR participants, and 3 of the 15 untreated participants were lost **Patients assessed:** Pentostam 28; AR 21, and untreated 12 **Age (years):** Pentostam; mean 29; AR: mean 25, and untreated: mean 36 years. **Sex:** M/F: 29/32 **Baseline imbalances:** no **Severity Illness:** The mean duration of at least 1 lesion self-reported by the participants was 3.6 months. For the groups, the mean duration was: Pentostam (3.9 months), AR (3.5 months), and untreated (3.2 months)

Interventions	**Type of interventions:**
	
	• **Intervention group:**
	  • Pentostam: 20 mg Sb/kg day, with no upper limit on daily dose, for 20 days intramuscularly
	  • Allopurinol ribonucleoside (1500 mg daily orally) plus probenecid (500 mg daily orally) for 28 days
	• **Control group:** untreated controls.
	
	Duration of intervention: Pentosmtam 20 days and allopurinol ribonucleoside 28 days. For the untreated controls the end of therapy was defined as 20 days after entering into the study
	
	Co-interventions: not reported

Outcomes	**Definition:** • ***Clinical cure:*** If the lesion had > 80% re-epithelialised by the first follow-up at 1½ months • ***Failure:*** If the lesion had < 80% re-epithelialised by the first follow-up at 1½ months • ***Relapse:*** If the lesion enlarged after initial healing **Time points reported:** The long and short axes of each lesion were measured by 1 observer to the nearest millimetre at the following times: prior to and after 1, 2 and 3 weeks of therapy, and after 4 weeks of therapy with allopurinol ribonucleoside. Participants in all groups were seen at 1½, 3, 6, and 12 months after the end of therapy **Adverse effects:** NR
Notes	**Ethical approval needed/obtained for study**: The protocol for this study was approved by the Central University of Ecuador and by the US Food and Drug Administration **Informed consent obtained:** participants signed informed consent **Study funding sources:** not stated **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

Guderian 1991 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "All patients were randomized in a ratio of 2:2:1" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment was described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 14 out of 75 (18.67%). Reasons were not reported Pentostam group: 2/30; AR group: 9/30; Untreated: 3/15
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section.
Other bias	High risk	Sample size calculation was not adequately reported

Guzman-Rivero 2014

Study characteristics	
Methods	**Study design:** Pilot randomised clinical trial **Setting/location:** healthcare centres of Isiboro-Secure park,Villa Tunari Hospital Cochabamba province; Bolivia **Period of study:** not stated **Sample size calculation:** not stated
Participants	**Type of Leishmania:** Not reported but in the introduction they stated that *L. braziliensis* was endemic in Bolivia **Inclusion criteria:** age 15 - 50 years, diagnosis of cutaneous leishmaniasis by any of the 2 laboratory tests described below, and no history of previous leishmaniasis episodes **Exclusion criteria:** mucosal or mucocutaneous leishmaniasis, presence of more than 2 cutaneous lesions, pregnancy, lactation, use of nutritional supplements, presence of diabetes mellitus, chronic renal failure, or liver disease **Randomized:** 34 **Withdrawals:** 5 **Patients assessed:** 29 **Age (years) and sex:** Median age (y): Women: 24 (15 - 47), Men: 22 (15 - 37) M/F: 18/11

Guzman-Rivero 2014 *(Continued)*

	Baseline data: no relevant differences between groups for plasma concentration of nutrient-related compounds, haematological parameters or inflammatory markers
Interventions	**Type of interventions:** All participants received for 20 days daily intramuscular injections of pentavalent antimony (Glucantime, Sanofi Aventis Farmaceutica Ltda, Sao Paulo, Brazil), 20 mg Sb/kg/day. The physicians in the healthcare centres of Isiboro-Secure park administered the injection • ***Intervention group:*** glucantamine + zinc capsule contained 315 mg of zinc gluconate (45 mg zinc) • ***Control group:*** glucantamine + placebo capsule contained 315 mg of corn starch 1 capsule a day (zinc or placebo) was taken after a meal coinciding with the time of antimony injection during the therapy period and continued at the same time thereafter. Compliance was assessed by daily reporting of given capsule by the physicians **Duration of intervention:** 60 days for placebo or zinc capsule **Co-interventions:** not stated **Duration of follow-up:** 60 days after supplementation with zinc or placebo
Outcomes	**Definition:** • ***Assessment of lesion healing:*** The cutaneous lesions were assessed in 2 time phases, the first one at 3, 9, 15, and 20 days, concomitant with antimony treatment and then every 10 days during the last 40 days. Area of lesion (mm^2) and presence of raised edge of lesion, inflammatory halo, satellite lesions, and purulent material were measured. The area was calculated using the formula for a circle or ellipse based on measurements with a caliper. The healing of lesions was expressed as percent reduction of the initial area **Adverse effects:** NR **Time points reported:** after 20 days at the end of antimony treatment (T1) and after 60 days of supplementation with zinc or placebo (T2)
Notes	**Ethical approval needed/obtained for study**: Ethics permission for procedures involving human volunteers was obtained from the Bolivian Ethics Committee of the Medical Faculty, Universidad Mayor de San Simón and the Regional Ethics Committee, Lund, Sweden (no. 2009/171) **Informed consent obtained:** All participants completed a health questionnaire prior to entering the study and signed a consent form for inclusion into the study **Baseline imbalances:** None relevant **Study funding sources:** collaborative program between Universidad Mayor de San Simón and Lund University on Health and Nutrition supported by SIDA (Swedish International Development Agency). Further support was obtained from the EU project ECNIS2 **Possible conflicts of interest:** The authors declare no conflict of interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to receive zinc or placebo coded capsules for 60 days." Comment: No detailed information provided
Allocation concealment (selection bias)	Unclear risk	No detailed information provided

Guzman-Rivero 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label". Comment: No detailed information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT analysis were performed Losses to follow-up: IMMA + Zinc: 1/15 (6.7%) (due to low adherence to the clinical follow-up); IMMA + Placebo: 4/19 (21%) (due to low adherence to the supplementation and clinical follow-up (3) and low adherence to the antimony treatment (1))
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Other bias	High risk	Leishmania sp was not confirmed and sample size calculation was not adequately reported

Hepburn 1994

Study characteristics	
Methods	**Study design:** Open, randomised and prospective study **Setting/location:** the army medical facility in Edinburgh, UK **Period of study:** Not described **Sample size calculation:** Not described
Participants	**Type of Leishmania:** cutaneous leishmaniasis caused by *L. braziliensis* and *L. mexicana* **Inclusion criteria:** patients were British soldiers who had contracted CL in Belize and who had not received any anti-leishmanial therapy for at least 3 months **Exclusion criteria:** Not described **Randomised:** Soldiers were randomly allocated to receive either aminosidine or sodium stibogluconate **Withdrawals:** Not described **Patients assessed:** 34 soldiers were enrolled into the study: 17 received aminosidine and 17 received sodium stibogluconate **Age (years) and sex:** Aminosidine: age 23.8 years (3.6); Sodium stibogluconate: age 23.5 years (3.8) **Baseline data:** Aminosidine: weight 72.8kg (7.1); number of lesions 1.58 (1 - 5); size of lesion at start of treatment: ulcer 18.6 (14.5), induration 28.0 (17.9); site of lesion: head and neck 4, trunk 1 limbs 12 Sodium stibogluconate: weight 73.3kg (6.6); number of lesions 1.76 (1 - 3); size of lesion at start of treatment: ulcer 11.8 (5.8), induration 25.4 (13.5); site of lesion: head and neck 4, trunk 1 limbs 12
Interventions	**Type of interventions:**

Hepburn 1994 *(Continued)*

- **Intervention 1:** Aminosidine, 14 mg/kg/d (max. 1 g daily) for 20 days
- **Intervention 2:** Sodium stibogluconate, 20 mg/kg/d for 20 days

Duration of intervention: 20 days

Co-interventions: Not described.

Duration of follow-up: the participants were followed for at least 6 months to ensure the lesion did not reactivate

Outcomes	**Definition:** Lesions were considered to have clinically healed when the ulcer had completely re-epithelialised and the scar was flat and non-indurated. Parasitological cure was defined as the absence of amastigotes and a negative culture **Adverse effects** **Time points reported:** during treatment, and again 2 weeks after treatment had finished. 6 weeks after the end of treatment
Notes	**Ethical approval needed/obtained for study**: EIt was approved by the Army Medical Services Research and Ethics Committee **Informed consent obtained:** All the participants gave their written informed consent **Study funding sources:** not stated **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Soldiers were randomly allocated to receive either aminosidine 14 mg/kg/d (max. 1 g daily) or sodium stibogluconate 20 mg/kg/d." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was open
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was open
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing results data
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	High risk	Sample size calculation was not adequately reported

Hu 2015

Study characteristics	
Methods	**Study design:** Randomised, single-blinded non-inferiority trial **Setting/location:** outpatient clinic of the Dermatology Service in Paramaribo. Suriname **Period of study:** 03 January 2010 - 30 April 2013 **Sample size calculation:** 70 participants per group were required to be 80% sure that the lower limit of a 90% 2-sided confidence interval will exclude a difference in favour of the standard 3-day regimen of more than 15% (non-inferiority margin), assuming a 85% clinical cure for both groups. The 15% non-inferiority margin was determined by consensus of a panel of dermatologists experienced in the treatment of CL and is in line with a similar study
Participants	**Type of Leishmania:** Not confirmed but reported that In Suriname CL is endemic and mainly caused by *L. guyanensis* **Inclusion criteria:** Eligible individuals were ≥ 16 years with laboratory-confirmed CL (histopathology and/or Giemsa smear of biopsy) who could be contacted by phone **Exclusion criteria:** CL patients treated in the previous 6 months, pregnancy or lactation, unable to attend 1 of the study visits, medical history of diabetes mellitus, cardiac, renal and hepatic disease, abnormal baseline values for amylase, AST, ALT, creatinine, glucose, haemoglobin, leucocytes, thrombocytes, and patients with known allergy to PI. **Randomised:** 163 **Withdrawals:** Study compliance was lower in the 3-day regimen group: at 6 weeks follow-up 32.9% (26/79) was either lost to follow-up (23) or did not show up (3) compared to 17.9% (15/84) in the 7-day regimen group, the difference being statistically significant (P = 0.013). At 12-week visit 40.5% (32/79) and 29.8% (25/84) respectively were lost to follow-up, the difference not being statistically significant (P = 0.074) **Patients assessed:** 84 + 79 analysed by ITT at 6 and 12 weeks **Age (years) and sex:** average age 7-day regimen: 33 y (16 - 59); 3-day regimen: 30 (18 - 75); M/F: 150/13 **Baseline data:** No. of lesions per participant (%): 7-day regimen, 3-day regimen: 1: 44 (52.4%) 40 (50.6%); 2: 15 (17.9%) 14 (17.7%); ≥ 3: 25 (29.8%) 25 (31.7%) Median no. of lesions (range): 7-day regimen 1 (1 – 101), 3-day regimen 1 (1 – 81)
Interventions	**Type of interventions:** • ***Intervention group:*** *2* intramuscular injections of 7 mg/kg pentamidine isethionate salt on days 1 and 3 (3-day regimen) • ***Control group:*** pentamidine isethionate 3 intramuscular injections of 4 mg/kg on days 1, 4 and 7 (7-day regimen) **Duration of intervention:** 3 - 7 days **Co-interventions:** none **Duration of follow-up:** 12 weeks after treatment.
Outcomes	**Definition:** Primary endpoint was clinical cure six weeks after end of treatment

Hu 2015 *(Continued)*

	Clinical cure was defined as complete re-epithelisation and absence of inflammatory signs (infiltration, erythema and/or scaling). ***Therapy failure*** was observed in case of incomplete re-epithelisation and/or inflammatory signs The secondary endpoints were clinical cure at 12 weeks, parasitological cure at 6 and 12 weeks, adverse and drug-related toxicity events 1 week after the end of treatment and HRLQ differences before treatment and at 6 weeks follow-up visit **Time points reported:** 6 weeks and 12 weeks
Notes	**Ethical approval needed/obtained for study**: This study was approved by the Medical Ethical Commission of the Ministry of Health Suriname (VG 006-2009) **Informed consent obtained:** Written informed consent has been obtained from all participants **Baseline imbalances:** none relevant. **Study funding sources:** Netherlands Foundation for Scientific Research/ Foundation for the Advancement of Tropical Research – Science for Global Development (NWO/WOTRO) [grant number WO16531300]. **Possible conflicts of interest:** The authors have declared that no competing interests exist

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by a computerized balanced block randomization scheme that was stratified on disease severity based upon the presence or absence of clinical loco regional lymphadenitis." Comment: randomisation method described
Allocation concealment (selection bias)	Unclear risk	Quote: "Injections were administered by the dermatologist aware of the intervention allocation." Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded for both
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Two independent blinded dermatologists with at least four years of diagnostic CL experience determined clinical cure (using standardized photographs of lesions). In case of disagreement a third blinded dermatologist passed the final judgment." Comment:
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis were performed. Losses to follow-up: Intervention (3-day regimen): 33/79 (41.7%); Control (7-day regimen): 27/84 (32.1%) Lost to follow-up in both groups but the difference was not statistically significant
Selective reporting (reporting bias)	Low risk	All expected relevant outcomes reported. Dutch Trial Register (NTR 2076).

Hu 2015 *(Continued)*

Other bias	High risk	*Leishmania* sp was not confirmed

Krolewiecki 2007

Study characteristics	
Methods	**Study design:** Randomised open-label study **Setting/location:** ambulatory setting; patients who came to the Instituto de Investigaciones en Enfermedades Tropicales at the Universidad Nacional de Salta in Orán, Argentina **Period of study:** March 2003 to September 2005 **Sample size calculation:** Calculations for sample size and confirmatory analysis were determined with an alpha of 0.05 and a power of 0.80, assuming a cure rate of 95% for MA and 65% for azithromycin according to the protocol definition of clinical cure and a 1:1 randomisation between groups
Participants	**Type of Leishmania:** *Leishmania* (*Viannia*) *braziliensis* identified in 17 patients **Inclusion criteria:** Patients with parasitologically-proven cutaneous leishmaniasis were eligible to participate in the study if they were ≥ 14 years of age, had lesions not longer than 3 months, and had stable residency in the area **Exclusion criteria:** if they had received any drug with activity against Leishmania in the previous 3 months, if they had mucosal lesions, electrocardiographic abnormalities that would pose a risk for the use of antimonial drugs, were pregnant or breastfeeding, or had other diseases or laboratory abnormalities that would compromise the analysis, such as elevated levels of transaminases (> 3 times the upper normal limit), active tuberculosis or immunodeficiencies (patients infected with HIV were excluded if they had CD4 cell counts < 200 cells/µL) **Randomized:** 45 **Withdrawals:** 0 **Patients assessed:** 45 **Age (years) and sex:** Age in years (mean ± SD): MA: 37 ± 11, AZ: 33 ± 13; M/F: 39/6 **Baseline data:** 33 participannts 1 lesion only, 7 participants 2 lesions, 4 participants ≥ 3 lesions
Interventions	**Type of interventions:** • ***Intervention group:*** Azithromycin (Zitromax"; Pfizer, New London, CT) was prescribed orally in 500 mg tablets at a dose of 2 tablets on the first day, followed by 1 tablet every 24 hours for another 27 days • ***Control group:*** Meglumine antimoniate (5 mL vials containing 1.5 g of antimony, corresponding to 425 mg of pentavalent Sb) intramuscular (the intravenous route was used for participants intolerant of the intramuscular route). A second cycle at the same doses and lasting 15 days (so not to delay the administration of standard care to treatment failures) was indicated for participants with clinical improvement without resolution 14 days after completing the first cycle. Participants were evaluated at baseline visit and then at days 14 and 28 during treatment. The dosing regimen for MA was based on the standard therapy in the study area, which has demonstrated a short-term efficacy of > 95% in an observational study. The dosing regimen for azithromycin was chosen on the basis of a duration that would equal that of MA for better comparison, at a dose with predictable acceptable tolerance **Duration of intervention:** 28 days **Co-interventions:** not stated **Duration of follow-up:** 12 months

Krolewiecki 2007 *(Continued)*

Outcomes	**Definition:** • ***Cure:*** a lesion was considered cured when it had complete re-epithelisation without signs of disease activity or inflammation, and remained so for 12 months after completing therapy • ***Time to clinical cure*** was calculated as the time in days elapsing from baseline to the moment a lesion was considered cured according to the study definition • ***Treatment failure*** was defined as the absence of cure of all lesions after 30 days of completion of treatment, new lesions after 48 hours of treatment, and mucosal lesions and/or relapse of cutaneous lesions within 12 months after treatment completion. Participants with lesions that were progressing after the first cycle were also considered treatment failures • ***Safety*** was assessed by the frequency and severity of adverse effects and laboratory abnormalities **Time points reported:** after 1 and 2 cycles, and at 1 year after completing the therapy
Notes	**Ethical approval needed/obtained for study**: The study protocol and the informed consent form were reviewed and approved by an independent ethics committee and by Provincial, National and University authorities **Informed consent obtained:** Yes (see above) **Baseline imbalances:** None relevant **Study funding sources:** supported by an educational grant from Pfizer and by research grant Ramón Carrillo-Arturo Oñativia 2002. CONAPRIS Res. 170/02 from the Ministerio de Salud- Presidencia de la Nación Argentina **Possible conflicts of interest:** Nothing declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote page 641: "The randomization sequence was obtained from a computer- generated random number table, the details of the series were unknown to the investigators and were contained in sealed envelopes sequentially numbered, each having on the outside only the name of the study, the strata, and the number." Comment: randomisation method described
Allocation concealment (selection bias)	Low risk	Quote page 641: "After acceptance of the patient to participate in the study and completion of the screening procedures, the appropriately numbered envelope was opened and the card indicated which treatment the patient would receive." Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote page 641: “All the authors participated in the design of the study, had access to all study data and take responsibility for data analysis.” Comment: Open-label. But the determination of the outcomes of treatment were performed by the trial physicians and by the physicians at the local hospital, who were not involved with the study
Incomplete outcome data (attrition bias)	Low risk	ITT analyses were performed, with the exception of cure at 6 mo for the MA group

Krolewiecki 2007 *(Continued)*

All outcomes		Losses to follow-up < 20%: 1/45 (2.2%). At 12 months of follow-up, a participant receiving MA moved away from the area and was lost to follow-up, although he had healed by the second month after completing therapy
Selective reporting (reporting bias)	Low risk	No study protocol available, but they report all relevant outcomes No clinical trials register number
Other bias	Low risk	All information was provided

Llanos-Cuentas 1997

Study characteristics	
Methods	**Study design:** randomized, open, controlled, comparative clinical trial. **Setting/location:** Subjects were recruited from two patients associations and two medical center in Cusco, Peru **Period of study:** January 1989 to February 1992. **Unit of randomisation:** patient **Unit of analysis:** patient **Sample size calculation:** - **Phase 1:** patients with severe and moderate. They calculated a sample size of 44 patients to detect a difference of efficacy of at least 40% (we expected a cure rate of 50% to be associated with sodium stibogluconate plus allopurinol). - **Phase 2:** only patients with moderate disease. The sample size was calculated as 59 patients to detect a difference of efficacy of 40% between both regimens (they expected a cure rate of 40% to be associated with sodium stibogluconate alone and a cure rate of 80% to be associated with sodium stibogluconate plus allopurinol), with an a error of 0.05 and a β error of 0.80 (considering losses of 5%).
Participants	**Type of Leishmania:** mucocutaneous leishmaniasis (MCL) caused by *Leishmania braziliensis* complex. **Inclusion Criteria:** Patients with severe or moderate MCL with age between 15 to 60 deemed sufficiently serious or when the patient developed any years of age were eligible for study enrolment if they had a systemic disease. **Exclusion Criteria:** Clinically similar diseases (such as tuberculosis, leprosy, lymphoma, and paracoccidioidimycosis), series concomitant diseases, pregnancy, known or suspected allergy to Sb5+ or allopurinol, and use of Sb5+, allopurinol, amphotericin B, or ketoconazole in the last 6 months before the study. **Randomized:** 81 **Withdrawals:** 0 **Patients assessed:** 22 patients in phase 1 and 59 in phase 2 were randomized to either group A (sodium stiboglu stibogluconate alone) or group B (sodium stibogluconate plus allopurinol). Phase 1: 11 group A and 11 group B; phase 2: 30 group A and 29 group B. **Age (years):** mean age phase 1: group A 34.3±6 and group B 36.1±8.6; phase 2: group A 33.0±7.9 and group B 32.8±8.9. **Sex:** All patients were males. **Baseline imbalances:** not stated

Llanos-Cuentas 1997 *(Continued)*

	Severity Illness: mean duration of disease in months phase 1: group A 105.1±55 and group B 71.9±23.4; phase 2: group A79.9±53.1 and group B 75.9±53.1. Mean duration of mucosal disease phase 1: group A 33.6±18.9 and group B 34.9±25.6; phase 2: group A 34.2±28.1 and group B 37.9±41.9
Interventions	**Type of interventions:** The study was divided into two phases because the rate of cure of MCL varies with the severity of the disease. • **Group A:** sodium stibogluconate alone (20 mg of Sb5// [kgrd] iv) for 28 days. • **Group B:** sodium stibogluconate (20 mg of Sb5//[kgrd]iv) plus allopurinol (20 mg/[kgrd] orally in four divided doses) for 28 days. **Duration of intervention:** 28 days **Co-interventions:** not stated
Outcomes	**Definition:** • ***Clinical cure:*** complete clinical healing of the lesions with disappearance of edema, induration, or other inflammatory signs (complete scarring or epithelialization) and negative culture or PCR tests for at least the 12-month follow-up period. • ***Clinical failure:*** both primary treatment failure and relapse apart from the results of culture or PCR analysis. **Time points reported:** 12-month follow-up period • **Adverse effects:** Side effects were managed according to by culture and/or PCR analysis. Before the administration of the next dose of therapy, the patients were asked daily about the presence of any new symptom. The adverse effects were recorded during a structured interview with a checklist.
Notes	**Ethical approval needed/obtained for study**: All changes in the study design were made and formalized by the I-CHEM Steering Committee of the Special Programme for Research and Training in Tropical Diseases of the World Health Organization (Geneva) and the Ethical Committee of Universidad Peruana Cayetano Heredia (Lima, Peru). **Informed consent obtained:** patients gave written informed **Study funding sources:** This work was supported by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (ID maniasis in Kenya was variable, with cure rates ranging from project 880174). **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At enrolment time, the patients were randomized according to a permuted-blocks scheme with a block size of 10 patients." Comment: randomisation methods considered adequate.
Allocation concealment (selection bias)	Unclear risk	It was not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias)	Unclear risk	Open study

Llanos-Cuentas 1997 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Two of 22 patients in phase 1 withdrew from the study, one because of severe thrombocytopenia and one because of anaemia. Nine of the 59 patients in phase 2 withdrew from the study because of toxicity related to the treatment. Therefore, 20 patients in phase 1 and 50 in phase 2 were included in the analysis of efficacy. Ninety percent of patients adhered to follow-up procedures, but all were evaluated at the 12-month follow-up" Comment: attrition bias unlikely.
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section.
Other bias	Low risk	All information was provided

Llanos-Cuentas 2007

Study characteristics	
Methods	**Study design:** Randomised open trial **Setting/location:** Cuzco, Peru **Period of study:** from October 1993 to May 1994 **Sample size calculation:** the sample size was calculated as 48 participants per study group to detect a difference in clinical cure rates of 30%, estimated as 70% with meglumine antimoniate and 40% with aminosidine sulphate, with an alfa error of 0.05 and beta error of 0.2
Participants	**Type of Leishmania:** Mucocutaneous leishmaniasis (MCL) caused by *Leishmania (Viannia) braziliensis* **Inclusion criteria:** adults between 18 and 60 years of age with moderate MCL, defined as involvement of the nasal and pharyngeal mucosa with or without laryngeal infection but without respiratory distress and with proven presence of parasites by culture, histology, and/or PCR on a biopsy specimen **Exclusion criteria:** patients who had received treatment in the previous 6 months with antileishmanial agents or who had failed on a course of treatment with amphotericin B, patients with known or suspected allergy to aminoglycosides or antimonials, pregnant or nursing women, and patients not willing to return for follow-up evaluations. Patients with severe concurrent illnesses such as tuberculosis, renal, liver, or heart disease, or alcoholism **Randomised:** 38 eligible participants were randomly allocated to the 2 study groups: aminosidine sulphate or meglumine antimonate **Withdrawals:** 0 **Patients assessed:** 38: Aminosidine sulphate: 21 and Meglumine antimoniate: 17 **Age (years) and sex:** All were men in both intervention groups. Mean age was 32.6 ± 8.4 in the aminosidine group and 33.2 ± 8.3 in the meglumine group **Baseline data:** Aminosidine group: mean of weight 55.0 ± 6.5 kg, mean duration of residence in an endemic area was 20.1 ± 32.0 months; mean duration of mucosal disease was 43.3 ± 52.2 months; active cutaneous disease 4; extension of mucosal involvement to nose, pharynx, and palate 5; nose, pharynx, palate, and epiglottis 5; and nose, pharynx, palate, epiglottis, and vocal cords 11. Meglumine antimonate group: mean weight 55.7 ± 6.4 kg, mean duration of residence in an endemic area was 19.4 ± 26.2 months; mean duration of mucosal disease was 33.2 ± 26.3 months; active cu-

Llanos-Cuentas 2007 *(Continued)*

	taneous disease 3; extension of mucosal involvement to nose, pharynx, and palate 9; nose, pharynx, palate, and epiglottis 4; and nose, pharynx, palate, epiglottis, and vocal cords 4
Interventions	**Type of interventions:** • **Intervention 1:** Aminosidine sulphate group: (AS: Gabbromicina; Carlo Erba Farmitalia, Milan, Italy), 14 mg/kg body weight, once daily, by intramuscular injection for 21 days (total dose of 294 mg/kg) • **Intervention 2:** Meglumine antimonate group: (MA: Glucantime; Rhone Poulenc Rorer, Paris, France), 20 mg of pentavalent antimonial/kg body weight in 250 mL 5% dextrose in water infused over a 20-minute period once daily for 28 days **Duration of intervention:** Aminosidine sulphate group: 21 days and Meglumine antimonate group: 28 days **Co-interventions:** not stated **Rescue therapy:** Participants were hospitalised throughout the period of treatment. No other antileishmanial drugs were allowed. A detailed history and complete physical examination was performed on admission **Duration of follow-up:** 1 year post-treatment
Outcomes	**Definition:** • **Cured**: if the lesions appeared completely healed and re-epithelialised, and there were no inflammatory changes visible 1 year after finishing treatment • **Clinical improvement**: was defined as reduction of the observed inflammatory area and no detection of parasites by culture or PCR of a biopsy specimen • **Failure:** was defined as < 50% healing of the mucosal lesion or when clinical improvement was seen but parasites were isolated on culture or PCR was positive • **Relapse:** was defined as enlargement of the initial mucosal lesion or appearance of new lesions in previously-spared mucosal or dermal areas after attaining clinical improvement or cure • **Adverse effects** **Time points reported:** Each day participants were questioned for adverse effects and were examined physically. Mucosal lesions were re-assessed at the end of treatment and every 3 months for 1 year. Parasitologic examination was repeated if lesions persisted
Notes	**Baseline imbalances:** all participants were men **Ethical approval needed/obtained for study**: Ethical approval was obtained from the Special Program for Research and Training in Tropical Diseases of the World Health Organization and from Universidad Peruana Cayetano Heredia's Institutional Review Board **Informed consent obtained:** Participants gave written consent to participate **Study funding sources:** this study was funded by a research grant from the UNDP/WOLRD Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) 930033 **Possible conflicts of interest:** the authors disclosed no conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated random table in a 1:1 ratio" Comment: randomisation method described
Allocation concealment (selection bias)	Unclear risk	Not described

Llanos-Cuentas 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further information about blinding of outcome assessment was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	Low risk	All information was provided

Lobo 2006

Study characteristics	
Methods	**Study design:** Randomised, clinical trial **Setting/location:** Bahía, Brazil **Period of study:** March 1997 to December 2000 **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL). *L. braziliensis* (endemic) **Inclusion criteria:** patients 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. They had to be willing to return for clinical and laboratory evaluation 14 and 28 d after initiating treatment and continue for clinical follow-up **Exclusion criteria:** Pregnant women were excluded, as were people who had contraindications for meglutamine antimonate (Glucantime; Rhodia) treatment, such as severe renal or cardiovascular disease **Randomised:** 37 participants were randomly placed into 2 groups, 17 receiving heat therapy and 20 receiving Glucantime **Withdrawals:** 1 participant treated with heat therapy was excluded from analysis because he had put gunpowder over his ulcer and burned it several days after day 14 evaluation **Patients assessed:** 17 receiving heat therapy and 20 receiving Glucantime **Age (years):** heat therapy: mean 34 ± 14.6, range 18 - 65; Glucantime mean 36 ± 17.2, range 18 - 67 **Sex:** M/F: 24/13; heat therapy: men 9 (53%) and women 8 (47%); Glucantime**:** men 15 (75%) and women 3 (15%) **Baseline imbalances:** no

Lobo 2006 *(Continued)*

	Severity Illness: number of lesions: 1 (heat therapy 16 (94) and Glucantime 13 (65)); 2 (heat therapy 1 (6) and Glucantime 7 (35)). Ulcer location: heat therapy (trunk 2 (12), upper limbs 3 (18), lower limbs 12 (70)); Glucantime (face 3 (15), trunk 2 (10), upper limbs 3 (15), lower limbs 12 (60)). Mean ulcer size: heat therapy 23 ± 9.3 and Glucantime 21 ± 10.2
Interventions	**Type of interventions:** • **Intervention group: Heat therapy.** This was given in a single session. The lesion was washed with saline, then iodine, and anaesthetised with 2% lidocaine. The fork-like applicator of the Thermo Surgery instrument, powered by batteries, was placed at the edge of the lesion pointing toward the centre and heat at 50 °C was applied for 30 secs, then the applicator was moved to an adjacent area until the lesion had been completely covered, taking 4 - 5 mins. The heat is completely localised and produced between the 2 electrodes of the applicator (an area approximately 3 × 4 mm). The lesion was then covered with a gauze bandage. No additional treatment was administered • **Control group: Antimony treatment.** Intravenous injections of Glucantime, 20 mg/kg/d, were given during 20 consecutive days for all participants in the antimony group starting at day 0 and to all participants in the heat therapy group after day 28. On day 14, the lesion was measured and signs of healing or secondary infection noted, and at that time another biopsy was taken for immunohistochemistry. The lesions were re-evaluated on day 28. Blood samples were taken for cytokine analysis on days 14 and 28 **Duration of intervention:** 28 days **Co-interventions:** If the lesion had a secondary infection, it was treated with local antibiotics before therapy was initiated
Outcomes	**Definition:** • ***Clinical cure:*** not stated **Adverse effects:** not stated **Time points reported:** 14 and 28 days after initiating treatment
Notes	**Ethical approval needed/obtained for study**: The protocol was approved by the IRB of the FIOCRUZ, Federal University of Bahia and Harvard School of Public Health **Informed consent obtained:** After receiving a detailed explanation of the procedures to be carried out, the participants signed an informed consent form **Study funding sources:** support of grants from NIH NIAID and the Fundaçao Bahiana de Infectologia in Salvador, Bahia **Possible conflicts of interest:** "The authors have no conflicts of interest concerning the work reported in this paper"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “At day 0, patients included in the study with a presumptive diagnosis of CL (as determined by a positive skin test and positive serology) were randomly assigned to the heat therapy or Glucantime treatment groups” Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated

Lobo 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding of personnel was provided but it is not likely to add risk of bias, being oral administration
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 1 out of 37 (2.7%)
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	High risk	*Leishmania* sp was not confirmed and sample size calculation was not adequately reported

Lopez-Jaramillo 2010

Study characteristics	
Methods	**Study design:** Double-blind, randomised placebo-controlled clinical trial **Setting/location:** Patients admitted to the local hospitals in Santander (El Carmen de Chucuri, San Vicente de Chucuri, Rionegro, El Playon, Lebrija, Cimitarra,and Landazuri), and Tolima (Rovira, Ortega, and Rio Blanco), Colombia **Period of study:** March 2007 to August 2008 **Sample size calculation:** not performed
Participants	**Type of Leishmania:** *L. panamensis* **Inclusion criteria:** male and female ≥ 10 years of age; a parasitological diagnosis of CL with demonstration of Leishmania amastigotes on smears or promastigotes in culture **Exclusion criteria:** any history of anti-Leishmania therapy in the last 3 months; presence of > 5 lesions; presence of lesions in the perimeter (< 2 cms) of mucosal areas, eyes, nose, mouth, or genitals **Randomised:** 178 (90 in the MA group and 88 in the NOP group) **Withdrawals:** 35 (13 in the MA group and 22 in the NOP group) **Patients assessed:** 143 (77 in the MA group and 66 in the NOP group) **Age (years) and sex:** M/F: 109/69 • Glucantime 58 men and 32 women, 64% of participants between 19 - 50 years • NOP 51 men and 37 women, 69% of participants between 19 - 50 years **Baseline data:** 43.8% of participants in the Glucantime group had 2 or more lesions, in comparison with 46.5% of participants in the NOP group (P = 0.9). There were no significant differences between groups in the initial size (26.4 ± 31.3 cm 2 versus 21.7 ± 33.4 cm 2, P = 0.35) or the evolution time (48.8 ± 28.6 days versus 49.0 ± 35.2 days, P = 0.67) of the lesions
Interventions	**Type of interventions:**

Lopez-Jaramillo 2010 *(Continued)*

- **Intervention 1:** Intramuscular Meglumine antimoniate (Glucantime) 20 mg/kg/day plus a placebo patch
- **Intervention 2:** Intramuscular placebo (5 – 20 cc/day), and topical nanofiber nitric oxide (NO) releasing patch (≈ 3.5 µmol NO/cm 2 /day, NOP)

Duration of intervention: 20 days

Co-interventions: not stated

Rescue Therapy: When therapeutic failure occurred, participants were treated with intramuscular Glucantime at doses of 20 mg/kg/d for 20 days

Duration of follow-up: 90 days after the beginning of the treatment

Outcomes

Definition:

- ***Clinical cure*** was defined as follows:
  - *Clinical response* when complete re-epithelisation of the ulcer was observed
  - *Clinical improvement* was determined when a decrease in the lesion size < 100% and ≥ 50% was observed
  - *No response* was registered when a decrease in the lesion size was < 50% or an increase of up to 50% of the initial size was observed
  - *Therapeutic failure* was registered when an increase ≥ 50% in the lesion size, lack of re-epithelisation at Day 90 of follow-up, or no response in 2 consecutive visits was observed
- ***Relapse:*** when a lesion appeared at the edges or center of the scar after complete re-epithelization of the lesion
- ***Reinfection:*** when a lesion appeared in a different site from the initial injury
- T**oxicity**: vital signs were recorded and examined. Laboratory tests to monitor blood creatinine, amylase, AST, and ALT concentrations were taken at baseline (Day 0) and at Day 1 after treatment (Day 21)

Adverse effects: Each day during the treatment period, participants were questioned about symptoms suggesting possible drug side effects, including fever, myalgia, arthralgia, nausea, vomiting, abdominal discomfort, hyporexia, local rash or pain, and headache

Time points reported: at Day 21 (1 day after the end of treatment) and at Days 45 and 90 after the beginning of the treatment

Notes

Ethical approval needed/obtained for study: This study was approved by the institutional review board at the Cardiovascular Foundation of Colombia, and the Health Departments of Santander and Tolima localities

Informed consent obtained: Informed consent was obtained from all participants or parents of minors before enrolment

Baseline imbalances: No statistically significant differences between groups for age, sex, body mass index and history of leishmaniasis

Study funding sources: This study was supported by a grant from the Institute for Science and Technology “COLCIENCIAS” (grant: 6566-04-18090). Melvin Yesid Rincon Acelas was also supported from a young investigator fellowship award from COLCIENCIAS

Possible conflicts of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization list was prepared using a computer program" Comment: randomisation method described

Lopez-Jaramillo 2010 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "The randomization process was blinded and centralized: once eligibility of a patient was established, the investigators informed the study headquarters. The assigned code was reported to the monitoring nurse who had no contact with the participants." Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Assigned code was reported to the monitoring nurse who had no contact with the participant" Quote: “This study was a double-blind, randomized clinical trial comparing…” Comment: assume participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: “This study was a double-blind, randomized clinical trial comparing…” Comment: Not specified whether the outcome assessor was blinded or not
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups ITT was not performed • MA group: 13/90 (13%): 9 voluntary withdrawal from the study; 3 geographic and economic difficulties to assist with follow-up visits: 1 discontinued intervention; traffic accident (number not reported) • NOP group: 22/88 (25%): 12 voluntary withdrawal from the study; 10 geographic and economic difficulties to assist to follow-up visits
Selective reporting (reporting bias)	Low risk	Study protocol not available but all outcomes described in the Methods section were reported in the Results
Other bias	High risk	Sample size calculation was not adequately reported

López 2018

Study characteristics	
Methods	**Study design:** Open-label, randomised, non-comparative phase Ib/II clinical trial **Setting/location:** recovery centre or adults attending the PECET Clinic, both locations in Colombia **Period of study:** February 2014 to July 2016 **Sample size calculation:** “It was calculated that a sample size of 36 subjects per treatment arm (36 three times per day and 36 twice per day) would provide a precision estimate of 15% with 95% CI, based on an anticipated cure rate at Day 90 of 70%. Accounting for 10% subjects lost during follow up, four more subjects were added resulting in sample size of 40 subjects per regimen, or 80 subjects in total.”
Participants	**Type of Leishmania:** CL caused by either *L. panamesis* or *L. braziliensis* (using PCR ± restriction fragment length polymorphism (PCR-RFLP)) *L. braziliensis:12; L. panamesis: 66; Both: 2* **Inclusion criteria:** Men and women, aged ≥ 18 and ≤ 60 years old, confirmed parasitological diagnosis of CL, people with ≤ 3 ulcerative lesions of ≥ 0.5 cm and ≤ 3 cm (longest diameter) not located on the ear, face, close to mucosal membranes, joints, or on a location that in the opinion of the principal investigator was difficult to maintain application of the study drug topically

López 2018 *(Continued)*

Exclusion criteria: women with a positive serum pregnancy test, breast-feeding, or of a fertile age but not agreeing to take appropriate contraception during treatment period up to Day 45; history of clinically-significant medical problems as determined by history or laboratory studies; previous use of antileishmanial drugs (within 8 weeks); or abnormal laboratory values at baseline (Hb < 10g; serum creatinine above normal level; ALT / AST 3 times above normal range)

Randomised: 80

Withdrawals: 6: Anfoleish twice a day: 2; Anfoleish thrice a day: 4

Patients assessed: 79

Age (years) and sex:

Age (Years) Median (IQR) 24 (21 ± 29); Anfoleish twice a day: 24 (21±29); Anfoleish thrice a day: 24 (21 ± 29)

M/F: 78/2: Anfoleish twice a day: 39/1; Anfoleish thrice a day: 39/1

Baseline data:

Lesions were ulcerative, and most participants had only 1 lesion (n = 72, 90%)

Size: Ulcer D1 (mm^2) Median (IQR): Anfoleish twice a day: 85.8 (37.3 ± 262.5); Anfoleish thrice a day: 59.4 (28.5 ± 174.2)

Anatomical location: Head and neck (%) twice a day: 6 (13.6); thrice a day: 6 (13.6); Thorax (%) twice a day: 2 (4.6); thrice a day: 5 (11.4); Upper limbs (%) twice a day: 30 (68.2); thrice a day: 25 (56.8); Lower limbs (%) twice a day: 6 (13.6); thrice a day: 8 (18.2)

Interventions

Type of interventions:

- **Intervention 1:** Anfoleish (amphotericin B at 3%) applied 3 times a day for 4 weeks
- **Intervention 2:** Anfoleish applied twice a day for 4 weeks

Duration of intervention: 4 weeks (28 days)

Co-interventions: not stated

Rescue therapy: Meglumine antimoniate at doses of 20 mg/SbV /kg body weight per day for 20 days as recommended by Colombian Ministry of Health guidelines was provided free of charge to all participants who met the failure criteria and those who, for whatever reason, decided to withdraw from the study

Duration of follow-up: 6 months

Evaluated on a weekly basis during the treatment, at the end of treatment (day 28) and then on day 45 ± 5 days and on Days 90 ± 14 and 180 ± 14 to assess initial and final cure respectively

Outcomes

Definition:

- ***Initial cure:*** Complete re-epithelialisation of all ulcers and complete disappearance of the induration at Day 90 after the start of treatment
- ***Final Cure:*** Initial cure plus the absence of relapses at Day 180
- ***Relapse:*** Lesion that achieved 100% re-epithelialisation by Day 90 that subsequently reopened by Day 180
- ***Failure:*** was defined as < 50% re-epithelialisation of lesion by nominal Day 45; < 100% re-epithelialisation of the lesion by nominal Day 90, and relapse of the lesion at any time between Day 90 and Day 180 and an increase of ≥ 100% in ulcer area as compare to baseline, at any time before Day 90
- **% of re-epithelialisation of the lesion(s):** was calculated by comparing the size of the ulcer at baseline against the size at the follow-up visit.

Time points reported: 180 days

López 2018 *(Continued)*

Notes	**Ethical approval needed/obtained for study**: "Approvals from Army's Research Unit and their Institutional Ethics Committee was also obtained." **Informed consent obtained:** "Recognizing the influences of the military command structure (in Colombia), the study consent was obtained by a study staff not affiliated to the army. The presence of army officers or any superior (in Colombia), at the time of the recruitment or during the consenting process was not allowed. Before entry into the study, investigators obtained written informed consent from all participants." **Baseline imbalances:** Apart from lesion size, randomisation successfully allocated participants with similar characteristics, into both treatment groups. Lesions in participants assigned to the twice-a-day group were significantly larger than the lesions of those assigned to the thrice-a-day group (P = 0.04) **Study funding sources:** "This study was supported by Drugs for Neglected Diseases initiative (DNDi). The founders were involved in study design, publish and preparation of the manuscript." **Possible conflicts of interest:** "The authors have declared that no competing interests exist."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A list of treatments, generated randomly in blocks of six (EpiInfo, version 3.1, CDC, Atlanta, GA), was used to assign each subject to a treatment group." Comment: randomisation method described
Allocation concealment (selection bias)	Low risk	Quote: "Numbered opaque envelopes were used to conceal the random allocation sequence. Only the study coordinator had access to the list and was in charge of assigning the treatments." Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open trial - but not sure if outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 7/80 (8.75%) of which 6 were lost during the follow-up period (2 and 4 in the twice- and thrice-a-day groups, respecitvely), and 3 participants were removed from the study because of the appearance of new lesions The efficacy of the treatments was calculated by ITT and per protocol (PP)
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods were reported in the Results section. Registered ClinicalTrials.gov NCT01845727
Other bias	Low risk	All information was provided

Machado 2007

Study characteristics

Machado 2007 *(Continued)*

Methods	**Study design:** Double-blind, placebo-controlled trial **Setting/location:** Corte de Pedra, Salvador-Bahia, Brazil **Period of study:** not described **Sample size calculation:** not described
Participants	**Type of Leishmania:** mucosal leishmaniasis. *L. braziliensis* (endemic) **Inclusion criteria:** patients aged 18 – 65 years and had severe mucosal leishmaniasis (defined as the presence of deep mucosal ulcers or septal infiltration or perforation, or both) **Exclusion criteria:** patients who had superficial mucosal ulcers (mild mucosal leishmaniasis), prior therapy for mucosal disease, diabetes, or co-infection with HIV, or who were unavailable for follow-up **Randomised:** 23 participants **Withdrawals:** 0 **Patients assessed:** 11 participants in the pentoxifylline with Sbv group and 12 in the Sbv treatment alone (placebo) **Age (years) and sex:** Placebo plus Sbv: median age 40, mean 42 ± 14; 8% women Pentoxifylline plus Sbv: median age 32, mean 37 ± 15; 27% women **Baseline data:** Placebo plus Sbv: 75% participants with previous cutaneous leishmaniasis; median duration of symptoms 12, mean 50 ± 79; median diameter measurement 22 mm, mean 25 ± 10; median follow-up 27 months, mean 28 ± 9 months. Median time to cure 105 days, mean 145 ± 99. Pentoxifylline plus Sbv: 64% participants with previous cutaneous leishmaniasis; median duration of symptoms 6, mean 18 ± 36; median diameter measurement 20 mm, mean 19 ± 4; median follow-up 23 months, mean 27 ± 10 months. Median time to cure 75 days, mean 83 ± 36
Interventions	**Type of interventions:** • **Intervention group:** intravenous Sbv (meglumine antimony; Aventis), at a dosage of 20 mg per kg of body weight per day, plus oral pentoxifylline (Pentox; Farmasa) at a dosage of 400 mg 3 times daily for 30 days • **Control group:** received the same Sbv schedule plus oral placebo pills that were formulated to appear identical to pentoxifylline 3 times daily for 30 days **Duration of intervention:** 30 days **Co-interventions:** not stated **Rescue therapy:** Participants who became worse or who had no change in the characteristics of their lesions received a second course of Sbv. Participants who demonstrated partial but not complete healing at 90 days after initiation of therapy were further evaluated for another 30 – 60 days, and those who did not experience complete healing underwent another round of treatment **Duration of follow-up:** 2 years post-treatment.
Outcomes	**Definition:** • ***Cure:*** defined as complete re-epithelisation of the mucosal tissue and no evidence of inflammatory activity in the 150 days after initiation of therapy

Machado 2007 *(Continued)*

	Time points reported: All participants were evaluated every 30 days by a blinded otolaryngology specialist. An interim analysis was performed at 90 days after initiation of therapy
Notes	**Ethical approval needed/obtained for study**: This study was approved by the ethical committee for research of the Hospital Universitário Prof. Edgard Santos, Salvador-Bahia, Brazil **Informed consent obtained:** yes **Study funding sources:** Howard Hughes Medical Institute (International Scholars Research Grant) and Fundação de Amparo a Pesquisa do Estado da Bahia **Possible conflicts of interest:** All authors: no conflicts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After consent was obtained, patients were randomized, through the use of a randomization table, to the combined treatment group or the control group" Comment: randomisation method described
Allocation concealment (selection bias)	Unclear risk	Quote: "This randomized, double-blind, placebo-controlled trial" Comment: No further information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both the otolaryngologist and participants were blinded to treatment assignment during all the steps of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both the otolaryngologist and participants were blinded including the follow-up period
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	High risk	*Leishmania* sp was not confirmed and sample size calculation was not adequately reported

Machado 2010

Study characteristics

Methods	**Study design:** Randomised, open-label, controlled clinical trial **Setting/location:** Bahia, Brazil **Period of study:** From July 2007 to August 2008

Machado 2010 *(Continued)*

	Sample size calculation: Sample size of 90 participants was obtained by calculating the number of participants needed for 80% power (ß = 0.2) to detect an absolute difference as large as 25% in the rate of cure between the 2 treatment groups with a statistical significance of 5% (α = 0.05)
Participants	**Type of Leishmania:** *Leishmania (Viannia) braziliensis* **Inclusion criteria:** age between 2 and 65 years; a maximum of 5 ulcers with no more than 2 body regions involved; lesion size between 10 and 50 mm in a single dimension; and a period of < 90 days from the onset of the first ulcer **Exclusion criteria:** patients with a prior history of CL or antimony use, patients with evidence of mucosal or disseminated disease, pregnant or breastfeeding mothers, and patients with HIV or any systemic severe disease **Randomised:** 90 participants (60 to receive miltefosine, 30 to receive Sb) **Withdrawals:** 3 participants. 2 (1 from miltefosine group and the other from Sbv group) were lost for follow-up after the end of the treatment. 1 participant in the miltefosine group was excluded by irregular use of the medication **Patients assessed:** 90 participants were randomly assigned in a rate of 2:1 **Age (years) and sex:** Male/female: 61/29; Age (years) ± SD (range): miltefosine group 22.7 ± 14.7 (7 – 65), Sbv group 22.0 ± 15.2 (4 – 59); No. of lesions: 1 (69), ≥ 2 (21); Area of lesion (mm^2): miltefosine group 410.6, Sbv group 461.2 **Baseline data:** NR
Interventions	**Type of interventions:** • **Intervention 1:** Miltefosine was administered orally at the total target daily dosage of 2.5 mg/kg of body weight (maximum daily dose of 150 mg) for 28 consecutive days. Daily dose was divided into two or three intakes, given always with meals according to a weight scale. • **Intervention 2:** Meglumine antimoniate (MA) was administered intravenously at a dose of 20 mg Sbv/kg/day for 20 consecutive days (maximum daily dose of 3 ampoules or 1215 mg/Sbv). **Duration of intervention:** Miltefosine for 28 days, MA for 20 days **Co-interventions:** not reported **Duration of follow-up:** 6 months
Outcomes	**Definition:** Primary endpoint: cure at 6 months after the end of therapy. Secondary endpoints: cure at 2 months after the end of therapy; data from clinical and laboratory adverse effects. All lesions were also categorised as either active or healed (cured) at follow-up visits. Only lesions with complete re-epithelialisation, without raised borders, infiltrations or crusts were considered healed. Adverse effects **Time points reported:** 2 weeks, 1, 2, 4 and 6 months.
Notes	**Ethical approval needed/obtained for study**: This study was approved by the Ethics Committee of the Federal University of Bahia, in Salvador, Brazil (CEP/MCO/UFBA-Par/Res 034/2007) **Informed consent obtained:** A written informed consent was obtained for all adult participants, and from parents or guardians of minors **Baseline imbalances:** overall, there was a predominance of male participants (67.8% vs 32.2%) **Study funding sources:** this study is part of a National Multicenter Clinical Trial for the evaluation of miltefosine in the treatment of cutaneous leishmaniasis caused by *L. (V.) braziliensis* and *L. (V.) guyanensis* in Brazil

Machado 2010 *(Continued)*

Possible conflicts of interest: the authors have declared that no competing interests exist.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization table was obtained with Statacorp LP 9, Texas. USA." Comment: method described
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This study is a randomized, open-label" Comment: participants not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "This study is a randomized, open-label" Comment: not clear if outcome assessments were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 90 participants were included in the trial and completed the treatment, and 87 were followed for the entire 6 months after therapy
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Low risk	All information was provided

Machado 2018

Study characteristics

Methods	**Study design:** Multi-arm, phase II, randomised and controlled study **Setting/location:** Patients were spontaneously seeking medical attention at the health centre of Corte de Pedra, in the state of Bahia, Brazil **Period of study:** November 2015 to November 2016 **Sample size calculation:** not stated
Participants	**Type of Leishmania:** positive culture or positive PCR for *L. braziliensis* **Inclusion criteria:** untreated CL with 1 – 3 months of active disease, with diagnostic confirmation through positive identification of amastigotes in histopathological examination or positive culture or positive PCR for *L. braziliensis*. Recruitment required individuals to be 18 – 65 years of age, with a number of lesions ranging from 1 - 5, with the presence of ulcerated lesions with sizes varying between 1 and 5 cm in diameter **Exclusion criteria:** pregnant or breastfeeding women, childbearing-age women unwilling to adhere to contraceptive measures during treatment and until 2 months after the end of treatment; previous history of leishmaniasis treatment; malnutrition; concomitant diseases such as cardiac, pulmonary, hepatic, cancer, tuberculosis, malaria, AIDS, any other infectious disease; laboratory evidence of liver or kidney disease

Machado 2018 *(Continued)*

Randomised: 38: Group 1: 15; Group 2: 11; Control: 12

Withdrawals: 2: Group 1: 1; Group 2: 0; Control: 1

Patients assessed: 38: Group 1: 15; Group 2: 11; Control: 12

Age (years) and sex:

Age (years): Group 1: 35 (24 – 47); Group 2: 43 (32 – 53); Group 3 (Control): 29 (19 – 44)

M/F: 23/15

Baseline data: Most participants presented with only 1 lesion (74%, 28/38) with mean duration of disease of at least 1 month

Number of lesions

Single: Group 1: 9 (75%); Group 2: 8 (73%); Control: 11 (73%)

> 1: Group 1: 3 (25%); Group 2: 3 (27%); Control: 4 (27%)

Area of the lesion (mm^2): Group 1: 208 (538); Group 2: 144 (245); Control: 165 (345)

Interventions	**Type of interventions:** All groups were treated with the standard regimen of SbV (meglumine antimoniate—Glucantime) 20 mg SbV/kg/ day, intravenously, daily for 20 days • **Intervention 1:** oral tamoxifen received 20 mg/ day tamoxifen citrate every 12 h for 20 consecutive days plus SbV • **Intervention 2:** topical tamoxifen (a cream formulated in oil-free vehicle at 0.1% tamoxifen citrate twice a day for 20 days plus SbV • **Control group:** SbV monotherapy **Duration of intervention:** 20 days **Co-interventions:** not stated **Duration of follow-up:** 6 months
Outcomes	**Definition:** *Primary outcome* • Complete epithelisation of the lesion(s) 6 months after the end of treatment • frequency and severity of adverse effects (AEs). *Secondary outcomes* • Initial cure at 2 months after the end of treatment **Time points reported:** 90 and 210 days (3 and 7 months) after recruitment into the study
Notes	**Ethical approval needed/obtained for study**: "All procedures involving human subjects were approved by the Human Research Ethics Committee of the Biomedical Sciences Institute of the University of Sao Paulo and by the Human Research Ethics Committee of Hospital Universitario Prof. Edgard Santos of the University Federal da Bahia" **Informed consent obtained:** "A signed term of informed consent was obtained from all subjects." **Baseline imbalances:** The frequency of lymphadenopathy in association with the cutaneous lesion was different between groups, being detected in 93% of participants treated only with SbV and observed in 64% and 33% of participants treated with the topical or oral association, respectively. Other characteristics did not vary significantly between groups

Machado 2018 *(Continued)*

Study funding sources: "This work was supported by Fundaçao de Amparo à Pesquisa do Estado de Sao Paulo (FAPESP 2015/09080-2). SRBU is the recipient of a senior researcher scholarship from CNPq."

Possible conflicts of interest: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised by www.randomization.com and allocated at a rate of 1:1:1 into three groups: oral tamoxifen plus SbV, topical tamoxifen plus SbV and SbV monotherapy. Randomisation codes were generated by MEFD in a single block (block size = 38)."
Allocation concealment (selection bias)	Low risk	Quote: "Sequentially coded numbers associated with intervention arm and allocation were kept under the responsibility of MEFD, and kept in opaque and sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Participants and care providers were not blinded because interventions were not similar."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Outcome assessment was performed based on physical examination and without collecting any information regarding use of medications or side effects by PRLM and by EMC (blinded)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 2/38 (5.3%) ITT analysis was performed 4 participants did not complete the study: 1 from the SbV, 1 from the SbV plus topical tamoxifen group and 2 from the oral tamoxifen group. 2 of these were lost to follow-up, and 2 had severe AEs with irregular use of medication
Selective reporting (reporting bias)	Low risk	The trial was registered at Plataforma Brasil (plataformabrasil.saude.gov.br) under the certificate CAAE: 42930015.6.3001.0049
Other bias	High risk	Sample size calculation was not adequately reported

Machado-Pinto 2002

Study characteristics

Methods	**Study design:** Double-blind, placebo-controlled trial **Setting/location:** Minas Gerais, Brazil **Period of study:** May 1998 to January 1999 **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** American cutaneous leishmaniasis (ACL). *L. braziliensis* (endemic)

Machado-Pinto 2002 *(Continued)*

	Inclusion criteria: age over 5 years, a parasitologically-confirmed diagnosis of cutaneous leishmaniasis, and an informed consent form signed by the patient or the parents/guardians of those under 16 years of age **Exclusion criteria:** NR **Randomised:** 102 **Withdrawals:** 3 were excluded due to previously-diagnosed cardiac arrhythmias and 3 were lost to follow-up (4 from group 1 and 2 from group 2) **Patients assessed:** vaccine 47 and placebo 49 **Age (years):** Vaccine: median 16 (5 - 65); placebo: median 29 (7 - 82) **Sex:** M/F: 57/39; Vaccine: 53.2% male and 46.8% female. Placebo: 65.3% male and 34.7% female **Baseline imbalances:** no **Severity Illness:** Median duration of disease: 60 days in both groups. Median number of lesions: vaccine 1 (1 - 8) and placebo 1 (1 - 7). Mean lesion size mm: vaccine 34.2 ± 25.8 and placebo 34.5 ± 25.6
Interventions	**Type of interventions:** they treated 102 participants with ACL using either a combination of a single-strain *Leishmania amazonensis* killed promastigote vaccine plus a half-dose of meglumine antimoniate, or placebo plus the same half-dose regimen of meglumine antimoniate, in 10-day series followed by 10-day intervals • **Intervention group: Vaccine.** The vaccine used was produced by BioBras, Montes Claros, Brazil, under conditions of GMP, using a WHO reference *Leishmania amazonensis* strain (IFLA/BR/1967/PH8) • **Control group: Placebo.** The diluent, a 0.1 m phosphate buffer solution at pH 7.4, with 100 µg/mL of thimerosal, was used as placebo to replace the vaccine, which is diluted in this buffered solution The pentavalent antimonial, Glucantime (N-methyl-glucamine antimoniate), produced by Rhodia in Brazil, was used. Glucantime is marketed in 5 mL ampoules containing 425 mg pentavalent antimony (the equivalent of 85 mg Sb(V)/mL) **Group 1:** daily subcutaneous injection of 0.5 mL of the vaccine plus 8.5 mg/kg (0.5 mL/5 kg body weight) intramuscular injection of antimonial Glucantime for 10 days followed by 10 days of rest **Group 2:** daily subcutaneous injection of 0.5 mL of placebo plus 8.5 mg/kg (0.5 mL/5 kg body weight) intramuscular injection of antimonial Glucantime for 10 days followed by 10 days of rest **Duration of intervention:** 10 days **Co-interventions:** not stated **Rescue therapy:** Participants were re-evaluated every 20 days and, if not cured (complete re-epithelialisation and no infiltration), a new cycle of treatment was started. Those who had not reached cure after 4 series of treatment were switched to a full-dose treatment schedule with antimonials (17 mg/kg/day without vaccine/placebo)
Outcomes	**Definition:** • ***Clinical cure:*** complete re-epithelialisation and no Infiltration • ***Adverse effects*** **Time points reported:** Participants were re-evaluated every 20 days
Notes	**Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** The informed consent form signed by the participant or the parents/guardians of those under 16 years of age

Machado-Pinto 2002 *(Continued)*

Study funding sources: Conselho Nacional de Pesquisas (CNPq), Fundação Nacional de Saude (FNS), Secretaria Municipal de Saude de Caratinga, and Santa Casa de Belo Horizonte, Brazil provided support.

Possible conflicts of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "double-blind, placebo-controlled trial was performed in which patients were allocated by chance to one of the two study arms" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, controlled trial" Comment: participants were likely blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment was described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 6 out of 102 (6%)
Selective reporting (reporting bias)	High risk	Outcomes were at times not reported by group
Other bias	High risk	*Leishmania* sp was not confirmed and sample size calculation was not adequately reported

Martínez 1992

Study characteristics

Methods	**Study design:** Open-label, randomised clinical trial **Setting/location:** Lopez de Micay on the southern Pacific coast of Colombia **Period of study:** 1988 - 1990 **Sample size calculation:** not described
Participants	**Type of Leishmania:** American Cutaneous Leishmaniasis caused by *Leishmania braziliensis panamensis* **Inclusion criteria:** patients who had disease proved by examination of a smear, culture, or biopsy and who had received no previous therapy were included in the study. In addition, to minimise the possibility of bacterial superinfection often associated with lesions of the lower extremities, patients were included in the study only if their lesions were confined to the upper portion of the trunk or the arms. Patients with a body weight within 20 percent of the ideal weight for their height

Martínez 1992 *(Continued)*

Exclusion criteria: patients were excluded if they or their parents did not give written informed consent; if they had a known or suspected allergy to antimony or allopurinol; if they were pregnant or nursing; if they had serious concomitant diseases or any disease other than leishmaniasis requiring treatment; or if they had a pre-existing skin rash or another disease of the skin

Randomised: 110

Withdrawals: 0

Patients assessed: 110: meglumine antimoniate: 33; combination of allopurinol and meglumine antimoniate: 35; allopurinol: 25 and untreated: 17

Age (years) and sex: Except for 2 girls 8 and 10 years of age, the participants were male, ranging in age from 11 to 40. meglumine antimoniate: 33 men; combination of allopurinol and meglumine antimoniate: 35 men; allopurinol: 23 men and 2 female and untreated: 17 men

Baseline data:

Meglumine antimonia t e: 1 lesion: 15; 2 lesions: 7; 3 lesions: 8; 4 lesions: 1; > 4 lesions: 2; lesion on face: 4; arms: 20; trunk: 2; < 2 mm diameter: 16; 2 - 4 mm: 14; 4 - 6mm: 3; > 6mm: 0

Combination of allopurinol and meglumine antimoniate: 1 lesion: 14; 2 lesions: 8; 3 lesions: 10; 4 lesions: 2; > 4 lesions: 1; lesion on face: 5; arms: 12; trunk: 3; < 2 mm diameter: 18; 2 - 4 mm: 12; 4 - 6 mm: 4; > 6 mm: 1

Allopurinol: 1 lesion: 3; 2 lesions: 6; 3 lesions: 5; 4 lesions: 3; > 4 lesions: 0; lesion on face: 3; arms: 18; trunk: 1; < 2 mm diameter: 13; 2 - 4 mm: 11; 4 - 6 mm: 1; > 6mm: 0

Untreated: 1 lesion: 7; 2 lesions: 7; 3 lesions: 3; 4 lesions: 0; > 4 lesions: 0; lesion on face: 2; arms: 14; trunk: 1; < 2 mm diameter: 9; 2 - 4 mm: 6; 4 - 6 mm: 2; > 6 mm: 0

Interventions

Type of interventions:

- Allopurinol was given orally for 15 days in a dosage of 20 mg per kilogram of body weight per day, given in 4 divided doses
- Meglumine antimoniate was given by injection at a dose of 20 mg of antimony per kilogram per day for 15 days

Duration of intervention: 15 days

Co-interventions: not stated

Duration of follow-up: 2 years

Outcomes

Definition:

- ***Cure:*** was defined as complete healing and scarring of a lesion, with the disappearance of oedema, induration, and other signs of inflammation and a negative culture of the healed lesion 3 months after the completion of treatment
- ***Definitive cure:*** was considered to have occurred if the lesion did not recur at the site after 1 year of follow-up after the end of therapy
- ***Improvement:*** was defined as a reduction in the size of a lesion 3 months after the end of therapy, incomplete scarring, or the persistence of parasites as determined on culture in a healed or healing lesion
- ***Failure:*** was defined as the absence of change in the lesion and as the persistence of parasites on culture 3 months after the end of therapy. Participants with multiple lesions were not considered to be cured unless all lesions were healed
- ***Adverse effects***

Time points reported: Clinical evaluations were performed at intervals of 1, 3, 6, and 12 months after the administration of the study drug. Evaluation of the cutaneous lesions, including culture, biopsy,

Martínez 1992 *(Continued)*

	and measurements of diameter, was performed before each participant's admission to the study, on days 7 and 15, and at intervals thereafter
Notes	**Baseline imbalances:** not reported. **Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** not stated **Study funding sources:** not stated **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A master randomization list was generated by a computer. Corresponding packets of consecutively numbered envelopes were provided, each of which contained a card indicating the treatment assignment." Quote: "Several patients elected not to participate, since they did not wish to receive injections. Others elected not to be treated at all. The patients in the former group received allopurinol alone, and those in the latter group were followed as untreated controls. Thus, the patients in these two groups were not randomized but were self-selected." Comment: randomisation method was described in detail
Allocation concealment (selection bias)	Unclear risk	Quote: "A master randomization list was generated by a computer. Corresponding packets of consecutively numbered envelopes were provided, each of which contained a card indicating the treatment assignment." Comment: No further information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up.
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	High risk	Sample size calculation was not adequately reported

Martínez 1997

Study characteristics

Methods	**Study design:** Open-label, randomised clinical trial

Martínez 1997 *(Continued)*

	Setting/location: southern Colombia **Period of study:** May 1989 to December 1991 **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL) caused by *L. braziliensis* **Inclusion criteria:** age between 10 and 50 years, presence of a single typical patient with cutaneous and mucocutaneous leishmaniasis **Exclusion criteria:** if they did not give written informed consent; if they had a known or suspected allergy to antimony or allopurinol; if they were pregnant or nursing; if they had serious concomitant diseases or any disease other than leishmaniasis requiring treatment; or if they had a pre-existing rash or another disease of the skin. To be enrolled, patients had to have body weights within 20% of the ideal weights for their height **Randomised:** 100; stibogluconate alone (49), and 51 received the combination regimen (stibogluconate + allopurinol) **Withdrawals:** 0 **Patients assessed:** stibogluconate 49 and stibogluconate + allopurinol 51 **Age (years):** 18 - 57 years. **Sex:** M/F: 86/14; Stibogluconate: 44 (90) men and 5 (10) women; Stibogluconate + allopurinol: 42 (82) men and 9 (18) women**Baseline imbalances:** no **Severity Illness:** number of lesions in Stibogluconate group: 1: 32 (65%); 2: 9 (18%); 3: 6 (12%); 4: 0; 5: 2 (4%). number of lesions in Stibogluconate + allopurinol group: 1: 32 (63%); 2: 8 (16%); 3: 6 (10%); 4: 6 (12); 5: 0.
Interventions	**Type of interventions:** • **Intervention 1:** Allopurinol was given orally for 15 days in a dosage of 20 mg/(kg*d) in 4 divided doses. • **Intervention 2:** Stibogluconate (Pentostam, donated by the Burroughs Wellcome Company (now Glaxo-Wellcome), Research Triangle Park, NC) was given by injection in a dosage of 20 mg/(kg/d) for 15 days **Duration of intervention:** 15 days **Co-interventions:** not stated
Outcomes	**Definition:** • ***Clinical cure:*** defined as a complete clinical and parasitological response without relapse during 1 year of follow-up (i.e. complete healing and scarring of a lesion in association with the disappearance of oedema, induration, and other signs of inflammation, and a negative culture of the healed lesion 3 months after the completion of treatment) • ***Improvement:*** defined as a reduction in the size of a lesion 3 months after the end of therapy, incomplete scarring, or the persistence of parasites in a culture of a healed or a healing lesion • ***Failure:*** was defined as the absence of change in a lesion and the persistence of parasites in culture 3 months after the end of therapy Participants with multiple lesions were not considered to be cured unless all lesions were healed **Adverse effects:** Participants were questioned about expected adverse effects

Martínez 1997 *(Continued)*

	Time points reported: Clinical evaluations were performed at intervals of 1 month, 3 months, 6 months, and 12 months after the administration of the study drug
Notes	**Ethical approval needed/obtained for study**: The protocol was approved by the Tropical Disease Research Section of the World Health Organization **Informed consent obtained:** Participants gave written informed consent **Study funding sources:** not stated **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A master randomization list was generated by computer at the Department of Statistics at Cauca University" Comment: randomisation method described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants lost to follow-up: SSG: 1/49; SSG + Allopurinol: 2/51; Withdrawal because of toxicity: SSG: 1/49; SSG + Allopurinol: 0/51 Total losses: 4/100 (4%); ITT analyses were performed
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	High risk	Sample size calculation was not adequately reported

Miranda-Verástegui 2005

Study characteristics

Methods	**Study design:** Double-blind, randomised trial **Setting/location:** provinces of Churin, Barranca, Yauyos, Satipo, Chachapoyas, Cuzco, and Madre de Dios, Peru **Period of study:** February 2001 to August 2002 **Unit of randomisation:** participant **Unit of analysis:** participant

Miranda-Verástegui 2005 *(Continued)*

	Sample size calculation: not stated
Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL): *L. (V.) peruviana* and *L. (V.) braziliensis* **Inclusion criteria:** each participat must have had parasitologically-confirmed cutaneous leishmaniasis and a history of 1 failed course of treatment with meglumine antimoniate **Exclusion criteria:** mucosal involvement, pregnancy, breast-feeding, 1 lesion with an area 125 cm^2, 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) **Randomised:** 40 **Withdrawals:** 0. **Patients assessed:** Imiquimod group 20 and vehicle group 20 **Age (years):** Imiquimod group: mean 14.1 ± 2.9, median 8.0 (1 - 41). Vehicle group: mean 19.25 ± 4.6, median 11 (1 - 78) **Sex:** M/F: 23/17; Imiquimod group: 10 male (50%) and 10 female (50%). Vehicle group: 13 (65%) male and 7 (35%) female. **Baseline imbalances:** no **Severity Illness:** Location of lesion: imiquimod group (face 26, upper extremity 4, and lower extremity 5); vehicle group (face 30, upper extremity 5, lower extremity 5). Total area for lesion in cm^2: Imiquimod group (mean 1.3 ± 3.0, median 8.8 (0.05 - 6.3), vehicle group (mean 2.3 ± 4.5, median 5.2 (0.06 - 15.2)
Interventions	**Type of interventions:** All 40 participants enrolled in the study received standard therapy (20 mg/kg per day) with meglumine antimoniate (Glucantime; Aventis Pharma) for 20 days. This drug was administered intramuscularly to 9 children 5 years of age (5 from the imiquimod group and 4 from the vehicle control group) or by slow intravenous infusion (over 15 min) in older participants • **Intervention group:** imiquimod 5% cream • **Control group:** placebo vehicle cream (the vehicle used for imiquimod but with inactive ingredients: isostearic acid, cetyl alcohol, steryl alcohol, white petroleum, polisorbate 60, sorbitan mosnosterate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben; 3M Pharmaceuticals) A thin layer of cream was applied to each lesion every other day for 20 days (i.e. 10 applications). Each numbered treatment package had 10 sachets that were identical in appearance and contained either the imiquimod cream or the vehicle cream. Each lesion typically received 125 – 250 mg of cream every other day. The entire area of each lesion (including a 0.5 cm margin of normal skin) was treated. Cream was applied in the morning by the physician and was rubbed into the lesion(s) until no longer visible. Occlusive dressings were not used, but a sterile plastic "cap" was used for the lesions not on the face, to prevent cream removal by clothing. Participants were instructed to remove the cap after ~ 1 h and to wash the lesions with soap and water after ~ 8 h **Duration of intervention:** 20 days **Co-interventions:** All participants had a full medical evaluation on enrolment. If the clinical presentation raised the possibility of a bacterial superinfection (e.g. surrounding cellulitis, actively weeping lesions, tissue maceration, and foul odour), treatment with local or systemic antibiotic therapy and daily cleaning of the lesion was initiated to resolve the infection prior to entry into the study **Rescue therapy:** At termination of the study (12 months), participants for whom therapy had failed were offered outpatient treatment with intravenous amphotericin B (0.5 mg/kg in 500 mL of 5% dextrose every other day, for a total cumulative dose of 7.5 – 15 mg/kg or a maximum of 1 g)
Outcomes	**Definition:**

Miranda-Verástegui 2005 *(Continued)*

- ***Clinical cure:*** defined as complete re-epithelialisation without signs of inflammation;
- ***Clinical improvement:*** defined as reduction in lesion size and inflammation but without full re-epithelialisation
- ***Failure:*** defined as no improvement, with the lesion unchanged or worse compared with its status at the start of treatment

Adverse effects: semi-quantitative grading scale for evaluating adverse effects was used: grade 1 was defined as no significant interference with daily activities; grade 2 was defined as mild interference with daily activities, but no treatment required; and grade 3 was defined as severe interference with daily activities and treatment or intervention required

Time points reported: Lesions and adverse effects were evaluated during treatment and at 1, 2, 3, 6, and 12 months after the treatment period

Notes	**Ethical approval needed/obtained for study**: The study protocol and consent form were approved by the Research Ethics Committees of McGill University and Universidad Peruana Cayetano Heredia (Lima, Peru) and followed the Helsinki Declaration of 2000 **Informed consent obtained:** All of the participants or their guardians provided written, informed consent **Study funding sources:** financial support of the World Health Organization/Tropical Disease Research and 3M Pharmaceuticals. G.M. and B.W. **Possible conflicts of interest:** All authors: no conflicts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were also randomized to receive either imiquimod 5% cream or placebo vehicle cream" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...we performed a randomized, double-blind, placebo- controlled trial using ..." Quote: “Each numbered treatment package had 10 sachets that were identical in appearance and contained either the imiquimod cream or the vehicle cream.” Comment: participants and personnel were likely blinded to treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment was described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 2/40 (5%)
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section

Miranda-Verástegui 2005 *(Continued)*

Other bias	High risk	*Leishmania* sp was not confirmed and sample size calculation was not adequately reported

Miranda-Verástegui 2009

Study characteristics	
Methods	**Study design:** Randomised double-blind clinical trial **Setting/location:** Lima and Cuzco, Peru. **Period of study:** 12 months. **Sample size calculation:** Sample size was estimated such that the log-rank test for equality of survival curves would have 80% power to detect a statistically significant difference in proportions cured at 3 months of at least 32% (hazard ratio of 2.6) (estimates of proportions cured at 3 months were based on previously published data)
Participants	**Type of Leishmania:** participants recruited in Lima are typically infected with *L. peruviana*, *L. guyanensis*, or *L. braziliensis,* while those recruited at the Cuzco site are infected predominantly with *L. braziliensis* **Inclusion criteria:** Male and female between 5 and 65 years of age; confirmed diagnosis of cutaneous leishmaniasis (i.e. presence of an active ulcerative cutaneous Leishmania lesion, and a positive identification of the parasite from the lesion. (smear microscopy, culture, or PCR); duration of disease > 4 weeks; No prior therapy with anti-Leishmania drugs; female patients of childbearing age: a negative urine pregnancy test, not breastfeeding, required to use adequate contraception during the 20-day treatment; informed written consent (self or parent for under-18 year-olds) for the trial and a separate additional consent for photos of lesions (at baseline and at follow-up time points).; willing to participate in all treatment and follow-up visits, and be reachable by study personnel **Exclusion criteria:** Lesion(s) 2500 $mm^{2;\ m}$More than 6 cutaneous lesions; mucosal lesion; previous exposure to imiquimod or anti-Leishmania treatment; participation in another experimental protocol and/or had received investigational products within previous 30 days; history of any acute or chronic illness (other than cutaneous leishmaniasis) or medication that, in the opinion of the investigators, may interfere with the evaluation of the trial (e.g. history of heart or liver illness); history of significant psychiatric illness; history of previous anaphylaxis or severe allergic reaction to 1 or more of the proposed drugs; unlikely to co-operate with the requirements of the study protocol; concomitant infection (i.e. bartonellosis, sporotrichosis, mycobacterial infection) **Randomised:** 80 participants (20 experimental and 20 control subjects at each site) **Withdrawals:** 5 participants (2 discontinued intervention; 3 los to follow-up) **Patients assessed:** 75 completed the study (Control n = 36; experimental arm n = 39) **Age (years) and sex:** age (mean ± SD): experimental arm (25.0 ± 10.3), control arm (25.9 ± 10.4); male/female: 62/18 **Baseline data:** study site (no. of participants): Lima (40), Cuzco (40); Occupation (no. of participants): agriculture (48), professional (3), mining (8), student (3), tourism (13), other (5); Region where leishmaniasis was acquired (no. of participants): mountains (14), jungle (66)
Interventions	**Type of interventions:** • **Control arm**: received the standard pentavalent antimony treatment plus an application of placebo vehicle cream applied to each lesion 3 times a week • **Experimental arm**: received pentavalent antimony plus 5% imiquimod cream identically applied

Miranda-Verástegui 2009 *(Continued)*

	Duration of intervention: Topical treatment was applied 3 times a week for a total of 9 applications during the 20-day course **Co-interventions:** not reported. **Duration of follow-up:** 12 months post-treatment period
Outcomes	**Definition:** The primary outcome was • ***Cure:*** defined as complete re-epithelisation with no inflammation assessed during the 12-month post-treatment period **Time points reported:** 1, 2, 3, 6, 9 and 12 months
Notes	**Ethical approval needed/obtained for study**: Approvals from the ethics review boards of Universidad Peruana Cayetano Heredia UPCH, McGill University, and the National Institute of Health in Peru (INS-Peru) were obtained **Informed consent obtained:** Written informed consent was obtained from each participant enrolled in the study and the participant/parent **Baseline imbalances:** Overall, there was a predominance of male participants. Lesions were on average larger in the Cuzco cohort **Study funding sources:** funded by the Drugs for Neglected Diseases Initiative (DNDi). The funders were involved in the study design but did not play a role in data collection and analysis, decision to publish, or preparation of the manuscript **Possible conflicts of interest:** the authors have declared that no competing interests exist

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization list generated by 3M Pharmaceuticals Inc." Comment: Each clinic recruited 20 experimental and 20 control participants and assigned treatment based on a 1:1 randomisation list generated by 3M Pharmaceuticals Inc
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study I.D. numbers and corresponding treatment packages were prepared so that both subjects and study investigators were blind to treatment allocation throughout the study." Comment: both participants and personnel were blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "randomized double-blind clinical trial." Comment: not clear if outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No ITT analyses were performed Losses to follow-up: 5/80 (6%) (reasons were provided)
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Low risk	All information was provided

Navin 1990

Study characteristics	
Methods	**Study design:** Randomised, placebo-controlled clinical trial **Setting/location:** Guatemala **Period of study:** not stated **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL): *Leishmania braziliensis* and *Leishmania mexicana* **Inclusion criteria:** age between 18 and 60 years and diagnosis of leishmania confirmed by positive thin smears of cultures, no previous treatment with antimonials, no serious concomitant medical problems, lesion < 25 cm^2 in size, and no visual evidence of mucosal involvement **Exclusion criteria:** patients 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. Patients with unilateral lymphadenopathy or subcutaneous nodules in an area of lymph drainage from the lesion **Randomised:** 66 **Withdrawals:** 14: 7 had lesions in difficult-to-treat locations (5 on the ear and 2 near the eye), 3 preferred not to receive experimental treatment, 2 had lymphadenopathy, and 2 had lesion area > 25 cm^2. **Patients assessed:** 22 receiving meglumine antimoniate (Glucantime), 22 receiving localised controlled heat from a radio-frequency generator, and 22 receiving treatment with placebo **Age (years):** participants were young men, average age 20 years **Sex:** all participants were male soldiers **Baseline imbalances:** no **Severity Illness:** participants had up to 6 lesions at the time of diagnosis, but most (68%) had only 1 lesion. The mean area of ulceration was 5.2 cm^2

Interventions	**Type of interventions:**
	
	• **Intervention group:**
	  • Meglumine antimoniate: 850 mg of pentavalent antimony im daily for 15 days
	  • Localised heat: 50 °C for 30 sec, 3 treatments at 7-day intervals
	• **Control group:** placebo treatment was produced with a machine identical in appearance to the heat apparatus but which did not produced heat
	
	The area to be treated with heat or placebo was anaesthetised with lidocaine HCL, thoroughly debrided, and moistened for 15 mins with cotton sponges soaked in 0.85% NaCl
	
	Duration of intervention: 15 days
	
	Co-interventions: not stated
	
	Rescue therapy: If a participant's lesion was not completely re-epithelialised by the 13-week follow-up examination, the participant was removed from the study and treated with meglumine antimoniate 850 mg each day for 15 days

Outcomes	**Definition:**

Navin 1990 *(Continued)*

	• ***Clinical cure:*** defined as a lesion that completely re-epithelialised and had no evidence of papules, inflammation, or induration • ***Reactivated lesion:*** defined as the appearance of lesion within or at the border of a previous lesion • ***New lesion:*** defined as those that appeared after treatment away from any previous lesions **Adverse** effects**:** Participants were evaluated daily during treatment for adverse effects **Time points reported:** Clinical response was evaluated 2, 6, 9, 13, 26 and 52 weeks after the star of treatment
Notes	**Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** informed consent was obtained from each participant **Study funding sources:** not stated **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "subjects were assigned randomly to 1 of the 3 treatment groups..." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single-blinded. Participants did not know whether they were receiving heat or sham treatments
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment was described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section.
Other bias	High risk	Sample size calculation was not adequately reported

Navin 1992

Study characteristics

Methods	**Study design:** Randomised, comparative trial **Setting/location:** Guatemala **Period of study:** January 1988 to November 1989

Navin 1992 *(Continued)*

	Unit of randomisation: participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL): *Leishmania braziliensis* and *L. mexicana* **Inclusion criteria:** confirmed diagnosis of leishmaniasis, no previous treatment with antimonials or imidazoles, no serious concomitant medical problems, availability for follow-up for 12 months, and no visible evidence of mucosal involvement **Exclusion criteria:** not stated **Randomised:** 120 participants were assigned randomly and equally to 1 of 3 treatment groups: sodium stibogluconate, ketoconazole, and placebo **Withdrawals:** 37 persons did not meet eligibility criteria (4 had received previous treatment and 33 were not available for 12 months of follow-up), and 5 did not want to participate in the study **Patients assessed:** this study included 21 civilians and 99 soldiers. Stibogluconate 40, Ketoconazole 38 and placebo 40 **Age (years): mean age±SD:** Stibogluconate: 19.1 ± 0.6, Ketoconazole 20.0 ± 1.2 and placebo 21.3 ± 1.4 **Sex:** all participants were men **Baseline imbalances:** no **Severity Illness:** Mean area of ulceration (cm^2): Stibogluconate 1.5 ± 0.3, Ketoconazole 2.2 ± 0.4, and placebo 2.0 ± 0.4. Number of lesions per participant: Stibogluconate 1.6 ± 0.2, Ketoconazole 1.5 ± 0.1, placebo 1.5 ± 0.2

Interventions	**Type of interventions:**
	
	• **Intervention groups:**
	  • Sodium stibogluconate: 20 mg of pentavalent antimony per kg of body weight per day intravenously for 20 days
	  • Ketoconazole: 600 mg orally each evening for 28 days
	• **Control group:** placebo. Half the participants assigned to the placebo group received saline infusions similar to the stibogluconate infusions, and half received tablets similar in form to ketoconazole
	
	Duration of intervention: 20 or 28 days
	
	Co-interventions: not stated
	
	Rescue therapy: Participants who were removed from the study were treated with meglumine antimoniate at 20 mg of antimony per kg per day for 20 days. Participants with clinically-healed but parasitologically-positive lesions at the 9-week examination were not necessarily retreated

Outcomes	**Definition:** • ***Clinical response:*** defined as a lesion that completely re-epithelialised and had no evidence of inflammation • ***Reactivated lesion:*** defined as the appearance of an ulcer within or at the border of a previous lesion **Adverse effects:** participants reported the number of adverse effects during treatment **Time points reported:** participants were evaluated at 1, 2, 3, 4, 6, 9, 26, and 52 weeks after the start of therapy
Notes	**Ethical approval needed/obtained for study**: not stated

Navin 1992 *(Continued)*

Informed consent obtained: not stated

Study funding sources: US Army Medical Research and Development Command

Possible conflicts of interest: Opinions. interpretations. conclusions, and recommendations are those of the authors and are not necessarily endorsed by the US Army

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized according to a preexisting list produced by a computer program that differed from a random number generator only in that it assigned equal numbers of patients into each treatment group." Comment: randomisation sequence method described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Half the patients assigned to the placebo group received saline infusions similar to the stibogluconate infusions, and half received tablets similar in form to ketoconazole." Comment: SSG was not blinded.Ketoconazole and placebo claimed to be similar, but not identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Clinical evaluation of all lesions was made by one physician (B.A.A.), who was not aware of what treatment a particular patient had received. In addition, two other physicians (F. A. Neva and C. Ponce), who also did not know what treatment patients had received, evaluated photographs of lesions before treatment and at the 9- or 13-week follow-up examination."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 7/120 (5.83%) Quote: "All but 2 of the 120 patients completed their treatments without interruption. Both patients who prematurely interrupted their treatments were receiving ketoconazole. Data on these two patients are not included in the analysis of response rates." Quote: "During the 12 months of observation, only 5 (4%) patients were lost to follow-up (3 in the stibogluconate group and 1 each in the ketoconazole and placebo groups)".
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	High risk	Sample size calculation was not adequately reported

NCT01011309

Study characteristics

Methods	**Study design:** Phase 2, randomised, open-label, controlled study **Setting/location:** A medical clinic at the Instituto de Medicina Tropical 'Alexander von Humboldt', Universidad Peruana Cayetano Heredia, Lima, Peru **Period of study:** October 2009 - December 2011

NCT01011309 *(Continued)*

Sample size calculation: Not reported, but a total of 150 patients was planned, including age de-escalation to adolescents after the first 60 adults enrolled. Owing to slow recruitment and insufficient evidence of efficacy in the immunotherapy group, enrolment was closed early

Participants

Type of Leishmania: *Leishmania peruviana* (confirmed by PCR)

Inclusion criteria: Male and female ≥ 12 years and < 70 years of age. In the first stage of the study, only adults aged ≥ 18 years and < 70 years will be enrolled. In the second stage, enrolment will also include adolescents aged ≥ 12 - < 18 years; must have a clinical diagnosis of cutaneous leishmaniasis confirmed by positive identification of Leishmania parasite and identification of L. peruviana by PCR; lesions must be clear of any superinfection prior to enrolment; female patients of childbearing age must have a negative serum pregnancy test at screening, a negative urine pregnancy test within 24 hours before the first vaccination or initiation of chemotherapy, must not be breast-feeding, and are required to use adequate contraception through Day 84 of the study. These precautions are necessary due to unknown effects that LEISH-F2 + MPL SE, sodium stibogluconate might have in a fetus or newborn infant; the following laboratory blood tests must have values within the normal ranges at screening: sodium, potassium, urea, total bilirubin, ALT, AST, glucose, creatinine, alkaline phosphatase, total WBC count and platelet count. Haemoglobin may exceed the ULN since patients reside in the Andes at very high altitude (up to 20 g/dL); the following serology tests must be negative at screening: HIV-1/2, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody. All patients (or their parents) will receive HIV-related counselling prior to testing. Patients with positive HIV test results will be referred for counselling and treatment as appropriate; potential study participants (or their guardians) must give written informed consent, be willing to be housed in Lima for a minimum of 20 days and up to 63 days, able to attend all required follow-up visits, have a permanent address, and be reachable by study site personnel

Exclusion criteria: Infection with species other than *L.peruviana* as confirmed by PCR; presence of 11 or more active cutaneous leishmaniasis lesions; the diameter of the ulcerated area of any single lesion is > 60 mm; presence of lesions with superinfection at time of enrolment; history of mucocutaneous leishmaniasis or diagnosis of mucocutaneous leishmaniasis at screening; history of previous exposure to Leishmania vaccines; known use of injected or oral corticosteroids within 6 weeks prior to the first vaccination or initiation of chemotherapy; participation in another experimental protocol or receipt of any investigational products within 30 days prior to the first vaccination or initiation of chemotherapy; history of autoimmune disease or other causes of immunosuppressive states; history or evidence of any acute or chronic illness that, in the opinion of the study clinician, may interfere with the evaluation of the safety or the immunogenicity of the vaccine. (Patients presenting with concomitant illness will be referred for standard clinical care); history of use of any medication that, in the opinion of the study clinician, may interfere with the evaluation of the safety or the immunogenicity of the vaccine; history of significant psychiatric illness; drug addiction including alcohol abuse; patients with a history of previous anaphylaxis, severe allergic reaction to vaccines or unknown allergens, or allergic reaction to eggs; patients who are unlikely to co-operate with the requirements of the study protocol; ECG with evidence of ventricular arrhythmias ≥ 4 extra systoles per minute;

known allergy or contraindication to chemotherapy (e.g. known reaction to pentavalent antimonials, cardiopathy, myocarditis)

Randomised: 45: Group 1: Immunotherapy v1.4/1.5: 14; Group 2: Immunotherapy v1.6: 10; Group 3: Sodium stibogluconate (SSG): 21

Withdrawals: 10: Group 1: Immunotherapy v1.4/1.5: 2; Group 2: Immunotherapy v1.6: 3; Group 3: Sodium stibogluconate (SSG): 5

Patients assessed: 35: Group 1: Immunotherapy v1.4/1.5: 12; Group 2: Immunotherapy v1.6: 7; Group 3: Sodium stibogluconate (SSG): 16

Age (years) and sex:

Age: 38.0 (14.0); Group 1: 8.3 (14.2); Group 2: 32.7 (6.8); Group 3: 40.2 (16.0)

Between 18 and 65 years: 44 participants; ≥ 65 years: 1 participant (SSG group)

M/F= 27/18, of which: Group 1 M/F: 9/5; Group 2 M/F: 5/5; Group 3 M/F: 13/8

NCT01011309 *(Continued)*

	Baseline data: No baseline data other than age and sex
Interventions	**Type of interventions:** • **Intervention 1:** 10 mcg LEISH-F2 antigen + 25 mcg MPL-SE adjuvant given as 3 subcutaneous injections on Days 0, 28, and 56 • **Intervention 2:** 10 mcg LEISH-F2 antigen + 25 mcg MPL-SE adjuvant given as 3 subcutaneous injections on Days 0, 14, and 28 • **Control:** Sodium stibogluconate (SSG) given 20 mg/kg/day IV for 20 days **Duration of intervention:** 56, 28 and 20 days respectively **Co-interventions:** Not reported **Duration of follow-up:** 336 days
Outcomes	**Definition:** *Primary Outcome Measures*: • Date of ***Clinical Cure*** (Day 84); (Designated as safety issue: No) Efficacy of immunotherapy with the LEISH-F2 + MPL-SE vaccine was compared to the efficacy of chemotherapy with sodium stibogluconate in the treatment of CL. Efficacy is measured by the date of clinical cure **Adverse effects:** Grade 1 severity or higher occurring in ≥ 3 participants during active treatment phase of the study. (Day 0 through Day 336) (designated as safety issue: Yes). Safety of immunotherapy with the vaccine was compared to the safety of chemotherapy with sodium stibogluconate. All adverse effects are listed regardless of relatedness *Secondary Outcome Measures*: • IgG Antibodies and T-cell Cytokine Responses (IFN-g and IL-10) (Days 0, 56 or 84, and 168) (Designated as safety issue: No). Immunogenicity of the vaccine was evaluated by measuring IgG antibody and T-cell responses to the LEISH-F2 protein and soluble Leishmania antigen (SLA). IgG antibodies were measured by ELISA and T-cell cytokine responses (IFN-g and IL-10) were measured by Luminex. Data are presented as median post:pre ratios comparing Days 56/84 or 168 to baseline at Day 0 **Time points reported:** Days 0, 56 or 84, 168, and 336
Notes	**Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** not stated **Baseline imbalances:** not stated **Study funding sources:** Study sponsored by IDRI (Infectious Disease Research Institute) **Possible conflicts of interest: "**Principal Investigators are NOT employed by the organization sponsoring the study". Unpublished study. Results published in ClinicalTrials.gov web site **Caveats: "**A total of 150 patients was planned, including age de-escalation to adolescents after the first 60 adults enrolled. Owing to slow recruitment and insufficient evidence of efficacy in the immunotherapy group, enrolment was closed early."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomized"

NCT01011309 *(Continued)*

		Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	None (open-label)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	None (open-label)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 10/45 (22.2%) Analyses were not done by ITT Reasons were provided: Adverse effects: G1: 2; G2: 1; G3: 2; Lack of efficacy: G2: 1; Protocol violation: G2: 1; G3:3
Selective reporting (reporting bias)	Low risk	All outcomes were reported and the trial was registered at ClinicalTrials.gov Registration. NCT01011309
Other bias	High risk	In clinical.trials in the Certain agreements section appears that: "There IS an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed."

Neva 1997

Study characteristics	
Methods	**Study design:** Double-blind, placebo-controlled clinical trial **Setting/location:** Village of San Juan Bautista, Municipality of Pespire, Department of Choluteca, and Village of Coyolito, Municipality of Ampala, Department of Valle, Honduras **Period of study:** not stated **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL): *Leishmania mexicana* and *L. chagasi* **Inclusion criteria:** not stated **Exclusion criteria:** not stated **Randomised:** Each participant was given a number in consecutive order. Assignment to receive drug or placebo was determined from a list of random numbers generated by Epi-Info software **Withdrawals:** 0 **Patients assessed:** 53 participants were enrolled in the study, 26 from San Juan Bautista and 27 from Coyolito

Neva 1997 *(Continued)*

	Age (years):. Cases were equally divided by sex and ranged in age from 3 to 36 years. Only 4 participants were over the age of 20 years, 1 was 18, and the remainder 16 years or less **Sex:** not stated **Baseline imbalances:** no **Severity Illness:** Most cases (70% - 90%) had only 1 or 2 lesions. Multiple lesions were somewhat more common in participants from Coyolito, 8 of the 27 having 3 or more
Interventions	**Type of interventions:** • **Intervention group:** the medication used contained 15% paromomycin and 10% urea in 30 g of white soft paraffin in collapsible tubes. • **Control group:** the placebo consisted of white soft paraffin only Parents and participants were instructed to apply the ointment to the lesions 3 times daily, including Saturdays and Sundays, for 4 weeks **Duration of intervention:** 4 weeks **Co-interventions:** not stated
Outcomes	**Definition:** • ***Clinical improvement:*** defined as any degree of flattening and loss of induration or reduction in lesion size, or both • ***Clinical cure:*** was defined as complete disappearance of the lesion **Adverse effects:** not stated **Time points reported:** Participants were checked and their lesions were evaluated and photographed before and at 2 and 4 weeks after therapy was started. A final evaluation including photography, of lesions was carried out 11 weeks after completion of 4 weeks of topical treatment
Notes	**Ethical approval needed/obtained for study**: The nature and purpose of the study was approved by a local research committee **Informed consent obtained:** not stated **Study funding sources:** Financial support for typing parasite strains was provided by the Walter Reed Army Institute of Research, USA **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Each patient was given a number in consecutive order. Assignment to receive drug or placebo was determined from a list of random numbers generated by Epi-Info software.” Comment: randomisation method was described
Allocation concealment (selection bias)	Low risk	Quote: “The code identifying the contents of each tube was know only to the Geneva participants (FM and PO)” Quote: “Disclosure of which ointment each patient had received was made only after this evaluation.” Comment: allocation was likely concealed

Neva 1997 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “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” Comment: referred to as "Double-blind" - likely blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment was described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	High risk	Sample size was not adequately reported

Neves 2011

Study characteristics	
Methods	**Study design:** Randomised clinical trial **Setting/location:** Manaus – Amazonas State, Brasilia – Federal District, Corte de Pedra – Bahia State, and Ribeirao Preto – Sao Paulo State **Period of study:** January 2009 - Feburary 2010 **Sample size calculation:** not stated
Participants	**Type of Leishmania:** *L. guyanensis* and *L. brasiliensis* **Inclusion criteria:** Weight > 8 kg; Gender: male or female patients; Clinical findings compatible with CL and positive direct examination (by smear) for Leishmania; disease duration: between 1 and 3 months; number of lesions: a maximum of 6 lesions (localised cutaneous leishmaniasis - LCL); presence of at least 1 ulcerated lesion; lack of mucosal involvement and no history, confirmed or not, of cutaneous leishmanial lesion; signing the Informed Consent Form (ICF). **Exclusion criteria:** Prior treatment with pentavalent antimonials or leishmanicidal drugs in the last 6 months; clinical and/or laboratory evidence of cardiac abnormalities (pre-treatment ECG changes); concomitant tuberculosis, leprosy, cancer, diabetes mellitus or other serious illness; uncontrolled hypertension (HTN ≥ 160/95 mmHg, verified at least 3 times on different days); evidence of peripheral vascular involvement (presence of varicose veins in the legs or ulcerated, flat, hyperpigmented, painful lesions, even in the absence of secondary infection); history of alcoholism; treatment with corticosteroids or other immunosuppressants; pregnancy; AST ≥ 3 times the upper limit of normal; ALT ≥ 3 times the upper limit of normal; serum creatinine or urea ≥ 1.5 times the upper limit of normal **Randomised:** 185 participants (NMG: 74 participants; Pentamidine 74 participants; Amphotericin B: 37 participants) **Withdrawals:** 5 participants from the antimonial group and 4 from the pentamidine group were lost during follow-up. 2 participants in the antimonial group and 1 in the pentamidine group withdrew from the study after randomisation, as they preferred other medications; 28 Amphotericin B participants withdrew after randomisation

Neves 2011 *(Continued)*

	Patients assessed: NMG: 58 participants; Pentamidine 58 patients ; Amhotericin B: 0 due to small number of patients (for clinical efficacy only patients with *L. guyanensis* were evaluated, with 11 participants being excluded from the antimonial group and 12 from the pentamidine group) **Age (years) and sex:** Both sexes: 44 women and 141 men, with ages ranging from 5 to 65 years **Baseline data:** location of the lesions: head (13), upper limbs (68), lower limbs (99), trunk (46)
Interventions	**Type of interventions:** • Group antimonial: the dose was 15 mg/kg/day for 20 days, administered intravenously (IV) or intramuscularly (IM) • Group pentamidine: 3 doses of 4 mg/kg were administered every 72 hours by deep IM injection with the participant in a supine position • Group amphotericin B: 1mg/kg/day was administered IV for 20 days **Duration of intervention:** 20 days **Co-interventions:** not reported **Duration of follow-up:** 6 months
Outcomes	**Definition:** • ***Cure:*** complete healing of all ulcers and absence of any signs of inflammatory reaction 180 days after completion of treatment • ***Adverse effects*** **Time points reported:** 30, 60 and 180 days after the end of the treatment
Notes	**Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** The study included those who agreed to participate in the investigation by signing the Informed Consent Form **Baseline imbalances:** overall, there was a predominance of male participants **Study funding sources:** Financiadora de Estudos e Projetos (Research and Projects Financing) of the Ministry of Science and Technology - FINEP **Possible conflicts of interest:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A list of random distribution was established for their allocation in the treatment groups. This list was generated by the biostatistician of the project." Comment: randomisation method was described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias)	Unclear risk	No information provided

Neves 2011 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons facross groups. In group that was unbalanced, results to be analysed separately
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	High risk	Sample size calculation was not adequately reported

Newlove 2011

Study characteristics	
Methods	**Study design:** Randomised, double-blind, placebo-controlled clinical trial (NCT00469495) **Setting/location:** Bahia, Brazil **Period of study:** 4 months **Sample size calculation:** The sample size of 90 provided 80% power to detect a difference of 25% in the rate of cure between the groups with $\alpha = 0.05$. The assumption that there would be a clinical difference in cure rate of 25% was based on a prior study showing response rates of 70% and 95% in helminth-positive versus helminth-negative subjects, respectively
Participants	**Type of Leishmania:** *Leishmania braziliensis* **Inclusion criteria:** age between 13 and 50 years; a maximum of 3 ulcers; lesion diameter between 5 and 50 mm; and a period of 15 to 60 days from the onset of the ulcer. Only patients with helminthic infection were included. **Exclusion criteria:** patients who had been treated for helminths within 6 months, patients with evidence of mucosal or disseminated disease, pregnant or breastfeeding mothers, and patients with diabetes mellitus **Randomised:** 90 (45 early-treatment group; 45 control group) **Withdrawals:** 0 **Patients assessed:** 90; all 90 participants completed primary endpoint **Age (years) and sex:** Early treatment group: 34 male and 11 female between ages 15 - 35; Control group: 32 male and 13 female between ages 15 - 35 **Baseline data:** body mass index (interquartile range): treatment group 21.3 (19.4 – 24.7), control group 22.3 (20.7 – 24.0); No. (%) with 1 lesion: treatment group 34 (75.6%), control group 34 (75.6%); No. (%) with 2 lesions: treatment group 7 (16.7%), control group 8 (17.8%); No. (%) with 3 lesions: treatment group 4 (8.9%), control group 3 (6.7%); Lesion size, median (interquartile range), mm^2: treatment group 180 (70 – 400), control group 198 (100 – 400)
Interventions	**Type of interventions:** • **Intervention group:** received albendazole (400 mg), ivermectin (200 µg/kg), and praziquantel (50 mg/kg) in an oral formulation at Days 0 and 30 and placebo at Day 60 • **Control group:** received placebo manufactured by Federal University of Bahia Pharmacy that was identical in form, colour, and number to the treatment group at Days 0 and 30 **Duration of intervention:** 30 days.

Newlove 2011 *(Continued)*

	Co-interventions: control: appropriate oral antihelminthic based on parasitological assay results on the 60-day visit **Duration of follow-up:** 90 days
Outcomes	**Definition:** • ***Cure:*** lesions with complete re-epithelialisation, without raised borders or eschars • ***Adverse effects*** **Time points reported:** 30, 60, and 90 days after initiation of Sb v therapy
Notes	**Ethical approval needed/obtained for study**: This study was approved by the Ethics Committees of the Federal University of Bahia, Brazil and Weill Cornell Medical College **Informed consent obtained:** Written informed consent was obtained from all participants **Baseline imbalances:** Most CL participants (73.3%) were male **Study funding sources:** this study was supported by NIH/FIC grant D43 TW007127 and NIH/NIAID K24AI078884 **Possible conflicts of interest:** the authors do not have commercial or other associations that might pose a conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “a randomization table was used for group assignment.” Comment: method was described
Allocation concealment (selection bias)	Low risk	Quote: “a randomization table was used for group assignment and sealed envelopes were used for allocation concealment.” Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blind” Quote: "placebo manufactured by Federal University of Bahia Pharmacy that was identical in form, color, and number to a treatment group at Days 0 and 30." Comment: likely blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "randomized, double-blind” Comment unclear if outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	Low risk	Comment: relevant outcomes reported
Other bias	High risk	*Leishmania* sp was not confirmed

Oliveira-Neto 1997

Study characteristics	
Methods	**Study design:** Randomised, double-blind, clinical trial **Setting/location:** Rio de Janeiro, Brazil **Period of study:** not stated **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL) caused by *L. braziliensis* **Inclusion criteria:** clinical appearance of lesions, positive MST and the presence of parasites either in in-prints, histological examination or isolation in culture **Exclusion criteria:** not stated **Randomised:** 23 participants were randomly assigned to receive either a high dose of antimony or a lower one **Withdrawals:** 0. **Patients assessed:** low-dose: 12 participants and high-dose: 11 participants **Age (years):** Ages ranged from 11 to 66 years. Mean age of participants: Low-dose 25.25 ± 4.03 and high-dose 25.72 ± 5.10 **Sex:** 14 were male and 9 female **Baseline imbalances:** no **Severity Illness:** Mean area of ulceration (cm^2): low-dose 3.73 ± 0.95 and high-dose 3.89 ± 1.11. Number of lesion for participant: low-dose 1 to 4 lesions and high-dose 1 to 7 lesions. Mean duration of lesions (months): low-dose 3.25 ± 0.79 and high-dose 2.54 ± 0.38
Interventions	**Type of interventions:** • **Intervention 1:** 5 mg/kg/day dose of antimony during 30 consecutive days (low-dose) • **Intervention 2:** 20 mg/kg/day dose of antimony during 30 consecutive days (high-dose) Medication was N-methyl glucantime and each 5 ml ampoule contain 425 mg of pentavalent antimony. The doses were administered by intravenous route, diluted in distilled water always with the same final volume of 20 ml **Duration of intervention:** 30 days **Co-interventions:** not stated
Outcomes	**Definition:** • ***Complete response:*** was defined as the complete epithelisation of all lesions with no residual erythema at the end of the third month after therapy and no relapses during the follow-up **Adverse effects:** Participants were examined for adverse side effects. **Time points reported:** Participants were examined for adverse side effects and response to treatment at the following times after the beginning of the treatment: weeks 1, 2, 3, 4, 6; months 2, 3, 4, 6 and 12 and then years
Notes	**Ethical approval needed/obtained for study**: not stated

Oliveira-Neto 1997 *(Continued)*

Informed consent obtained: not stated

Study funding sources: Faper J. (N-E26/170-825/95)

Possible conflicts of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly and equally assigned to received either...." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Treatments were given in a double-blind fashion" Comment: likely blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	High risk	Sample size calculation was not adequately reported

Oster 1985

Study characteristics

Methods	**Study design:** Randomised clinical trial **Setting/location:** Walter Reed Army Medical Center, Washington, DC **Period of study:** February 1978 to January 1982 **Sample size calculation:** not described
Participants	**Type of Leishmania:** American cutaneous leishmaniasis caused by *L. braziliensis*, *L. mexicana*, and *L. chagasi* **Inclusion criteria:** the patient had not previously been treated with antileishmanial drugs, and the patient was at least 18 years of age and gave informed consent to participate in the trial **Exclusion criteria:** not described **Randomised:** 36 **Withdrawals:** 0

Oster 1985 *(Continued)*

	Patients assessed: 36 participants were randomly assigned to 1 of 3 experimental treatment schedules, 12 participants in each group **Age (years) and sex:** not described **Baseline data:** lesion size in the groups A = 3.0 ± 0.4 cm (mean ± SE), B = 2.8 ± 0.5, C = 2.5 ± 0.4, STD = 2.5 ± 0.3
Interventions	**Type of interventions:** • **Group A:** 600 mg Sb once daily x 10 days • **Group B:** Loading dose of 600 mg Sb followed by 600 mg Sb/day (continuous infusion) x 9 days • **Group C:** Loading dose of 600 mg Sb followed by 200 mg Sb every 8 hrs x 9 days **Duration of intervention:** 10 days **Co-interventions:** not stated **Rescue therapy:** Participants failing this second course of therapy were then treated with the regimen they had not yet received. Participants in group STD received standard therapy when retreated for a failure **Duration of follow-up:** 1 year post-treatment
Outcomes	**Definition:** • ***Cure:*** was defined as complete healing of lesions and a negative aspiration culture after treatment **Time points reported:** All participants were examined daily for signs of response to therapy and questioned daily about the occurrence of any new symptoms possibly. Patients were asked to return 1, 3, 6, and 12 months after apparent cure, at which time an interval history, physical examination, and lesion aspiration for culture were obtained
Notes	**Baseline imbalances:** not described sex and age. **Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** yes **Study funding sources:** not stated **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Assignment to one of three treatment groups was made according to a predetermined randomized schedule which was balanced for every three patients." Comment: method was described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided

Oster 1985 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment was described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	There was insufficient information to evaluate the risk of bias

Palacios 2001

Study characteristics	
Methods	**Study design:** Randomised, controlled, clinical trial **Setting/location:** Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM) in Cali and Tumaco, Colombia **Period of study:** April 1996 to March 1997 **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** The sample size to detect a 25% or greater difference in efficacy between the 10- and 20-day treatment groups with a 95% confidence level and a beta error of 20% was 42 patients per group. A 25% difference was considered clinically significant, taking into account the potential benefits of a 10-day treatment as opposed to 20 days, the high efficacy of pentavalent antimonials reported in the literature for the treatment of New World cutaneous leishmaniasis (88% – 100%) and the 100% cure we obtained in a previous pilot study involving 10 adult patients treated with meglumine antimonate for 10 days (Ochoa MT, unpublished data). The number of participants in the total study population was increased to 136 to compensate for the expected loss to follow-up
Participants	**Type of Leishmania:** *L. braziliensis* and *L. panamensis* **Inclusion criteria:** patients who had a parasitological diagnosis of cutaneous leishmaniasis **Exclusion criteria:** Patients who had been treated previously with antimonials, ketoconazole, or another imidazole, amphotericin B or pentamidine, as well as those with mucosal leishmaniasis, severe cardiovascular, renal, hepatic, or pancreatic disease, and pregnant or nursing women **Randomised:** 136 **Withdrawals:** 54 (40%) were not included in the efficacy analysis: 6 received an inadequate dose, 32 were non-adherent to treatment, 13 did not return for the 13-week follow-up examination, and 3 did not return for the 52-week evaluation. A total of 46 in the 10-day group and 36 in the 20-day group were analysed for final response **Patients assessed:** 10 days of treatment with meglumine antimoniate: 68 and 20 days of treatment with meglumine antimoniate: 68 **Age (years):** median age 10 days: 10 years old, and 20 days: 11 years old **Sex:** M/F: 76/60; 10 days: male 40 (58.8%), female 28 (41.2%); and 20 days: male 36 (52.9%), female 32 (47.1%)

Palacios 2001 *(Continued)*

	Baseline imbalances: no **Severity Illness:** Lesion characteristics in the group of 10 days were: ulcer 119 (71%), plaque 29 (17%), nodule 10 (6%), papule 8 (5%), regional adenopathy 35 (29%), satellite lesion 39 (23%). Lesion characteristics in the group of 20 days were: ulcer 119 (77%), plaque 21 (14%), nodule 9 (5%), papule 5 (4%), regional adenopathy 27 (17%), satellite lesion 45 (29%). Median area of lesion: 10 days 391.8 mm^2 and 20 days 430.9 mm^2
Interventions	**Type of interventions:** Meglumine antimoniate was prescribed according to the current recommendations of the Pan-American Health Organization/World Health Organization (PAHO/WHO), and the Ministry of Health of Colombia at a dosage of 20 mg Sb/Kg/day with no upper limit on the daily dose. Treatment was applied intramuscularly, once a day for 10 or 20 days, depending on the study group **Duration of intervention:** 10 and 20 days **Co-interventions:** not stated **Rescue therapy:** Participants in either group who were classified as a clinical failure received a new treatment with meglumine antimoniate at the same dose for 20 days
Outcomes	**Definition:** • ***Initial clinical response:*** if the participant had complete re-epithelialisation and absence of inflammatory signs of all lesions • ***Final clinical response:*** participants with initial clinical response without relapses of lesions between 13 and 52 weeks of follow-up • ***Clinical failure:*** defined as cases where the lesions failed **Adverse effects:** The adverse effects of antimonials were monitored over the treatment period using a structured questionnaire. Study personnel or health volunteers questioned participants about the presence of malaise, headache, myalgias, arthralgias, and anorexia. No laboratory tests were performed to evaluate toxicity of the treatments **Time points reported:** all participants were clinically evaluated at 13, 26, and 52 weeks after initiation of treatment
Notes	**Ethical approval needed/obtained for study**: All protocols were reviewed and approved by the Institutional Review Board of CIDEIM in accordance with the guidelines of the United States Federal Policy for Protection of Human Subjects (Title 45, Code of Federal Regulations, Part 46) and the Colombian Ministry of Health **Informed consent obtained:** the signed consent was obtained from each participant or from the guardian in the case of children less than 18 years of age **Study funding sources:** This work was supported by the Ministry of Health of Colombia and by a Young Investigator Studentship Grant from Colciencias to Ricardo Palacios **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed using permuted block randomization" Comment: method was described
Allocation concealment (selection bias)	Unclear risk	It was not stated

Palacios 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Due to the ethical considerations of applying a placebo by intramuscular injection over 10 days, the administration of treatment was not masked." Comment: Patients were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all patients were clinically evaluated at 13, 26, and 52 weeks after initiation of treatment by a physician other than the one prescribing treatment and who was masked with respect to which study group the patient belonged." Comment: masked examiners evaluated clinical responses
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up: 54 out of 136 (39.7%): 10-day group: 22/68; 20-day group: 32/68 Reasons were provided in Fig 1 of the publication and included inadquate dose given, not adhering to treatment or missing follow-up appointments.
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	Low risk	All information was provided

Prates 2017

Study characteristics	
Methods	**Study design:** Parallel, single-blind randomised controlled clinical trial **Setting/location:** Outpatients from the health post of Corte de Pedra, Bahia, Brazil **Period of study:** February 2014 to April 2015 **Sample size calculation:** The sample size of 70 patients was obtained considering a variation of 30% of the cure rate (55% in the control vs 85% in the study group), with an α value of 0.10% and 80% power
Participants	**Type of Leishmania:** A positive PCR result for *L. braziliensis* was found in 94.3% (50 of 53) **Inclusion criteria:** diagnosis of CL based on case definition; illness duration >1 month and < 3 months; age 18 – 65 years; 1 – 3 ulcerated lesions; major ulcer diameter ranging from 10 to 50 mm **Exclusion criteria:** pregnancy or breastfeeding among women; any uncontrolled active infectious or severe disease; allergy to fluconazole or Sbv **Randomised:** 53: Fluconazole (N = 27) and Sbv (N = 26) **Withdrawals:** 2 in the fluconazole group **Patients assessed:** 53 (ITT analysis) **Age (years) and sex:** M/F: 35/18, and age ranged from 18 to 53 years. **Baseline data:** Fluconazole group: M/F: 15/27; No. of lesions (Mean ± SD): 1.2 (0.4); Lesions in inferior limbs (%) 26/27 (96.3); Ulcer area, mean (SD), 270.6 (247.6) mm^2 Sbv group: M/F: 20/26; No. of lesions (Mean ± SD): 1.3 (0.6); Area of lesions (mm^2) (M ± SD): 132 ± 248; Lesions in inferior limbs (%) 17/26 (65.4) Ulcer area, mean (SD), 393 (337.9)

Prates 2017 *(Continued)*

Interventions	**Type of interventions:** • **Intervention:** administered orally in capsules containing 150 mg of the drug at a dosage of 6.5 – 8 mg/kg/d for 28 days • **Control:** Sbv (Glucantime), administered intravenously at a dosage of 20 mg/kg/d for 20 days **Duration of intervention:** 20 days (control) and 28 days (intervention) **Co-interventions:** not stated **Duration of follow-up:** at 2 weeks and 1, 2, and 6 months after therapy
Outcomes	**Definition:** • ***Initial and definitive Cure:*** complete epithelialisation of all lesions without raised borders, infiltrations, or crusts • ***Speed of healing*** *:* method not reported **Adverse effects:** Clinical and laboratory AEs were graded according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute **Time points reported:** Initial and definitive clinical cure were assessed 2 and 6 months after the end of each treatment, respectively. Interim analysis to access efficacy and safety was performed 3 times by the data safety and monitoring board, 8 months after the beginning of the study and then at 2-month intervals
Notes	**Ethical approval needed/obtained for study**: **Informed consent obtained:** The study was approved by the Ethics Committee of the Federal University of Bahia, Brazil (registration 296.392/2013). **Baseline imbalances:** Comparison between groups showed a lower mean age in the fluconazole group (P = 0.01). The groups also differed in the location of ulcerated lesions, with 26 of 27 participants (96.3%) in the fluconazole arm presenting with ulcers on the lower limbs, compared with 17 of 26 (65.4%) in the Sbv arm (P = 0.005) **Study funding sources:** This work was supported by the National Council of Scientific and Technological Development (MCTI/CNPq/MS-SCTIE-Decit 40/2012; Research for Neglected Diseases grant 404129/2012-9) **Possible conflicts of interest:** The authors declare that they have no conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Patients were randomized by a computer list obtained in www.randomization.com and allocated at a rate of 1:1 into 2 groups: fluconazole (intervention) and Sbv (control).” Comment: method was described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: “A single- blind randomized controlled clinical trial was performed. Both clinicians and subjects were instructed to not exchange any information regarding the treatment." Comment: not clear if blinding was broken

Prates 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Clinicians blinded to the assignment group performed the physical examination to evaluate cure. Both clinicians and subjects were instructed to not exchange any information regarding the treatment." Comment: outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analyses were performed, although 1 participant in the fluconazole group discontinued treatment because of malaise, headache, and moderate dizziness 2 losses to follow-up (< 5%)
Selective reporting (reporting bias)	Low risk	All outcomes were reported and the trial was registered at Clinical Trials Registration. NCT01953744
Other bias	Low risk	All information was provided

Ravis 2013

Study characteristics	
Methods	**Study design:** Randomised, double-blind, 2-group trial **Setting/location:** Lima, Peru, and Panama City, Panama **Period of study:** 20 days **Sample size calculation:** not stated
Participants	**Type of Leishmania:** cutaneous leishmaniasis (sp unknown) **Inclusion criteria:** not stated **Exclusion criteria:** not stated **Randomised:** Adult: Paromomycin = 13; WR 279,3 = 13 Child: Paromomycin = 18 WR 279,3 = 16 **Withdrawals:** 0 **Patients assessed:** Day 20: Adult: Paromomycin = 13 WR 279,3 = 13 Child: Paromomycin = 18 WR 279,3 = 16 **Age (years) and sex:** adult/paromomycin: Age, yrs 37 (14); Sex, M/F 10/3. Adult/ WR 279,396: Age, yrs 36 (12); Sex, M/F 8/5. Child/paromomycin: Age, yrs 11.4 (4.1); Sex, M/F 14/4. Child/ WR 279,396: Age, yrs 10.3 (2.9); Sex, M/F 13/3 **Baseline data:** adult/paromomycin: Wt, kg 74 (19); Lesion size mm^2 332 (317). Adult/ WR 279,396: Wt, kg 77 (15); Lesion size mm^2 175 (163) Child/paromomycin: Wt, kg 40.6 (17.6); Lesion size mm^2 155 (158). Child/ WR 279,396: Wt, kg 35.8 (12.7); Lesion size mm^2 112 (175)
Interventions	**Type of interventions:** • **Intervention 1:** receive either WR 279,396 (each gram of cream contains 150 mg (15% (wt/wt)) paromomycin USP base and 5 mg (0.5% (wt/wt)) gentamicin USP base) • **Intervention 2:** receive either paromomycin alone (each gram of cream contains 150 mg (15% (wt/wt)) paromomycin USP base).

Ravis 2013 *(Continued)*

	Duration of intervention: 20 days **Co-interventions:** not described **Duration of follow-up:** not reported
Outcomes	**Definition:** The lower limits of quantitation(LLOQ)were 13.20 ng/ml for gentamicin C1, 12.25 ng/ml for gentamicin C1a, 21.25 ng/ml for gentamicin C2, and 50.0 ng/ml for gentamicin (total) and paromomycin. The total body clearance value was the mean of the 2 reported estimates for 12 mg/kg-of-body-weight- and 15 mg/kg single-intramuscular -paromomycin-dose groups **Time points reported:** days 1 and 20
Notes	**Ethical approval needed/obtained for study**: In Peru, the protocol was approved by the Independent Ethics Committee (IEC) of the Universidad Peruana Cayetano Heredia (UPCH) and the IEC of Hospital Nacional Cayetano Heredia (HNCH) in Lima City. The Ministry of Health of Peru approved importation of the study drug. In Panama, the protocol was approved by the Panamanian National Committee of Bioethics for Research, Panama City, Panama. In the United States, the protocol was approved by the Human Research Protections Office, U.S. Army Medical Research and Materiel Command, Ft. Detrick, MD **Informed consent obtained:** Written informed consent was obtained from all adult participants and from the legal representatives of all minors. In addition, all minors provided witnessed assent **Baseline imbalances:** not described. **Study funding sources:** this work was supported by the Department of the Army **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details were provided
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Referred to as "double-blind" so assume participants and personnel were blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	Registered at ClinicalTrials.gov under registration no. NCT01032382 and NCT01083576. All outcomes described in the registration were reported
Other bias	Unclear risk	There was insufficient information to evaluate the risk of bias

Rubiano 2012

Study characteristics	
Methods	**Study design:** Randomised, open-label, non- inferiority clinical trial **Setting/location:** 3 geographic locations in Colombia: the municipalities of Chaparral (Tolima), Tumaco (Nariño) and Cali (Valle) **Period of study:** July 2007 to November 2009. The last 26-week follow-up was completed in June 2010 **Sample size calculation:** Sample size estimate assumed 20% treatment failure for meglumine antimoniate and 15% for miltefosine and a 15% maximum inferiority of miltefosine. 62 children per group were necessary to demonstrate this difference with an α value of 0.05 (1 tail) and a power of 90%. The 15% maximum difference was determined by consensus of a panel of physicians experienced in the treatment of leishmaniasis
Participants	**Type of Leishmania:** Parasites were isolated and identified in 51.7% of participants (60/116) from samples obtained at the baseline visit. Most (71.6%) were *L. panamensis*, followed by *L. guyanensis* (26.6%) **Inclusion criteria:** children aged 2 – 12 years with parasitologically-confirmed cutaneous leishmaniasis who were available to receive supervised treatment for up to 28 days and participate in follow-up for 26 weeks **Exclusion criteria:** weight < 10 kg, mucocutaneous disease, use of anti-Leishmania medications during the month prior to diagnosis, medical history of cardiac, renal, or hepatic disease, menarche, and baseline values for haemoglobin, amylase,AST, ALT, creatinine, and serum urea nitrogen outside the normal range **Randomised:** 116 **Withdrawals:** 5 (2 in the MA group and 3 in the miltefosine group) **Patients assessed:** 116 by ITT and 111 per protocol (56 in the MA group and 55 in the miltefosine group) **Age (years) and sex:** MA group: age, median (range),y: 7 (2 - 11) and M/F: 31/27; Miltefosine group: age, median (range),y: 7 (2 - 12) and M/F: 24/34 **Baseline data:** Lesions per person, median (range), No.: 2 (1 - 7) in the MA group and 2 (1 - 8) in the miltefosine group; Lesion size, median (range) mm^2: MA group, 209 (28 - 1764); Miltefosine group: 277 (2 - 2441); Location of lesion, N°: Head and neck: 48 (MA) and 31 (Miltefosine), Upper limbs: 37 (MA) and 48 (Miltefosine); Lower limbs: 23 (MA) and 31 (Miltefosine); Trunk: 15 (MA) and 10 (Miltefosine)
Interventions	**Type of interventions:** • ***Intervention group:*** miltefosine (10 mg miltefosine/capsule) at 1.5 – 2.5 mg/kg/d by mouth during 28 consecutive days, divided into 2 or 3 daily doses • ***Control group:*** intramuscular meglumine antimoniate (81 mg Sb/mL) at 20 mg Sb/kg/d for 20 consecutive days When participants met definitions of therapeutic failure (at any of the follow-up visits), follow-up was concluded, and alternative treatment was provided **Duration of intervention:** miltefosine 28 days; antimoniate 28 days **Co-interventions:** not stated **Duration of follow-up:** 26 weeks after initiation of treatment
Outcomes	**Definition:** *Primary outcomes* Initial therapeutic response at week 13:

Rubiano 2012 *(Continued)*

- ***Cure:*** complete re-epithelisation and the absence of inflammatory signs for all cutaneous leishmaniasis lesions
- ***therapeutic failure*** was defined as incomplete re-epithelisation and/or the presence of induration, raised borders, or redness in any lesion or the appearance of new lesions

Initial therapeutic response at week 26:

- initial clinical therapeutic response attained by week 13 and maintained until week 26 without the appearance of new lesions
- therapeutic failure was defined as the presence of inflammatory signs (induration, raised borders, or redness) or ulceration in any of the original lesions or the appearance of new lesions

Adverse effects were identified by study personnel using a structured questionnaire to record constitutional and gastrointestinal symptoms. AEs were classified according to Common Terminology Criteria for Adverse Events, version 3.0

Secondary outcome

Parasitologic response, defined as failure to culture parasites from lesion aspirates obtained at the end of treatment

Time points reported: End of treatment, at 13 and 26 weeks after initiation of treatment

Notes

Ethical approval needed/obtained for study: The study was approved by the institutional ethical review boards of Centro Internacional de Entrenamiento e Investigaciones Medicas (CIDEIM) and Centro Dermatologico Federico Lleras Acosta, the national reference center for dermatologic disease

Informed consent obtained: Legal guardians of all participants provided written informed consent; patients aged ≥7 years provided written informed assent.

Baseline imbalances: The only significant difference between groups for baseline characteristics was more frequent presence of palpable lymphatic involvement along the trajectory-draining lesions in the miltefosine group

Study funding sources: Colombian national Departamento Administrativo de Ciencia, Tecnología e Innovación (COLCIENCIAS) (grant 2229-343-19253). Capacity building for the ethical conduct of clinical trials at the study sites was supported by the National Institute of Allergy and Infectious Diseases International Collaborations in Infectious Disease Research Program (grant 1 U19AIO65866) and Fogarty Global Infectious Diseases Research Training Program (grant D43 TW006589).

Possible conflicts of interest: MCM. joined Sanofi Pasteur in July 2009, a year after the start of this non-inferiority trial. All other authors declare no potential conflicts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computerized balanced block randomization scheme was used to generate group assignment, which was stratified according to study site and age group (2 to < 7 and 7–12 years)." Comment: randomisation method described
Allocation concealment (selection bias)	Low risk	Quote: "To ensure allocation concealment, treatment was assigned by the coordinating center (CIDEIM) via phone call from the study site at subject inclusion. Directly observed treatment was administered daily by study personnel." Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias)	High risk	Quote: “Double blinding was not undertaken because of the different routes of administration of the study medications and the unjustified and unethical risk of injection placebo.

Rubiano 2012 *(Continued)*

All outcomes		Comment: Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Masked evaluation" "To eliminate ascertainment bias, treatment outcome was determined by a masked evaluator using standardized photographs of lesions. In case of disagreement between the clinical evaluation by study site physicians and the masked evaluator, the photos were evaluated by a second masked dermatologist. This occurred in 4 cases; outcome assessment by the 2 masked evaluators concurred in all cases." Comment: outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Subjects withdrawn from the study or unavailable for follow-up were considered therapeutic failures for ITT analysis and excluded from PP analysis." Comment: Few losses in follow-up, distributed in both treatment groups (1 and 2)
Selective reporting (reporting bias)	Low risk	Reported all relevant outcomes that were planned in the Protocol Clinical Trial Registration: NCT00487253
Other bias	Low risk	All information was provided

Saenz 1987

Study characteristics	
Methods	**Study design:** Randomised study **Setting/location:** rural areas of the provinces of Panama and Colon **Period of study:** February 1983 to July 1985 **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL) by *L. braziliensis panamensis.* Diagnostic confirmation by culture or biopsy **Inclusion criteria:** confirmed diagnosis of leishmaniasis **Exclusion criteria:** prior treatment for leishmaniasis **Randomised:** 59 participants were randomised into 2 groups: 29 received Glucantime and 30 received pentostam glucantime **Withdrawals:** 9 participants are excluded because they had < 6 months follow-up **Patients assessed:** glucantime: 29 and pentostam: 30 **Age (years):** the average age was 29.6 y for glucantime and 26.4 y for pentostam **Sex:** M/F: 47/12; ratio m/f: glucantime 9:1 and pentostam 2:1 **Baseline imbalances:** no

Saenz 1987 *(Continued)*

	Severity Illness: type lesion was ulcerative in all participants
Interventions	**Type of interventions:** • **Glucantime:** 20 mg de Sb per kg daily, IM, for 20 days, maximum 850 mg per day • **Pentostam:** 20 mg de Sb per kg, IM, for 20 days, maximum 850 mg per day **Duration of intervention:** 20 days **Co-interventions:** not described
Outcomes	**Definition:** • ***Clinical cure:*** A cure was defined as a participant whose previous ulcer had complete re-epithelialisation • ***Relapse:*** reactivation of the disease at the site of the initial injury • ***Failure:*** incomplete healing and persistence of parasites to 2 months after treatment **Adverse effects:** They evaluated adverse effects such as myalgia, arthralgia, headache, fever, malaise, pain at the injection site and allergy **Time points reported:** every 3 months to complete 1 year
Notes	**Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** not stated **Study funding sources:** Partly funded by UNDP/World Bank/WHO Special Program for Research and Training in Tropical diseases **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Los pacientes fueron distribuidos al azar en dos grupos terapeuticos..." Translated quote: "The patients were randomized into two therapeutic groups..." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment was described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 9 out of 59 (15.3%)

Saenz 1987 *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	High risk	Sample size calculation was not adequately reported

Saenz 1990

Study characteristics	
Methods	**Study design:** Randomised study **Setting/location:** Panama **Period of study:** March 1986 to March 1988 **Unit of randomisation:** participaent **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL) caused by *L. panamensis* and *L. mexicana* **Inclusion criteria:** Panamanians with cutaneous lesions clinically diagnosed as leishmaniasis and who gave informed consent **Exclusion criteria:** if they had facial or mucosal lesions, significant concomitant disease of any organ, or abnormalities on subsequent baseline tests (complete blood count, determination of serum levels of glucose, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, bilirubin, alkaline phosphatase, urea nitrogen, creatinine, cholesterol, and calcium; electrocardiogram; chest radiograph) **Randomised:** 41 **Withdrawals:** 0 **Patients assessed:** 22 participants were entered into the ketoconazole group, and 19 participants were randomised into the Pentostam group **Age (years):** Ketoconazole group: the age range was 16 to 48 years; the mean age was 25 years and 18 of 22 (82%) were between 16 and 30 years of age. Pentostam group: the age range was 17 to 67 years; the mean age was 34 years and 11 of 19 (58%) were 16 to 30 years of age **Sex:** All participants were male **Baseline imbalances:** no **Severity Illness:** There was a mean of 2.1 lesions per ketoconazole-treated participant, and 23 of the 35 lesions (66%) were on the upper extremities. There was a mean of 2.6 lesions perpPentostam-treated participant, with 25 of 49 lesions (51%) being on the upper extremities. For the ketoconazole group, there was a mean ± SD duration of disease of 8.2 ± 3.5 weeks; for the pentostam group, there was a duration of 12.5 ± 3.0 weeks. The mean ± SD area of the lesions on ketoconazole-treated a was 333 ± 319 mm^2. The size of the lesions on pentostam-treated participants was 350 ± 470mm^2
Interventions	**Type of interventions:** • **Intervention 1:** 3 x 200 mg tablets of ketoconazole, a total of 600 mg, before sleep each day for 28 days • **Intervention 2:** 20 mg antimony Sb/kg/day with a maximum of 850 mg Sb/day, intramuscularly for 20 days **Duration of intervention:** 20 or 28 days

Saenz 1990 *(Continued)*

	Co-interventions: not described **Rescue therapy:** Participants in whom ketoconazole, pentostam, or placebo therapy failed were re-treated 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, intramuscularly for 12 days), and all were cured
Outcomes	**Definition:** • ***Healed:*** if it had undergone complete re-epithelialisation. A lesion was definitively healed if it had not clinically relapsed by the 12-month follow-up examination • ***Failed therapy:*** if it had diminished by < 25% by the l-month follow-up examination (i.e. was > 75% of its original size by 1 month after the end of the approximately l-month period of treatment) • ***Relapsed:*** if it underwent a 100% enlargement after initial diminution or if a new lesion appeared adjacent to the original lesion • ***Cured:*** of leishmaniasis if all lesions had undergone definitive healing Therapy failed in a person if any lesion failed to respond to therapy or relapsed. Although the clinician who initially judged the clinical status of the lesion was aware of the participant's treatment group, photographs of the lesions provided objective evidence of clinical status **Adverse effects:** During treatment, participants were asked daily for symptomatic complaints, and blood was drawn weekly for complete blood counts and serum chemistries **Time points reported:** In clinic 1,2,3,6, and 12 months after the end of treatment. At these times, any no- healed lesion was measured
Notes	**Ethical approval needed/obtained for study**: not stated. **Informed consent obtained:** participant gave informed consent **Study funding sources:** not stated **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was accomplished by card drawing" Comment: adequate method given
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Clinicians were aware of the treatment, but we do not know whether participants were aware of the allocated treatment or not
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Although the clinician who initially judged the clinical status of the lesion was aware of the patient's treatment group, photographs of the lesions provided objective evidence of clinical status." Comment: outcomes unlikely to be affected (objective assessment)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up

Saenz 1990 *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	High risk	Sample size calculation was not adequately reported

Saheki 2017

Study characteristics	
Methods	**Study design:** Phase III, randomised, controlled, single-blind, non-inferiority trial **Setting/location:** Evandro Chagas National Institute of Infectious Diseases (INI), Oswaldo Cruz Foundation (Fiocruz),Rio de Janeiro State, Brazil **Period of study:** October 2008 to July 2014 **Sample size calculation:** calculated "To calculate the sample size, we have used estimates from the largest clinically acceptable margin derived from historical data. Sample size calculations were inflated to allow for the possibility of up to a 10% withdrawal rate from the study. With these assumptions, a statistical power (1 - β) of 80%, and α level of 5% (one-sided test), a total of 72 patients would be required to determine non-inferiority."
Participants	**Type of Leishmania:** 54 samples were identified as *Leishmania (Viannia) braziliensis* through species characterisation by multi-locus enzyme electrophoresis (MLEE) **Inclusion criteria:** at least 13 years or older and had parasitological diagnosis of cutaneous leishmaniasis by at least one of the following methods: direct examination (scraping or imprint), histopathology, culture, immunohistochemistry or PCR **Exclusion criteria:** prior treatment with meglumine antimoniate (MA); concomitant mucosal leishmaniasis, lack of exposure in an endemic area of Rio de Janeiro State; women in reproductive age not using contraceptives; pregnancy; mmunosuppressive therapy; ongoing treatment for tuberculosis or leprosy; presence of severe or worse changes in baseline clinical evaluation; presence of moderate or worse changes in baseline laboratory evaluation; presence of moderate or worse changes in baseline electrocardiographic evaluation or baseline corrected QT interval (cQT) >460 ms **Randomised:** 72 (high-dose MA (N = 36) and low-dose MA (N = 36)) **Withdrawals:** 1 (High dose MA group) **Patients assessed:** 72 included in the ITT and 71 in the PP analyses **Age (years) and sex:** Low dose/high dose: 13 - 20 years 6 (16.7)/ 4 (11.1); 21 - 35 years 8 (22.2)/ 13 (36.1); 36 - 50 years 11 (30.6)/ 8 (22.2); > 50 years 11 (30.6)/ 11 (30.6) **Sex (M/F):** 51/21**:** Low-dose (25/11); High-dose (26/10) **Baseline data:** Low dose/high dose: No. of lesions per participant 1.0 (1 ± 2.5)/ 1.0 (1.0 ± 1.0); Feature of the main lesion-ulcerated, n (%) 34 (94.4)/ 33 (91.7); Site of the main lesion-lower limbs, n (%) 11 (30.6)/ 18 (50.6); lymph node involvement, n (%) 9 (25.0)/ 11 (30.6); Mean diameter of the main lesion, mm 33.8 (10.1)/ 31.6 (17.3); mean diameter of the main ulcer, mm 22.7 (8.1)/ 19.9 (7.8); MST mm 14.1 (8.8)/ 18.2 (8.5); MST positivity, n/N (%) 29/33 (87.9)/ 29/30 (96.7); positive culture for Leishmania in skin biopsy, n (%) 32 (94.1)/ 31 (91.2)

Saheki 2017 *(Continued)*

Interventions	**Type of interventions:** • **Intervention 1:** 20 mg Sb5+/kg/day (high dose) • **Intervention 2:** 5 mg Sb5+/kg/day (low dose) **Duration of intervention:** 20 days (intervention 1) and 30 days (intervention 2) **Co-interventions:** not described **Rescue therapy:** Participants received alternative therapies according to clinician's preferences and standard local practices if they had not achieved clinical cure or were unable to tolerate the allocated treatment **Duration of follow-up:** 3.78 years (95% CI, 3.36 to 4.19).
Outcomes	**Definition:** • ***Clinical cure:*** epithelialisation within 120 days, scarring within 360 days, absence of clinical worsening, absence of relapse and no appearance of mucosal lesion • ***Scarring*** was assessed at each visit and was defined as the presence of the following criteria: complete healing of all lesions characterised by complete epithelialisation and absence of crusts, infiltration, desquamation, or erythema • ***Clinical worsening*** was defined as deterioration of presenting signs or appearance of satellite lesions • ***Relapse*** was defined as the reappearance of inflammatory signs in the scar or development of new cutaneous lesions in other locations after scarring was established **Adverse effects**: Major adverse effects were defined as presence of severe or worse changes in clinical evaluation, presence of moderate or worse changes in laboratory evaluation, presence of moderate or worse changes in electrocardiographic evaluation or corrected QT interval (cQT) > 460 ms **Time points reported:** Clinical cure at 360 days of follow-up. Clinical assessment with enquiry about adverse effects was done every 10 days during treatment, and every month thereafter for 2 months
Notes	**Baseline imbalances:** There were a few statistically non-significant but noteworthy imbalances: male predominance, the high-dose group had a lower median age, a greater percentage of subjects with diabetes and lesions located in lower limbs **Ethical approval needed/obtained for study**: Ethical approval was granted by the ethics committee at the Evandro Chagas National Institute of Infectious Diseases under number 0055.0.009.000-07 on 17 October 2007 **Informed consent obtained:** Participants gave their informed consent **Study funding sources:** The authors received no specific funding for this work. However, this research was partially funded by Conselho Nacional de Desenvolvimento Científico e Tecnológico - CNPq, grants 304335/ 14-2, 304786/2013-6 and 307090/2004-3, and by Fundacão de Amparo à Pesquisa do Rio de Janeiro - FAPERJ, grants E-26/202.911/2015, E26/ 201.537/2014, E-26/102.183/2013 and E26/101-511/2010. AdOS is supported by CNPq, grant 304335/14-2, and FAPERJ, grant E-26/202.911/ 2015. MFM is supported by CNPq, grant 304786/ 2013-6, and FAPERJ, grant E26/201.537/2014. CMVR is supported by FAPERJ, grant E-26/ 102.183/2013. MCAM is supported by CNPq, grant 307090/2004-3. SRLP is supported by FAPERJ, grant E26/101-511/2010 **Possible conflicts of interest:** The authors have declared that no competing interests exist

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomization was performed by a statistician with no clinical involvement in the trial using a random allocation sequence generated by Epi Info, version 6.04d, in blocks of size 12”

Saheki 2017 *(Continued)*

		Comment: method described
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence was concealed in sequentially numbered, opaque and sealed envelopes until interventions were assigned. Envelopes were kept by an independent pharmacist in a safe deposit box at the pharmacy of INI. To ensure allocation concealment, after the written informed consents were obtained from eligible subjects, treatment was assigned by a second independent pharmacist at the pharmacy of INI." Comment: allocation likely concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "While treatment assignment obviously could not be masked to subjects due to the intramuscular injections, they were instructed before each visit not to discuss any aspects of the treatment with the examiners."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Clinicians involved in subjects' enrolment and adverse effects management were masked to lesion assessment and group assignment. Dermatologists who assessed the lesions were masked to group assignment, clinical data and adverse events." Quote: "All clinical, dermatological, electrocardiographic (ECG) and laboratory assessments were performed masked with respect to the treatment allocation, which was not revealed until the database had been closed at the end of the trial." Quote: "A second trial statistician responsible solely for undertaking the analyses was masked to the randomization sequence and to the treatment allocation until all analyses had been done." Comment: outcome assessment blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analyses were reported by ITT and per protocol. Reasons for dropouts were not provided High-dose group: 1 died
Selective reporting (reporting bias)	Low risk	Study protocol was available and registered (ClinicalTrials.gov: NCT01301924) Outcomes reported in Methods were reported in Results
Other bias	Low risk	All information was provided

Sampaio 2019

Study characteristics	
Methods	**Study design:** Phase II, open-label, randomised clinical trial **Setting/location:** Hospital Universitário de Brasília (HUB) in Brazil, to which patients are referred by primary care facilities for diagnostic confirmation of suspected cases of ATL **Period of study:** January 2010 to December 2016 **Sample size calculation:** "sample size of 40 patients was expected. This population was defined based on the availability of the tested drug, whichis not yet commercially available in Brazil"
Participants	**Type of Leishmania:** The subgenus of the detected parasitewas identified using PCR-restriction fragment length polymorphism (PCR-RFLP). Amastigote forms were found in the histopathological exam-

Sampaio 2019 *(Continued)*

	inations of 6% of participants. PCR using kinetoplastid DNA (kDNA) from nasal swabs was positive in 58.82% of participants, where *Leishmania (V.) braziliensis* was detected **Inclusion criteria:** clinical (the presence of any infiltration or ulceration in nasopharyngeal or oral structures) and an epidemiological history compatible with ML, in addition to parasite visualisation (culture, direct examination, histopathology), or at least2 of the following exams compatible with the diagnosis: MST, compatible histopathological infiltrate, and indirect immunofluorescence **Exclusion criteria:** > 70 years old or < 18 years old, who underwent specific treatment for leishmaniasis < 6 months before recruitment, who showed any evidence of immunosuppression (e.g. HIV, immunosuppressive drugs), or who had any clinical condition that contraindicated the use of medications (e.g. pregnancy, renal failure, cardiopathy) **Randomised:** 40: Intervention group: Control group: 20 **Withdrawals:** 8: Intervention group: 2; Control group: 6 **Patients assessed:** 32/40 (ITT analysis) "Quote: “we performed two analyses: a per-protocol analysis including only patients who concluded treatment and excluding patients who lost the analyzed outcome, and an intention-to-treat-analysis, performed at 90 days and four years after treatment, in which any patient that missed a follow-up visit was considered a therapeutic failure.” Intervention group: 18; Control group: 14 **Age (years) and sex:** Age (years): Intervention group: 61.2 (SD 11.3); Control group: 50.8 (SD 13.0) M/F: 18/22: Intervention group: 9/11; Control group: 9/9 **Baseline data:** Active cutaneous lesions n (%): Intervention group: 3 (15.0); Control group: 1 (5.6) Disease time (months): Intervention group: 112.4 (SD 133.3); Control group: 141.5 (SD 152.5)
Interventions	**Type of interventions:** Although there is no current consensus about the dose of MILT for the treatment of New World leishmaniasis, the WHO suggests a dose of 2 mg/kg/day, while the PAHO suggests 1.5 – 2 mg/kg/day. This drug is not commercialised in Brazil • **Intervention 1:** miltefosine 1.3 – 2 mg/kg/day (2 capsules) for 28 days • **Control group:** intravenous 20 mg SbV/kg/day of meglumine antimoniate (N-MA) for 30 days **Duration of intervention:** 20 and 30 days respectively **Co-interventions:** not stated **Duration of follow-up:** 6 months and some up to 4 years
Outcomes	**Definition:** • The main outcome was defined as complete re-epithelisation and the absence of any inflammation of the lesion 4 years after the end of treatment • Adverse effects Any participant that missed a follow-up visit was considered a therapeutic failure **Time points reported:** The participants were actively recruited at the hospital for clinical evaluation at 0, 30, 60, 90, and 180 days, as well as every 6 months up to 4 years after treatment.

Sampaio 2019 *(Continued)*

Notes	**Ethical approval needed/obtained for study**: "The study complied with the Declaration of Helsinki (1964 and subsequent revisions). The study was approved by the Ethics Committee of the Faculty of Medicine, University of Brasilia (076/2008)." **Informed consent obtained:** "All patients with a confirmed diagnosis of ML were consecutively included after signing an informed consent form" **Baseline imbalances:** Differences between the 2 experimental groups in characteristics, such as age and disease time, likely occurred due to chance **Study funding sources**: "The drug MILT (Impavido ®) was donated by Laboratorio Æterna Zentaris GmbH. This work was supported by grant number 478575/2008-4 from Conselho Nacional de Desenvolvimento Científico e Tecnológico." **Possible conflicts of interest:** "The authors declare no conflicts of interest"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patient allocation was made following a random assignment in fixed block sizes of four patients. A staff member, who was different from the principal investigator, randomly created a list containing ten groups of four patients. Two patients from each group were allocated to each block."
Allocation concealment (selection bias)	Low risk	Quote: "The generated list was kept by an administrative employee who was not involved in either the intervention or the outcome measurements"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding Quote: "The absence of blinding or sham intervention may have weakened the allocation concealment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further information about blinding of outcome assessment was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 8/40 (20%) However, both per protocol and ITT analyses were performed. Reasons: 2 losses in the MILT group and 6 losses in the N-MA group. In the MILT group, 1 participant had their treatment suspended due to abdominal pain and elevation of serum amylase at 231 U/L (reference values: 20 – 160 U/L), while the second participant abandoned clinical follow-up after treatment completion. In the N-MA group, 2 participants did not complete the study due to treatment suspension related to an adverse prolonged corrected QTc interval. In the N-MA group, 2 participants declined to participate in the study after randomisation prior to the first medication dose, alleging that the pentavalent antimonial side effects were too severe. 2 additional participants also abandoned clinical follow-up after treatment completion.
Selective reporting (reporting bias)	Low risk	Study protocol was registered in ClinicalTrials.gov database (NCT01377974)
Other bias	Low risk	All information was provided

Santos 2004

Study characteristics	
Methods	**Study design:** Randomised, double-blind, placebo-controlled study **Setting/location:** Corte de Pedra, Bahia, Brazil **Period of study:** not stated **Unit of randomization:** participant **Unit of analysis:** participant **Sample size calculation:** not stated
Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL). *L. braziliensis* (endemic) **Inclusion criteria:** 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 (also called "the Montenegro skin test") to Leishmania antigen **Exclusion criteria:** pregnancy, an age of < 15 or > 50 years, other associated acute or chronic illness, and a history of allergy to GM-CSF or antimony or both **Randomised:** 22 **Withdrawals:** 22 participants were initially assigned to the 2 groups. 2 participants (1 in each of the groups) were excluded, because the topical medication was administered by use of a different wound compress **Patients assessed:** 10 participants received antimony plus topical Granulocyte-macrophage colony-stimulating factor (GM-CSF), and 10 received antimony plus placebo (saline) **Age (years):** mean age GM-CSF + antimony group: 28 ± 14, placebo + antimony group: 29 ± 1 **Sex:** GM-CSF + antimony group: included 7 male (70%) and 3 female (30%); placebo + antimony group: included 9 male (90%), and 1 female (10%) **Baseline imbalances:** no **Severity Illness:** Mean size of the lesions before treatment in the group treated with GM-CSF + antimony was 25 ± 5.8 mm and in the group treated with placebo + antimony was 24 ± 5 mm
Interventions	**Type of interventions:** antimony plus topical Granulocyte-macrophage colony-stimulating factor (GM-CSF), and antimony plus placebo • **Intervention group:** antimony 20 mg/kg of body weight daily for 20 days plus GM-CSF. The participants in the GM-CSF group were treated as follows: ulcers were cleansed with 0.9% sodium-chloride solution and were sprinkled with 1 mL of GMCSF working solution (10 mg of GM-CSF/mL in 0.9% sodium chloride solution) per 10 cm2 of ulcer area, providing a final dose between 1 and 2 mg/cm^2 of ulcer area. A non-adhesive hydrophobic wound compress (Adaptic; Johnson & Johnson) was secured over the area with a cotton bandage and a short stretch compression bandage (Colban; 3M). 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) • **Control group:** placebo group: antimony plus saline. The participants in the placebo group received saline applied locally instead of GM-CSF All of the participants received intravenous pentavalent antimonial treatment (meglumin antimoniate; Roche) daily for 20 days, at 20 mg/ kg of body weight **Duration of intervention:** antimony 20 days and GM-CSF 3 weeks

Santos 2004 *(Continued)*

	Co-interventions: not described **Rescue therapy:** participants with failed treatment received an additional course of intravenous pentavalent antimonial therapy (20 mg/kg of body weight daily for 20 days)
Outcomes	**Definition:** • ***Clinical cure:*** was defined as complete re-epithelialisation of the ulcer • ***Failure:*** was defined as a persistent, non-healing ulcer 3 months after the initiation of treatment **Adverse effects:** To maintain the double-blind nature of the study, 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 (such as general malaise and myalgias) **Time points reported:** For 6 months after treatment was initiated, the participants were evaluated every 15 days; afterward, they were evaluated every 2 months until 1 year of follow-up was completed
Notes	**Ethical approval needed/obtained for study**: the study was approved by the Ethics Committee of the Hospital Universitário Professor Edgard Santos, Bahia, Brazil **Informed consent obtained:** Written, informed consent was obtained from all participants > 18 years old and from parents of younger participants **Study funding sources:** not stated **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “The patients who met the inclusion criteria were randomized by use of a randomization table; the randomization was performed by a statistician." Comment: randomisation method considered adequate
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Both the patients and the physicians who performed the clinical follow-up were blinded.” Comment: double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Two physicians independently examined the patients on all visits. Two independent physicians examined the participants 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.” Comment: outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “Two patients (1 in each of the groups) were excluded, because the topical medication was administered by use of a different wound compress."
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	High risk	*Leishmania* sp was not confirmed and sample size calculation was not adequately reported

Sosa 2013

Study characteristics	
Methods	**Study design:** Randomised, double-blinded Phase 2 trial **Setting/location:** area surrounding Panama City, Panama, where *L. panamensis* is prevalent **Period of study:** February 2010 to 28 March 2011 **Sample size calculation:** Quote."As the study was primarily a PK (pharmacokinetics) evaluation that was not designed to compare the efficacy of the two topical creams, the selection of the number of subjects (15 in each arm) was based on the following objectives: 1) to obtain PK data which, when combined with PK data from a similarly designed Phase 2 study in Peru, would provide a collective body of data to determine the extent of systemic drug exposure; and, 2) to obtain sufficient data to have a preliminary estimation of the initial clinical cure rate as a basis for calculating sample sizes for a possible larger trial."
Participants	**Type of Leishmania:** 14/26 positive to *L. panamiensis* **Inclusion criteria:** Eligible patients were male or non-pregnant/non-lactating women; ≥ 5 years of age; with ≤ 10 lesions; and with 1 of these lesions (the index lesion) having the following characteristics: ulcerative, at least 1 cm, and < 5 cm in greatest diameter of lesion, including induration, and confirmed to contain Leishmania by culture or microscopic examination of lesion material. The reason to designate 1 lesion as the index lesion is that the response of at least that lesion would reflect the efficacy of treatment on an ulcer known to be caused by Leishmania **Exclusion criteria:** signs of disseminated disease, against which a topical treatment would not be expected to be effective or recent treatment (within 8 weeks of starting study treatments) with a recognised antileishmanial **Randomised:** 30 **Withdrawals:** none **Patients assessed:** 30 **Age (years) and sex:** 6 (5 - 11 years), 7 (12 - 17 years), 17 adults; M/F: 24/6 **Baseline data:** Total number of lesions (N) WR: 34, PA: 30; Number of lesions per participant: mean (SD): WR: 2.3 (1.7), PA: 2.0 (1.0); Duration of disease before treatment (days), mean (SD): WR: 94 (97). PA: 68 (18)
Interventions	**Type of interventions:** • ***Intervention group:*** WR 279,396 WR 279,396 (15% paromomycin + 0.5% gentamicin) • ***Control group:*** Paromomycin alone (15% paromomycin) **Duration of intervention:** Participants were treated once daily for 20 days with the topical creams **Co-interventions:** not stated **Duration of follow-up:** Blood samples for PKs were collected during the first 20 days, local application site toxicity was assessed daily, and lesion sizes were measured 5 times during the treatment period. Participants were followed at weekly intervals after completing treatment of safety and efficacy up to Day 63, and then had final follow-up visits at Days 100 and 168
Outcomes	**Definition:** • Clinical endpoints criteria. ○ ***Final clinical cure*** was defined as (A and C) or (B and C), where A = participant had initial clinical cure (100% re-epithelialisation of index lesion by nominal Day 63); B = participant had initial clinical improvement (> 50% re-epithelialisation of index lesion by nominal Day 63 followed by 100%

Sosa 2013 *(Continued)*

re-epithelialisation of the index lesion on or before nominal Day 100; and C = participant had no relapse of index lesion. ***Relapse*** was defined as an index lesion meeting the criteria for initial clinical cure or initial clinical improvement that had any new ulceration (> 0 + 0 mm measurement) by nominal Day 168.

- The protocol-specified primary efficacy endpoint was the number of participants with an index lesion that exhibited final clinical cure. If the participant was withdrawn early from the study, they were considered a treatment failure
- Secondary endpoints included number of participants where all baseline lesions that received treatment met the definition for final clinical cure and all lesions treated independently of the participant

Adverse effects: the safety endpoints were adverse events in general, application site reactions, and aminoglycoside renal toxicity determined by serum creatinine measurements at the end of therapy on Day 20

Time points reported: Participants were followed at weekly intervals after completing treatment of safety and efficacy up to Day 63, and then had final follow-up visits at Days 100 and 168

Notes

Ethical approval needed/obtained for study: The protocol was approved by the Panamanian National Committee of Bioethics for Research, Panama City, Panama, and by the Human Research Protections Office, U.S. Army Medical Research and Materiel Command, Ft. Detrick, Maryland

Informed consent obtained: Informed consent was obtained from all study participants and/or guardians before enrolment

Baseline imbalances: none relevant

Study funding sources: sponsored by the Office of the Surgeon General, Department of the Army, USA, and it is registered with ClinicalTrials.gov identifier NCT01083576

Possible conflicts of interest: Nothing declared. However, "The opinions or assertions contained herein are the private views of the authors, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote p 558: "After establishing eligibility for the study, a total of 30 patients were randomly assigned in 1:1 allocation to the two treatment groups in a blinded manner. To balance treatment assignments by age group, a permuted block randomization method was used to generate the treatment randomization within age groups. Subjects were stratified by age group: 5–11 years, 12–7 years, and ≥ 18 years of age. No more than 18 subjects could be randomized in any age range, so that there would be at least six subjects in each age stratum evaluable for the PK analysis." Comment: randomisation method described
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as “double-blinded”. Assume participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Mentioned as “double-blinded” - not clear if outcome assessors were blinded

Sosa 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote page 559: " Six subjects in the Paromomycin Alone group and one subject in the WR 279,396 group were withdrawn from the study by the investigator before the final visit at Day 168 because of treatment failure. All of these subjects were included in the ITT analysis." Comment: Losses to follow-up > 20%: Paromomycin alone: 6/15 (40%), WR 279,396: 1/15 (6.7%).Withdrawals were due to treatment failure. ITT analysis performed
Selective reporting (reporting bias)	Low risk	Efficacy and safety data were secondary endpoints in this study. Protocol available (ClinicalTrials.gov identifier: NCT 01083576)
Other bias	Low risk	All information was provided

Sosa 2019

Study characteristics	
Methods	**Study design:** Phase 3, randomised, double-blind study **Setting/location:** Instituto Conmemorativo Gorgas de Estudios de la Salud, Panama City, Panama. The study was condcuted at three sites in Panama: Penonome, Panama City, and Changuinola **Period of study:** May 2013 to January 2016 **Sample size calculation:** "The sample size of the study was adjusted to 400 total subjects, adding 50 subjects to each study arm to maintain at least 90% power with a two-sided alpha of 0.05 to detect statistically significant superiority of paromomycin-gentamicin over paromomycin alone for *L. panamensis* patients"
Participants	**Type of Leishmania:** Whenever possible, infecting species of *Leishmania* were determined by PCR followed by restriction fragment length polymorphism (RFLP) using the heat shock protein 70 for discrimination of *Leishmania* species and isoenzyme analysis (multilocus enzyme electrophoresis (MLEE)). Of 399 participants, 398 were typed using PCR/RFLP. Of those, a total of 312 (78%) were identified as infected with *L. panamensis*, 78 (20%) with *L. guyanensis*, 8 (2%) with *L.braziliensis,* and 1(0.3%) with *L. naiffi* **Inclusion criteria:** Male or female aged at least 2; participant or legal guardian able to give written informed consent or assent, as appropriate; diagnosis of CL in at least 1 lesion by at least 1 of the following methods: positive culture for promastigotes,or microscopic identification of amastigotes in stained lesion tissue; at least 1 ulcerative lesion ≥ 1 cm and ≤ 5 cm that has a diagnosis of CL; willing to forego other forms of treatments for CL including other investigational treatments during the study; in the opinion of the investigator, participant (or their legal guardian), is capable of understanding and complying with the protocol; if female and of child-bearing potential, must have a negative serum pregnancy test during screening and agree to use an acceptable method of birth control during the treatment phase and for 1 week after treatment is completed **Exclusion criteria:** Lesion due to leishmania that involves the nasal or oral mucosa or any signs of mucosal disease that might be due to Leishmania; only a single lesion on the ear with erosive cartilage; signs and symptoms of disseminated disease in the opinion of the investigator; > 10 lesions; woman who is breast-feeding; significant organ abnormality, chronic disease such as diabetes, severe hearing loss, evidence of renal or hepatic dysfunction, or creatinine, AST, or ALT > 15% above the upper limit of normal (ULN) as defined by the clinical laboratory-defined normal ranges; received treatment for leishmaniasis including any medication with pentavalent antimony including sodium stibogluconate (Pentostam™), meglumine antimoniate (Glucantime™); amphotericin B (including liposomal amphotericin B and amphotericin B deoxycholate); or other medications containing paromomycin (administered parenterally or topically) or methyl benzethonium chloride (MBCL); gentamicin; fluconazole; ke-

Sosa 2019 *(Continued)*

	toconazole; pentamidine; miltefosine, azithromycin or allopurinol that was completed within 56 days of starting study treatments; history of known or suspected hypersensitivity or idiosyncratic reactions to aminoglycosides **Randomised:** 400, although 1 randomised participant in Group 2 (a minor) was later determined to not be properly consented (legal guardian could not provide documentation) and was not included in the analysis. Thus, 399 of which: Group 1: WR 279,396: 201; Group 2: Paromomycin alone: 198 (after excluding the minor) **Withdrawals:** 16: Group 1: WR 279,396: 9; Group 2: Paromomycin alone: 67 **Patients assessed:** 387: Group 1: WR 279,396: 195; Group 2: Paromomycin alone: 192 **Age (years) and sex:** Overall: 23 ± SD: 16 (2 – 78): G1: 23 ± 17 (2 – 78), G2: 24 ± 15 (2 – 73) ≤ 18 years: G1: 105; G2: 110 M/F= 250/149 of which: Group 1 M/F: 125/76; Group 2 M/F: 125/73 **Baseline data:** **Total number of lesions:** Group 1: 417; Group 2: 396 **Area of all lesion ulcers (mm^2): mean ± SD (range):** Group 1: 120 ± 146 (0.2 – 1053); Group 2: 121 ± 152 (5.2 – 1158) **Number of baseline lesions (standard deviation):** Group 1: 2.3 ± 1.7 (1 – 10); Group 2 2.1 ± 1.6 (1 – 9) **Length of time in days before treatment that lesions were first noticed:** Group 1: 59.7 ± 53.6 (15 – 374); Group 2: 62.1 ± 57.7 (10 – 559)
Interventions	**Type of interventions:** • **Intervention 1:** WR 279,396 is a topical cream of paromomycin 15% and gentamicin 0.5% • **Intervention 2:** Paromomycin (15% paromomycin topical cream) A vehicle-control group was not included as it was considered unethical to withhold treatment based on the standard of care in Panama and the results of the Phase 3 Tunisian study, which showed the statistical superiority of paromomycin-gentamicin and paromomycin alone compared with the vehicle-control **Duration of intervention:** once daily for 20 days **Co-interventions:** not described **Rescue therapy:** "Subjects who fail therapy (see definition of failure below) will be taken off study and may be administered rescue therapy at the discretion of the subject's personal physician." **Duration of follow-up:** 168 days
Outcomes	**Definition:** *Primary Outcome Measures*: Percentage of participants with final clinical cure. ***Final clinical cure*** was defined as: initial clinical cure (100% re-epithelialisation of index lesion by nominal Day 63) or initial clinical improvement (> 50% re-epithelialisation of index lesion by nominal Day 63) followed by 100% re-epithelialisation of the index lesion on or before nominal Day 100. In addition, no relapse of index lesion by nominal Day 168 The safety endpoints were **adverse effects** (AEs) including application site reactions (pain, erythema, oedema, and vesicles) and increased creatinine and transaminases. Examination of the nasal and oral mucosa was performed at baseline and Days 63, 100, and 168 for evidence of mucosal disease. Evidence of mucosal leishmaniasis was also considered an adverse effect

Sosa 2019 *(Continued)*

	Secondary Outcome Measures: Percentage of participants with all lesions cured, defined as final clinical cure (as defined above) and cure of all other lesions by nominal Day 100 (100% re-epithelialisation of all ulcerated lesions and resolution of all other types of lesions); and median time to initial clinical cure (100% re-epithelialisation of the index lesion) **Time points reported:** Days 0, 2 - 9 daily, day 20, day 35, 49, 63, 100, and 168
Notes	**Ethical approval needed/ btained for study**: The protocol was approved by the Gorgas Institutional Bioethics Committee, the National Committee of Bioethics for Research, Panama and by the Human Research Protections Office, U.S. Army Medical Research and Materiel Command. **Informed cosent obtained:** All participants or their legal representatives provided written informed consent, and minors also provided assent **Baseline imbalances:** There was a slightly higher proportion of males (62.7%) than females and adults constituted 53.9% of participants studied. Baseline characteristics were not significantly different between groups **Study funding sources:** This study was funded by the U.S. Army Medical Materiel Development Activity (USAMMDA), U.S. Army Medical Research and Materiel Command. USAMMDA also provided the investigational product for the study **Possible conflicts of interest:** "Principal Investigators are NOT employed by the organization sponsoring the study" Unpublished study. Results published in ClinicalTrials.gov website

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "If eligible, subjects will be randomized in a targeted 1:1 ratio (200 subjects per group) using site as a stratification variable" Comment: randomisation method seems adequate
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double (Participant, Investigator)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The modified intention-to-treat (mITT) population (N = 399) and the safety population consisted of all subjects who received any administration of investigational product and was used as the primary analytic population for efficacy and safety analyses. The evaluable population (N = 387) included all subjects who received daily doses of investigational product for at least 18 of the total 20 days and did not have missing lesion measurements at day 63 and 168. Final clinical cure rates of the index lesion and all lesions (proportions) were compared between the two treatment groups by uncorrected chi-square test using the mITT group." Comment: Losses to follow up: 16/399 = 4.01% A total of 16 participants, 9 in the WR 279,396 group and 7 in the paromomycin-alone group missed at least 1

Sosa 2019 *(Continued)*

		day of application of investigational product. 2 participants missed treatment due to adverse effects of mild and transient hypoacusia or vomiting, neither of which were considered to be related to study cream
Selective reporting (reporting bias)	Low risk	All outcomes were reported and the trial was registered at Clinical Trials Registration. NCT01790659
Other bias	Unclear risk	There was insufficient information to evaluate the risk of bias

Soto 1994a

Study characteristics	
Methods	**Study design:** Randomised study **Setting/location:** Colombia **Period of study:** January to December 1992 **Sample size calculation:** 90 consecutive patients who met eligibility requirements
Participants	**Type of Leishmania:** Cutaneous leishmaniasis (CL) caused by *L. panamensis* **Inclusion criteria:** adults between 18 and 60 years old, had cutaneous leishmaniasis proven parasitologically, had not used putative antileishmanial compounds in the previous 9 months, and gave written informed consent to participate **Exclusion criteria:** Patients were excluded from the study if there were serious concomitant medical problems in their history or abnormalities in baseline laboratory tests (blood levels of white cells or haemoglobin, serum levels of AST or urea nitrogen (BUN), urine analysis) **Randomised:** The 90 participants were randomly assigned to receive 1 of the 3 treatments with aminosidine sulphate. Because the original intention was to compare group (i) with group (ii), the first 60 participants were randomly allocated equally between those 2 groups. When 50 participants (25 in each group) had been entered, it became clear that aminosidine efficacy was less than expected. They therefore decided to add group (in). The final 40 participants of the study were randomly allocated to groups (i), (ii) and (iii) in the ratio of 5:5:30 **Withdrawals:** 1 participant in group (ii) was lost to follow-up **Patients assessed:** There were 30 evaluable participants in groups (i) and (iii), and 29 in group (ii) **Age (years) and sex:** All participants were men and were aged 18 - 60 **Baseline data:** the mean size of lesions in-group (i) was 143 mm^2, smaller than the mean sizes of lesions in groups (ii) (305 mm^2) and (iii) (288 mm^2)
Interventions	**Type of interventions:** The 90 participants were randomly assigned to receive 1 of the following 3 treatments with aminosidine sulphate: • Group (i), 12 mg base (16 mg salt)/kg/d (maximum 850 mg base/d) for 7 days • Group (ii), 12 mg base/kg/d (maximum 850 mg/d) for 14 days • Group (iii), 18 mg base/kg/d (maximum 850 mg/d) for 14 days **Duration of intervention:** 7 - 14 days **Co-interventions:** not described

Soto 1994a *(Continued)*

	Duration of follow-up: 1½ months follow-up
Outcomes	**Definition:** The definitions of response were based on clinical criteria. Each lesion was judged to have enlarged, undergone no appreciable change, improved, or to have healed on the basis of comparison with its original size: enlarged if > 150% of original size, no change if 50% - 150% of the original size, improved if l% - 49% of the original size, and healed if the lesion was no longer present • ***Cured:*** if all lesions had healed by the 1½ months follow-up visit • ***Failed therapy:*** if at least 1 lesion had enlarged or had undergone no change at 1½ months • ***Ultimately cured:*** if none of the initially-healed lesions relapsed by the end of 12 months after treatment, if lesions that had been improved at 1½ months subsequently healed and did not relapse, and if no new lesion emerged **Adverse effects:** In all participants, the levels of white cells and haemoglobin in the blood and the levels of AST and BUN in the serum were within normal limits (AST: < 27 units/L; BUN: < 20 mgL) before starting therapy. There was no abnormal haematological value after therapy. In only 3 participants were the AST or BUN values after therapy > 25% above the upper limit of normal. 1 participant in group (ii) had an AST value 50% above the upper limit of normal, and 2 participants in group (i) had AST values 100% and 200% above the upper limit. No participant had impaired hearing ability after therapy **Time points reported:** 1½, 3, 6 and 12 months after the end of treatment, when the lesions were re-measured
Notes	**Ethical approval needed/obtained for study**: The study was approved by the Ethical Review Committee of Bogota Military Hospital. **Informed consent obtained:** yes **Baseline imbalances:** Do not describe mean or median age **Study funding sources:** Farmitalia Carlo Erba, Milano, Italy **Possible conflicts of interest:** Dr. Olliaro was employed at Farmitalia Carlo Erba during the initial phase of this work.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The 90 patients were randomly assigned to receive one of the 3 treatments with aminosidine sulphate"..."Because the original intention was to compare group (i) with group (ii), the first 60 patients were randomly allocated equally between those 2 groups. When 50 patients (25 in each group) had been entered, it became clear that aminosidine efficacy was less than expected. We therefore decided to add group (in). The final 40 patients of the study were randomly allocated to groups (i), (iii) and (iii) in the ratio of 5:5:30." Comment: randomisation method described
Allocation concealment (selection bias)	Unclear risk	It was not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No further information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further information about blinding of outcome assessment was provided

Soto 1994a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant in group (ii) was lost to follow-up
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	High risk	Sample size calculation was not adequately reported

Soto 1998

Study characteristics	
Methods	**Study design:** Randomised, partially double-blind, controlled phase 3 trial **Setting/location:** Colombia **Period of study:** not described **Sample size calculation:** not described
Participants	**Type of Leishmania:** American cutaneous leishmaniasis caused by *L. braziliensis* and *L. panamensis* **Inclusion criteria:** adults between 18 and 60 years old, had cutaneous leishmaniasis proven parasitologically, had not used putative antileishmanial compounds in the previous 9 months, and gave written informed consent to participate **Exclusion criteria:** serious concomitant medical problems in their history or abnormalities in baseline laboratory tests (blood levels of white cells or haemoglobin, serum levels of AST or urea nitrogen (BUN), urine analysis) **Randomised:** 150 **Withdrawals:** Because of a protocol error, 1 participant randomised to group 1 was instead treated with Sb for 20 days and was analysed as a member of group 4 **Patients assessed:** Group 1: 59 participants, group 2: 30 participants; group 3: 30 participants, group 4: 31 participants. **Age (years) and sex:** All participants were men and were aged 18 - 60 **Baseline data:** the mean number lesions per participant in groups 1, 2 and 3 were 1.4, and 1.2 in group 4. The mean lesion size in group 1 was 224 ± 210 mm^2, in group 2 was 202 ± 221, in group 3 was 302 ± 423 and in group 4 was 267 ± 331
Interventions	**Type of interventions:** • **Group 1 (experimental group):** topical paromomycin/MBCL twice a day for 10 days plus injectable Sb for 7 days • **Group 2 (first negative control group):** topical placebo twice a day for 10 days plus injectable Sb for 7 days • **Group 3 (second negative control group):** topical paromomycin/MBCL twice a day for 10 days plus injectable Sb for 3 days • **Group 4 (positive control group):** injectable Sb for 20 days. Since both groups 1 and 2 administered received a topical cream for 10 days in addition to Sb for 7 days, the study was double-blinded for those 2 groups **Duration of intervention:** 3, 7, or 20 days.

Soto 1998 *(Continued)*

	Co-interventions: not described **Duration of follow-up:** 12 months of follow-up
Outcomes	**Definition:** • ***Failure:*** defined as worsening of disease (> 50% enlargement of any lesion at any time), inability to initially heal (< 75% re-epithelialisation of any lesion by the first follow-up 1½ months after the end of therapy) • ***Relapse:*** enlargement of a lesion that had completely or partially healed by the end of 9 – 12 months of follow-up • ***Cure:*** defined as an initial cure (complete healing of all lesions by the end of therapy or by the 1½-month follow-up) with no relapse **Time points reported:** 1.5, 9 and 12 months after the end of follow-up Adverse effects were not reported
Notes	**Ethical approval needed/obtained for study**: The study was approved by the Ethical Review Committee of the Universidad Militar Nueva Granada, Bogata **Informed consent obtained:** not stated **Baseline imbalances**: Do not describe mean or median age **Study funding sources:** This work was supported in part by the AB Foundation for Medical Research **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned in unequal allocation (2:1:1:1) to four groups" Quote: "Because of a protocol error, one patient who was randomized to group 1 was instead treated with Sb for 20 days and was analyzed as a memember of group 4" Comment: randomisation method described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Since both groups 1 and 2 received a topical cream for 10 days in addition to Sb for 7 days, the study was double-blinded for those two groups" "the study was double-blinded for group 1 and 2" Comment: it is a partially double-blind controlled phase III trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further information about blinding of outcome assessment was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Because of a protocol error, 1 participant who was randomised to group 1 was instead treated with Sb for 20 days and was analysed as a member of group 4. No dropouts were reported

Soto 1998 *(Continued)*

Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	High risk	Sample size calculation was not adequately reported

Soto 2002

Study characteristics	
Methods	**Study design:** Phase II pilot study **Setting/location:** Colombia **Period of study:** not described **Sample size calculation:** not described
Participants	**Type of Leishmania:** American cutaneous leishmaniasis caused by *L. panamensis* **Inclusion criteria:** patients with mild-to-moderate but not severe disease, and with ulcerative disease. Total ulcer lesion size was < 2000 mm^2, lymphadenopathy was < 1 cm in diameter, and there was no disease of the oronasal mucosa. In addition, screening laboratory values (such as serum levels of creatinine) had to be within normal limits and the patients had to be without concomitant medical problems **Exclusion criteria:** Patients with papular or nodular lesions **Randomised:** 45 **Withdrawals:** 8 **Patients assessed:** Of 45 participants, 33 were randomied to the WR279396 group (active group) and 12 to the placebo group **Age (years) and sex:** All participants were men aged ~ 25 years; mean age was 23 ± 2.6 in the WR279396 group and 26 ± 9 in the placebo group **Baseline data:** The pre-therapy lesion sizes were a mean of 166 mm^2. There was no statistical difference in pretreatment lesion sizes between the active and the placebo group (P = 0.4, t-test). The mean number of lesions was 1.6 per participant
Interventions	**Type of interventions:** Each ulcerative lesion was treated twice a day for 20 days with 0.0005 mL/mm^2 of WR279396 or placebo **Duration of intervention:** 20 days. **Co-interventions:** not described. **Duration of follow-up:** 6 months of follow-up
Outcomes	**Definition:** • ***Lesion cure:*** defined as 100% re-epithelialisation of the lesion without relapse by the 6-month follow-up • ***Lesion failure:*** defined as lack of 100% re-epithelialisation by 6 months or doubling of the lesion size at a previous examination period, at which point the participant was removed from the protocol and treated with meglumine antimonate Determination of lesion cure and failure was made by a clinician blinded as to the treatment group. For a participant to be cured, all lesions had to resolve

Soto 2002 *(Continued)*

	Adverse reactions: In the active group, 18 (55%) of 33 participants experienced local reactions, all of which were reported as having a pain grade of 1 and lasting a mean of 3.6 days, except for 1 participant, who had Grade 2 erythema for 1 day. 4 (33%) of 12 placebo participants reported a pain grade of 1 for a mean of 2.5 days each **Time points reported:** 20 days of therapy and at 1½, 3, and 6 months after the beginning of therapy
Notes	**Ethical approval needed/obtained for study**: Approved by the Hospital Militar Central, the Walter Reed Army Institute of Research, and the Human Subject Review Board, Office of the Surgeon General, Department of the Army **Informed consent obtained:** yes **Study funding sources:** the financial support was of the U.S. Army Medical Research and Material Command and the A. B. Foundation for Medical Research **Possible conflicts of interest:** The opinions or assertions contained in this paper are those of the authors and are not to be construed as the official or reflecting the views of the Department of Defense or the United States Army

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Admitted patients were randomly assigned to treatment with WR279396 or placebo (the base used in WR279396) in a 2:1 allocation. The reason for the lack of exact 2:1 assignment was that randomization was performed for a possible total of 60 patients to allow for drop-outs, and a relatively large number of active treatments were randomized to the first 45 patients." Comment: randomisation method described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment was described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "The 5 nonassessable patients in the active group were so designated because they absconded after treatment (n=1), they self-administered glucantime after treatment (n=1), they had initial disease of the lip and were admitted via a protocol violation (n=1), they demonstrated one cured lesion and one lesion that failed to cure (n=1), and the lesion size diminished by 90% but not by 100% (n1). The 3 nonassessable patients in the placebo group all had lesions that at the end of therapy were relatively unchanged but were parasitologically positive. These patients were removed from the protocol and treated with glucantime at the patients' request". Comment: 8/45 (17.8%). Reasons for exclusion were provided
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	High risk	Sample size calculation was not adequately reported

Soto 2004a

Study characteristics	
Methods	**Study design:** Randomised, double-blinded comparative trial **Setting/location:** Bolivia and Colombia **Period of study:** October 2001 to February 2003 **Sample size calculation:** Not described.
Participants	**Type of Leishmania:** American cutaneous leishmaniasis caused by *L. panamensis* **Inclusion criteria:** patients ≥ 18 years old with parasitologically-proven cutaneous leishmaniasis **Exclusion criteria:** mucosal disease, previous treatment with antimonials, concurrent treatment with hepatotoxic, pancreaticotoxic, or cardiotoxic drugs, and any concurrent systemic medications except common drugs for symptomatic relief **Randomised:** 114 **Withdrawals:** 0 **Patients assessed:** • Bolivian participants: 20 received Glucantime, 8 received pentostam and 17 received generic stibogluconate • Colombian participants: 30 received Glucantime, 8 received pentostam and 31 received generic stibogluconate **Age (years) and sex:** • Bolivian participants: Glucantime group men 100%, mean age 34 (18 - 65); pentostam group: men 87%, mean age 20 (20 - 61); stibogluconate group: men 88%, mean age 37 (18 - 63) • Colombian participants: Glucantime group men 70%, mean age 25 (18 - 70), pentostam group: men 75%, mean age 28 (22 - 65); stibogluconate group: men 81%, mean age 31 (19 - 71) **Baseline data:** Bolivian participants: in 45 participants, the mean number of lesions per participant was 1.8 and the mean lesion size was 397 mm^2 • Glucantime group: number of lesions 43, mean ulcer size 281 ± 304 • Pentostam group: number of lesions 14, mean ulcer size 633 ± 1122 • Stibogluconate group: number of lesions 37, mean ulcer size 406 ± 442 Colombian participants: In 69 participants, the mean number of lesions per participant was 1.9 and the mean lesion size was 328 mm^2 • Glucantime group: number of lesions 53, mean ulcer size 333 ± 314 • Pentostam group: number of lesions 14, mean ulcer size 316 ± 195 • Stibogluconate group: number of lesions 62, mean ulcer size 327 ± 292
Interventions	**Type of interventions:** Each agent was administered at a dose of 20 mg of Sb/kg/ day (there was no upper limit on the daily dose) intramuscularly for 20 consecutive days **Duration of intervention:** 20 days **Co-interventions:** Not described. **Duration of follow-up:** 6 months after the end of treatment

Soto 2004a *(Continued)*

Outcomes	**Definition:** • ***Lesion failure:*** defined by clinical criteria, i.e. enlargement of lesion area by > 100% during therapy, no diminution (Colombia) or < 50% diminution (Bolivia) of lesion area by 1½ months after the end of therapy, lack of complete healing of the lesion by 3 months after therapy, or relapse of an initially-healed lesion by 6 months after the end of treatment • ***Lesion cure:*** the absence of lesion failure. For a participant to be cured, each lesion had to be cured • ***Adverse effects*** **Time points reported:** day 10 of therapy, at the end of therapy on day 20, and 15 days after therapy
Notes	**Ethical approval needed/obtained for study**: The study protocol and amendments were reviewed and approved by the responsible authorities at the Bolivian and Colombian study sites: Colegio Medico in Bolivia and Comite de Etica en Investigacion, Hospital Militar Central, Bogota for Colombia **Informed consent obtained:** All participants provided informed consent **Study funding sources:** the AB Foundation supported this study **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomized by playing cards to receive either Pentostam or Glucantime at an allocation ratio of 1:1" Comment: randomisation method described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was a randomised, double-blinded comparative trial. Assume participants and study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing results data
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Sample size calculation was not adequately reported

Soto 2004b

Study characteristics

Methods	**Study design:** Randomised, placebo-controlled, double-blind multicentre trial

Soto 2004b *(Continued)*

	Setting/location: In Colombia, the participants were both civilians and soldiers who acquired infection in the provinces of Uraba and Carmen de Chucuri and who were evaluated in local hospitals for diagnosis and treatments. In Guatemala, the participants 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. Study conducted in Colombia and Guatemala **Period of study:** June 2000 to December 2002 **Sample size calculation:** not stated
Participants	**Type of Leishmania:** In Colombia, all parasites were *L. panamensis* via monoclonal antibody binding. In Guatemala, 63% were *L. braziliensis*, and 37% of speciated parasites were *L. mexicana* via PCR **Inclusion criteria:** Either sex; aged > 12 years; parasitologically-confirmed CL; no mucosal involvement; previous treatment for the disease was permitted if the therapy had stopped > or 4 weeks earlier and the lesions were not improving **Exclusion criteria:** significant concomitant diseases were excluded by history and by the requirement for approximately normal complete blood cell counts (i.e. WBC count, haemoglobin level, and platelet count), liver transaminase levels (i.e. AST and ALT levels), and kidney function test results (i.e. creatinine and blood urea nitrogen level); pregnancy and lactation, and significant concomitant diseases **Randomised:** 133 (intervention group (N = 89) and control (N = 44)) **Withdrawals:** 8 (intervention group (N = 7) and control (N = 1)) **Patients assessed:** 125 (ITT and per-protocol analyses were carried out) **Age (years) and sex:** Age, mean years ± SD: Miltefosine (Colombia): 24 ± 10; M/F 42/7; Miltefosine (Guatemala): 26 ± 10; M/F 18/6; Placebo (Colombia): 25 ± 13; M/F 39/1; Placebo (Guatemala): 28 ± 12; M/F 20/0 Overall M/F: 119/14 **Baseline data:** Median no. of lesions (range): Miltefosine (Colombia): 1 (1 – 8); Miltefosine (Guatemala): 1 (1 – 10); Placebo (Colombia): 1 (1 – 5); Placebo (Guatemala): 1 (1 – 3) Ulcer size, median mm^2 (range): Miltefosine (Colombia): 171 (72 – 1775); Miltefosine (Guatemala): 165 (6 – 1650); Placebo (Colombia): 238 (6 – 2110); Placebo (Guatemala): 154 (6 – 3300) No. (%) of participants with previous therapy failure: Miltefosine (Colombia): 3 (6); Miltefosine (Guatemala): 10 (25); Placebo (Colombia): 2 (8) ;Placebo (Guatemala): 8 (40)
Interventions	**Type of interventions:** • **Intervention:** Miltefosine orally (50 mg) • **Control:** Placebo administered like miltefosine **Duration of intervention:** 28 days **Co-interventions:** not stated **Duration of follow-up:** 6 months
Outcomes	**Definition:** • ***Cure:*** complete healing of all lesions by 6 months after the end of therapy. Thus, for a participant to be cured, no lesion could enlarge by 50%, be parasite-positive, relapse, or heal incompletely, and no new Leishmania-positive lesion could appear

Soto 2004b *(Continued)*

- ***Treatment failure:*** if a lesion enlarged by 50% or was positive for parasites 2 weeks to 6 months after the end of therapy, relapsed (enlarged) after previously diminishing in size, or did not completely re-epithelialise by 6 months after the end of therapy. Appearance of a new lesion from which *Leishmania* could be demonstrated was also a criterion for failure

Adverse effects: Subjective and laboratory adverse events were graded according to the Common Toxicity Criteria (CTC) of the National Cancer Institute (ctep.cancer.gov/reporting/ctc.html)

Time points reported: Cure was assessed at 2 weeks, 2 months, and 6 months after the end of therapy

Notes	**Ethical approval needed/obtained for study**: The study protocol and amendments were approved by the responsible authority at the Colombian study site (Comite de Etica en Investigacion, Hospital Militar Central, Bogota, Colombia) and at the Guatemalan study site (Universidad del Valle Ethics Committee) **Informed consent obtained:** not stated **Baseline imbalances:** Prominence of men. In the Guatemalan site 40% of placebo participants had previous treatment failure vs 25% in the miltefosine group **Study funding sources:** Zentaris (to J.S. and B.A.A.) **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"This was a randomized, placebo controlled, double-blind multicenter trial of miltefosine" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind - assume participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 8 out of 133 (6%). Reasons were provided ITT and PP analyses were carried out.
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	High risk	Sample size calculation was not adequately reported

Soto 2008

Study characteristics

Soto 2008 *(Continued)*

Methods	**Study design:** Randomised, unblinded clinical trial **Setting/location:** Bolivian provinces of Beni or La Paz from which we recruited mucosal patients and treated them at the community clinic of Palos Blancos **Period of study:** November 2005 to March 2007 **Sample size calculation:** No. "The number of patients and patient allocation (2 miltefosine: 1 antimony) was chosen based on resource constraints and the desire to provide more patients for the experimental (miltefosine) group."
Participants	**Type of Leishmania:** *Leishmania braziliensis* **Inclusion criteria:** skin ulcer confirmed to be caused by leishmania by visualisation of parasites in lesion material by Giemsa staining; either sex; ≥ 12 years of age **Exclusion criteria:** mucosal disease or anti-leishmanial therapy for at least 6 months; significant concomitant disease by history, physical examination, or blood tests; pregnancy or lactation **Randomised:** 62 **Withdrawals:** 5, 3 in miltefosine group and 2 in glucantime group **Patients assessed:** 57 **Age (years) and sex:** 25 – 30 years of age; 51 male and 11 female **Baseline data:** median of 1 ulcer per participant with an average area of ~ 300 mm^2
Interventions	**Type of interventions:** • ***Intervention group:*** Oral miltefosine (2.5 mg/kg/d for 28 days) • ***Control group:*** intramuscular antimony (20 mg/kg/d for 20 days) **Duration of intervention:** 28 days miltefosine and 20 days antimony **Co-interventions:** none. **Duration of follow-up:** 6 months
Outcomes	**Definition:** • ***Efficacy*** was evaluated by measuring the size of the ulcer (maximum length and width) at baseline, at the end of therapy, and at 1, 3, and 6 months after the end of therapy • ***Lesion*** was defined as a failure if it enlarged by 50% at the end of therapy or at 1 month after therapy, did not diminish by 50% at 3 months after therapy, did not heal (completely re-epithelialise) by 6 months after the end of therapy, or relapsed (enlarged after previously diminishing in size) • ***Lesion cure*** was the opposite of failure: complete healing of all lesions by 6 months after the end of therapy. For a participant to be cured, all lesions had to cure. Cure rate at time X" means the % of participants in whom all lesions had healed by time X **Time points reported:** 1, 3 and 6 months
Notes	**Ethical approval needed/obtained for study**: The study was approved by the Comité de Etica, Colegio Médico, La Paz, Bolivia **Informed consent obtained:** All participants signed informed consent **Baseline imbalances:** none relevant **Study funding sources:** AB Foundation

Soto 2008 *(Continued)*

Possible conflicts of interest: "J. Berman is an officer of the AB Foundation, the funder of the study. This statement is made in the interest of full disclosure and not because the author considers this to be a conflict of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote p 210: "The number of patients and patient allocation (2 miltefosine: 1 antimony) was chosen based on resource constraints and the desire to provide more patients for the experimental (miltefosine) group. The patients were randomized in a 2:1 allocation." Comment: No information provided
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up (5 in total accounting for 8%): 3 in miltefosine group and 2 in glucantime group
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	High risk	*Leishmania* sp was not confirmed and sample size calculation was not adequately reported

Soto 2013

Study characteristics

Methods	**Study design:** Randomised, open clinical trial **Setting/location:** Chapare province, Bolivia **Period of study:** May 2011 to January 2012. **Sample size calculation:** "The sample size, based on feasibility of accrual over 6 months, was adequate to differentiate putative cure rates of 80% (IL Sb group) vs 10% (placebo group)."
Participants	**Type of Leishmania:** ILSb: *L. braziliensis* (15) and *L. amazonensis* (2); Cryotherapy: *L. braziliensis* (7) and *L. guyanensis* (1); Placebo; *L. braziliensis* (14), *L. lainsoni* (2) and *L. guyanensis* (1). **Inclusion criteria:** ≥ 12 years of age; 1 ulcerative lesion ≤ 30 mm in largest diameter, thus with a total lesion area of ≤ 900 mm^2; parasitological diagnosis by visualisation in the direct smear or biopsy, or culture from a lesion aspirate

Soto 2013 *(Continued)*

Exclusion criteria: specific or putatively specific antileishmanial therapy (Sb, pentamidine, amphotericin B, miltefosine, imidazoles, allopurinol) in the last 3 months; mucosal lesions in the nose and mouth by physical examination; and history of concomitant diseases including immunosuppression that would be likely to interact, either positively or negatively, with IL Sb treatment

Randomised: 80

Withdrawals: 3 participants lost to follow-up, one in each group

Patients assessed: 77

Age (years) and sex: Mean age 29 ± 12 y (ILSb: 29 ± 13 y, Cryotherapy: 26 ± 11 y, Placebo: 32 ± 13 y); sex information not provided

Baseline data: Lesion size, mm^2, mean (SD): ILSb: 259 (191), Cryo: 205 (118), Placebo: 188 (145); Lesion location, No. (%) IlSb, Cryo, Placebo: arms/hand: 3 (10%), 6 (30%), 8 (27%); head/neck: 3 (10%), 2 (10%), 6 (20%); chest/back: 2 (7%), 1 (5%), 0 (0%); leg: 22 (73%), 11 (55%), 16 (53%)

Interventions

Type of interventions:

- ***Intervention 1:*** Intralesional Sb (N-methylglucamine (Glucantime Rhodia Laboratories, France: 81 mg/mL) was administered on each of days 1, 3, and 5. A small button of Xylocaine was applied by means of a thin needle at the 4 cardinal points of the lesion. Sb was then administered with a small-gauge (23 g) needle at each cardinal point, with the needle being moved in all directions to infiltrate the whole lesion. The amount injected was 650 µg (0.008 µL)/mm2 of lesion area
- ***Intervention 2*:** Cryotherapy. Liquid nitrogen was sprayed using a CryAc device (Brymill Co) for 5 – 20 seconds until the lesion and 1 – 2 mm of surrounding normal tissue appeared frozen. Cryotherapy was performed on days 1 and 14. Postoperative care included daily cleansing with an antiseptic solution and cream for 1 week following each cryotherapy application
- ***Control group:*** Placebo. An emollient cream compounded by the Facultad de Farmacia, Universidad Mayor de San Simón (Cochabamba, Bolivia), was spread evenly over the lesion daily for 20 days. Application was administered by medical personnel 1 – 2 times a week during clinic visits at those times and by the participant on the other days. The composition of the cream was 40% liquid paraffin, 9% hard paraffin, 7% wax, 9% glycerin, 35% water, and 0.1 g propylparaben

Duration of intervention: Intralesional Sb (N-methylglucamine) was administered on each of days 1, 3, and 5; Cryotherapy was performed on days 1 and 14. Placebo was spread evenly over the lesion daily for 20 days. Application was administered by medical personnel 1 – 2 times a week during clinic visits at those times and by the participant on the other days

Co-interventions: For all experimental groups, apparent superinfection upon entrance into the study was treated with soap and water plus fusidic acid cream twice a day for 4 – 7 days, augmented by dicloxacillin if necessary (1.5 g orally for 7 days), prior to antileishmanial treatment

Duration of follow-up: 6 months after the end of treatment and seen x 3 times during that time: at 1 month, 3 months, and 6 months after the end of therapy

Outcomes

Definition: The endpoint parameter was reduction in lesion size.

Lesion size: defined as the area of the lesion ulcer, and was computed as maximum ulcer width × maximum ulcer length. Lesion size was measured at study entry, then at 1 month, 3 months, and 6 months after the end of therapy. The change in lesion size was calculated by expressing lesion sizes after therapy as a percentage of the lesion size prior to therapy

Lesion failure: doubling of lesion size by 1 month after therapy, < 50% diminution in lesion size at 3 months after therapy, relapse (substantial enlargement after previous diminution), and not achieving a lesion size of 0 mm^2 at 6 months after therapy. Any lesion that did not fail was considered to be cured. Thus, for a participant to be cured, the lesion could not have doubled soon after therapy (1 month), failed to make substantial progress toward healing (at least 50% resolution by 3 months), relapsed, or failed to completely re-epithelialise at 6 months

Adverse effects: Local and systemic

Soto 2013 *(Continued)*

	Time points reported: 1 month, 3 months and 6 months
Notes	**Ethical approval needed/obtained for study**: The study was approved by the Comité de Bioética de la Facultad de Medicina, Universidad Mayor de San Simón, Cochabamba, Bolivia **Informed consent obtained:** Participants in the Chapare province, Bolivia, catchment area were identified and, after signing informed consent and meeting entrance criteria, were treated at the Hospital Local, Chipiriri, Bolivia **Baseline imbalances:** none relevant. **Study funding sources:** AB Foundation **Possible conflicts of interest:** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to the 3 groups via a randomized deck of cards in the ratio 3:2:3” Comment: method described
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “The original design was a 4-arm, open-label comparison” Comment: blinding not done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported although they stated it is open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analyses were performed Losses to follow-up < 20%: 3/80 (3.8%), 1 in each group
Selective reporting (reporting bias)	Low risk	Protocol available (NCT01300975). All relevant outcomes reported
Other bias	Low risk	All information was provided

Soto 2016a

Study characteristics

Methods	**Study design:** Parallel, open-label phase II, randomised clinical trial **Setting/location:** outpatients from Chapare, Los Yungas, and Santa Cruz, Bolivia **Period of study:** March 2013 - November 2014. **Sample size calculation:** “Formal sample size calculations were not used for this hypothesis-generating phase 2 study.”

Soto 2016a *(Continued)*

Participants	**Type of Leishmania**: *L. braziliensis*, *L amazonensis, L. lainson* and *L. guyanensis*. by PCR; *L. braziliensis* (17), *Leishmania braziliensis/amazonensis/lainsoni/guyanensis* (4) **Inclusion criteria:** to have 1 ulcerative lesion ≤ 30 mm in largest diameter and ≤ 500 mm^2 in total area. Other entrance characteristics were identical to that for the previous study (see notes below): either gender, ≥ 12 years, parasitologically-diagnosed, no antileishmanial therapy in the last 3 months, no mucosal lesions, and no history of concomitant diseases including immunosuppression **Exclusion criteria:** None specified **Randomised:** 90 **Withdrawals:** 2 **Patients assessed:** 88 **Age (years) and sex:** mean age 29 years; sex not available Age (years): mean (SD): ILSb-3 injections: 28 10); ILSb-5: 30 (13); ILPenta-120-3: 30 (11) **Baseline data:** 310 mm mean baseline lesion size. Mean weight 62 kg
Interventions	**Type of interventions:** • ***Intervention group I:*** ILSb (N-methylglucamine (Glucantime®; 81 mg Sb/mL) was administered on each of days 1, 3, and 5 (ILSb-3 injections) • ***Intervention group II:*** ILSb (N-methylglucamine on each of days 1, 3, 5, 8, and 11 (ILSb-5 injections) at a dose of 650 µg Sb (8 µL)/mm^2 of lesion area per day • ***Intervention group III:*** IL pentamidine (30 mg/mL; Pentacarinat®) was administered at a dose of 120 µg (4 µL)/mm^2 of lesion area (ILpenta-120-3 injections) or 240 µg (8 µL)/mm^2 of lesion area (ILpenta-240-3 injections) on each of days 1, 3, and 5 **Duration of intervention:** from 5 to 11 days **Co-interventions:** none reported. **Duration of follow-up:** up to 6 months after the end of therapy
Outcomes	**Definitions:** • ***Efficacy:*** reduction in lesion size. The change in lesion size was calculated by expressing lesion sizes after therapy as a percentage of the lesion size before therapy • ***Failure*** *:* substantial enlargement (doubling) of lesion size by 1 month after therapy, non-substantial (< 50%) diminution in lesion size at 3 months after therapy, relapse (enlargement after previous diminution), not being completely re-epithelialised ("re-epithelialized" = lesion size of "0" mm^2) at 6 months after therapy. Any lesion that did not fail was considered "cured". • ***Cure:*** the lesion could not have doubled soon after therapy (1 month), failed to make substantial progress toward healing (at least 50% resolution by 3 months), or relapsed and must have completely re-epithelialised at 6 months **Adverse effects:** patients were evaluated for local pain and irritation (defined as erythema and/or edema and/or itching and/or burning sensation and/ or scaling), which could be caused by any agent. Each adverse effect other than pain was graded on a 0 – 3 scale defined as follows: 0 = absent, 1 = mild (present but treatment not required), 2 = moderate (present and needed specific treatment), and 3 = severe (present with such intensity that antileishmanial therapy had to be stopped). The 0 – 3 scale for pain was as follows: 0 = absent; 1 = mild (present but expected with injections, treatment not required); 2 = moderate (present and more than expected with injections, treatment not required); and 3 = severe (present with such intensity that analgesics were required) **Time points reported:** at 1 month, 3 months, and 6 months after the end of therapy

Soto 2016a *(Continued)*

Notes	**Ethical approval needed/obtained for study:** The study was approved by the Comité de Bioética de la Facultad de Medicina, Universidad Mayor de San Simón, Cochabamba, Bolivia **Baseline imbalances:** none detected **Study funding sources:** Funded by a grant from the AB Foundation to Jaime Soto **Possible conflicts of interest:** The authors declared they have no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Through a randomized list generated by a computer program" Comment: method described
Allocation concealment (selection bias)	Unclear risk	No information was provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open label". Study not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open label". Study not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 losses to follow-up (1 in each of 2 groups) Analyses were reported by ITT and per protocol. Reasons for dropouts were not provided, but < 5% were lost to follow-up
Selective reporting (reporting bias)	Low risk	Study protocol not available although these trials were a continuation of the investigations of the prior publication, study procedures closely followed those previously reported in Soto 2013: NCT01300975
Other bias	Low risk	All information was provided

Soto 2016b

Study characteristics

Methods	**Study design:** parallel, Open-label phase II, randomised clinical trial **Setting/location:** outpatients from Chapare, Los Yungas, and Santa Cruz, Bolivia **Period of study:** March 2013 - November 2014 **Sample size calculation:** "Formal sample size calculations were not used for this hypothesis-generating phase 2 study."
Participants	**Type of Leishmania**: L. braziliensis by PCR: *L. braziliensis* (13), *Leishmania sp* (2) **Inclusion Criteria:** to have 1 ulcerative lesion ≤ 30 mm in largest diameter and ≤ 500 mm^2 in total area. Other entrance characteristics were identical to that for the previous study (see notes below): either

Soto 2016b *(Continued)*

	gender, ≥ 12 years, parasitologically-diagnosed, no antileishmanial therapy in the last 3 months, no mucosal lesions, and no history of concomitant diseases including immunosuppression **Exclusion Criteria:** None specified **Randomised:** 60 **Withdrawals:** 1 in the ILPenta-240-3 group **Patients assessed:** 59. **Age (years) and sex:** mean age 27 years; sex not available Age (years): mean (SD): ILSb-5: 25 (7); ILPenta-240-3: 28 (7) **Baseline data:** 260 mm mean baseline lesion size. Mean weight 60 kg
Interventions	**Type of interventions:** • ***Intervention group I:*** ILSb (N-methylglucamine on each of days 1, 3, 5, 8, and 11 (ILSb-5 injections) at a dose of 650 µg Sb (8 µL)/mm^2 of lesion area per day • ***Intervention group II:*** IL pentamidine 240 µg (8 µL)/mm^2 of lesion area (ILpenta-240-3 injections) on each of days 1, 3, and 5 **Duration of intervention:** 5 to 11 days **Co-interventions:** none reported. **Duration of follow-up:** up to 6 months after the end of therapy
Outcomes	**Definitions:** • ***Efficacy:*** reduction in lesion size. The change in lesion size was calculated by expressing lesion sizes after therapy as a percentage of the lesion size before therapy • ***Failure:*** substantial enlargement (doubling) of lesion size by 1 month after therapy, non-substantial (< 50%) diminution in lesion size at 3 months after therapy, relapse (enlargement after previous diminution), not being completely re-epithelialised ("re-epithelialized" = lesion size of "0" mm^2) at 6 months after therapy. Any lesion that did not fail was considered "cured". • ***Cure:*** the lesion could not have doubled soon after therapy (1 month), failed to make substantial progress toward healing (at least 50% resolution by 3 months), or relapsed and must have completely re-epithelialised at 6 months **Adverse effects:** patients were evaluated for local pain and irritation (defined as erythema and/or oedema and/or itching and/or burning sensation and/ or scaling), which could be caused by any agent. Each adverse effect other than pain was graded on a 0 – 3 scale defined as follows: 0 = absent, 1 = mild (present but treatment not required), 2 = moderate (present and needed specific treatment), and 3 = severe (present with such intensity that antileishmanial therapy had to be stopped). The 0 – 3 scale for pain was as follows: 0 = absent; 1 = mild (present but expected with injections, treatment not required); 2 = moderate (present and more than expected with injections, treatment not required); and 3 = severe (present with such intensity that analgesics were required) **Time points reported:** at 1 month, 3 months, and 6 months after the end of therapy
Notes	**Ethical approval needed/obtained for study:** The study was approved by the Comité de Bioética de la Facultad de Medicina, Universidad Mayor de San Simón, Cochabamba, Bolivia **Baseline imbalances:** none detected **Study funding sources:** Funded by a grant from the AB Foundation to Jaime Soto **Possible conflicts of interest:** The authors declared they have no conflicts of interest

Soto 2016b *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Through a randomized list generated by a computer program" Comment: randomisation method described
Allocation concealment (selection bias)	Unclear risk	No information was provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open label". Study not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open label". Study not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 lost to follow-up
Selective reporting (reporting bias)	Low risk	Study protocol not available although these trials were a continuation of the investigations of the prior publication, study procedures closely followed those reported" in a previous article (Soto 2013: NCT01300975)
Other bias	Low risk	All information was provided

Soto 2019

Study characteristics

Methods	**Study design:** Randomised double-blind placebo-controlled clinical trial **Setting/location:** Outpatients at Centro de Salud de la Asunta, Hospital Palos Blancos, Bolivia **Period of study:** April 2017 to April 2018 **Sample size calculation:** "The sample size calculation was based on the primary outcome variable (cure) for paromomycin-Aquaphilic vs Aquaphilicvehicle. We assumed that the lowest cure rate that a product such as paromomycin-Aquaphilic could have and still be clinically attractive is 65%. We also assumed that the negative (Aquaphilic-vehicle) control cure rate could be as high as 25%. With a paromomycin-Aquaphilic cure rate of 65% and an Aquaphilic-vehicle cure rate of 25%, alpha of 0.05, beta of 0.80, and an allocation ratio of 2 (paromomycin-Aquaphilic) to 1 (Aquaphilic-vehicle), 34 patients were needed in paromomycin-Aquaphilic and 17 patients were needed in Aquaphilic-vehicle. The extra patients (6 in paromomycin-Aquaphilic and 3 in Aquaphilic-vehicle) were enrolled to protect against possible losses to follow-up. We also assigned 20 patients to the positive control, IL-pentamidine."
Participants	**Type of Leishmania:** cutaneous leishmaniasis: *L. braziliensis* (endemic), although only 7 patients had *L. braziliensis* (5 in the intervention group and 1 in each of the control groups) **Inclusion criteria:** 1 to 2 ulcerative lesions, each ≤ 30 mm in largest diameter and with a total lesion area ≤ 900 mm^2; ≥ 12 years old; parasitologically-diagnosed by visualisation of amastigotes or culture of promastigotes from lesion material; no antileishmanial therapy in the last 3 months; no mucosal lesions; and no history of significant concomitant diseases, including immunosuppression

Soto 2019 *(Continued)*

Exclusion criteria: Previous treatment for leishmaniasis with Sb, pentamidine, amphotericin B, miltefosine, imidazoles, allopurinol in the last 3 months; other diseases that would be likely in the PI's opinion to interact, either positively or negatively, with treatment

Randomised: 80: Intervention: 40; active control: 20; placebo control: 20

Withdrawals: 6: Intervention: 2; active control: 2; placebo control: 2

Patients assessed: 80 (ITT analysis performed)

Age (years) and sex:

Age in years, as mean (SD): Overall: 28 (9.1): intervention: 27 (6.9); active control: 25 (8.5); placebo control: 32 (11)

Male and female were included but the proportions were not reported

Baseline data:

Lesion size in mm^2, as mean (SD): Overall 299 (138): intervention: 338 (108); active control: 310 (132); placebo control: 304 (134)

Interventions	**Type of interventions:** • **Intervention**: 15% paromomycin in aquafilm base twice a day for 20 consecutive days • **Active control:** IL Pentamidine (30 mg/mL; Pentacarinat Sanofi-Aventis, Bogota, Colombia) was administered intralesionally at a dose of 120 µg (4 µL)/mm^2 of the lesion area on days 1, 3, and 5 • **Placebo control**: 10% Urea in parafilm cream, 2 times a day for 20 days **Duration of intervention:** 20 days (paromomycin and placebo groups) **Co-interventions:** Treatment for pruritus, erythema or swelling or both was cortisone 1% cream twice a day for 2 to 4 days. Treatment for pain was paracetamol 500 mg orally as 1 or 2 tablets a day for 1 to 3 days **Duration of follow-up:** 6 months
Outcomes	**Definition:** • ***Efficacy:*** was reduction in lesion size. Lesion size was defined as the area of the lesion ulcer, computed as maximum ulcer width × maximum ulcer length. Lesion size was measured at the time of study entry, then at 1 month, 3 months, and 6 months after the end of therapy • ***Failure:*** the same as before: substantial enlargement (doubling) of lesion size by 1 month after therapy; non-substantial (< 50%) diminution in lesion size at 3 months after therapy; relapse (enlargement after previous diminution); or not being completely re-epithelialised (re-epithelialised = lesion size of 0 mm^2) at 6 months after therapy • ***Cure:*** Any lesion that did not fail was considered cured and, for a participant with 1 lesion, constituted cure of the participant. For a participant with 2 lesions, if 1 lesion met the failure criteria, that participant was considered a failure and, conversely, both lesions had to not fail for the participant to be considered cured. **Adverse effects:** Local (erythema, swelling, hard oedema, superficial necrosis, pruritis, and pain) were assessed on treatment days when treatments were applied by study personnel. A 0 – 3 scale was used, where 0 meant absent; 1 meant mild (present but treatment not required); 2 meant moderate (present and needed specific treatment); and 3 meant severe (present with such intensity that antileishmanial therapy had to be stopped) **Time points reported:** 1, 3 and 6 months
Notes	**Ethical approval needed/obtained for study**: "This study was approved by the Comité de Bioética de la Facultad de Medicina, Universidad Mayor de San Simón, Cochabamba, Bolivia."

Soto 2019 *(Continued)*

Informed consent obtained: "After signing informed consent and meeting entrance criteria, the patients were treated at Centro de Salud de la Asunta, Hospital Palos Blancos, Bolivia"

Baseline imbalances: "In spite of randomization, the entrance age was higher for the Aquaphilic group than for the other 2 groups (P = .02–0.06 in t-test)."

Study funding sources: "This work was supported by a grant from the AB Foundation to J. S."

Possible conflicts of interest: "J. S. has received research funding from the AB Foundation. J. B. is an officer of the AB Foundation. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This was a randomized evaluation of 3 interventions." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Low risk	Quote: "Treatments were distributed by the study pharmacist to the study staff." Comments: Allocation likely concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Staff and patients were blinded with respect to whether the patient was receiving Aquaphilic-vehicle or paromomycin- Aquaphilic" Comment: Intralesional injection of pentamidine group was not masked
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis was performed Losses to follow-up: 6/80 (7.5%), 2 in each intervention group although reasons were not provided
Selective reporting (reporting bias)	Low risk	Clinical trial was registered (NCT03096457). All outcomes described in the protocol were reported in the study
Other bias	Unclear risk	*Leishmania* sp was claimed to be endemic although it was confirmed in 7 participants. The method used to confirm the type of Leishmania was not described

Souza 1998

Study characteristics

Methods	**Study design:** Randomised comparative study **Setting/location:** Brazil **Period of study:** not reported

Souza 1998 *(Continued)*

	Sample size calculation: not stated
Participants	**Type of Leishmania:** American cutaneous leishmaniasis (sp unknown) **Inclusion Criteria:** 1 to 10 lesions for a maximum of 6 months **Exclusion Criteria:** not stated **Randomised:** 172: Group A - 66 cases received pentamidine injections; Group B - 54 cases received glucantime injections; Group C 52 cases were treated with glucantime injections **Withdrawals:** not stated **Patients assessed:** Number of participants assessed unknown **Age (years) and sex:** ages varied from 14 to 40 years old. M/F: 145/27 **Baseline data:** They presented 1 to 10 lesions, present for a maximum of 6 months
Interventions	**Type of interventions:** • Group A: received pentamidine injections 4 mg/kg/dose - 3 doses with 2-day interval • Group B: received glucantime injections 15 mg/kg/day for 20 days • Group C: were treated with glucantime injections 7.5 mg/kg/day for 15 days **Duration of intervention:** 6 - 20 days. **Co-interventions:** not stated **Duration of follow-up:** Unknown
Outcomes	**Definition:** not stated **Time points reported:** not stated
Notes	**Ethical approval needed/obtained for study**: not stated **Informed consent obtained:** not stated **Baseline imbalances:** Males predominance (145 males and 27 females presented) **Study funding sources:** not stated **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk; authors did not judge if the outcome is likely to be influenced by lack of blinding

Souza 1998 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Neither the number of withdrawals nor the number of participants assessed were reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	There was insufficient information to evaluate the risk of bias

Toledo 2014

Study characteristics	
Methods	**Study design:** Multicentre, randomised, open-label, 2-arm parallel-group, non-inferiority clinical trial **Setting/location:** All of the treatments were performed in an ambulatory setting.The René Rachou Research Centre Oswaldo Cruz Foundation (CPqRR/FIOCRUZ), and Montes Claros State University (Unimontes). Both centers are located in Minas Gerais, Brazil **Period of study:** August 2008 to March 2012 **Sample size calculation:** Initially, a sample size of 310 participants in each group was calculated using an accuracy method, with an α error = 0.05 and a power = 0.8, and considering a 60% cure rate in both arms. The inferior limit of the 95% confidence interval (1-sided) between the azithromycin and meglumine antimoniate cure rates should not have been less than −10% in order to consider the azithromycin treatment as non-inferior. The final sample size was 682 participants, which took into consideration a possible loss of follow-up period of 10%
Participants	**Type of Leishmania:** *L. (Viannia) braziliensis* was the species identified in DNA samples extracted from biopsy fragments of 29 participants. *Leishmania (Viannia) braziliensis* is the most common species found in the patients at the study reference centre (> 90%) (unpublished data) and in the study area (92.5%) **Inclusion criteria:** Treatment-naïve patients with localised cutaneous leishmaniasis were included in the study after signing the informed consent form if they met the following inclusion criteria: age between 14 to 65 years; ≤ 6 apparent cutaneous lesions that were compatible with CL and a positive MST test (≥ 5mm), followed by parasitological or molecular confirmation of the CL infection (which included a direct exam, culture, pathological exam, and/or kDNA detection by PCR) **Exclusion criteria:** disseminated leishmaniasis; the presence of mucosal lesions; pregnancy (confirmed by β-hCG in their blood sample); breast feeding; diseases that interfere with scar healing; primary or acquired immunodeficiency; immunosuppressive drug use; use of any topical or oral medication that could interfere with the healing process or with potential leishmanicidal action, including antibiotics; decompensated chronic diseases; any ECG abnormalities that contra-indicated meglumine antimoniate use; use of any medication that could prolong the QTc interval; any diseases or conditions that may lead to non-compliance with protocol, including alcohol abuse; and intolerance to azithromycin, macrolides or meglumine antimoniate **Randomised:** 48 (MA: 24, AZ: 24) **Withdrawals:** 4 participants from the meglumine antimoniate group withdrew during treatment, due to adverse effects. All of the participants enrolled in the azithromycin group completed their treatment. During the 3 months post-treatment, 5 participants were lost to follow-up, which included 3 from the azithromycin group and 2 from the meglumine antimoniate group **Patients assessed:** 43: 21 azithromycin group and 18 meglumine antimoniate group

Toledo 2014 *(Continued)*

	Age (years) and sex: M/F: 38/10 where most participants were male (38 - 79.2%); ages ranged from 15 to 56 years (mean 34.5 ± 12.2) **Baseline data:** Almost 2/3 of the participants had only 1 lesion, and the time since the first lesion occurred ranged from 15 to 425 days (mean 98.6 ± 67.5). The lesions of 29 (61.7%) participants had ≤ 90 days of progression. The mean lesion area was 5.17 cm^2 (SD =10.11). There were no baseline demographic and clinical characteristic differences between both groups
Interventions	**Type of interventions:** • ***Intervention group:*** 15 mg/kg/day of intravenous or intramuscular meglumine antimoniate (maximum daily dose of 1215 mg) (Glucantime® - Aventis, batch number: 605022) • ***Control group:*** one 500 mg azithromycin tablet a day (Zitromax® - GSK, batch numbers 6186401403; 0864009) **Duration of intervention:** 20 consecutive days **Co-interventions:** Nothing stated **Duration of follow-up:** 3 and 6 months after completion of treatment
Outcomes	**Definition:** The primary efficacy end point was CL cure rate by ITT and per protocol (PP) analyses. • ***Cure:*** defined as complete lesion healing and re-epithelialisation without inflammatory infiltration and erythema until 90 days after the treatment ended. Patients withdrawn from the study due to AEs or loss to follow-up were considered treatment failures in the ITT analysis The secondary endpoints were as follows: • ***Delayed CL cure:*** (180 days after treatment), CL recurrence between cure and 180 days after treatment, and the percentage of healed lesions at the end of treatment and at 30, 60, and 90 days after the treatment ended • ***Recurrence:*** defined by the reappearance of a previous lesion or a new cutaneous or mucosal lesion. Participant lost to follow-up were considered as recurrences in the ITT analysis All of the secondary efficacy endpoints were analysed by ITT and per protocol (PP). The safety analysis included all patients who received at least 1 dose of study drugs. Clinical, laboratory and ECG abnormalities were categorised according to the AIDS clinical trial group (ACTG) criteria **Time points reported:** Months 1, 2, 3, and 6 after treatment
Notes	**Ethical approval needed/obtained for study**: The clinical study protocol and informed consent were reviewed and approved by the Rene Rachou Research Centre, Oswaldo Cruz Foundation [Centro de Pesquisa René Rachou, Fundação Oswaldo Cruz (CPqRR, FIOCRUZ)], (CAAE 0010.0.246.000-06/CEPSH-CPqRR 20/2006) and Montes Claros State University - Unimontes (Comitê de Ética em Pesquisa da Universidade Estadual de Montes Claros 2050) ethics committees. The Brazilian National Council on Ethics in Research (CONEP) accredits these committees. The project has also been approved by the Ethics Review Committee of the University of Brasilia from where a third trial site was expected to be coordinated but was cancelled due to the study interruption **Informed consent obtained:** Written informed consent was obtained for every participant prior to enrolment. For participants younger than 18 years of age, a written informed consent was also obtained from their legal representative **Baseline imbalances:** There were no baseline demographic and clinical characteristic differences between the groups. However, 79% of participants had 1 lesion in the AZ group vs 50% in the MA group; the area of lesions (2.93% vs 13.22%) and the mean time (in days) since the first lesion (41.0% vs 85.3%) were lower in the AZ group **Study funding sources:** supported by Conselho Nacional de Desenvolvimento Científi co e Tecnológico (CNPq), Fundaçãode Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) and Fundação Oswaldo Cruz (FIOCRUZ). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

Toledo 2014 *(Continued)*

Possible conflicts of interest: The authors declare that there is no conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization used blocks of six and a 1:1 allocation rates were generated by using the Web site Randomization.com [http://www.randomization.com]." Comment: randomisation method was described
Allocation concealment (selection bias)	Low risk	Quote: "Envelopes that were sequentially numbered, opaque and sealed were provided to the local clinical coordinator. Allocation followed the recruitment sequence, and the patient's name was written on the envelope before it was opened." Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label - participants and study personnel not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label. However it is quite unlikely that lack of blinding of outcome evaluators could result in bias when assessing main outcome (cure was defined as complete lesion healing and re-epithelialisation without inflammatory infiltration and erythema until 90 days after the treatment ended)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants withdrawn from the study due to AEs or loss to follow-up were considered treatment failures in the ITT analysis. 4 participants from the meglumine antimoniate group withdrew during treatment due to adverse events. During the 3 months post-treatment, 5 participants were lost to follow-up, which included 3 from the azithromycin group and 2 from the meglumine antimoniate group
Selective reporting (reporting bias)	Low risk	The article presents all relevant primary and secondary outcomes stated in the study protocol (ClinicalTrials.gov: NCT00682656)
Other bias	Low risk	All information was provided

Vélez 1997

Study characteristics

Methods	**Study design:** Randomised, controlled, and partially double-blinded phase III study **Setting/location:** Colombia **Period of study:** April 1992 to November 1995 **Unit of randomisation:** participant **Unit of analysis:** participant **Sample size calculation:** not stated

Vélez 1997 *(Continued)*

Participants	**Type of Leishmania:** cutaneous leishmaniasis (CL): *L. panamensis* and *L. braziliensis* **Inclusion criteria:** patients aged 6 to 60 years, had cutaneous leishmaniasis 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 follow-up **Exclusion criteria:** presence of concomitant diseases that required medical intervention, abnormalities in the complete blood count, abnormal glutamate oxaloacetate aminotransferase levels, abnormal creatinine levels, abnormal uric acid levels, and pregnancy **Randomised:** 187 **Withdrawals:** 5 of the original 187 randomly-assigned participants were excluded from the study: 2 participants violated the study protocol, 1 had an uncertain parasitologic diagnosis, 1 had a clinical course that could not be interpreted, and 1 had co-infection with *Sporothrix schenckii.* 4 participants were excluded from the placebo group and 1 from the glucantime group **Patients assessed:** Allopurinol group: 60; placebo group: 56; and glucantime group: 66 **Age (years):** mean age allopurinol group: 29 ± 12, placebo group: 25 ± 13 and glucantime group: 25 ± 13 **Sex:** M/F: 114/62; allopurinol group: 63% male, 37% female; placebo group: 63% male, 37% female; and glucantime group: 62% male and 38% female **Baseline imbalances:** no **Severity Illness:** mean lesions per participant: allopurinol group: 2.8 ± 2.8, placebo group: 3.3 ± 3.4 and glucantime group: 2.9 ± 3.8. Location of lesions: allopurinol group (upper body 32%, lower body 43%, upper and lower body 25%); placebo group: (upper body 45%, lower body 29%, upper and lower body 27%) and glucantime group: (upper body 38%, lower body 44%, upper and lower body 18%).

Interventions	**Type of interventions:**
	
	• **Intervention groups:**
	  • Allopurinol: 300 mg (3 x 100-mg tablets) 4 times daily for 28 days, so that the dosage given was approximately 5 mg/kg 4 times daily or 20 mg/kg daily for 28 days
	  • Glucantime: 20 mg of antimony/kg daily (no maximum daily dose) intramuscularly for 20 days
	• **Control group:** placebo, 3 tablets 4 times daily for 28 days
	
	Duration of intervention: antimony and placebo: 28 days and glucantime: 20 days
	
	Co-interventions: not described

Outcomes	**Definition:** • ***Complete clinical response:*** Complete re-epithelialisation of the ulcer and disappearance of all induration. Lesions that showed a complete clinical response were followed for as long as 12 months to verify lack of relapse • ***Clinical improvement:*** 50% to 99% re-epithelialisation of the ulcer area and diminution of induration relative to the previous examination. Lesions that showed clinical improvement at the end of therapy or 1½ months after the end of therapy were followed until either a complete clinical response or no clinical response was seen at subsequent follow-up sessions • ***No clinical response:*** < 50% enlargement or diminution of the ulcer area and of induration. If no clinical response was seen at the end of therapy, the lesion was monitored further • ***Failure to respond:*** > 50% enlargement of lesion size at the end of therapy or at subsequent follow-up, or no clinical response at an examination done 1½ months or more after the end of therapy • ***Relapse:*** The reappearance of the lesion at the original site after a complete clinical response or the appearance of lesions involving the mucosa

Vélez 1997 *(Continued)*

	A participant was considered cured if all of their lesions had a complete clinical response by the third month of therapy and no relapse had occurred by the 12-month follow-up appointment. Therapy was considered to have failed if any of the participant's lesions did not respond to therapy or relapsed **Adverse effects**: Toxicity was determined by 1 evaluator before the code was broken. The occurrence and severity of anticipated adverse effects were recorded at each monitoring session **Time points reported**: Lesions were examined before the start of therapy; at the end of therapy; and 1.5, 3, 6, 9, and 12 months after the end of therapy
Notes	**Ethical approval needed/obtained for study**: The ethical review committee of the Antioquia University School of Medicine and Hospital San Vicente de Paul, Medellin, Colombia, approved the study **Informed consent obtained:** all participants gave written informed consent **Study funding sources:** By UNDP/World Bank/World Health Organization Special Programme for Research and Trainiing in Tropical Disease (Dr. Vélez) **Possible conflicts of interest:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomization code was broken after the end of follow-up for the last patient." Comment: method of generation of randomisation sequence (in this case the code) was not clearly described
Allocation concealment (selection bias)	Low risk	Quote: "The randomization code was broken after the end of FU for the last patient." Comment: allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "partially double-blinded phase III study" Comment: not clear who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "After the end of follow-up for the last patient, three independent, blinded evaluators determined efficacy and reached a consensus for each patient." Comment: outcome assessment blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 5/187 (2.67%). Reasons were provided
Selective reporting (reporting bias)	Low risk	All expected/predicted outcomes were reported in the Results section
Other bias	High risk	Sample size calculation was not adequately reported

Vélez 2010

Study characteristics

Vélez 2010 *(Continued)*

Methods	**Study design:** Randomised, open-label Phase III clinical trial **Setting/location:** 5 military health establishments located in central, northeast, and southern Colombia **Period of study:** June 2006 to April 2008 **Sample size calculation:** The sample size was calculated assuming an expected effectiveness of at least 78% for miltefosine and 90% for the pentavalent antimonials, 95% confidence interval (CI) and a power of 80%. An additional 20% was added to the calculated sample size to compensate for loss during the follow-up period. On the basis of these figures, the sample size was calculated as 144 participants per group, for a total of 288 for both groups
Participants	**Type of Leishmania:** *L. (V.) panamensis* (n = 86; MA group: 32, Thermotherapy group: 24, and MF group: 30). *L. (V.) braziliensis* (n = 162; MA group: 52, Thermotherapy group: 59, and MF group: 51) **Inclusion criteria:** a confirmed parasitological diagnosis of leishmaniasis; received no treatment for the current infection during the past 6 weeks; normal renal, hepatic, pancreatic, and haematological functions; volunteered to participate in the study **Exclusion criteria:** serious concomitant illnesses; lesions with mucosal involvement; disseminated cutaneous leishmaniasis (presence of 10 or more cutaneous lesions and a negative MST) **Randomised:** 437 (MF (N = 145), Thermotherapy (N = 149), and MA (N = 143)) **Withdrawals:** 60 (23 in the MF group, 15 in the Thermotherapy group, and 22 in the MA group) **Patients assessed:** 437 (all participants were assessed by ITT analysis) **Age (years) and sex:** Age (years) (median (min – max)): MA group. 23 (19 – 38), Thermotherapy group: 23 (19 - 39), and MF group: 23 (19 – 37); adult men serving in the Colombian Army **Baseline data:** 68% only 1 lesion; 31% 2 or more. Type of lesion: 95% ulceration of lesions: 81% upper part of the body
Interventions	**Type of interventions:** • ***Intervention group 1:*** 1 x 50 mg capsule of miltefosine (Impávido ®, Zentaris, Frankfurt, Germany) was administered orally 3 times a day for 28 days. Capsules were administered after each meal, for a daily dose of 150 mg and a total dose of 4200 mg per participant • ***Intervention group 2:*** Thermotherapy (Thermomed®, Thermosurgery Inc. Phoenix-USA) lesions. Each thermal application was at 50 °C and lasted for 30 seconds; the number of applications depended on the size of the lesion. After the thermotherapy session and over the next 10 days, an antibiotic ointment (fusidic acid) was applied over the lesions • ***Control group:*** Meglumine antimoniate (Glucantime ®, Aventis, Paris, France) was administered intramuscularly at a dose of 20 mg/kg body weight per day for 20 days **Duration of intervention:** 20 days antimoniate, 28 days miltefosine, and a single session in the thermotherapy group **Co-interventions:** In the thermotherapy group after the the single session and over the next 10 days, an antibiotic ointment (fusidic acid) was applied over the lesions to prevent secondary infections **Duration of follow-up:** 6 months

Outcomes	**Definition**
	
	• **Clinical cure:**
	  ○ ***Initial cure*** **:** Complete re-epithelialisation of all ulcers and complete disappearance of the induration up to 3 months after the end of treatment.
	  ○ ***Definitive cure*** **:** Initial cure plus the absence of recurrences or MCL for 6 months after the end of treatment

Vélez 2010 *(Continued)*

- ***Clinical improvement*** **:** Re-epithelialisation and at least 50% reduction of the area induration relative to previous observation. Lesions that presented clinical improvement 6 weeks after the end of treatment were monitored for an additional 3 months, after which time the lesion should have completely healed; if not, the case was classified as therapeutic failure

- **Recurrence**: Reactivation of the lesion at the original site after cure or mucosal compromise during follow-up
- **Reinfection**: Appearance of new lesions at anatomical sites different from the sites of the original lesions after the participant was evaluated as cured and returned to endemic areas

Adverse effects: evaluated according to standard criteria used in therapy of cancer v.3 (CTCAE)

Time points reported: end of treatment, 6 weeks, 3 months and 6 months after completion of treatment

Notes

Ethical approval needed/obtained for study: The protocol was approved by the bioethics committee for research on humans in the Sede de Investigación Universitaria (CBEIH-SIU) of the University of Antioquia and by the ethics committee of the General Health Directorate of the Colombian Army

Informed consent obtained: All participants signed an informed consent form in the presence of 2 witnesses

Baseline imbalances: none relevant.

Study funding sources: Funding was provided by the Social Protection Ministry of the Republic of Colombia, which did not participate in the design, implementation, analysis or report of this project

Possible conflicts of interest: "The authors hereby state they have no conflict of interest in this study."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote p 352: "Subjects were randomly assigned to the treatment groups. A list of treatments, generated randomly in blocks of eight (EpiInfo, version 3.1, CDC, Atlanta, GA), was used to assign each subject to a treatment group."
Allocation concealment (selection bias)	Low risk	Quote: "Only the clinical coordinator of the study had access to the list and was in charge of allocating treatments." Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open-label" - so participants and study personnel were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"open-label" - unclear if outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analyses were reported by ITT and per protocol. Reasons for dropouts were provided. MF group: 2 participants (1.4%) did not complete the treatment because of secondary effects and 21 (14.7%) were lost during the 6-month follow-up, so 122 (84.1%) completed the study according to the protocol Thermotherapy group: end of treatment (2) and 6 months follow-up (13)

Vélez 2010 *(Continued)*

		MA group: 18 (12.6%) were lost during the 6-month follow-up, 2 (1.4%) left the army before completing the study, and 2 (1.4%) were killed in combat, so 121 participants (84.6%) completed the study according to the protocol
Selective reporting (reporting bias)	Low risk	Protocol available, all relevant outcomes were reported ClinicalTrials.gov: NCT00471705
Other bias	Low risk	All information was provided

ACML: American cutaneous and mucocutaneous leishmaniasis; AL: allopurinol; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AS: aminosidine sulphate; AST: aspartate aminotransferase; ATL: American tegumentary leishmaniasis; C: Calculated; CL: cutaneous leishmaniasis; D: design; Dropouts: ND = no dropouts; ECG: electrocardiogram; Excl: exclusion criteria; FU: follow-up; GM-CSF: Granulocyte macrophage colony-stimulating factor; h: hour(S); HRLQ: health-related life quality; IFT: immunofluorescence test; IL: intralesional; IM: intramuscular; Incl: inclusion criteria; IV: intravenous; M/F: male/female ratio; MA: meglumine antimoniate; MBCL: methylbenzethonium chloride; MDLBT: Median duration of lesions before therapy; MNL: Median number of lesions; MSL: Median size of lesions; MST: Montenegro skin test; NC: Not calculated; NR: not reported; OD: once daily; PCR: polymerase chain reaction; PI: pentamidine isethionate; PR: paromomycin; Px: participants; Sample size: Small = < 50 participants; Medium = 51 - 150 participants; Large = > 150 participants; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; SSG: sodium stibogluconate; T1: treatment 1; T2: Treatment 2; T3: treatment 3; T4: treatment 4.

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

Study	Reason for exclusion
Armijos 2004B	Excluded in the previous review (use of vaccines alone, aimed at preventing cutaneous leishmaniasis)
De Luca 1999	Excluded in the previous review (use of vaccines alone, aimed at preventing cutaneous leishmaniasis)
De Luca 2001	Excluded in the previous review (use of vaccines alone, aimed at preventing cutaneous leishmaniasis)
De Luca 2003	Excluded in the previous review (use of vaccines alone, aimed at preventing cutaneous leishmaniasis)
Deps 2000	Excluded in the previous review (inadequate method of randomisation sequence)
Fagundes 2007	Excluded in the previous review (ineligible study design)
Falquete 2002	Ineligible study design
Gardlo 2003	Ineligible study design
Hendrickx 1998	Ineligible study design
Hepburn 1993	Ineligible study design
Hepburn 1994b	Excluded in the previous review (no outcome of interest)
Herwaldt 1992	Ineligible study design
Krause 1999	Ineligible study design
Laguna-Torres 1999	Excluded in the previous review (ineligible study design)

Study	Reason for exclusion
Llanos 1991	Excluded in the previous review (no outcome of interest)
Llanos-Cuentas 2010	Ineligible comparator
Monjour 1994	Excluded in the previous review (use of vaccines alone)
Motta 2012	Ineligible study design
Nascimento 1990	Excluded in the previous review (use of vaccines alone, aimed at preventing cutaneous leishmaniasis)
Oliveira-Neto 2000	Excluded in the previous review (ineligible study design)
Rodriguez 1995	Excluded in the previous review (no outcomes of interest)
Saldanha 2000	Excluded in the previous review (no outcome of interest)
Soto 1994b	Excluded in the previous review (inadequate method of randomisation sequence)
Soto 1995	Ineligible study design
Soto-Mancipe 1993	Excluded in the previous review (inadequate method of randomisation sequence)
Urcuyo 1982	Ineligible study design
Veiga 1985	Ineligible study design
Vélez 2005	Excluded in the previous review (use of vaccines alone, aimed at preventing cutaneous leishmaniasis)
Wortmann 2002	Excluded in the previous review (mixed Old World and New World forms of CL)

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT00004755

Methods	Treatment, randomised, open label, parallel assignment, safety/efficacy study
Participants	Total enrolment: 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 < 3 months duration) No mucocutaneous leishmaniasis No prior leishmaniasis --Prior/concurrent therapy -- No prior treatment for leishmaniasis -- Px characteristics --

NCT00004755 *(Continued)*

	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 contra-indication to protocol therapy; no pregnant or nursing women
Interventions	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
Outcomes	Not reported
Notes	Recruitment status: completed

NCT00111514

Methods	Treatment, randomised, double-blind, placebo-control, parallel assignment, safety study
Participants	Total enrolment: 48 Ages eligible for study: 18 - 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 3 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: • Occurrence of dose-limiting toxicity • Adverse effects Secondary outcome measures: • IgG and T-cell response to Leish-111f vaccine • Leish-111f skin test reactivity • Safety of the vaccine with respect to the clinical course of mucocutaneous leishmaniasis
Notes	Recruitment status: completed

NCT00111553

Methods	Treatment, randomised, double-blind, active control, parallel assignment, safety study
Participants	Total enrolment: 45 Ages eligible for study: 18 - 60 years; genders eligible for study: both Inclusion criteria: • Confirmed diagnosis of cutaneous leishmaniasis defined as positive identification of parasite from lesion biopsy • Normal lab values and electrocardiogram (ECG) • Negative for HIV, hepatitis B and C, and Chagas disease Exclusion criteria: • 9 or more active cutaneous lesions • Lesion diameter > 60 mm • Previous exposure to Leishmania vaccines or to MPL-SE • Pregnant or breast-feeding woman
Interventions	This study is a phase 1, randomised, double-blind, placebo controlled, sequential dose-escalating trial to evaluate the safety and immunogenicity of 3 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: • Occurrence of dose-limiting toxicity • Adverse effects Secondary outcome Measures: • IgG and T-cell response to Leish-111f vaccine • Leish-111f skin test reactivity • Safety of the vaccine with respect to the clinical course of cutaneous leishmaniasis
Notes	Recruitment status: completed

NCT00317980

Methods	Treatment, randomised, single-blind, active control, parallel assignment, safety/efficacy study
Participants	Total enrolment: 324 Ages eligible for study: 7 - 50 years; genders eligible for study: both Accepts healthy volunteers Inclusion criteria: • Presence of 1 to 9 cutaneous lesions clinically compatible with leishmaniasis • Disease duration of 2 to 20 weeks • Positive leishmanin skin test • Parasitological diagnosis confirmed through culture or genus-specific PCR for Leishmania spp Exclusion criteria:

NCT00317980 *(Continued)*

	• History of past episode of leishmaniasis
	• Mucocutaneous disease
	• Disseminated disease
	• Use of drugs with anti-leishmanial activity
	• Contraindications for using pentavalent antimony:
	  ○ pregnancy
	  ○ renal failure
	  ○ heart failure
	  ○ hepatic failure
	• Other diseases: active tuberculosis, hanseniasis

Interventions	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.
Outcomes	The clinical outcomes of cure or failure will be evaluated until the third month of follow-up Primary outcome measures: • Proportion of clinically-cured Px at the third month after treatment • Proportion of Px with early failure during the first 3 months after treatment Secondary outcome measures: • Proportion of Px with adherence to the protocol-prescribed drug • Proportion of Px with adverse effects • Proportion of Px with late failure after the first 3 months of follow-up
Notes	Recruitment status: completed

NCT00973128

Methods	Randomised, safety/efficacy study, parallel assignment, single-blind (Investigator), treatment
Participants	Total enrolment: 40 Ages eligible for study: 15 - 50 years; genders eligible for study: both Accepts healthy volunteers: No Inclusion criteria: • Age between 15 and 50 years • Either gender • Diagnosis of cutaneous leishmaniasis • < 60 days of disease Exclusion criteria: • Any history of prior anti-leishmania therapy • Negative parasitology (aspirate/smear)or negative Montenegro test • Pregnancy • Age < 15 and > 50 years • Other associated acute or chronic illnesses • History of allergy to GM-CSF and/or antimony

NCT00973128 *(Continued)*

	• HIV, HTLV-1 infections or diabetes
	• Administrative reasons:
	  • Lack of ability or willingness to give informed consent (patient and/or parent / legal representative)
	  • Anticipated non-availability for study visits/procedures

Interventions	Intervention 1: Antimony (20 mg/daily for 10 days) plus GM-CSF treatment: antimony (20 mg/daily for 10 days) plus GM-CSF (400 µg, divided in 2 doses a week apart) Active comparator: Antimony (20 mg/daily for 20 days) plus saline administered in an identical fashion to the GM-CSF
Outcomes	Primary outcome measures: • Cure rate or complete cicatrisation of the ulcer 3 months after treatment. Designated as safety issue: Yes Secondary outcome measures: • Initial cure rate or complete cicatrisation of the ulcer 2 months after treatment. Designated as safety issue: Yes
Notes	Recruitment status: completed

NCT01380301

Methods	Randomised, safety/efficacy study, parallel assignment, open label, treatment
Participants	Total enrolment: 19 Ages eligible for study: 12 - 75 years; genders eligible for study: both Accepts healthy volunteers: No Type of leishmaniasis: cutaneous leishmaniasis Inclusion criteria: • Parasitological confirmation • at least 1 lesion must be ulcerative • No specific antileishmanial therapy during the previous 6 months Exclusion criteria: • Concomitant diseases such as tuberculosis, HIV, diabetes, renal failure, liver disease • abnormalities CTC 2 in blood, liver, kidney test or EKG
Interventions	Experimental: Miltefosine and Antimony Miltefosine 1.5 to 2.5 mg/kg/d during 14 days simultaneously with meglumine antimoniate 20 mg/kg/d during 10 days Active comparator: Miltefosine alone: Miltefosine 1.5 to 2.5 mg/kg/d during 14 days
Outcomes	Primary outcome measures: • Healing of ulcers by 45 days. Designated as safety issue: Yes Secondary outcome measures:

NCT01380301 *(Continued)*

	• Clinical findings and Laboratory parameters in normal ranges at 28 days. Designated as safety issue: Yes
Notes	Recruitment status: Terminated (low efficacy rates)

NCT01380314

Methods	Randomised, efficacy study, parallel assignment, double-blind (participant, investigator), treatment
Participants	Total enrolment: 60 Ages eligible for study: 12 years and older; genders eligible for study: both Accepts healthy volunteers: No Type of leishmaniasis: cutaneous leishmaniasis Inclusion criteria: • Gender: male or female • Age: > 12 yrs of age • Presentation: At least 1 lesion must be ulcerative. No more than 3 lesions. Parasitology: Parasitological confirmation of 1 lesion will be made by visualisation or culture of leishmania from the biopsy or aspirate of the lesion • No specific or putatively specific therapy (Sb, pentamidine, amphotericin B, imidazoles, allopurinol) in the last 6 months Exclusion criteria: • Previous treatment for leishmaniasis • Concomitant diseases by history • Abnormal complete blood counts (white blood count, haemoglobin, platelet count), values of liver transaminases (SGOT), kidney function tests (creatinine) • Pregnancy or breastfeeding or not willing to take contraception for 3 months after the end of treatment
Interventions	Intervention 1: Miltefosine 150 mg x day during 28 days + Imiquimod 5% every other day during 3 weeks Placebo comparator: Miltefosine 150 mg x day during 28 days + Placebo every other day during 3 weeks
Outcomes	Primary outcome measures: • Healing of ulcers by 45 days. Designated as safety issue: No Secondary outcome measures: • Clinical findings and normal laboratory parameters at 28 days. Designated as safety issue: Yes
Notes	Recruitment status: completed

NCT01464242

Methods	Randomised, safety/efficacy study, parallel assignment, double-blind (participant, caregiver, investigator), treatment
Participants	Total enrolment: 100 Participants aged 18 to 65 years; genders eligible for study: both Accepts healthy volunteers: No Inclusion criteria: • Patients with clinical diagnosis of cutaneous leishmaniasis (parasitologic confirmation or presumptive biopsy plus a positive Montenegro skin test) • Age between 18 and 65 years • Lesions of a duration ≥ 1 month • More than one lesion or single lesion > 3 cm in diameter • Willingness to participate in the study after being informed through a consent process approved by the institutional ethical review committee Exclusion criteria: • Pregnant or lactating women, and women who are planning to conceive during the study or that reject the use of birth control methods • Medical conditions that compromise the immune system (HIV infection, neoplasias, diabetes mellitus, autoimmune diseases, or use of corticosteroids, immunomodulators or antineoplastic drugs) • Medical conditions that preclude the use of antimonials or pentoxifylline (cardiac, renal, hepatic or pancreatic disease or abnormalities) • Alcohol abuse or use of recreational drugs that interfere with adherence to treatment • Use of drugs with antileishmanial potential during the previous 13 weeks, including pentavalent antimonials, amphotericin B, miltefosine, and pentamidine • Use of Theophylline, anticoagulants or antiarrhythmics • Diffuse or disseminated leishmaniasis • Mucosal involvement secondary to Leishmania infection • Incapacity to attend the study visits or any other condition that according to the investigator could interfere with adherence to study procedures
Interventions	Intervention group: Glucantime® 20 mg/kg/day intramuscular injection (IM) daily + pentoxifylline 400 mg orally 3 times a day Control group: Glucantime® 20 mg/kg/day IM each day + placebo 400 mg orally 3 times a day Frequency: 20 days
Outcomes	Primary outcome measures: • Primary efficacy outcome: Definitive Cure: participants will be followed up to 26 weeks.Designated as safety issue: No. Definitive cure, defined as complete re-epithelialisation and absence of inflammatory signs in all cutaneous leishmaniasis lesions, and absence of new leishmaniasis lesions • Primary safety outcome: Adverse effects: participants will be followed up to 26 weeks. Designated as safety issue: Yes. Clinical and laboratory adverse effects will be qualified according to the Common Toxicity Criteria for Adverse Effects (CTCAE). All unexpected non-serious adverse effects will be notified and expected adverse effects of moderate or higher category will be reported. All serious adverse effects will be reported Secondary outcome measures: • In vitro lymphoproliferation: participants will be followed for an average of 20 days. Designated as safety issue: No. Proliferation of peripheral blood mononuclear cells (PBMCs) after stimulation in vitro with L. panamensis antigens will be measured by tritiated thymidine uptake

NCT01464242 *(Continued)*

	• Cytokine secretion by PBMCs: participants will be followed for an average of 20 days. Designated as safety issue: No. Secretion of a panel of cytokines relevant to the inflammatory and immune responses will be measured in supernatants from PBMCs cultured with L. panamensis antigens using Luminex technology • Macrophage leishmanicidal capacity: participants will be followed for an average of 20 days. Designated as safety issue: No. Macrophages will be differentiated from peripheral blood monocytes and their leishmanicidal capacity will be measured by luminometry after infection with luciferase-transfected promastigotes • Macrophage inducible nitric oxide synthase (iNOS) expression: participants will be followed for an average of 20 days. Designated as safety issue: No. Macrophage expression of iNOS after infection will be measured by quantitative real-time PCR (RT-PCR)
Notes	Recruitment status: completed

NCT03294161

Methods	Single-blinded, parallel, randomised clinical trial
Participants	N = 50 Ages eligible for study: 18 - 65 years (Adult, Older Adult); gender eligible for study: both Accepts healthy volunteers: no Corte de Pedra Health Post, Bahia, Brazil Inclusion criteria: • Newly-diagnosed (untreated) cutaneous leishmaniasis or early cutaneous leishmaniasis with localised lesions and a positive culture or diagnosed by PCR methods or by intradermal skin testing (Montenegro test) • Number of lesions: 1 to 3 ulcerative lesions • Lesion's diameter: 1 to 5 cm • Disease duration: up to 3 months Exclusion criteria: • Aspartate aminotransferase, alanine aminotransferase > 3 times upper limit of normal range • Serum creatinine or blood urea nitrogen > 1.5 times upper limit of normal range • Evidence of serious underlying disease (cardiac, renal, hepatic or pulmonary) • Immunodeficiency or antibody to HIV • Any non-compensated or uncontrolled condition, such as active tuberculosis, malignant disease, severe malaria, HIV, or other major infectious diseases • Lactation, pregnancy (to be determined by adequate test) or inadequate contraception in women of childbearing potential for treatment period plus 2 months • Negative parasitology (aspirate/biopsy/PCR) or negative Montenegro test • Any history of prior anti-leishmania therapy • Any condition which compromises ability to comply with the study procedures • Lack of ability or willingness to give informed consent (patient and/or parent / legal representative) • Anticipated non-availability for study visits/procedure
Interventions	Intervention: Immucillin DI4G Immucillin DI4G was administered by topical use at 2% concentration once a day for 20 days associated with Meglumine antimoniate administered by intravenous route at a dosage of 20 mg/kg/day, during 20 days.Other Name: Fourth-generation Immucillin Derivative

NCT03294161 *(Continued)*

	Active comparator: Meglumine antimoniate Placebo for topical use once a day at the ulcer for 20 days associated with Meglumine antimoniate administered as the standard treatment for cutaneous leishmaniasis by intravenous route at a dosage of 20 mg/kg/day, during 20 days.Other Name: Glucantime
Outcomes	**Primary outcomes:** • Cure rate or complete cicatrisation of the ulcer by 6 months after treatment **Secondary outcomes:** • Initial cure rate or complete cicatrisation of the ulcer by 2 months after treatment
Notes	Recruitment status: completed

Silva 2006

Methods	Double-blind, randomised, double-masked, placebo-controlled clinical trial
Participants	Total enrolment: 620 Ages eligible for study: 18 - 50 years; genders eligible for study: both Accepts healthy volunteers: No Inclusion criteria: • Men and women between 18 and 50 years old • Cutaneous ulcers of > 2 weeks of evolution • Positive parasitological diagnosis for CL • Patients that voluntarily agree to participate in the study and sign the informed consent • Disposition to attend all the visits punctually (initial, treatment and follow-up) • Acceptation of not using any other treatment for CL while in the study Exclusion criteria: • Pregnant women • Presence of any condition or disease that compromises the patient immunologically (i.e. diabetes, cancer, etc.) or any other that, based on the judgement of the researcher, could alter the course of CL • Diffuse CL or > 5 active lesions • Mucocutaneous leishmaniasis (no lesion must be located < 2 cm from the nasal, urogenital, and/or anal mucous membranes or from the edge of the lips) • Visceral leishmaniasis • Complete or incomplete treatment with antimony compounds in the last 3 months • Patients with history of hepatic, renal or cardiovascular disease • Mentally or neurologically disabled patients that are considered not fit to approve their participation in the study
Interventions	Group 1: For 20 days this group will receive simultaneously IMMA (Glucantime®) 20 mg/kg/day with a maximum dose of 3 ampoules a day; and a NOP placebo Group 2: For 20 days this group will receive simultaneously placebo of IMMA (5 - 15 cc/day) and an active NOP
Outcomes	Primary outcome measures:

Silva 2006 *(Continued)*

	• Complete re-epithelisation 3 months after the beginning of the treatment • Absence of reactivation and effects on the mucous membranes during the 6 months of the study Secondary outcome measures: • Incomplete re-epithelisation 3 months after the beginning of the treatment • Increase in the size of the ulcer by > 50% in relation to the last clinical evaluation • Reactivation and/or effects on the mucous membranes during the 6 months of the study
Notes	Recruitment status: Terminated (an interim analysis showed that nitric oxide patches are not effective)

CL: cutaneous leishmaniasis; GM-CSF: Granulocyte macrophage colony-stimulating factor; HIV: human immunodeficiency viruses; HTLV-1: Human T-cell lymphotropic virus type 1; IgG: immunoglobulin G; IM: intramuscular; IV: intravenous; PCR: polymerase chain reaction; Px: participants; MA: meglumine antimoniate; NOP: Nitric oxide patch; NR: not reported.

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

NCT00537953

Study name	Efficacy and safety of a short course of the combination of miltefosine and antimony to treat cutaneous leishmaniasis in Bolivia
Methods	Interventional Treatment, randomised, open label, active control, parallel assignment, safety/efficacy study
Participants	Ages eligible forsStudy: 18 - 65 years; genders eligible for study: male Accepts healthy volunteers: No Inclusion criteria: • Gender: male; Age: adults; Presentation: At least 1 lesion must be ulcerative; Parasitology: parasitological confirmation of 1 lesion will be made by visualisation or culture of leishmania from the biopsy or aspirate of the lesion. Exclusion criteria: • Previous treatment for leishmaniasis, specific or putatively specific therapy (Sb, pentamidine, amphotericin B, imidazoles, allopurinol) • Other concomitant diseases by history and by approximately normal complete blood counts (white blood count, haemoglobin, platelet count), values of liver transaminases (SGOT), values of pancreatic function (lipase), kidney function tests (creatinine), and EKG
Interventions	Not reported
Outcomes	Not reported
Starting date	Not reported
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: 28 September 2007 ClinicalTrials.gov Identifier: NCT00537953

NCT00537953 *(Continued)*

	Health Authority: Bolivia: Ministry of Health
Notes	Recruitment status: unknown

NCT01301937

Study name	Phase III clinical trial for mucosal or mucocutaneous leishmaniasis. Comparison between the standard and alternative antimonial schemes
Methods	Interventional Allocation: randomised Intervention model: parallel assignment Masking: triple (care provider, investigator, outcomes assessor) Primary purpose: treatment
Participants	Estimated enrolment: 76 Ages eligible for study: 13 years and older; gender: both Inclusion criteria: • Mucosal or mucocutaneous leishmaniasis with parasitological diagnosis by 1 or more of the following methods: direct examination (imprint), histopathology, culture, immunohistochemistry, or PCR Exclusion criteria: • Women who do not use contraceptives or do it badly • Pregnant women • Children under 13 years • Previous antimonial treatment for LM • Immunosuppressive therapy (steroids, cancer chemotherapy) or medicines for tuberculosis or leprosy • Presence of altered baseline clinical adverse effect level equivalent to > G3 • Presence of altered basal laboratory adverse effect level equivalent to > G2 • Presence of baseline electrocardiographic changes equivalent to an adverse effect level > G4 and/or baseline QTc > 0.46 ms (equivalent to AE level G1)
Interventions	Intervention 1: high continuous dose: IM Meglumine antimoniate 20 mg/kg/day for 30 continuous days Intervention 2: low continuous dose: IM Meglumine antimoniate 5 mg/kg/day for up to 120 continuous days according to clinical cure
Outcomes	Primary outcome measures: • Efficacy of meglumine antimoniate in the treatment of mucosal leishmaniasis: 6 years This study is designed to evaluate the efficacy of high and low doses of meglumine antimoniate in the treatment of mucosal or mucocutaneous leishmaniasis Secondary outcome measures: • Safety of meglumine antimoniate in the treatment of mucosal leishmaniasis: 6 years

NCT01301937 *(Continued)*	
	This study is designed to evaluate the safety of high and low doses of meglumine antimoniate in the treatment of mucosal or mucocutaneous leishmania
Starting date	October 2008
Contact information	Contact: Armando O. Schubach, MD, PhD; and Claudia M. Valete-Rosalino, MD, PhD e-mail: vigileish@ipec.fiocruz.br Tel: (55)(21)38659541 ClinicalTrials.gov Identifier: NCT01301937 Other Study ID Numbers: low dosage ML Study first received: 20 February 2011 Last updated: 20 May 2017
Notes	Recruitment status: recruiting

NCT02530697	
Study name	The association of miltefosine and pentoxifylline to treat mucosal leishmaniasis: an open-label, randomised clinical trial in Brazil
Methods	Randomised, safety/efficacy study, parallel assignment, open label, treatment
Participants	Total enrolment: 40 Participants aged 18 to 80 years; genders eligible for study: both Accepts healthy volunteers: No Inclusion criteria: • Mucosal leishmaniasis, not treated or at least 6 months without any treatment to leishmaniasis • Ages between 18 and 80 years • Fertile women should use at least 2 contraceptive methods (hormonal and barrier) • Agree to participate in the study and sign the informed consent term Exclusion criteria: • Use of any leishmanicidal drugs 6 months prior • Clinical or laboratory evidence of electrocardiographic disorders • Renal, hepatic, cardiac diseases, uncontrolled diabetes or AIDS • Hypersensitivity to meglumine antimoniate • Pregnancy or lactation • Fertile women that do not agree to use contraceptive methods • Patients that do not agree to the informed consent term
Interventions	Intervention group 1: Miltefosine 2.5 mg/kg/day up to 50 mg 2x/daily. Pentoxifylline 20 mg/kg/day up to 400 mg 3x/daily Control group: Intervention group 1: 20 mgSb + 5 /kg/day meglumine antimoniate intravenous. Pentoxifylline 20 mg/kg/day up to 400 mg 3x/daily Frequency: 28 days

NCT02530697 *(Continued)*

Outcomes	Primary outcome measures: • Cure at 90 days. (Designated as safety issue: No). Complete healing of previous lesions until the 90th day after the beginning of the treatment • Failure at 90 days. (Designated as safety issue: No). Lesions fail to heal until the 90th day after the beginning of the treatment • Relapse at 90 days. (Designated as safety issue: No). Lesions that reappear on the scar of a previously-healed lesion
Starting date	August 2015
Contact information	Sofia S Martins, email: sofiasalesm@gmail.com Raimunda Sampaio, email: raimunda.sampaio@gmail.com ClinicalTrials.gov Identifier: NCT02530697 Other Study ID Numbers: 40068714.1.0000.5558 Study first received: 19 August 2015 Last updated: 22 May 2016 Health Authority: Brazil: National Committee of Ethics in Research
Notes	Recruitment status: recruiting

NCT02687971

Study name	A randomised, open label, multicentre study to determine the efficacy and safety of combining thermotherapy and a short course of miltefosine for the treatment of uncomplicated cutaneous leishmaniasis in the New World
Methods	Study type: interventional Study design: allocation: randomised Intervention model: parallel assignment Masking: none (open label) Primary purpose: treatment
Participants	Estimated enrolment: 130 Ages eligible for study: 18 - 60 years (adult); genders eligible for study: all Accepts healthy volunteers: no Inclusion criteria: Patient with a confirmed diagnosis of CL in at least 1 lesion by at least 1 of the following methods: microscopic identification of amastigotes in stained lesion tissue, or demonstration of Leishmania by PCR, or positive culture for promastigotes Patient has a lesion that satisfies the following criteria: • Lesion size ≥ 0.5 cm and ≤ 4 cm (longest diameter) • Not located on the ear, face, close to mucosal membranes, joints or on a location that in the opinion of the PI is difficult to apply TT

NCT02687971 *(Continued)*

	• Patient with ≤ 4 CL lesions • Duration of lesion < 4 months by patient history • Patient able to give written informed consent, and in the opinion of the investigator, the patient is capable of understanding and complying with the protocol Exclusion criteria: • Woman with a positive urine pregnancy test at screening or who is breast-feeding, lactating, or woman at a fertile age who does not agree to take appropriate contraception during treatment period and up to D90 • History of clinically-significant medical problems/treatment that might interact, either negatively or positively, with topical treatment of leishmaniasis, including any immunocompromising condition • Within 8 weeks (56 days) of trial Day 1, received treatment for leishmaniasis with any medication including antimonials likely, in the opinion of the PI, to modify the course of the Leishmania infection • Has diagnosis or suspected diagnosis of mucocutaneous leishmaniasis based on physical exam • History of known or suspected hypersensitivity or idiosyncratic reactions to trial medication or excipients • Patient who is not willing to attend the trial visits, or is not able to comply with follow-up visits up to 6 months • Known history of drug addiction and/or alcohol abuse
Interventions	Active Comparator: Thermotherapy alone Local heat will be applied using a Localised Current Field radio-frequency generating device manufactured by Thermo-Med Technologies, Inc. A wand with 2 electrodes is connected to the main housing by a thin wire. The electrodes are applied to the skin. We will use electrodes 6 mm long, separated by 4 mm.1 single session at the site of the lesion(s) at 50 °C for 30-second applications will be used. Depending on the size of the lesion, more than 1 application may be administered Experimental: Thermotherapy plus Miltefosine In addition to receiving 1 single session of thermotherapy as described above, participants will receive oral miltefosine 2 or 3 capsules a day, which is the equivalent of 100 to 150 mg respectively for 21 days. Miltefosine capsules will be taken after breakfast, lunch and dinner, i.e. after food. The daily dose of miltefosine will depend on the weight of each participant. According to dosage instructions if the participant is taking the miltefosine twice a day, it must be taken in the morning and at night (dose of 100 mg/Kg/day); if the participant is taking miltefosine 3 times a day, it must be taken in the morning, at noon and at night (dose of 150 mg/Kg/day)
Outcomes	Primary outcome measures: • Initial cure rate at Day 90, after start of treatment. Initial cure: ulcerated lesions: 100% re-epithelialisation of the lesion(s) by Day 90 Non-ulcerated lesions: flattening and/or no signs of induration of the lesion(s) by Day 90.The percentage of re-epithelialisation of the lesion(s) is calculated by comparing the size of the ulcer at Day 7 against the size at the follow-up visit Secondary outcome measures: • Final cure rate at Day 180, after star of treatment. The number of participants who fulfil the criteria of initial cure and have no relapse by Day 180 • Frequency and severity of adverse effects by Day 45. Frequency and severity of adverse effects by treatment group
Starting date	December 2016
Contact information	**Colombia**

NCT02687971 *(Continued)*

	Programa de Estudios y Control de Enfermedades Tropicales (PECET), Universidad de Antioquia Recruiting, Medellin, Colombia Contact: Ivan Velez: idvelez@pecet-colombia.org Principal Investigator: Ivan Dario Velez **Peru** IMT Alexander Von Humboldt Recruiting, Lima, Peru Contact: Alejandro Llanos-Cuentas, Dr +51 1 482 7739 alejandro.llanos.c@upch.pe Contact: Braulio Valencia, MD +5114827739 braulio.valencia@upch.pe ClinicalTrials.gov Identifier: NCT02687971 Other Study ID Numbers: DNDi-MILT-07-CL Study first received: 17 February 2016 Last updated: 25 April 2017
Notes	Recruitment status: recruiting

NCT03023111

Study name	Miltefosine and GM-CSF in cutaneous leishmaniasis: a randomised and controlled trial
Methods	Study type: interventional (clinical trial) Allocation: randomised Intervention model: parallel assignment Masking: quadruple (participant, care provider, investigator, outcomes assessor) Primary purpose: treatment
Participants	Estimated enrolment: 300 participants Ages eligible for study: 18 - 65 years (adult, older adult) Sexes eligible for study: all Accepts healthy volunteers: no Inclusion criteria: • Untreated ulcerative cutaneous leishmaniasis, with laboratory diagnosis obtained through at least 1 of the following tests: direct examination of the lesion, positive culture or PCR for Leishmania • Age: 18 to 65 years • Sex: men and women • Presence of at least 1 ulcerated lesion at any location • Presence of a maximum of 3 ulcerated lesions • Diameter of lesions varying between 1 and 5 cm • Clinical evolution of the disease of not less than 1 month and not more than 3 months Exclusion criteria:

NCT03023111 *(Continued)*

	• Evidence of severe underlying disease (cardiac, renal, hepatic, pulmonary) or malignant disease • Participants with immunodeficiency or HIV carriers • Serious protein or caloric malnutrition, or both • Active and uncontrolled infectious-contagious disease such as tuberculosis, leprosy, systemic fungal disease (histoplasmosis, paracoccidioidomycosis) or any other similar condition • Women who are pregnant or breastfeeding • Allergy to Sbv or miltefosine • Previous treatment for leishmaniasis • Lack of capacity or willingness to provide informed consent (participant or parent/legal representative) • Absence of availability for the visits or to comply with the study procedures
Interventions	• Active comparator: Sbv Meglumine antimoniate (Glucantime): Dosage: 20 mg/kg/day, intravenously, during 20 days • Experimental: Miltefosine plus placebo: Miltefosine (28 days / 2.5 mg/Kg/day at a maximum dose of 150 mg/day orally) + topical placebo (gel cream, 2 times a day for 28 days) • Experimental: Miltefosine plus GM-CSF: Miltefosine (28 days / 2.5 mg/kg/day at a maximum dose of 150 mg/day orally) + topical GM-CSF (0.01% gel cream, 2 times a day for 28 days)
Outcomes	Primary outcome measures • Final cure rate or complete cicatrisation of the ulcer at 6 months after the end of treatment. All lesions will be categorised as either active or healed (cured) at follow-up visits. Only lesions with complete re-epithelialisation, without raised borders, infiltrations or crusts will be considered healed. Evaluation of the lesions will be performed by 2 clinicians who will be unaware of the group assignment of all participants. Bidirectional measurements of ulcers will be taken of the participants' lesions at the initial visit, and at each follow-up visit with standardised caliper. The area involved will be calculated as the product of the 2 measurements Secondary outcome measures • Initial cure rate or initial cicatrisation of the ulcer at 2 months after the end of treatment]. All lesions will be categorised as either active or healed (cured) at follow-up visits. Only lesions with complete re-epithelialisation, without raised borders, infiltrations or crusts will be considered healed. Evaluation of the lesions will be performed by 2 clinicians who will be unaware of the group assignment of all participants. Bidirectional measurements of ulcers will be taken of the participants' lesions at the initial visit, and at each follow-up visit with standardised caliper. The area involved will be calculated as the product of the 2 measurements • Healing time up to 2 months after the end of treatment. Time (in days) to achieve complete cicatrisation will be recorded • Clinical and laboratory adverse effects during treatment and through study completion, an average of 1 year. Clinical and laboratory adverse effects will be recorded and graded according to the Common Terminology Criteria for Adverse Event (CTCAE) of the National Cancer Institute
Starting date	March 2017
Contact information	Contact: Paulo RL Machado, MD, PhD 55-71-32377353 prlmachado@hotmail.com Contact: Edgar M Carvalho, MD, PhD 55-71-32377353 edgar@ufba.br
Notes	Recruitment status: not yet recruiting

NCT03084952

Study name	A phase 2, randomised, unicentric clinical trial with dose scaling for safety, tolerability and efficacy assessment of 18-Methoxycoronaridine administered to cutaneous leishmaniasis patients

NCT03084952 *(Continued)*

Methods	Study type: interventional Study design: allocation: randomised Intervention model: sequential assignment Masking: none (open label) Primary purpose: treatment
Participants	Estimated enrolment: 52 Ages eligible for study: 18 - 59 years (Adult); genders eligible for study: all Accepts healthy volunteers: no Inclusion criteria: • Age between 18 and 59 years of age • Clinical diagnosis of leishmaniasis with at least 1 ulcerated lesion with evolution time from 1 month • Parasitological confirmation • Women of childbearing potential should not be pregnant or breast-feeding, confirmed by examination of b-HCG (Gonadotrophic-Chorionic Hormone beta) at the time of screening • Men and women should use barrier contraceptive methods during the course of the study Exclusion criteria: • History of any disease or co-morbidities that, in the opinion of the investigator, can either put the individual at risk or influence the results and ability of the patient to participate in the study • History or presence of gastrointestinal, hepatic, cardiac, renal disease or any other known condition that may interfere with the absorption, distribution, metabolism or excretion of the investigational product • Any evidence of underlying serious disease (cardiac, renal, hepatic or pulmonary) • Pregnancy or the patient's unwillingness to use barrier contraceptive methods during and 3 months after therapy • History of gastrointestinal ulcer disease, inflammatory bowel disease, symptoms of indigestion • Any clinically important abnormality in biochemistry, haematology, urinalysis or clinical outcomes judged by the investigator • Any positive screening result for hepatitis B antigens, hepatitis C antibodies, and HIV • Any clinically significant abnormalities in the rate, or driving the resting ECG morphology that may interfere with the interpretation of the QT interval variations • History of cancer • History of drug abuse, judged by the investigator • History of alcohol abuse or excessive alcohol consumption, judged by the investigator • History of smoking • History of severe allergy/hypersensitivity, judged by the investigator • History of hypersensitivity to drugs with similar chemical structure
Interventions	Experimental: 18-Methoxycoronaridine • 1 mg/d • 4 mg/d • 8 mg/d • 12 mg/d • Best dose 18-MC • Minimum effective dose 18-MC

NCT03084952 *(Continued)*

	Active comparator: Glucantime
Outcomes	Primary outcome measures: • Lesion reduction and re-epithelisation - Definitive cure by 6 months at the follow-up visit. Complete epithelisation of all ulcers and complete disappearance of inflammatory hardening of all lesions at 6 months at the follow-up visit • Lesion reduction and re-epithelisation - Partial cure by 6 months at the follow-up visit. Incomplete epithelialisation or incomplete regression of inflammatory hardening of 1 or more lesions, and without the appearance of new lesions. • Apparent cure: complete epithelisation of all ulcers and regression ≥ 70% of the inflammatory hardening of all lesions • Clinical failure by 6 months at the follow-up visit. Any of the following topics as clinical failure: residual readers with the presence of non-GiemsaDiff-Quick print parasites, or the appearance of new lesions or ≥ 20% increase or no improvement of lesions previously documented
Starting date	November 2017
Contact information	Jan Carlo Delorenzi, PhD +55(11)989780869 jancarlo@hebron.com.br ClinicalTrials.gov Identifier: NCT03084952 History of Changes Other Study ID Numbers: HB/F2-002/2016 Study first received: 14 March 2017 Last Updated: 15 August 2017
Notes	Recruitment status: not yet recruiting

NCT03829917

Study name	Oral miltefosine plus topical paromomycin In American cutaneous leishmaniasis
Methods	Study type: interventional (clinical trial) Allocation: randomised Intervention model: parallel assignment Masking: double (participant, investigator) Primary purpose: treatment
Participants	Estimated enrolment: 120 participants Ages eligible for study: 12 years and older (child, adult, older adult); genders eligible for study: all Accepts healthy volunteers: no Inclusion and exclusion criteria: • Gender: male or female • Age: > 12 yrs of age • Presentation: 1 - 2 ulcerative lesions, each < 30 mm in largest diameter and with a total lesion area < 900 mm^2 • Parasitology: Parasitological confirmation of the lesion will be made by visualisation or culture of Leishmania from the biopsy or aspirate of the lesion • Previous treatment for leishmaniasis:

NCT03829917 *(Continued)*

	◦ No specific or putatively specific therapy (Sb, pentamidine, amphotericin B, miltefosine, imidazoles, allopurinol) in the last 3 months • Other diseases: No concomitant diseases by history that would be likely in the PI's opinion to interact, either positively or negatively, with treatment
Interventions	• Experimental: paromomycin and miltefosine paromomycin-aquaphilic cream applied topically once daily for 28 days plus oral miltefosine pills 2.5 mg/day (50 mg 3 times a day) for 28 days • Active comparator: miltefosine pills alone 2.5 mg/day (50 mg 3 times a day) for 28 days. This group will also receive aquaphilic-vehicle cream for 28 days • Active comparator: paromomycin: paromomycin-aquaphilic cream applied topically once daily for 28 days
Outcomes	Primary outcome measures: Change in size of cutaneous ulcers at 2, 3, 4 and 6 months after the beginning of therapy Complete healing of all lesions by 6 months after the beginning of therapy. Thus for a participant to be cured: no lesion could enlarge by 50%, relapse, or heal incompletely; and no new Leishmania-positive lesion can have appeared
Starting date	01 February 2019
Contact information	Contact: Patricia Gutierrez, Ms, 33515152 pgutierrezduenas@gmail.com Contact: Paula Soto, MD, 33515152 dra.paula.dermalaser@gmail.com
Notes	Recruitment status: recruiting

NCT04072874

Study name	Evaluation of the safety and clinical activity of Curaleish lotion and cream in the topical treatment of cutaneous leishmaniasis in Colombia
Methods	Study type: interventional (clinical trial) Allocation: randomised Intervention model: parallel assignment Intervention model description: An open-label, randomised, non-comparative, two-arm exploratory study. After all the screening evaluations have been completed, the principal investigator or his designee will confirm the participant's eligibility on Day 1, and the randomisation will be determined by IWRS where randomised identification of the participant will be provided. The treatment allocation will be performed according to a computer-generated random code Masking: none (open label) Primary purpose: treatment
Participants	Estimated enrolment: 50 participants Ages eligible for study: 18 - 60 years (adult); genders eligible for study: all Accepts healthy volunteers: no Inclusion criteria: • Men and women between 18 - 60 years

NCT04072874 *(Continued)*

- Patient with confirmed parasitological diagnosis of CL in at least 1 lesion, performed at least through the following methods: microscopic identification of amastigotes in tissue of the lesion; Leishmania diagnose through PCR; positive culture for promastigotes
- Patient with a lesion that meets the following criteria: ulcer or nodule with a maximum size of 4 cm (the largest diameter)
- Not located on the ear, face, near mucous membranes, joints, or in places that, in the opinion of the PI, the study medication is difficult to apply topically
- Patient with a maximum of 4 CL lesions
- The duration of the lesion < 3 months according to the patient's history
- The patient is able to give written informed consent
- Patients who the investigator believes are able to understand and are willing to comply with the requirements of the protocol

Exclusion criteria:

- Women with positive pregnancy test during the screening process, or who are lactating; or women of childbearing age who do not agree to take contraceptives during treatment and until Day 45
- The person has a history of significant medical conditions or treatments that may interact negatively or positively with the topical treatment of Leishmaniasis, including any immune-compromised condition
- Within 8 weeks (56 days) of beginning the study treatments, having received treatment for Leishmaniasis through any medication, including Glucantime that might, in the opinion of the principal investigator (PI),modify the course of the infection by Leishmania
- Based on physical examinations performed, they have been diagnosed, or a diagnosis of Mucocutaneous Leishmaniasis is suspected
- Known history or suspected hypersensitivity or idiosyncratic reactions to the study medication
- Patients who do not wish to attend study appointments or who cannot keep up with follow-up visits for up to 6 months

Interventions	Active comparator: Regimen 1: Curaleish lotion applied 3 times a day in combination with Curaleish cream applied twice a day for 4 weeks For both treatments, the participant applies Curaleish lotion in the morning, afternoon, and evening, i.e. 3 times a day, and Curaleish cream in the morning and afternoon, i.e. twice a day. Drug: Experimental topical (Curaleish Topical) Active Comparator: Regimen 2: Curaleish lotion applied three times a day in combination with Curaleish cream applied twice a day for 6 weeks For both treatments, the participant applies Curaleish lotion in the morning, afternoon, and evening, i.e. 3 times a day, and Curaleish cream in the morning and afternoon, i.e. twice a day
Outcomes	Primary outcome measures • post-treatment (healing) by day 180. Healing: initial healing without relapse and/or mucous commitment for the post-treatment evaluation of Day 180. Initial healing is defined as 100% re-epithelialisation of the lesion(s) following Day 90 post-treatment Secondary outcome measures • Adverse effects, measured at 28 days and 42 days depending on the duration of each treatment group. Adverse effects (AEs) will be evaluated according to the seriousness, temporal relationship, relationship with the study medication, and severity. The recording will be carried out through clinical examination, telephone calls, and through the completion of the participant's diary The local AEs that will be evaluated are:

NCT04072874 *(Continued)*

- Erythema
- Burning
- Pain
- Pruritus
- Irritation

The following evaluations will be made:

- Frequency and severity (mild, moderate, severe) of AEs by treatment group
- Status (area of lesions, induration, erythema, etc.) in each measurement. Additionally, before starting treatment and at the end of it, renal (creatinine) and liver function (transaminases) tests will be performed on volunteers

Starting date	January 2020
Contact information	Contact: Ivan D Velez +574 2196501 idvelez@pecet-colombia.org Contact: Liliana Lopez +574 2196506 liliana.lopez@pecet-colombia.org
Notes	Recruitment status: not yet recruiting

NTR2076

Study name	Clinical, parasitological and pharmaco-economical evaluation of a 3 days versus 7 days pentamidine isethionate regimen for cutaneous leishmaniasis in Suriname
Methods	2-arm parallel randomised controlled clinical trial
Participants	Age: NR Gender: NR N° of participants: 220 Inclusion criteria: • Patient is 16 years and older • Histopathology and/or smear of skin biopsy confirms diagnosis of CL • Willingness to attend all study visits (treatment (1, 2 and 3) and follow-up (1, 2 and 3) • Patient can be contacted by phone, either directly or through family living (in the vicinity of Paramaribo) Exclusion criteria: • Patients with CL treated in the past 6 months • Pregnancy or lactation • Potential loss to follow-up (unable to attend 1 of the study visits, either treatment or follow-up) • Patients with a history of liver disease and/or elevated transaminase levels of more than twice the normal value (normal values ≤ 40 U/l) at the time of enrolment • Patients with a history of kidney disease and/or elevated plasma creatinine level of > 40% the upper limit of the normal range (normal values = 70 - 110 umol/l) at the time of enrolment • Patients with a history of pancreas disease and/or elevated amylase levels of > 3 times the normal value (normal value = 32 U/l) at the time of enrolment • Patients with anaemia (haemoglobin level < 7.5 mmol/l), leucocytopenia (leucocytes < 4 x 109/l) and thrombopenia (thrombocytes < 150 x 109/l) at the time of enrolment • Patients with a history of heart disease

NTR2076 *(Continued)*

	• Patients with diabetes • Patients with a known allergy to Pentamidine Isethionate
Interventions	1. A standard course of pentamidine isethionate 4 mg/kg body weight IM at day 1, 4 and 7 (control/usual care arm) 2. A short course regimen of pentamidine isethionate 7 mg/kg body weight IM on day 1 and day 3 (case/intervention arm)
Outcomes	Primary outcomes: To establish if a short course of pentamidine isethionate 7 mg/kg body weight given intramuscular at days 1 and 3 (short course) is as effective as the standard course pentamidine isethionate 4 mg/kg intramuscular at days 1, 4 and 7 (standard course) in people with CL. CL is diagnosed by the detection of leishmaniasis organisms (in a skin smear or a biopsy by light microscope or by the detection of leishmaniasis nucleic acid sequences through NAAT) in a clinically- suspected lesion 1. Clinical relapse 2. Parasitological cure rate 6 and 12 weeks after completion of the treatment Secondary outcomes: 1. To establish if the short course has an equal rate of participant-reported side effects and clinically-determined drug-related toxicity effects as the standard course 2. To establish if the short course is equal to the standard course for health-related quality of life measured by validated self-report questionnaires (Generic QoL measured by the EQ-5D and EQ-VAS questionnaires and disease-specific QoL measured by the SKINDEX questionnaire) 3. To establish if the short course is equal to the standard course for cost effectiveness based on a cost survey questionnaire. The appropriate type of economic evaluation is conditional on the results of the primary objective (relapse rate) and health-related quality of life (HR-QoL) 4. To establish the effect on participant compliance of the short-course regimen versus the standard-course regimen
Starting date	11 January 2009
Contact information	Name: Ricardo Hu Address: Dienst dermatologie, Tourtonnelaan 5 Paramaribo Suriname Telephone: 597-474315 Email: ricarhu@gmail.com
Notes	Recruitment status: recruiting

PER-007-16

Study name	A randomised open-label multicentre study to determine the efficacy and safety of combining thermotherapy and a short course of miltefosine for the treatment of uncomplicated cutaneous leishmaniasis in the New World
Methods	Randomised, open-label, multicentre clinical superiority trial
Participants	Target sample size: 65 Age: 18 - 60; genders: both

PER-007-16 *(Continued)*

	Inclusion criteria:
	• Men or women aged ≥ 18 and ≤ 60 years old (Peru)
	• Patient with a confirmed diagnosis of CL in at least 1 lesion by at least 1 of the following methods: microscopic identification of amastigotes in stained lesion tissue; or demonstration of Leishmania by PCR; or positive culture for promastigotes
	• Patient has a lesion that satisfies the following criteria:
	  • Lesion size ≥ 0.5 cm and < 4 cm (longest diameter)
	  • Not located on the ear, face, close to mucosal membranes, joints or on a location that in the opinion of the PI is difficult to apply TT
	  • Patient with < 4 CL lesions
	  • Duration of lesion < 4 months by patient history
	• Patient able to give written informed consent
	• In the opinion of the investigator, the patient is capable of understanding and complying with the protocol
	
	Exclusion criteria:
	• Woman with a positive urine pregnancy test at screening or who is breast-feeding, lactating, or woman of fertile age who does not agree to take appropriate contraception during treatment period and up to D90
	• History of clinically-significant medical problems/treatment that might interact, either negatively or positively, with topical treatment of leishmaniasis including any immunocompromising condition
	• Within 8 weeks (56 days) of study Day 1, received treatment for leishmaniasis with any medication including antimonials likely, in the opinion of the PI, to modify the course of the Leishmania infection
	• Has diagnosis or suspected diagnosis of mucocutaneous leishmaniasis based on physical exam
	• History of known or suspected hypersensitivity or idiosyncratic reactions to study medication
	• Patient who is not willing to attend the study visits, or is not able to comply with follow-up visits up to 6 months
	• Known history of drug addiction and/or alcohol abuse

Interventions	Intervention 1: Thermotherapy (1 application session, 50 °C for 30 seconds) Intervention 2: Thermotherapy (1 application session, 50 °C for 30 seconds) + miltefosine 2.5 mg/kg/day for 21 days All participants will have a follow-up visit at Days 7, 14, 21, 45, 63, 90 and 180 after the beginning of treatment to assess efficacy, as measured by the number who fulfil the initial and final cure criteria at Day 90 and Day 180, respectively
Outcomes	Primary outcome(s): The proportion of initial clinical cure rate in each regimen (TT & TT + miltefosine) measured at Day 90 Initial cure: Ulcerated lesions: 100% re-epithelialisation* of the lesion(s) by Day 90. Non-ulcerated lesions: flattening and/or no signs of induration of the lesion(s) by Day 90 Secondary outcome(s) The number of participants who fulfil the criteria of initial cure and have no relapse by Day 180 (final cure) Frequency and severity of adverse effects by treatment group The number of participants with lesions 100% re-epithelialised/flattened at each measurement time point

PER-007-16 *(Continued)*

	The number of participants with 100% re-epithelialisation/flattening of lesions by Leishmania species over time
Starting date	04 April 2016
Contact information	Name: Alejandro Llanos Address: Avenida el Derby Nro. 250 Oficina 1204-Santiago de Surco Santiago de Surco Lima Lima Perú Telephone: 994273050 Email: elmer.llanos@upch.pe Affiliation: Peruvian Clinical Research S.A.C
Notes	Recruitment status: active

RBR-5r93wn

Study name	Efficacy and safety of Miltefosin in comparison with Liposomal Anfotericin B for the treatment of Mucosal Leishmaniasis
Methods	Study type: intervention Study design: Open, randomised-controlled, in parallel 3-arms treatment study Phase: 3
Participants	Target sample size: 116 Age: 18 years and older Inclusion criteria: • Both sexes • Age > 18 years • Mucosal impairment • parasitological confirmation of Leishmania infection by 1 or more of the following methods: parasitological examination (direct examination or culture), histopathology, immunohistochemistry or molecular test; consent form signed; availability for the schedule of the study Exclusion criteria: • Women of reproductive age with positive (serum) pregnancy test at the time of screening • Lactating women, or women who can not or will not use contraception during and for up to 3 months after discontinuation of treatment • Carriers of HIV infection or other immunodebilitating condition • Hepatic enzyme levels 3 times above the upper limit of normal, according to reference values • Previous treatment for LM in the 6 months prior to study inclusion • Previous treatment with leishmanicidal drugs indicated for the treatment of other diseases in the last 6 months prior to inclusion • use of medications that interfere with the therapeutic response or that cause interactions with drug of the study • A history of hypersensitivity to the drugs being tested • Renal, cardiac, hepatic or psychiatric disease that at the discretion of the investigator represents a contraindication to the use of some of the treatment alternatives included in this study • Disseminated leishmaniasis concomitant with mucosal involvement

RBR-5r93wn *(Continued)*

	• intravenous drug users or other chemical dependencies • Sjogren-Larson syndrome
Interventions	• Miltefosine group: 46 participants will receive Miltefosine, 2.5 mg/kg/day orally, with a maximum of 150 mg/day, 2 or 3 times daily for 28 days • Amphotericin B liposomal daily infusion: 46 participants will receive liposomal amphotericin B, 3 - 5 mg/kg/day intravenously up to the cumulative total dose of 30 mg/kg. • Group Amphotericin B Liposomal weekly infusion: 24 participants will receive liposomal amphotericin B, dose of 10 mg/kg/day intravenously, 3 administrations with interval of 7 days
Outcomes	Primary outcome(s) • Cure rate with the treatments evaluated by the absolute number and percentage of cured participants compared to treated participants. Cure is defined by absence of inflammation at 180 days Secondary outcome(s) • Late cure rate of the treatments evaluated by the absolute number and percentage of cured participants compared to treated participants. Cure is defined by absence of inflammation at 360 days • Adverse effects rate with the treatment evaluated by the number of participants with adverse effects compared to all treated participants; a clinical and laboratory record previously set will be used
Starting date	01 March 2018
Contact information	Name: Gláucia Fernandes Cota Address: Av Augusto de Lima, 1715 30190-002 Belo Horizonte Brazil Telephone: 553133497712 Email: cota@minas.fiocruz.br Affiliation: Centro de Pesquisa Rene Rachou, Fundação Oswaldo Cruz
Notes	Recruitment status: not yet recruiting

RBR-6mk5n4

Study name	Multicentre study evaluating the efficacy and safety of intralesional administration of Meglumine Antimoniate compared to systemic treatment for cutaneous leishmaniasis
Methods	Phase III clinical trial of treatment randomised-controlled, parallel, 2-arms open trial
Participants	Nº of participants: 250 from 7 recruiting centres Age: 13 - 100 years Gender: NR Inclusion criteria: • Patients who are able to sign the informed consent and willing to participate in the study as participants attending the follow-up visits as scheduled • Patients who present up to a maximum of 3 lesions with or without ulceration • Patients with confirmed parasitic infection by Leishmania by scraping or imprint or histopathological examination or culture or immunohistochemistry or by PCR

RBR-6mk5n4 *(Continued)*

	• Patients who present lesions with a maximum of 5 cm in diameter for a single lesion or up to 3 cm for 2 lesions or up to 2 cm in the case of 3 lesions; Exclusion criteria: • Women of childbearing age who do not use contraceptive methods or do so improperly • Pregnant women; • Children under the age of 13 • Patients with lesions in the cephalic segment • Patients who have had previous treatment with MA • Patients with disseminated or diffuse or recidiva cutis leishmaniasis • Patients with any form of leishmaniasis with mucous membrane involvement • Patients with concomitant use of any medication with recognised toxic interactions with Sb5+ which cannot be substituted over the study period • Patients with comorbid conditions such as heart or kidney or liver diseases
Interventions	Group 1 (intervention): 125 participants with confirmed cutaneous leishmaniasis will be treated with intralesional meglumine antimoniate in a total of 3 infiltrations with a 14-day interval (with a maximum limit of 3 ampoules IL/day) Group 2 (control): 125 participants with confirmed cutaneous leishmaniasis will be treated with 10 - 20 mg/kg/day meglumine antimoniate systemically for 20 days (a maximum limit of 3 ampoules a day)
Outcomes	Primary outcome: The efficacy of intralesional therapy with meglumine antimoniate for localised cutaneous leishmaniasis is expected to be no less than 20% as described with systemic therapy. The outcome will be evaluated within 180 days. Cure will be measured by the clinical evaluation of healed leishmaniasis lesions (complete epithelialisation and total involution of the infiltration interpreted as definitive healing) Secondary outcome: Frequency and severity of adverse effects 20% lower in the group treated with intralesional infiltration. The extent of adverse effects will be assessed by the number of adverse effects reported in the adverse event records by the physician on days 15, 20 and 45 of the start of treatment
Starting date	01 December 2017
Contact information	Name: Liliane Fátima Antonio Olivieira Address: Av Brasil, 4365 - Manguinhos 21040-360 RIO DE JANEIRO Brazil Telephone: 55(21)38659609 Email: lilianedefatima@gmail.com Affiliation: Instituto Nacional de Infectologia Evandro Chagas (INI) -Fiocruz
Notes	Recruitment status: recruiting Financial support: Organização Pan-Americana de Saúde (OPAS) - Brasília, DF, Brazil

AE: adverse effects; CL: cutaneous leishmaniasis; D90: day 90; GM-CSF: Granulocyte macrophage colony-stimulating factor; HIV: human immunodeficiency viruses; IL: intralesional; IM: intramuscular; IWRS: Interactive Web Response System; LM: leishmaniasis; PCR: polymerase chain reaction; PI: principal investigator; Px = participants; MA: meglumine antimoniate; MC: Methoxycoronardine; NR: not reported; TT: thermotherapy.

DATA AND ANALYSES

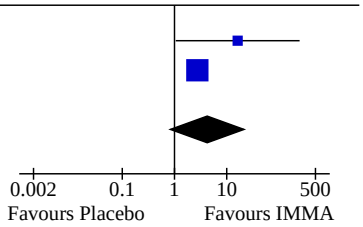
Comparison 1. IM Meglumine Antimoniate (20 mg/kg/d for 20 d) *vs* placebo (3 tablets/4 times a day for 28 d) in *L. braziliensis* and *L. panamensis*; FU: 3 months and 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Complete cure	2	157	Risk Ratio (M-H, Random, 95% CI)	4.23 [0.84, 21.38]
1.2 Adverse effects (FU one year)	1	134	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.17, 1.96]
1.3 Recurrence (FU one year)	1	127	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.17, 19.26]

Analysis 1.1. Comparison 1: IM Meglumine Antimoniate (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

	IMMA		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Saenz 1990	13	19	0	11	24.4%	16.20 [1.06 , 248.50]	
Vélez 1997	52	67	17	60	75.6%	2.74 [1.80 , 4.18]	
Total (95% CI)		**86**		**71**	**100.0%**	**4.23 [0.84 , 21.38]**	
Total events:	65		17				

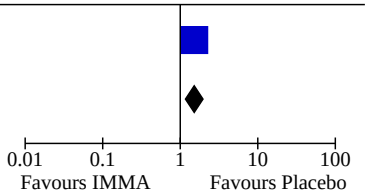
Heterogeneity: Tau² = 0.86; Chi² = 1.86, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 1.74 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: IM Meglumine Antimoniate (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 2: Adverse effects (FU one year)

	IMMA		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Vélez 1997	53	67	35	67	100.0%	1.51 [1.17 , 1.96]	
Total (95% CI)		**67**		**67**	**100.0%**	**1.51 [1.17 , 1.96]**	
Total events:	53		35				

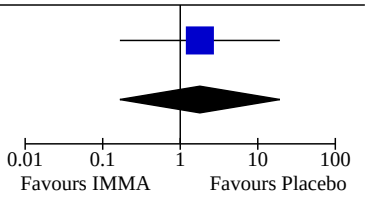
Heterogeneity: Not applicable
Test for overall effect: Z = 3.13 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: IM Meglumine Antimoniate (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 3: Recurrence (FU one year)

Study or Subgroup	IMMA Events	IMMA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Vélez 1997	2	67	1	60	100.0%	1.79 [0.17 , 19.26]
Total (95% CI)		**67**		**60**	**100.0%**	**1.79 [0.17 , 19.26]**
Total events:	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



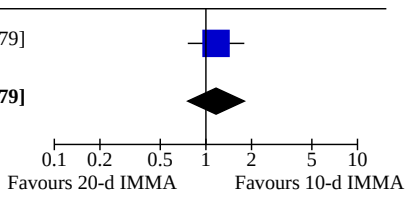
Comparison 2. 10-day IM Meglumine Antimoniate 20 mg/Kg/day *vs* 20-day IM Meglumine Antimoniate in *L. braziliensis* and *L. panamensis*; FU: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Complete cure	1	136	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.76, 1.79]
2.2 Complete cure in children	1	54	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.58, 1.30]
2.2.1 Under 5 years old	1	17	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.05, 4.02]
2.2.2 5 to 15 years old	1	37	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.59, 1.34]
2.3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.3.1 Anorexia	1	136	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.52, 1.94]
2.3.2 Headache	1	136	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.29, 1.01]
2.3.3 Myalgias	1	136	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.55, 2.12]
2.3.4 Malaise	1	136	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.27, 1.18]
2.3.5 Arthralgias	1	136	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.14, 0.94]

Analysis 2.1. Comparison 2: 10-day IM Meglumine Antimoniate 20 mg/Kg/day *vs* 20-day IM Meglumine Antimoniate in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 1: Complete cure

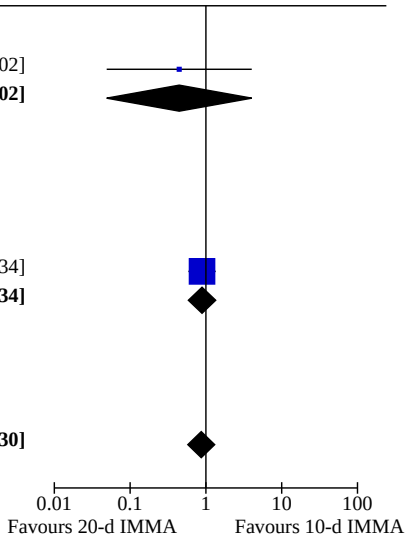
Study or Subgroup	10-d IMMA Events	10-d IMMA Total	20-d IMMA Events	20-d IMMA Total	Weight	Risk Ratio M-H, Random, 95% CI
Palacios 2001	28	68	24	68	100.0%	1.17 [0.76 , 1.79]
Total (95% CI)		**68**		**68**	**100.0%**	**1.17 [0.76 , 1.79]**
Total events:	28		24			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable

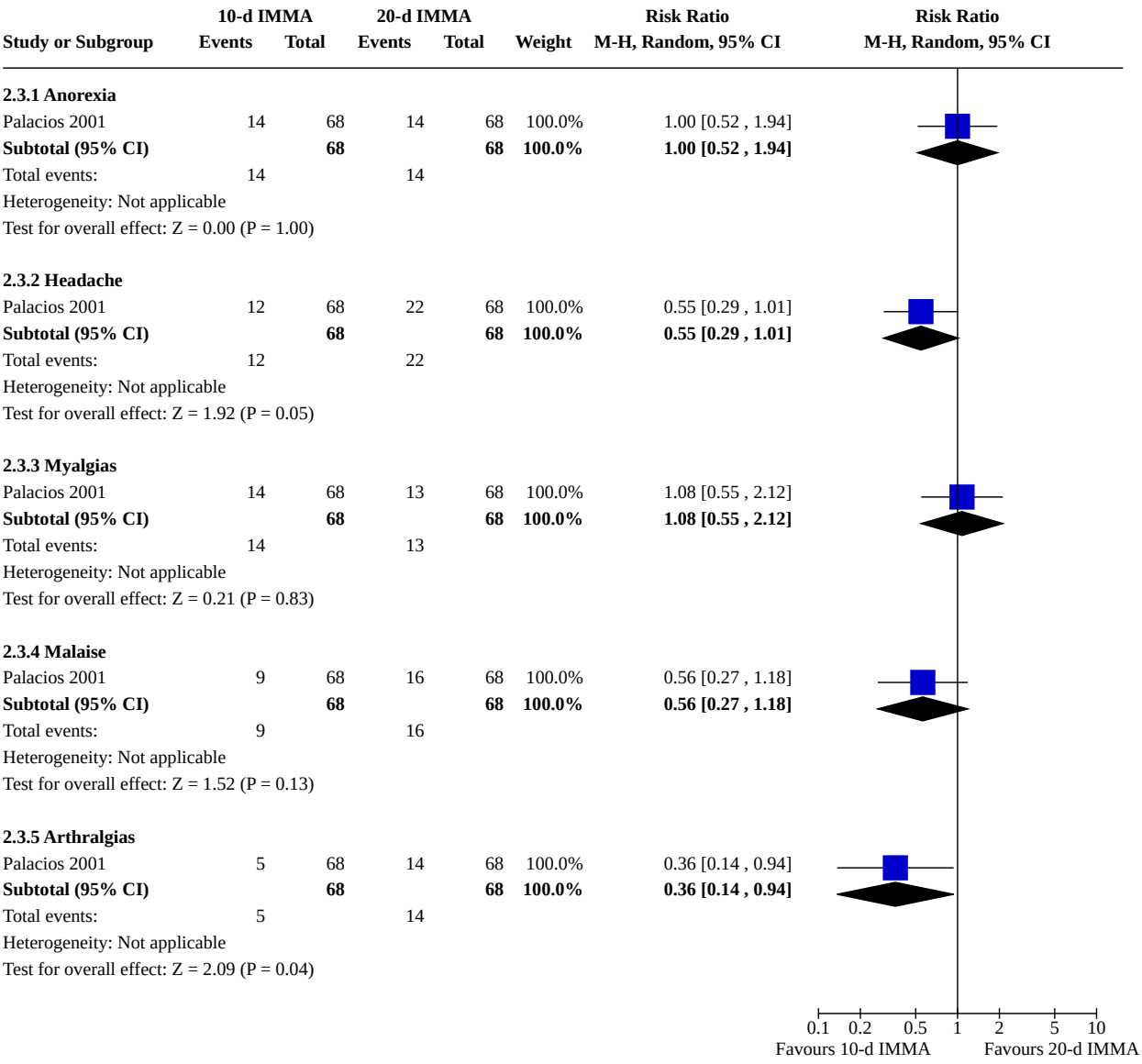


Analysis 2.2. Comparison 2: 10-day IM Meglumine Antimoniate 20 mg/Kg/day *vs* 20-day IM Meglumine Antimoniate in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 2: Complete cure in children

Study or Subgroup	10-d IMMA Events	10-d IMMA Total	20-d IMMA Events	20-d IMMA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Under 5 years old						
Palacios 2001	1	9	2	8	3.4%	0.44 [0.05 , 4.02]
Subtotal (95% CI)		**9**		**8**	**3.4%**	**0.44 [0.05 , 4.02]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
2.2.2 5 to 15 years old						
Palacios 2001	14	21	12	16	96.6%	0.89 [0.59 , 1.34]
Subtotal (95% CI)		**21**		**16**	**96.6%**	**0.89 [0.59 , 1.34]**
Total events:	14		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
Total (95% CI)		**30**		**24**	**100.0%**	**0.87 [0.58 , 1.30]**
Total events:	15		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.54), I² = 0%						



Analysis 2.3. Comparison 2: 10-day IM Meglumine Antimoniate 20 mg/Kg/day *vs* 20-day IM Meglumine Antimoniate in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 3: Adverse effects



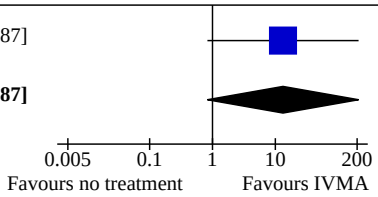
Comparison 3. IV Meglumine Antimoniate 20 mg/kg/d for 15 d *vs* no treatment in *L. panamensis*; FU: 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Complete cure	1	50	Risk Ratio (M-H, Random, 95% CI)	13.24 [0.83, 210.87]
3.2 Recurrence	1	50	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.35, 6.85]

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

Study or Subgroup	IVMA Events	IVMA Total	no treatment Events	no treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
Martínez 1992	12	33	0	17	100.0%	13.24 [0.83 , 210.87]
Total (95% CI)		**33**		**17**	**100.0%**	**13.24 [0.83 , 210.87]**
Total events:	12		0			

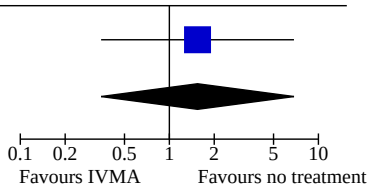
Heterogeneity: Not applicable
Test for overall effect: Z = 1.83 (P = 0.07)
Test for subgroup differences: Not applicable



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

Study or Subgroup	IVMA Events	IVMA Total	No Treatment Events	No Treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
Martínez 1992	6	33	2	17	100.0%	1.55 [0.35 , 6.85]
Total (95% CI)		**33**		**17**	**100.0%**	**1.55 [0.35 , 6.85]**
Total events:	6		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable



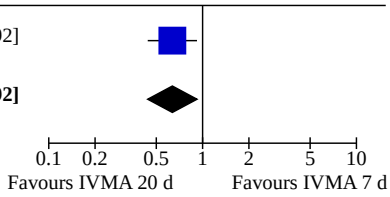
Comparison 4. IV Meglumine Antimoniate for 7 days + placebo topically TD for 10 d *vs* IV Meglumine Antimoniate for 20 d in *L. braziliensis* & *L. panamensis*; FU: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Complete cure	1	61	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.44, 0.92]

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

Study or Subgroup	IV MA 7 d Events	IV MA 7 d Total	IV MA 20 d Events	IV MA 20 d Total	Weight	Risk Ratio M-H, Random, 95% CI
Soto 1998	16	30	26	31	100.0%	0.64 [0.44 , 0.92]
Total (95% CI)		**30**		**31**	**100.0%**	**0.64 [0.44 , 0.92]**
Total events:	16		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.41 (P = 0.02)
Test for subgroup differences: Not applicable



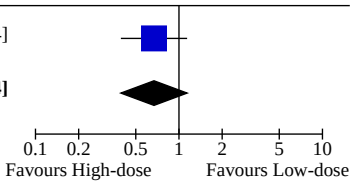
Comparison 5. IV Meglumine Antimoniate 15% (14 mg/kg/d) *vs* IV Meglumine Antimoniate 30% (28 mg/kg/d) ; FU: 2 years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Complete cure (CL plus MCL)	1	43	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.39, 1.14]
5.2 Complete cure CL form	1	26	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.81, 2.78]
5.3 Complete cure MCL form	1	17	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.53, 3.86]

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

Study or Subgroup	Low-dose MA (15%) Events	Total	High-dose MA (30%) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Figueiredo 1999	11	24	13	19	100.0%	0.67 [0.39 , 1.14]
Total (95% CI)		**24**		**19**	**100.0%**	**0.67 [0.39 , 1.14]**
Total events:	11		13			

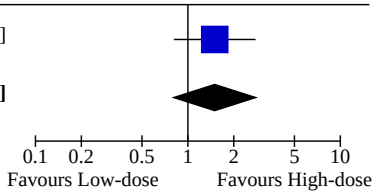
Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable



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

Study or Subgroup	High-dose Events	Total	Low-dose Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Figueiredo 1999	9	12	7	14	100.0%	1.50 [0.81 , 2.78]
Total (95% CI)		**12**		**14**	**100.0%**	**1.50 [0.81 , 2.78]**
Total events:	9		7			

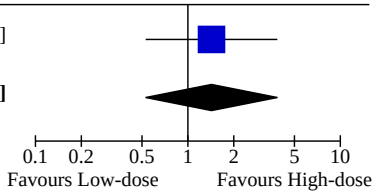
Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable



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

Study or Subgroup	High-dose Events	Total	Low-dose Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Figueiredo 1999	4	7	4	10	100.0%	1.43 [0.53 , 3.86]
Total (95% CI)		**7**		**10**	**100.0%**	**1.43 [0.53 , 3.86]**
Total events:	4		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable



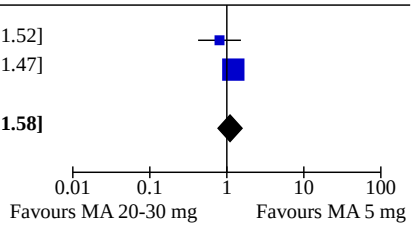
Comparison 6. Meglumine Antimoniate low dosage (5mg/kg/day) (30 to 120 days) up to *vs* high dosage (20-30 mg+/kg/day) (20-30 days) in *L. braziliensis*; FU: 12-45 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Complete cure	2	89	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.77, 1.58]
6.2 Adverse effects	1	23	Risk Ratio (M-H, Random, 95% CI)	3.27 [0.83, 12.95]

Analysis 6.1. Comparison 6: Meglumine Antimoniate low dosage (5mg/kg/day) (30 to 120 days) up to *vs* high dosage (20-30 mg+/kg/day) (20-30 days) in *L. braziliensis*; FU: 12-45 months, Outcome 1: Complete cure

Study or Subgroup	MA 5 mg Events	Total	MA 20-30 mg Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ferreira 2014	5	8	7	9	23.7%	0.80 [0.42 , 1.52]
Saheki 2017	34	36	28	36	76.3%	1.21 [1.00 , 1.47]
Total (95% CI)		**44**		**45**	**100.0%**	**1.10 [0.77 , 1.58]**
Total events:	39		35			

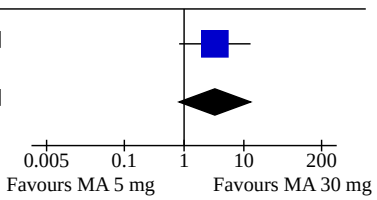
Heterogeneity: Tau² = 0.03; Chi² = 1.59, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 0.53 (P = 0.60)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Meglumine Antimoniate low dosage (5mg/kg/day) (30 to 120 days) up to *vs* high dosage (20-30 mg+/kg/day) (20-30 days) in *L. braziliensis*; FU: 12-45 months, Outcome 2: Adverse effects

Study or Subgroup	MA 5 mg Events	Total	MA 30 mg Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Oliveira-Neto 1997	6	11	2	12	100.0%	3.27 [0.83 , 12.95]
Total (95% CI)		**11**		**12**	**100.0%**	**3.27 [0.83 , 12.95]**
Total events:	6		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.69 (P = 0.09)
Test for subgroup differences: Not applicable



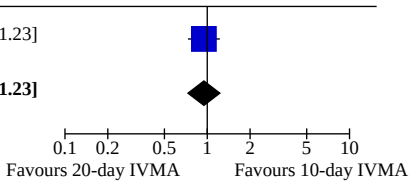
Comparison 7. 10-day IV Meglumine Antimoniate 20mg/kg/day + 10-day placebo *versus* 20-day IV Meglumine Antimoniate in *L. braziliensis* and *L. mexicana*; FU: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Complete cure	1	44	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.73, 1.23]
7.2 Adverse effects: arthralgia	1	44	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.06]

Analysis 7.1. Comparison 7: 10-day IV Meglumine Antimoniate 20mg/kg/day + 10-day placebo *versus* 20-day IV Meglumine Antimoniate in *L. braziliensis* and *L. mexicana*; FU: 1 year, Outcome 1: Complete cure

Study or Subgroup	10-day IVMA + placebo Events	Total	20-day IVMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Arana 1994	18	22	19	22	100.0%	0.95 [0.73 , 1.23]
Total (95% CI)		**22**		**22**	**100.0%**	**0.95 [0.73 , 1.23]**
Total events:	18		19			

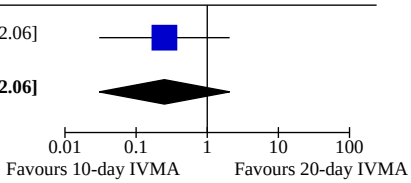
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: 10-day IV Meglumine Antimoniate 20mg/kg/day + 10-day placebo *versus* 20-day IV Meglumine Antimoniate in *L. braziliensis* and *L. mexicana*; FU: 1 year, Outcome 2: Adverse effects: arthralgia

Study or Subgroup	10-day IVMA + placebo Events	Total	20-day IVMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Arana 1994	1	22	4	22	100.0%	0.25 [0.03 , 2.06]
Total (95% CI)		**22**		**22**	**100.0%**	**0.25 [0.03 , 2.06]**
Total events:	1		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable

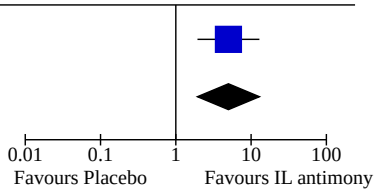


Comparison 8. Intralesional antimony (650 µg/mm^2) *vs* placebo in *L. braziliensis, L. amazonensis, L. guyanensis and L. lainsoni;* FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Complete cure	1	60	Risk Ratio (M-H, Random, 95% CI)	5.00 [1.94, 12.89]

Analysis 8.1. Comparison 8: Intralesional antimony (650 µg/mm^2) *vs* placebo in *L. braziliensis, L. amazonensis, L. guyanensis and L. lainsoni;* FU: 6 months, Outcome 1: Complete cure

Study or Subgroup	IL antimony Events	IL antimony Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Soto 2013	20	30	4	30	100.0%	5.00 [1.94 , 12.89]
Total (95% CI)		**30**		**30**	**100.0%**	**5.00 [1.94 , 12.89]**
Total events:	20		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.33 (P = 0.0009)						
Test for subgroup differences: Not applicable						

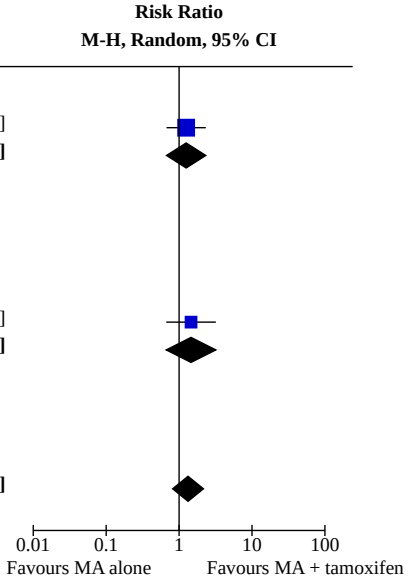


Comparison 9. Meglumine antimoniate 20 mg/kg/day plus oral tamoxifen 40 mg/day *versus* meglumine antimoniate alone in *L. braziliensis*; FU: 3-6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Complete cure at 3-6 months	1	54	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.82, 2.16]
9.1.1 Cure at 3 months	1	27	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.67, 2.32]
9.1.2 Cure at 6 months	1	27	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.67, 3.19]
9.2 Recurrence at 6 months	1	27	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.06, 6.09]

Analysis 9.1. Comparison 9: Meglumine antimoniate 20 mg/kg/day plus oral tamoxifen 40 mg/day *versus* meglumine antimoniate alone in *L. braziliensis*; FU: 3-6 months, Outcome 1: Complete cure at 3-6 months

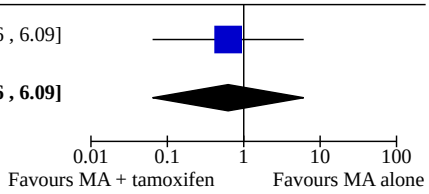
Study or Subgroup	MA + tamoxifen Events	MA + tamoxifen Total	MA alone Events	MA alone Total	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 Cure at 3 months						
Machado 2018	8	12	8	15	61.5%	1.25 [0.67 , 2.32]
Subtotal (95% CI)		**12**		**15**	**61.5%**	**1.25 [0.67 , 2.32]**
Total events:	8		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
9.1.2 Cure at 6 months						
Machado 2018	7	12	6	15	38.5%	1.46 [0.67 , 3.19]
Subtotal (95% CI)		**12**		**15**	**38.5%**	**1.46 [0.67 , 3.19]**
Total events:	7		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.34)						
Total (95% CI)		**24**		**30**	**100.0%**	**1.33 [0.82 , 2.16]**
Total events:	15		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.14 (P = 0.25)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² = 0%						



Analysis 9.2. Comparison 9: Meglumine antimoniate 20 mg/kg/day plus oral tamoxifen 40 mg/day *versus* meglumine antimoniate alone in *L. braziliensis*; FU: 3-6 months, Outcome 2: Recurrence at 6 months

Study or Subgroup	MA + tamoxifen Events	Total	MA alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Machado 2018	1	12	2	15	100.0%	0.63 [0.06 , 6.09]
Total (95% CI)		**12**		**15**	**100.0%**	**0.63 [0.06 , 6.09]**
Total events:	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable

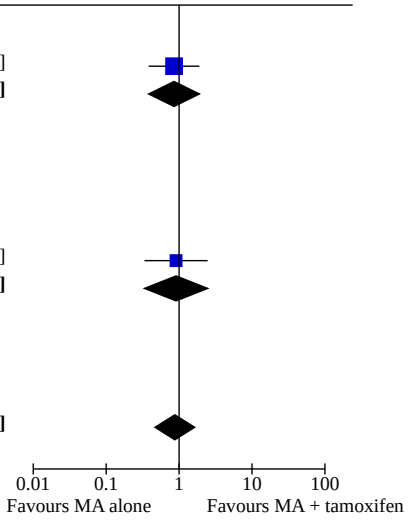


Comparison 10. Meglumine antimoniate 20 mg/kg/day plus topical tamoxifen for 20 days (0.1% citrate) *versus* meglumine antimoniate alone in *L. braziliensis*; FU: 3-6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Complete cure at 3-6 months	1	52	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.47, 1.63]
10.1.1 Cure at 3 months	1	26	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.38, 1.90]
10.1.2 Cure at 6 months	1	26	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.34, 2.47]
10.2 Recurrence at 6 months	1	26	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.07, 6.61]

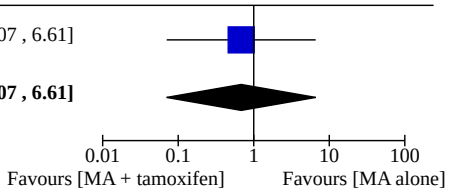
Analysis 10.1. Comparison 10: Meglumine antimoniate 20 mg/kg/day plus topical tamoxifen for 20 days (0.1% citrate) *versus* meglumine antimoniate alone in *L. braziliensis*; FU: 3-6 months, Outcome 1: Complete cure at 3-6 months

Study or Subgroup	MA + tamoxifen Events	MA + tamoxifen Total	MA alone Events	MA alone Total	Weight	Risk Ratio M-H, Random, 95% CI
10.1.1 Cure at 3 months						
Machado 2018	5	11	8	15	60.7%	0.85 [0.38 , 1.90]
Subtotal (95% CI)		**11**		**15**	**60.7%**	**0.85 [0.38 , 1.90]**
Total events:	5		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
10.1.2 Cure at 6 months						
Machado 2018	4	11	6	15	39.3%	0.91 [0.34 , 2.47]
Subtotal (95% CI)		**11**		**15**	**39.3%**	**0.91 [0.34 , 2.47]**
Total events:	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						
Total (95% CI)		**22**		**30**	**100.0%**	**0.87 [0.47 , 1.63]**
Total events:	9		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						



Analysis 10.2. Comparison 10: Meglumine antimoniate 20 mg/kg/day plus topical tamoxifen for 20 days (0.1% citrate) *versus* meglumine antimoniate alone in *L. braziliensis*; FU: 3-6 months, Outcome 2: Recurrence at 6 months

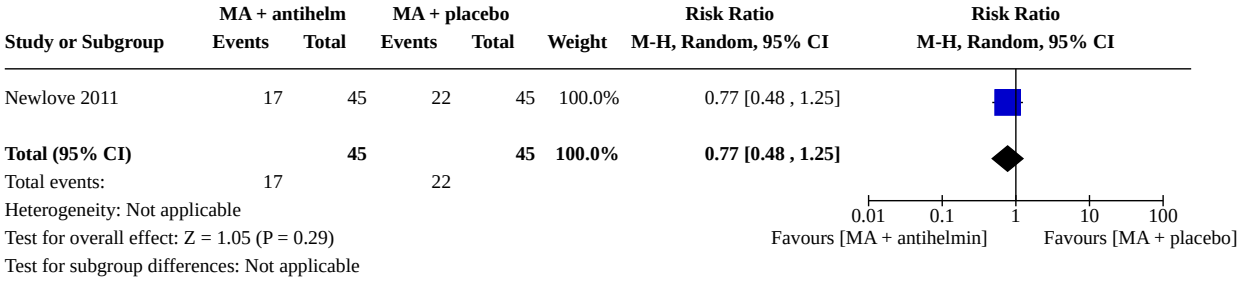
Study or Subgroup	MA + tamoxifen Events	MA + tamoxifen Total	MA alone Events	MA alone Total	Weight	Risk Ratio M-H, Random, 95% CI
Machado 2018	1	11	2	15	100.0%	0.68 [0.07 , 6.61]
Total (95% CI)		**11**		**15**	**100.0%**	**0.68 [0.07 , 6.61]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Not applicable						



Comparison 11. IV meglumine antimoniate (IVMA) plus antihelminthic treatment versus IVMA plus placebo in *L.braziliensis*; FU: 90 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Complete cure	1	90	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.48, 1.25]

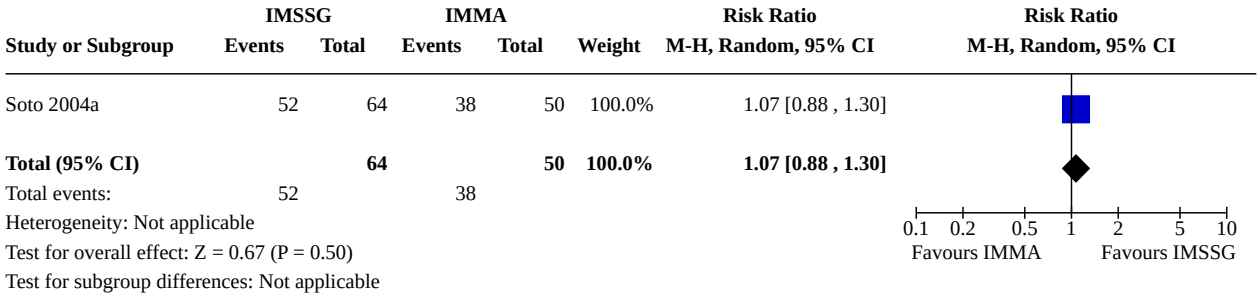
Analysis 11.1. Comparison 11: IV meglumine antimoniate (IVMA) plus antihelminthic treatment versus IVMA plus placebo in *L.braziliensis*; FU: 90 days, Outcome 1: Complete cure



Comparison 12. IM Sodium Stibogluconate 20 mg/kg/d for 20d *vs* IM Meglumine Antimoniate (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
12.1 Complete cure	1	114	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.88, 1.30]
12.2 Adverse effect Overall	1	59	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.78, 1.91]
12.3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.3.1 Myalgias	1	114	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.50, 1.22]
12.3.2 Headache	1	114	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.37, 1.26]
12.3.3 Metallic taste	1	114	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.27, 0.92]
12.3.4 Abdominal pain	1	114	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.32, 1.94]
12.4 Recurrence	1	119	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.45, 2.05]
12.5 Microbiological or histopathological cure of skin lesions	1	59	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.85, 1.19]

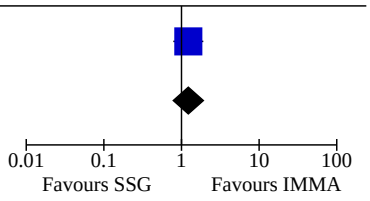
Analysis 12.1. Comparison 12: IM Sodium Stibogluconate 20 mg/kg/d for 20d *vs* IM Meglumine Antimoniate (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months, Outcome 1: Complete cure



Analysis 12.2. Comparison 12: IM Sodium Stibogluconate 20 mg/kg/d for 20d *vs* IM Meglumine Antimoniate (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months, Outcome 2: Adverse effect Overall

Study or Subgroup	IMSSG Events	IMSSG Total	IMMA Events	IMMA Total	Weight	Risk Ratio M-H, Random, 95% CI
Saenz 1987	19	30	15	29	100.0%	1.22 [0.78 , 1.91]
Total (95% CI)		**30**		**29**	**100.0%**	**1.22 [0.78 , 1.91]**
Total events:	19		15			

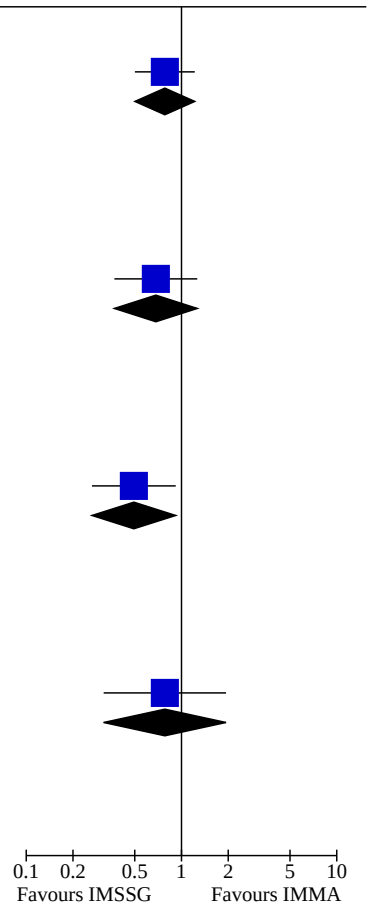
Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable



Analysis 12.3. Comparison 12: IM Sodium Stibogluconate 20 mg/kg/d for 20d *vs* IM Meglumine Antimoniate (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months, Outcome 3: Adverse effects

Study or Subgroup	IMSSG Events	IMSSG Total	IMMA Events	IMMA Total	Weight	Risk Ratio M-H, Random, 95% CI
12.3.1 Myalgias						
Soto 2004a	23	64	23	50	100.0%	0.78 [0.50 , 1.22]
Subtotal (95% CI)		**64**		**50**	**100.0%**	**0.78 [0.50 , 1.22]**
Total events:	23		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.28)						
12.3.2 Headache						
Soto 2004a	14	64	16	50	100.0%	0.68 [0.37 , 1.26]
Subtotal (95% CI)		**64**		**50**	**100.0%**	**0.68 [0.37 , 1.26]**
Total events:	14		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
12.3.3 Metallic taste						
Soto 2004a	12	64	19	50	100.0%	0.49 [0.27 , 0.92]
Subtotal (95% CI)		**64**		**50**	**100.0%**	**0.49 [0.27 , 0.92]**
Total events:	12		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.23 (P = 0.03)						
12.3.4 Abdominal pain						
Soto 2004a	8	64	8	50	100.0%	0.78 [0.32 , 1.94]
Subtotal (95% CI)		**64**		**50**	**100.0%**	**0.78 [0.32 , 1.94]**
Total events:	8		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.59)						

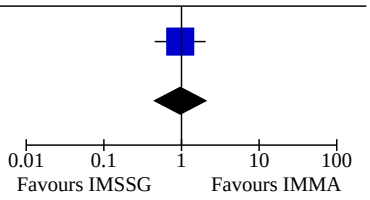
Test for subgroup differences: $Chi^2 = 1.49$, df = 3 (P = 0.68), $I^2 = 0\%$



Analysis 12.4. Comparison 12: IM Sodium Stibogluconate 20 mg/kg/d for 20d *vs* IM Meglumine Antimoniate (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months, Outcome 4: Recurrence

Study or Subgroup	IMSSG Events	IMSSG Total	IMMA Events	IMMA Total	Weight	Risk Ratio M-H, Random, 95% CI
Saenz 1987	20	89	7	30	100.0%	0.96 [0.45 , 2.05]
Total (95% CI)		**89**		**30**	**100.0%**	**0.96 [0.45 , 2.05]**
Total events:	20		7			

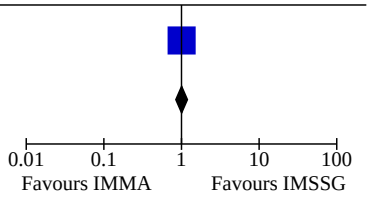
Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable



Analysis 12.5. Comparison 12: IM Sodium Stibogluconate 20 mg/kg/d for 20d *vs* IM Meglumine Antimoniate (20 mg/kg/d for 20d) in *L. panamensis*; FU: 6 months, Outcome 5: Microbiological or histopathological cure of skin lesions

Study or Subgroup	IMSSG Events	IMSSG Total	IMMA Events	IMMA Total	Weight	Risk Ratio M-H, Random, 95% CI
Saenz 1987	27	30	26	29	100.0%	1.00 [0.85 , 1.19]
Total (95% CI)		**30**		**29**	**100.0%**	**1.00 [0.85 , 1.19]**
Total events:	27		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable



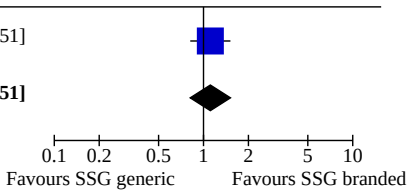
Comparison 13. IM Sodium Stibogluconate (branded) *vs* IM Sodium Stibogluconate (generic). Dose: 20 mg/kg/d for 20 d in *L.panamensis*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Complete cure	1	64	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.82, 1.51]
13.2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.2.1 Myalgias	1	64	Risk Ratio (M-H, Random, 95% CI)	1.93 [1.04, 3.58]
13.2.2 Headache	1	64	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.65, 4.25]
13.2.3 Metallic taste	1	64	Risk Ratio (M-H, Random, 95% CI)	2.14 [0.79, 5.82]
13.2.4 Abdominal pain	1	64	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.85, 10.63]

Analysis 13.1. Comparison 13: IM Sodium Stibogluconate (branded) *vs* IM Sodium Stibogluconate (generic). Dose: 20 mg/kg/d for 20 d in *L.panamensis*; FU: 6 months, Outcome 1: Complete cure

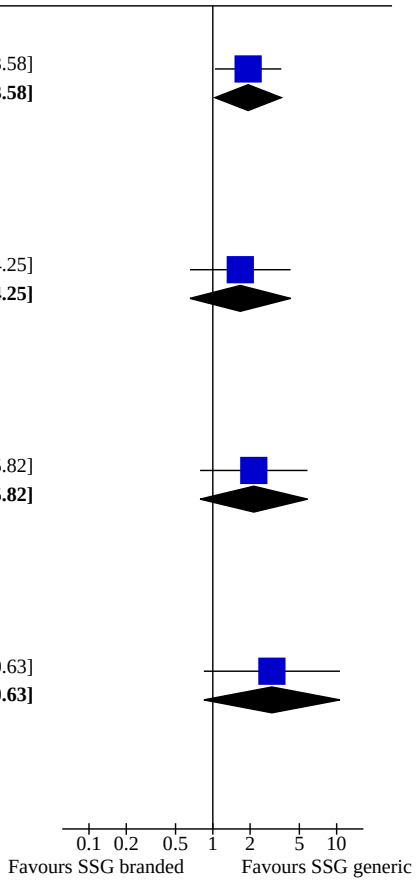
Study or Subgroup	SSG branded Events	Total	SSG generic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Soto 2004a	40	48	12	16	100.0%	1.11 [0.82 , 1.51]
Total (95% CI)		**48**		**16**	**100.0%**	**1.11 [0.82 , 1.51]**
Total events:	40		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 13.2. Comparison 13: IM Sodium Stibogluconate (branded) *vs* IM Sodium Stibogluconate (generic). Dose: 20 mg/kg/d for 20 d in *L.panamensis*; FU: 6 months, Outcome 2: Adverse effects

Study or Subgroup	SSG branded Events	Total	SSG generic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
13.2.1 Myalgias						
Soto 2004a	9	16	14	48	100.0%	1.93 [1.04 , 3.58]
Subtotal (95% CI)		**16**		**48**	**100.0%**	**1.93 [1.04 , 3.58]**
Total events:	9		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.09 (P = 0.04)						
13.2.2 Headache						
Soto 2004a	5	16	9	48	100.0%	1.67 [0.65 , 4.25]
Subtotal (95% CI)		**16**		**48**	**100.0%**	**1.67 [0.65 , 4.25]**
Total events:	5		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
13.2.3 Metallic taste						
Soto 2004a	5	16	7	48	100.0%	2.14 [0.79 , 5.82]
Subtotal (95% CI)		**16**		**48**	**100.0%**	**2.14 [0.79 , 5.82]**
Total events:	5		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
13.2.4 Abdominal pain						
Soto 2004a	4	16	4	48	100.0%	3.00 [0.85 , 10.63]
Subtotal (95% CI)		**16**		**48**	**100.0%**	**3.00 [0.85 , 10.63]**
Total events:	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						

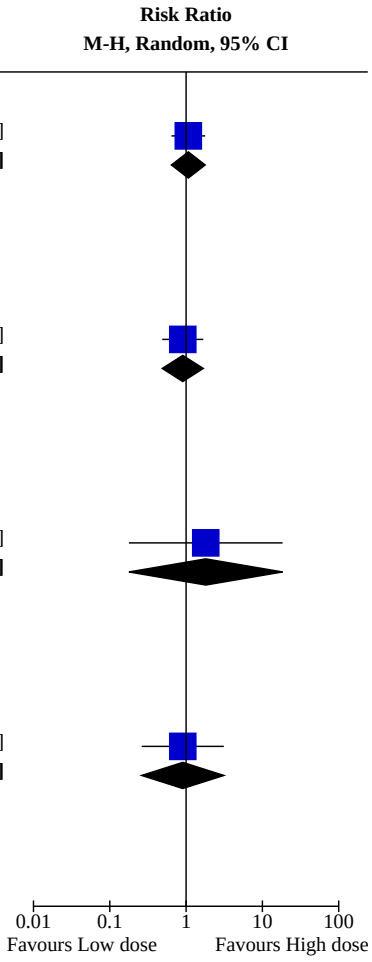


Comparison 14. Low dose of IV sodium stibogluconate 20 days versus high doses in *L.panamensis* and *L. chagasi; FU: 1 year*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1.1 Muscle-joint stiffness	1	40	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.64, 1.78]
14.1.2 Increses in liver enzymes	1	40	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.49, 1.68]
14.1.3 Mild leukopenia	1	40	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.18, 18.39]
14.1.4 Electrographic abnormalities	1	40	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.26, 3.12]

Analysis 14.1. Comparison 14: Low dose of IV sodium stibogluconate 20 days versus high doses in *L.panamensis* and *L. chagasi; FU: 1 year*, Outcome 1: Adverse effects

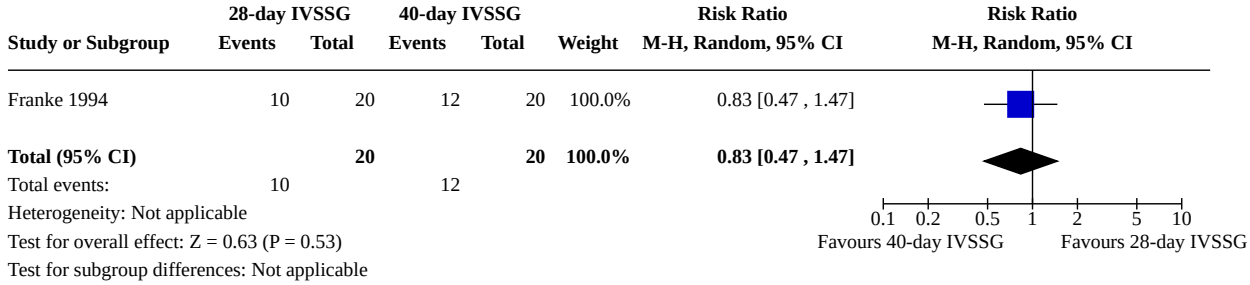
Study or Subgroup	Low dose Events	Low dose Total	High doses Events	High doses Total	Weight	Risk Ratio M-H, Random, 95% CI
14.1.1 Muscle-joint stiffness						
Ballou 1987	13	21	11	19	100.0%	1.07 [0.64 , 1.78]
Subtotal (95% CI)		**21**		**19**	**100.0%**	**1.07 [0.64 , 1.78]**
Total events:	13		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
14.1.2 Increses in liver enzymes						
Ballou 1987	10	21	10	19	100.0%	0.90 [0.49 , 1.68]
Subtotal (95% CI)		**21**		**19**	**100.0%**	**0.90 [0.49 , 1.68]**
Total events:	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
14.1.3 Mild leukopenia						
Ballou 1987	2	21	1	19	100.0%	1.81 [0.18 , 18.39]
Subtotal (95% CI)		**21**		**19**	**100.0%**	**1.81 [0.18 , 18.39]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
14.1.4 Electrographic abnormalities						
Ballou 1987	4	21	4	19	100.0%	0.90 [0.26 , 3.12]
Subtotal (95% CI)		**21**		**19**	**100.0%**	**0.90 [0.26 , 3.12]**
Total events:	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						



Comparison 15. IV Sodium Stibogluconate 20mg/kg for 28 days *vs* IV Sodium Stibogluconate for 40 days in *L. braziliensis*; FU: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Complete cure	1	40	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.47, 1.47]

Analysis 15.1. Comparison 15: IV Sodium Stibogluconate 20mg/kg for 28 days *vs* IV Sodium Stibogluconate for 40 days in *L. braziliensis*; FU: 1 year, Outcome 1: Complete cure



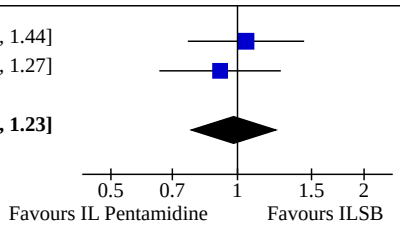
Comparison 16. IL Sodium Stibogluconate (650 µg; Sb 8 µL/mm^2) *vs* IL pentamidine (240 µg; 8 µL/mm^2) in *L. braziliensis and L. braziliensis/amazonensis/lainsoni/guyanensis*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Complete cure	2	120	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.78, 1.23]
16.2 Adverse effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.2.1 Myalgia	2	120	Risk Ratio (M-H, Random, 95% CI)	3.93 [0.45, 34.54]
16.2.2 Local irritation	2	120	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.55, 2.58]
16.2.3 Local pain	2	120	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.79, 3.83]
16.3 Recurrence	1	60	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.25, 99.95]

Analysis 16.1. Comparison 16: IL Sodium Stibogluconate (650 µg; Sb 8 µL/mm²) *vs* IL pentamidine (240 µg; 8 µL/mm²) in *L. braziliensis and L. braziliensis/amazonensis/lainsoni/guyanensis*; FU: 6 months, Outcome 1: Complete cure

Study or Subgroup	ILSB Events	Total	ILPentamidine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Soto 2016a	22	30	21	30	52.2%	1.05 [0.76 , 1.44]
Soto 2016b	20	30	22	30	47.8%	0.91 [0.65 , 1.27]
Total (95% CI)		**60**		**60**	**100.0%**	**0.98 [0.78 , 1.23]**
Total events:	42		43			

Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable



Analysis 16.2. Comparison 16: IL Sodium Stibogluconate (650 µg; Sb 8 µL/mm²) *vs* IL pentamidine (240 µg; 8 µL/mm²) in *L. braziliensis and L. braziliensis/amazonensis/lainsoni/guyanensis*; FU: 6 months, Outcome 2: Adverse effects

Study or Subgroup	ILSB Events	Total	ILPentamidine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
16.2.1 Myalgia						
Soto 2016a	1	30	0	30	47.3%	3.00 [0.13 , 70.83]
Soto 2016b	2	30	0	30	52.7%	5.00 [0.25 , 99.95]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**3.93 [0.45 , 34.54]**
Total events:	3		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.23 (P = 0.22)

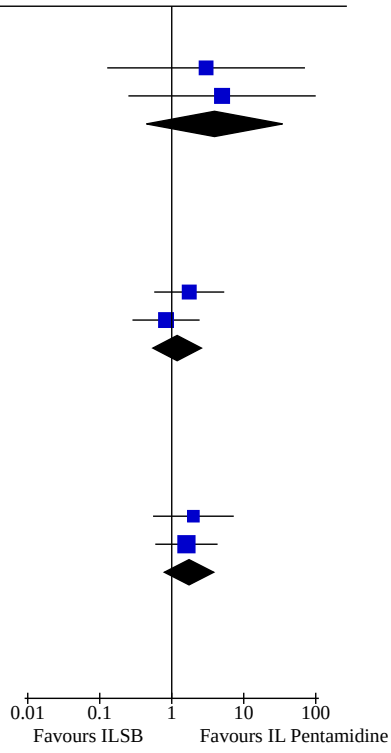
16.2.2 Local irritation						
Soto 2016a	7	30	4	30	47.9%	1.75 [0.57 , 5.36]
Soto 2016b	5	30	6	30	52.1%	0.83 [0.28 , 2.44]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**1.19 [0.55 , 2.58]**
Total events:	12		10			

Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)

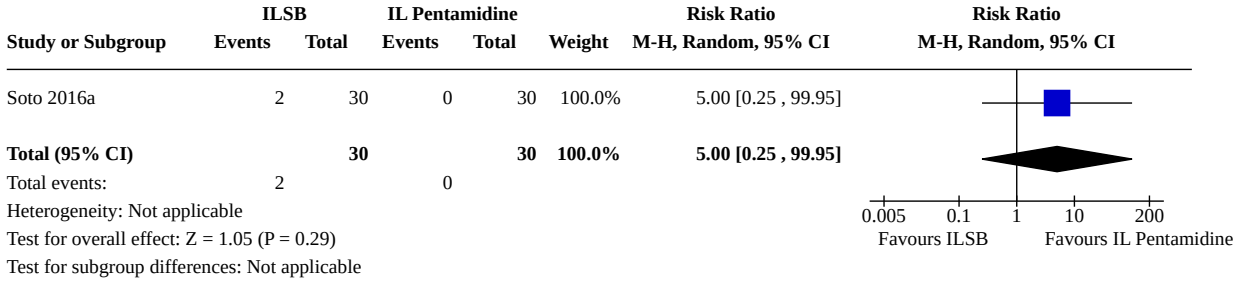
16.2.3 Local pain						
Soto 2016a	6	30	3	30	37.3%	2.00 [0.55 , 7.27]
Soto 2016b	8	30	5	30	62.7%	1.60 [0.59 , 4.33]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**1.74 [0.79 , 3.83]**
Total events:	14		8			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.38 (P = 0.17)

Test for subgroup differences: Chi² = 1.23, df = 2 (P = 0.54), I² = 0%



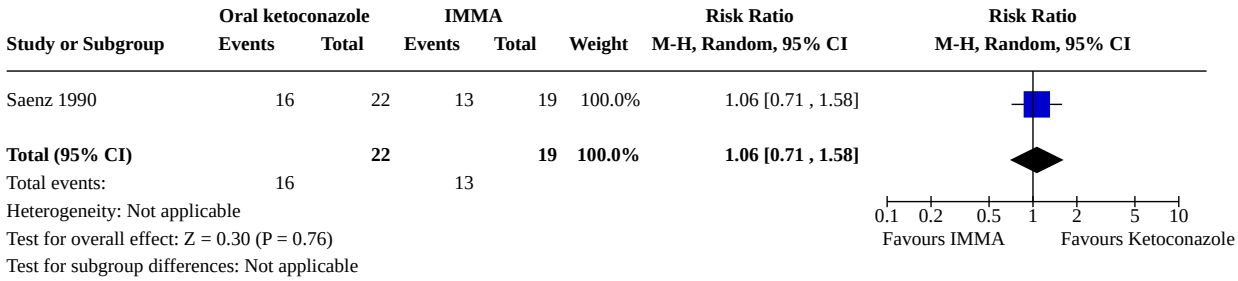
Analysis 16.3. Comparison 16: IL Sodium Stibogluconate (650 µg; Sb 8 µL/mm²) *vs* IL pentamidine (240 µg; 8 µL/mm²) in *L. braziliensis and L. braziliensis/amazonensis/lainsoni/guyanensis*; FU: 6 months, Outcome 3: Recurrence



Comparison 17. Oral ketoconazole 200 mg for 28 days *vs* IM Meglumine Antimoniate 20 mg/kg for 20 days in *L. panamensis* and *L. mexicana*; FU: 3 months

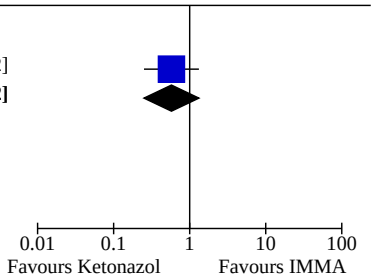
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Complete cure	1	41	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.71, 1.58]
17.2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.2.1 Laboratory abnormalities	1	41	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.25, 1.32]
17.3 Speed to healing (% of complete re-epithelization of lesions at 1 month in cured patients)	1	29	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.54, 2.03]
17.4 Miocrobiological cure of skin lesions (% in cured patients)	1	29	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.46, 1.43]

Analysis 17.1. Comparison 17: Oral ketoconazole 200 mg for 28 days *vs* IM Meglumine Antimoniate 20 mg/kg for 20 days in *L. panamensis* and *L. mexicana*; FU: 3 months, Outcome 1: Complete cure



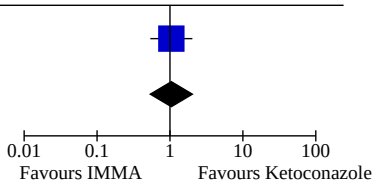
Analysis 17.2. Comparison 17: Oral ketoconazole 200 mg for 28 days *vs* IM Meglumine Antimoniate 20 mg/kg for 20 days in *L. panamensis* and *L. mexicana*; FU: 3 months, Outcome 2: Adverse effects

Study or Subgroup	Oral ketoconazole Events	Total	IMMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
17.2.1 Laboratory abnormalities						
Saenz 1990	6	22	9	19	100.0%	0.58 [0.25 , 1.32]
Subtotal (95% CI)		**22**		**19**	**100.0%**	**0.58 [0.25 , 1.32]**
Total events:	6		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
Test for subgroup differences: Not applicable						



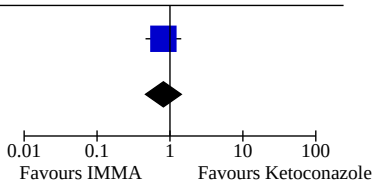
Analysis 17.3. Comparison 17: Oral ketoconazole 200 mg for 28 days *vs* IM Meglumine Antimoniate 20 mg/kg for 20 days in *L. panamensis* and *L. mexicana*; FU: 3 months, Outcome 3: Speed to healing (% of complete re-epithelization of lesions at 1 month in cured patients)

Study or Subgroup	Oral ketoconazole Events	Total	IMMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Saenz 1990	9	16	7	13	100.0%	1.04 [0.54 , 2.03]
Total (95% CI)		**16**		**13**	**100.0%**	**1.04 [0.54 , 2.03]**
Total events:	9		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
Test for subgroup differences: Not applicable						



Analysis 17.4. Comparison 17: Oral ketoconazole 200 mg for 28 days *vs* IM Meglumine Antimoniate 20 mg/kg for 20 days in *L. panamensis* and *L. mexicana*; FU: 3 months, Outcome 4: Miocrobiological cure of skin lesions (% in cured patients)

Study or Subgroup	Oral ketoconazole Events	Total	IMMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Saenz 1990	9	16	9	13	100.0%	0.81 [0.46 , 1.43]
Total (95% CI)		**16**		**13**	**100.0%**	**0.81 [0.46 , 1.43]**
Total events:	9		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
Test for subgroup differences: Not applicable						



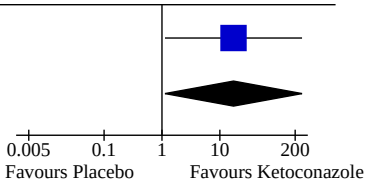
Comparison 18. Oral ketoconazole 200 mg *vs* oral placebo for 28 days in *L. panamensis* and *L. mexicana*; FU: 3 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Complete cure	1	33	Risk Ratio (M-H, Random, 95% CI)	17.22 [1.13, 262.82]

Analysis 18.1. Comparison 18: Oral ketoconazole 200 mg *vs* oral placebo for 28 days in *L. panamensis* and *L. mexicana*; FU: 3 months, Outcome 1: Complete cure

Study or Subgroup	Oral ketoconazole Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Saenz 1990	16	22	0	11	100.0%	17.22 [1.13 , 262.82]
Total (95% CI)		**22**		**11**	**100.0%**	**17.22 [1.13 , 262.82]**
Total events:	16		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.05 (P = 0.04)
Test for subgroup differences: Not applicable



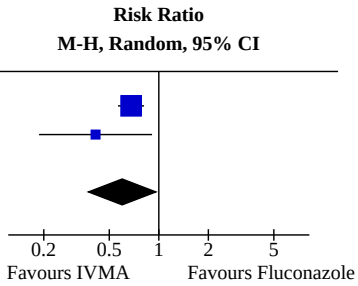
Comparison 19. 300-450 mg oral Fluconazole *vs* 20mg/kg/d IV Meglumine Antimoniate 20 mg/kg in *L. braziliensis*; FU: 3-6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Complete cure	2	173	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.37, 0.96]
19.2 Adverse effects	1	53	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.52, 2.20]
19.3 Needed rescue therapy	1	53	Risk Ratio (M-H, Random, 95% CI)	2.20 [1.09, 4.46]
19.4 Speed to healing (days)	1	53	Mean Difference (IV, Random, 95% CI)	40.40 [11.27, 69.53]

Analysis 19.1. Comparison 19: 300-450 mg oral Fluconazole *vs* 20mg/kg/d IV Meglumine Antimoniate 20 mg/kg in *L. braziliensis*; FU: 3-6 months, Outcome 1: Complete cure

Study or Subgroup	Fluconazole Events	Total	IVMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Alves Noroes 2015	40	60	59	60	75.0%	0.68 [0.57 , 0.81]
Prates 2017	6	27	14	26	25.0%	0.41 [0.19 , 0.91]
Total (95% CI)		**87**		**86**	**100.0%**	**0.60 [0.37 , 0.96]**
Total events:	46		73			

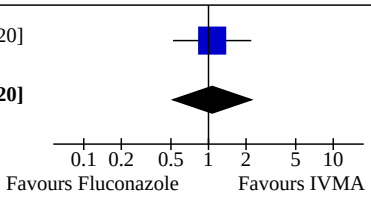
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 1.80$, df = 1 (P = 0.18); $I^2 = 44\%$
Test for overall effect: Z = 2.13 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 19.2. Comparison 19: 300-450 mg oral Fluconazole *vs* 20mg/kg/d IV Meglumine Antimoniate 20 mg/kg in *L. braziliensis*; FU: 3-6 months, Outcome 2: Adverse effects

Study or Subgroup	Fluconazole Events	Fluconazole Total	IVMA Events	IVMA Total	Weight	Risk Ratio M-H, Random, 95% CI
Prates 2017	10	27	9	26	100.0%	1.07 [0.52 , 2.20]
Total (95% CI)		**27**		**26**	**100.0%**	**1.07 [0.52 , 2.20]**
Total events:	10		9			

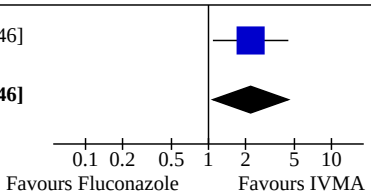
Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.85)
Test for subgroup differences: Not applicable



Analysis 19.3. Comparison 19: 300-450 mg oral Fluconazole *vs* 20mg/kg/d IV Meglumine Antimoniate 20 mg/kg in *L. braziliensis*; FU: 3-6 months, Outcome 3: Needed rescue therapy

Study or Subgroup	Fluconazole Events	Fluconazole Total	IVMA Events	IVMA Total	Weight	Risk Ratio M-H, Random, 95% CI
Prates 2017	16	27	7	26	100.0%	2.20 [1.09 , 4.46]
Total (95% CI)		**27**		**26**	**100.0%**	**2.20 [1.09 , 4.46]**
Total events:	16		7			

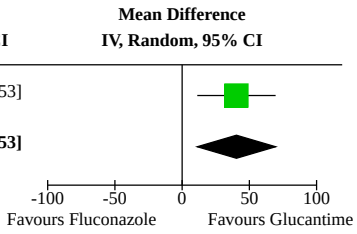
Heterogeneity: Not applicable
Test for overall effect: Z = 2.19 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 19.4. Comparison 19: 300-450 mg oral Fluconazole *vs* 20mg/kg/d IV Meglumine Antimoniate 20 mg/kg in *L. braziliensis*; FU: 3-6 months, Outcome 4: Speed to healing (days)

Study or Subgroup	Fluconazole Mean	Fluconazole SD	Fluconazole Total	IVMA Mean	IVMA SD	IVMA Total	Weight	Mean Difference IV, Random, 95% CI
Prates 2017	157.6	55.7	27	117.2	52.5	26	100.0%	40.40 [11.27 , 69.53]
Total (95% CI)			**27**			**26**	**100.0%**	**40.40 [11.27 , 69.53]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.72 (P = 0.007)
Test for subgroup differences: Not applicable



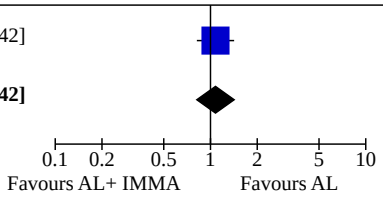
Comparison 20. Oral Allopurinol 20 mg/kg/d (4 doses) for 15d *vs* Allopurinol + IM Meglumine Antimoniate 20 mg/kg (same regimen) in *L. panamensis*; FU: 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 Complete cure	1	60	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.82, 1.42]
20.2 Recurrence	1	60	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.07, 7.30]

Analysis 20.1. Comparison 20: Oral Allopurinol 20 mg/kg/d (4 doses) for 15d *vs* Allopurinol + IM Meglumine Antimoniate 20 mg/kg (same regimen) in *L. panamensis*; FU: 12 months, Outcome 1: Complete cure

Study or Subgroup	AL Events	AL Total	AL+IMMA Events	AL+IMMA Total	Weight	Risk Ratio M-H, Random, 95% CI
Martínez 1992	20	25	26	35	100.0%	1.08 [0.82 , 1.42]
Total (95% CI)		**25**		**35**	**100.0%**	**1.08 [0.82 , 1.42]**
Total events:	20		26			

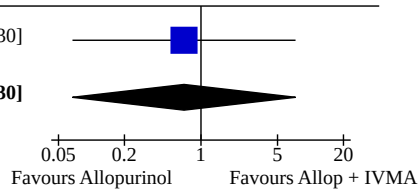
Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)
Test for subgroup differences: Not applicable



Analysis 20.2. Comparison 20: Oral Allopurinol 20 mg/kg/d (4 doses) for 15d *vs* Allopurinol + IM Meglumine Antimoniate 20 mg/kg (same regimen) in *L. panamensis*; FU: 12 months, Outcome 2: Recurrence

Study or Subgroup	Allopurinol Events	Allopurinol Total	Allop + IVMA Events	Allop + IVMA Total	Weight	Risk Ratio M-H, Random, 95% CI
Martínez 1992	1	25	2	35	100.0%	0.70 [0.07 , 7.30]
Total (95% CI)		**25**		**35**	**100.0%**	**0.70 [0.07 , 7.30]**
Total events:	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Not applicable



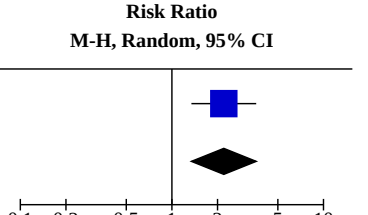
Comparison 21. Oral Allopurinol 20 mg/kg/d (4 doses) x 15d *vs.* IV Meglumine Antimoniate (same regimen) in *L. panamensis*; FU: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 Complete cure	1	58	Risk Ratio (M-H, Random, 95% CI)	2.20 [1.34, 3.60]
21.2 Recurrence	1	58	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.06, 6.88]

Analysis 21.1. Comparison 21: Oral Allopurinol 20 mg/kg/d (4 doses) x 15d *vs.* IV Meglumine Antimoniate (same regimen) in *L. panamensis*; FU: 1 year, Outcome 1: Complete cure

Study or Subgroup	Allopurinol Events	Allopurinol Total	IVMA Events	IVMA Total	Weight	Risk Ratio M-H, Random, 95% CI
Martínez 1992	20	25	12	33	100.0%	2.20 [1.34 , 3.60]
Total (95% CI)		**25**		**33**	**100.0%**	**2.20 [1.34 , 3.60]**
Total events:	20		12			

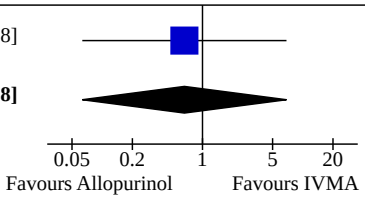
Heterogeneity: Not applicable
Test for overall effect: Z = 3.14 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 21.2. Comparison 21: Oral Allopurinol 20 mg/kg/d (4 doses) x 15d *vs.* IV Meglumine Antimoniate (same regimen) in *L. panamensis*; FU: 1 year, Outcome 2: Recurrence

Study or Subgroup	Allopurinol Events	Total	IVMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Martínez 1992	1	25	2	33	100.0%	0.66 [0.06 , 6.88]
Total (95% CI)		**25**		**33**	**100.0%**	**0.66 [0.06 , 6.88]**
Total events:	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable



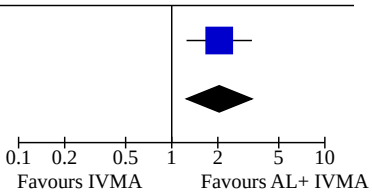
Comparison 22. Oral Allopurinol 20 mg/kg/d + IV Meglumine Antimoniate (20 mg/kg/d (4 doses) for 15d) *vs* IV Meglumine Antimoniate (same regimen) in *L. panamensis*; FU: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 Complete cure	1	68	Risk Ratio (M-H, Random, 95% CI)	2.04 [1.25, 3.34]
22.2 Recurrence	1	68	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.14, 6.31]

Analysis 22.1. Comparison 22: Oral Allopurinol 20 mg/kg/d + IV Meglumine Antimoniate (20 mg/kg/d (4 doses) for 15d) *vs* IV Meglumine Antimoniate (same regimen) in *L. panamensis*; FU: 1 year, Outcome 1: Complete cure

Study or Subgroup	AL+ IVMA Events	Total	IVMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Martínez 1992	26	35	12	33	100.0%	2.04 [1.25 , 3.34]
Total (95% CI)		**35**		**33**	**100.0%**	**2.04 [1.25 , 3.34]**
Total events:	26		12			

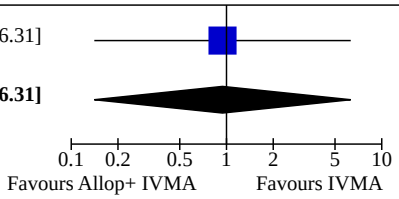
Heterogeneity: Not applicable
Test for overall effect: Z = 2.85 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 22.2. Comparison 22: Oral Allopurinol 20 mg/kg/d + IV Meglumine Antimoniate (20 mg/kg/d (4 doses) for 15d) *vs* IV Meglumine Antimoniate (same regimen) in *L. panamensis*; FU: 1 year, Outcome 2: Recurrence

Study or Subgroup	Allop + IVMA Events	Total	IVMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Martínez 1992	2	35	2	33	100.0%	0.94 [0.14 , 6.31]
Total (95% CI)		**35**		**33**	**100.0%**	**0.94 [0.14 , 6.31]**
Total events:	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable

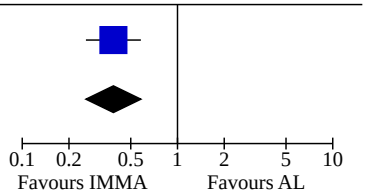


Comparison 23. Oral Allopurinol 300 mg for 28d *vs* IM Meglumine Antimoniate 20mg/kg/d for 20 d in *L braziliensis* and *L. panamensis* ; FU: 12 month

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.1 Complete cure	1	127	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.26, 0.58]
23.2 Recurrence	1	127	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.29, 9.69]

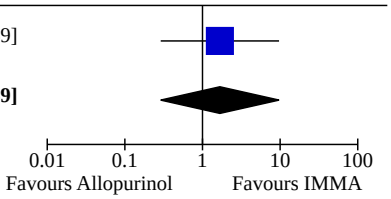
Analysis 23.1. Comparison 23: Oral Allopurinol 300 mg for 28d *vs* IM Meglumine Antimoniate 20mg/kg/d for 20 d in *L braziliensis* and *L. panamensis* ; FU: 12 month, Outcome 1: Complete cure

Study or Subgroup	AL Events	AL Total	IMMA Events	IMMA Total	Weight	Risk Ratio M-H, Random, 95% CI
Vélez 1997	18	60	52	67	100.0%	0.39 [0.26 , 0.58]
Total (95% CI)		**60**		**67**	**100.0%**	**0.39 [0.26 , 0.58]**
Total events:	18		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.57 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Analysis 23.2. Comparison 23: Oral Allopurinol 300 mg for 28d *vs* IM Meglumine Antimoniate 20mg/kg/d for 20 d in *L braziliensis* and *L. panamensis* ; FU: 12 month, Outcome 2: Recurrence

Study or Subgroup	AL Events	AL Total	IMMA Events	IMMA Total	Weight	Risk Ratio M-H, Random, 95% CI
Vélez 1997	3	60	2	67	100.0%	1.68 [0.29 , 9.69]
Total (95% CI)		**60**		**67**	**100.0%**	**1.68 [0.29 , 9.69]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Test for subgroup differences: Not applicable						



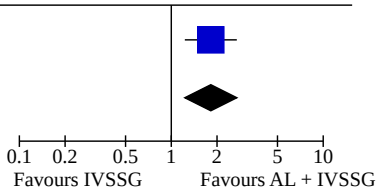
Comparison 24. Oral Allopurinol 20 mg/k/d + IV Sodium Stibogluconate (20 mg/kg/d (4 doses) x 15d) *vs* IV Sodium Stibogluconate (same dose) in *L. braziliensis*; FU: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1 Complete cure	1	100	Risk Ratio (M-H, Random, 95% CI)	1.82 [1.23, 2.70]
24.2 Complete cure; Oral AL plus IVSSG vs IVSSG	2	168	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.40, 2.59]

Analysis 24.1. Comparison 24: Oral Allopurinol 20 mg/k/d + IV Sodium Stibogluconate (20 mg/kg/d (4 doses) x 15d) *vs* IV Sodium Stibogluconate (same dose) in *L. braziliensis*; FU: 1 year, Outcome 1: Complete cure

Study or Subgroup	AL + IVSSG Events	AL + IVSSG Total	IVSSG Events	IVSSG Total	Weight	Risk Ratio M-H, Random, 95% CI
Martínez 1997	36	51	19	49	100.0%	1.82 [1.23 , 2.70]
Total (95% CI)		**51**		**49**	**100.0%**	**1.82 [1.23 , 2.70]**
Total events:	36		19			

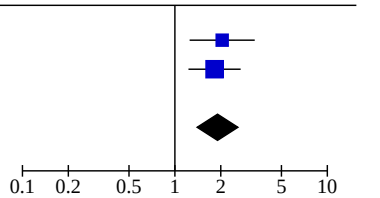
Heterogeneity: Not applicable
Test for overall effect: Z = 2.98 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 24.2. Comparison 24: Oral Allopurinol 20 mg/k/d + IV Sodium Stibogluconate (20 mg/kg/d (4 doses) x 15d) *vs* IV Sodium Stibogluconate (same dose) in *L. braziliensis*; FU: 1 year, Outcome 2: Complete cure; Oral AL plus IVSSG vs IVSSG

Study or Subgroup	AL+ IVSSG Events	AL+ IVSSG Total	IVSSG Events	IVSSG Total	Weight	Risk Ratio M-H, Random, 95% CI
Martínez 1992	26	35	12	33	39.1%	2.04 [1.25 , 3.34]
Martínez 1997	36	51	19	49	60.9%	1.82 [1.23 , 2.70]
Total (95% CI)		**86**		**82**	**100.0%**	**1.90 [1.40 , 2.59]**
Total events:	62		31			

Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 4.11 (P < 0.0001)
Test for subgroup differences: Not applicable



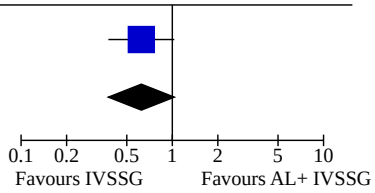
Comparison 25. Oral Allopurinol 20 m/k/d + IV Sodium Stibogluconate (20 mg/kg/d (4 doses) for 28d) *vs* IV Sodium Stibogluconate (same dose); FU: 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.1 Complete cure	1	81	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.38, 1.03]
25.2 Recurrence	2	181	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.73, 1.85]

Analysis 25.1. Comparison 25: Oral Allopurinol 20 m/k/d + IV Sodium Stibogluconate (20 mg/kg/d (4 doses) for 28d) *vs* IV Sodium Stibogluconate (same dose); FU: 12 months, Outcome 1: Complete cure

Study or Subgroup	AL+ IVSSG Events	AL+ IVSSG Total	IVSSG Events	IVSSG Total	Weight	Risk Ratio M-H, Random, 95% CI
Llanos-Cuentas 1997	14	40	23	41	100.0%	0.62 [0.38 , 1.03]
Total (95% CI)		**40**		**41**	**100.0%**	**0.62 [0.38 , 1.03]**
Total events:	14		23			

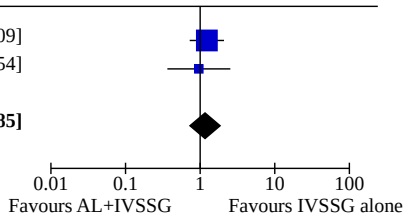
Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 25.2. Comparison 25: Oral Allopurinol 20 m/k/d + IV Sodium Stibogluconate (20 mg/kg/d (4 doses) for 28d) *vs* IV Sodium Stibogluconate (same dose); FU: 12 months, Outcome 2: Recurrence

Study or Subgroup	AL+ IVSSG Events	AL+ IVSSG Total	IVSSG Events	IVSSG Total	Weight	Risk Ratio M-H, Random, 95% CI
Llanos-Cuentas 1997	18	40	15	41	77.1%	1.23 [0.72 , 2.09]
Martínez 1997	7	51	7	49	22.9%	0.96 [0.36 , 2.54]
Total (95% CI)		**91**		**90**	**100.0%**	**1.16 [0.73 , 1.85]**
Total events:	25		22			

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.53)
Test for subgroup differences: Not applicable



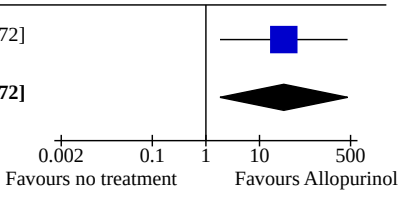
Comparison 26. Oral Allopurinol 20 mg/kg/d (4 doses) for 15 d *vs* no treatment in *L. panamensis*; FU: 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.1 Complete cure	1	42	Risk Ratio (M-H, Random, 95% CI)	28.38 [1.83, 439.72]
26.2 Recurrence	1	42	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.03, 3.46]

Analysis 26.1. Comparison 26: Oral Allopurinol 20 mg/kg/d (4 doses) for 15 d *vs* no treatment in *L. panamensis*; FU: 12 months, Outcome 1: Complete cure

Study or Subgroup	Allopurinol Events	Allopurinol Total	no treatment Events	no treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
Martínez 1992	20	25	0	17	100.0%	28.38 [1.83 , 439.72]
Total (95% CI)		**25**		**17**	**100.0%**	**28.38 [1.83 , 439.72]**
Total events:	20		0			

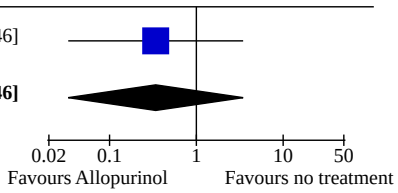
Heterogeneity: Not applicable
Test for overall effect: Z = 2.39 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 26.2. Comparison 26: Oral Allopurinol 20 mg/kg/d (4 doses) for 15 d *vs* no treatment in *L. panamensis*; FU: 12 months, Outcome 2: Recurrence

Study or Subgroup	Allopurinol Events	Allopurinol Total	no treatment Events	no treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
Martínez 1992	1	25	2	17	100.0%	0.34 [0.03 , 3.46]
Total (95% CI)		**25**		**17**	**100.0%**	**0.34 [0.03 , 3.46]**
Total events:	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable



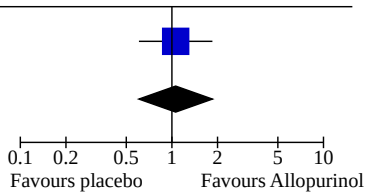
Comparison 27. Oral Allopurinol 300 mg 28 days *vs* placebo in *L. braziliensis* and *L. panamensis*; FU: 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.1 Complete cure	1	120	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.61, 1.85]
27.2 Relapse	1	120	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.32, 28.03]

Analysis 27.1. Comparison 27: Oral Allopurinol 300 mg 28 days *vs* placebo in *L. braziliensis* and *L. panamensis*; FU: 12 months, Outcome 1: Complete cure

Study or Subgroup	Allopurinol Events	Allopurinol Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Vélez 1997	18	60	17	60	100.0%	1.06 [0.61 , 1.85]
Total (95% CI)		**60**		**60**	**100.0%**	**1.06 [0.61 , 1.85]**
Total events:	18		17			

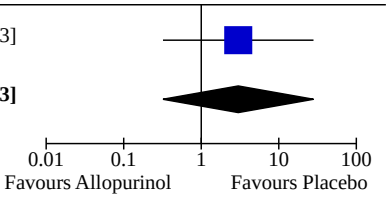
Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable



Analysis 27.2. Comparison 27: Oral Allopurinol 300 mg 28 days *vs* placebo in *L. braziliensis* and *L. panamensis*; FU: 12 months, Outcome 2: Relapse

Study or Subgroup	Allopurinol Events	Allopurinol Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Vélez 1997	3	60	1	60	100.0%	3.00 [0.32 , 28.03]
Total (95% CI)		**60**		**60**	**100.0%**	**3.00 [0.32 , 28.03]**
Total events:	3		1			

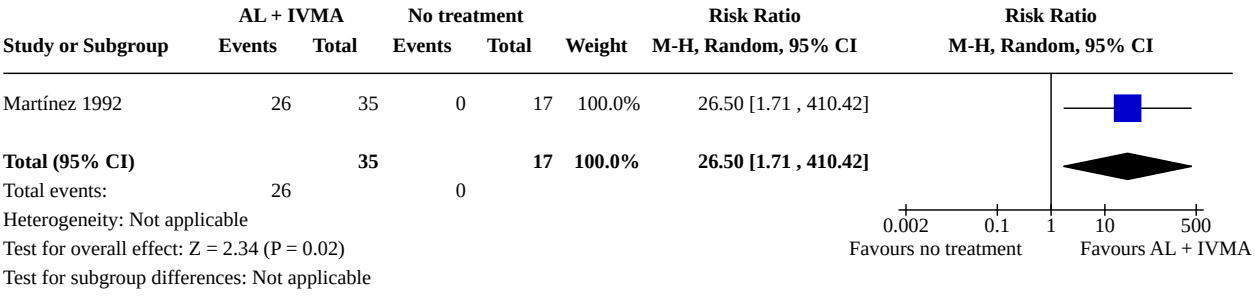
Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable



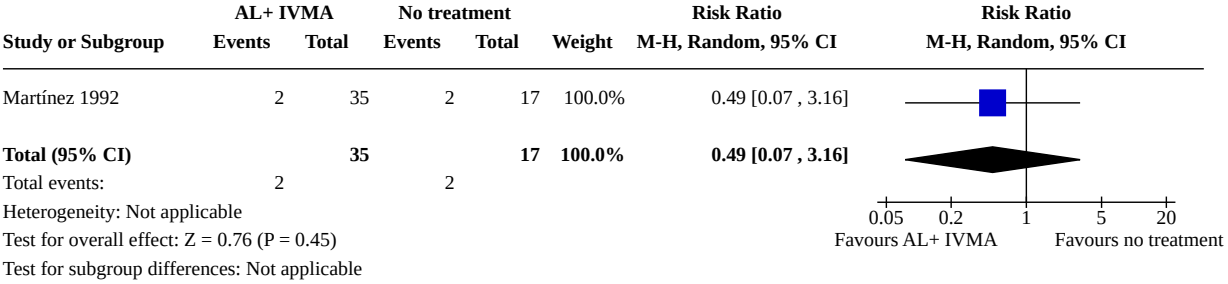
Comparison 28. Oral Allopurinol 20 mg/kg/d + IV Meglumine Antimoniate (20 mg/kg/ d in 4 doses for 15d) *vs* no treatment in *L. panamensis*; FU: 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.1 Complete cure	1	52	Risk Ratio (M-H, Random, 95% CI)	26.50 [1.71, 410.42]
28.2 Recurrence	1	52	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.07, 3.16]

Analysis 28.1. Comparison 28: Oral Allopurinol 20 mg/kg/d + IV Meglumine Antimoniate (20 mg/ kg/ d in 4 doses for 15d) *vs* no treatment in *L. panamensis*; FU: 12 months, Outcome 1: Complete cure



Analysis 28.2. Comparison 28: Oral Allopurinol 20 mg/kg/d + IV Meglumine Antimoniate (20 mg/ kg/ d in 4 doses for 15d) *vs* no treatment in *L. panamensis*; FU: 12 months, Outcome 2: Recurrence



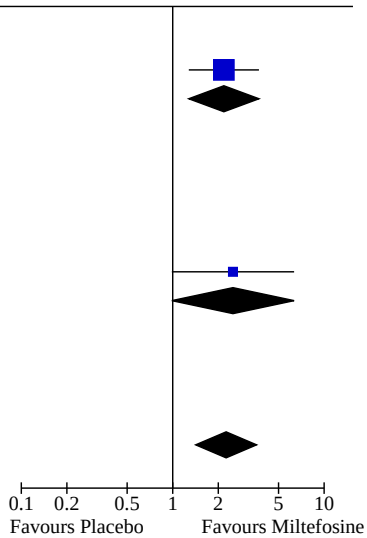
Comparison 29. Oral miltefosine 50 mg for 28 d *vs* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29.1 Complete cure	1	133	Risk Ratio (M-H, Random, 95% CI)	2.25 [1.42, 3.58]
29.1.1 Colombia	1	73	Risk Ratio (M-H, Random, 95% CI)	2.18 [1.28, 3.71]
29.1.2 Guatemala	1	60	Risk Ratio (M-H, Random, 95% CI)	2.50 [0.99, 6.33]
29.2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29.2.1 Nausea	1	133	Risk Ratio (M-H, Random, 95% CI)	3.96 [1.49, 10.48]
29.2.2 Motion sickness	1	133	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.68, 2.42]
29.2.3 Headache	1	133	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.67, 2.59]
29.2.4 Vomiting	1	133	Risk Ratio (M-H, Random, 95% CI)	6.92 [2.68, 17.86]
29.2.5 Diarrhoea	1	133	Risk Ratio (M-H, Random, 95% CI)	2.47 [0.57, 10.80]
29.2.6 Creatinine	1	133	Risk Ratio (M-H, Random, 95% CI)	3.58 [1.34, 9.56]
29.2.7 Aspartate aminotransferase	1	133	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.17, 1.12]
29.2.8 Alanine aminotransferase	1	133	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.32, 2.50]
29.3 Recurrence	1	133	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.37, 23.89]

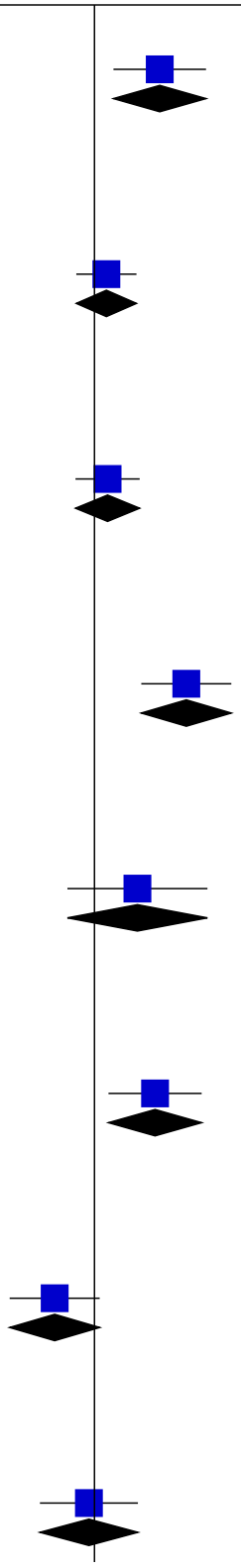
Analysis 29.1. Comparison 29: Oral miltefosine 50 mg for 28 d *vs* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months, Outcome 1: Complete cure

Study or Subgroup	Miltefosine Events	Miltefosine Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
29.1.1 Colombia						
Soto 2004b	40	49	9	24	75.2%	2.18 [1.28 , 3.71]
Subtotal (95% CI)		**49**		**24**	**75.2%**	**2.18 [1.28 , 3.71]**
Total events:	40		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.86 (P = 0.004)						
29.1.2 Guatemala						
Soto 2004b	20	40	4	20	24.8%	2.50 [0.99 , 6.33]
Subtotal (95% CI)		**40**		**20**	**24.8%**	**2.50 [0.99 , 6.33]**
Total events:	20		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.93 (P = 0.05)						
Total (95% CI)		**89**		**44**	**100.0%**	**2.25 [1.42 , 3.58]**
Total events:	60		13			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 3.44 (P = 0.0006)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.80), I² = 0%						



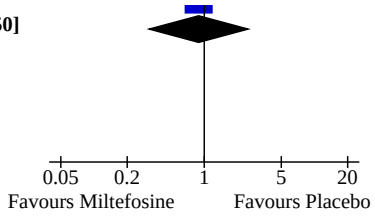
Analysis 29.2. Comparison 29: Oral miltefosine 50 mg for 28 d *vs* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months, Outcome 2: Adverse effects

Study or Subgroup	Miltefosine Events	Total	placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
29.2.1 Nausea						
Soto 2004b	32	89	4	44	100.0%	3.96 [1.49 , 10.48]
Subtotal (95% CI)		**89**		**44**	**100.0%**	**3.96 [1.49 , 10.48]**
Total events:	32		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.77 (P = 0.006)						
29.2.2 Motion sickness						
Soto 2004b	26	89	10	44	100.0%	1.29 [0.68 , 2.42]
Subtotal (95% CI)		**89**		**44**	**100.0%**	**1.29 [0.68 , 2.42]**
Total events:	26		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.44)						
29.2.3 Headache						
Soto 2004b	24	89	9	44	100.0%	1.32 [0.67 , 2.59]
Subtotal (95% CI)		**89**		**44**	**100.0%**	**1.32 [0.67 , 2.59]**
Total events:	24		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
29.2.4 Vomiting						
Soto 2004b	56	89	4	44	100.0%	6.92 [2.68 , 17.86]
Subtotal (95% CI)		**89**		**44**	**100.0%**	**6.92 [2.68 , 17.86]**
Total events:	56		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.00 (P < 0.0001)						
29.2.5 Diarrhoea						
Soto 2004b	10	89	2	44	100.0%	2.47 [0.57 , 10.80]
Subtotal (95% CI)		**89**		**44**	**100.0%**	**2.47 [0.57 , 10.80]**
Total events:	10		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
29.2.6 Creatinine						
Soto 2004b	29	89	4	44	100.0%	3.58 [1.34 , 9.56]
Subtotal (95% CI)		**89**		**44**	**100.0%**	**3.58 [1.34 , 9.56]**
Total events:	29		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.55 (P = 0.01)						
29.2.7 Aspartate aminotransferase						
Soto 2004b	7	89	8	44	100.0%	0.43 [0.17 , 1.12]
Subtotal (95% CI)		**89**		**44**	**100.0%**	**0.43 [0.17 , 1.12]**
Total events:	7		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.73 (P = 0.08)						
29.2.8 Alanine aminotransferase						
Soto 2004b	9	89	5	44	100.0%	0.89 [0.32 , 2.50]
Subtotal (95% CI)		**89**		**44**	**100.0%**	**0.89 [0.32 , 2.50]**
Total events:	9		5			



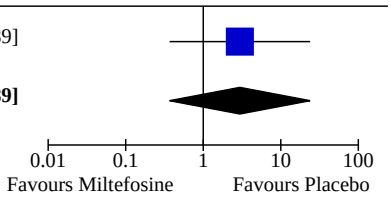
Analysis 29.2. (Continued)

Subtotal (95% CI)		**89**		**44**	**100.0%**	**0.89 [0.32 , 2.50]**
Total events:	9		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.82)						



Analysis 29.3. Comparison 29: Oral miltefosine 50 mg for 28 d *vs* placebo (same regimen) in *L. mexicana*, *L. panamensis* and *L. braziliensis*; FU: 6 months, Outcome 3: Recurrence

	Miltefosine		placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Soto 2004b	6	89	1	44	100.0%	2.97 [0.37 , 23.89]	
Total (95% CI)		**89**		**44**	**100.0%**	**2.97 [0.37 , 23.89]**	
Total events:	6		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							
Test for subgroup differences: Not applicable							

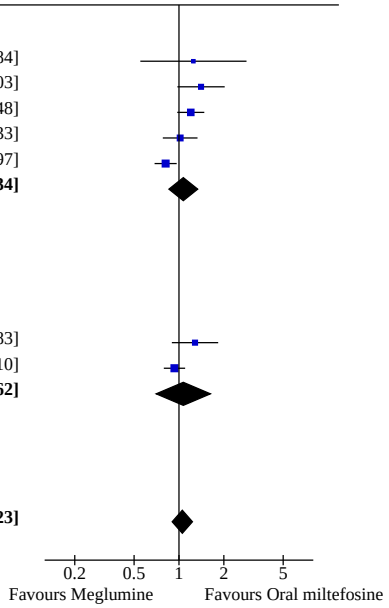


Comparison 30. Oral Miltefosine *vs* Meglumine Antimoniate; FU: 6-12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30.1 Complete cure	7	676	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.90, 1.23]
30.1.1 6 months FU	5	534	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.86, 1.34]
30.1.2 12 month FU	2	142	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.70, 1.62]
30.2 Complete cure in children 2 to 12 years old	2	144	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.98, 1.46]
30.3 Adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
30.3.1 Nausea	3	464	Risk Ratio (M-H, Random, 95% CI)	2.45 [1.72, 3.49]
30.3.2 Vomiting	3	464	Risk Ratio (M-H, Random, 95% CI)	4.76 [1.82, 12.46]
30.4 Speed to healing (% of complete re-epithelization of lesions at 1 month in cured patients)	1	60	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.59, 0.89]

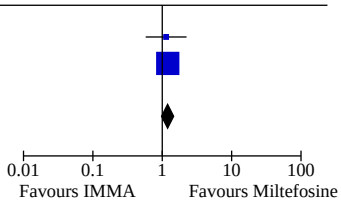
Analysis 30.1. Comparison 30: Oral Miltefosine *vs* Meglumine Antimoniate; FU: 6-12 months, Outcome 1: Complete cure

Study or Subgroup	Oral miltefosine Events	Total	Meglumine antimoniate Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
30.1.1 6 months FU						
Garcia 2014	5	8	5	10	3.2%	1.25 [0.55 , 2.84]
Machado 2010	45	60	16	30	10.9%	1.41 [0.98 , 2.03]
Rubiano 2012	48	58	40	58	18.3%	1.20 [0.97 , 1.48]
Sampaio 2019	11	12	9	10	15.1%	1.02 [0.78 , 1.33]
Vélez 2010	85	145	103	143	20.5%	0.81 [0.69 , 0.97]
Subtotal (95% CI)		**283**		**251**	**68.0%**	**1.07 [0.86 , 1.34]**
Total events:	194		173			
Heterogeneity: Tau² = 0.04; Chi² = 12.20, df = 4 (P = 0.02); I² = 67%						
Test for overall effect: Z = 0.59 (P = 0.55)						
30.1.2 12 month FU						
Chrusciak-Talhari 2011	41	56	16	28	11.2%	1.28 [0.90 , 1.83]
Soto 2008	36	41	16	17	20.8%	0.93 [0.79 , 1.10]
Subtotal (95% CI)		**97**		**45**	**32.0%**	**1.07 [0.70 , 1.62]**
Total events:	77		32			
Heterogeneity: Tau² = 0.07; Chi² = 4.61, df = 1 (P = 0.03); I² = 78%						
Test for overall effect: Z = 0.31 (P = 0.75)						
Total (95% CI)		**380**		**296**	**100.0%**	**1.05 [0.90 , 1.23]**
Total events:	271		205			
Heterogeneity: Tau² = 0.02; Chi² = 14.83, df = 6 (P = 0.02); I² = 60%						
Test for overall effect: Z = 0.65 (P = 0.52)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



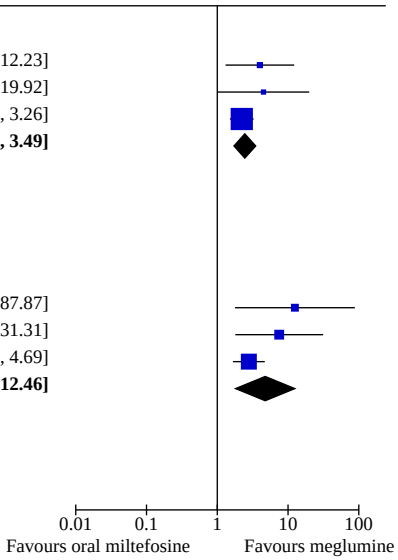
Analysis 30.2. Comparison 30: Oral Miltefosine *vs* Meglumine Antimoniate; FU: 6-12 months, Outcome 2: Complete cure in children 2 to 12 years old

Study or Subgroup	Oral miltefosine Events	Total	Meglumine antimoniate Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chrusciak-Talhari 2011	12	19	5	9	8.7%	1.14 [0.58 , 2.24]
Rubiano 2012	48	58	40	58	91.3%	1.20 [0.97 , 1.48]
Total (95% CI)		**77**		**67**	**100.0%**	**1.19 [0.98 , 1.46]**
Total events:	60		45			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.74 (P = 0.08)						
Test for subgroup differences: Not applicable						



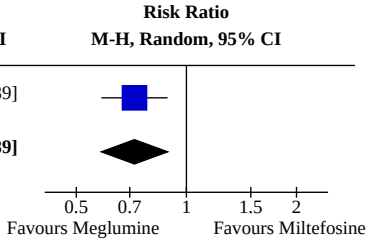
Analysis 30.3. Comparison 30: Oral Miltefosine *vs* Meglumine Antimoniate; FU: 6-12 months, Outcome 3: Adverse events

Study or Subgroup	Oral miltefosine Events	Total	Meglumine antimoniate Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
30.3.1 Nausea						
Machado 2010	24	60	3	30	10.0%	4.00 [1.31 , 12.23]
Rubiano 2012	9	57	2	57	5.7%	4.50 [1.02 , 19.92]
Vélez 2010	59	129	27	131	84.3%	2.22 [1.51 , 3.26]
Subtotal (95% CI)		**246**		**218**	**100.0%**	**2.45 [1.72 , 3.49]**
Total events:	92		32			
Heterogeneity: Tau² = 0.00; Chi² = 1.71, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 4.97 (P < 0.00001)						
30.3.2 Vomiting						
Machado 2010	25	60	1	30	17.8%	12.50 [1.78 , 87.87]
Rubiano 2012	15	57	2	57	26.9%	7.50 [1.80 , 31.31]
Vélez 2010	44	129	16	131	55.3%	2.79 [1.66 , 4.69]
Subtotal (95% CI)		**246**		**218**	**100.0%**	**4.76 [1.82 , 12.46]**
Total events:	84		19			
Heterogeneity: Tau² = 0.37; Chi² = 3.84, df = 2 (P = 0.15); I² = 48%						
Test for overall effect: Z = 3.17 (P = 0.002)						



Analysis 30.4. Comparison 30: Oral Miltefosine *vs* Meglumine Antimoniate; FU: 6-12 months, Outcome 4: Speed to healing (% of complete re-epithelization of lesions at 1 month in cured patients)

Study or Subgroup	Oral miltefosine Events	Total	Meglumine antimoniate Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Soto 2008	31	44	16	16	100.0%	0.72 [0.59 , 0.89]
Total (95% CI)		**44**		**16**	**100.0%**	**0.72 [0.59 , 0.89]**
Total events:	31		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.07 (P = 0.002)						
Test for subgroup differences: Not applicable						



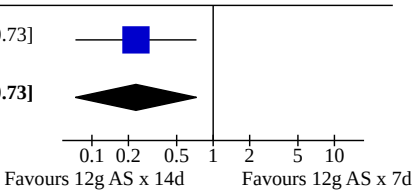
Comparison 31. Different regimens of IM Aminosidine in *L. panamensis*; FU: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.1 Complete cure; AS 12-g base x 7 days versus AS 12-g base x 14 days	1	60	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.07, 0.73]
31.2 Complete cure; AS 12-g base x 7d *versus* AS 18-g base for 14 d	1	60	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.06, 0.62]
31.3 Complete cure; AS 12-g base x 14 d *versus* AS 18-g base x 14 d	1	60	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.50, 1.49]
31.4 Adverse effects: AST level 50% higher that normal	1	60	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.19, 20.90]

Analysis 31.1. Comparison 31: Different regimens of IM Aminosidine in *L. panamensis*; FU: 1 year, Outcome 1: Complete cure; AS 12-g base x 7 days versus AS 12-g base x 14 days

Study or Subgroup	12g AS x 7d Events	Total	12g AS x 14d Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Soto 1994a	3	30	13	30	100.0%	0.23 [0.07 , 0.73]
Total (95% CI)		**30**		**30**	**100.0%**	**0.23 [0.07 , 0.73]**
Total events:	3		13			

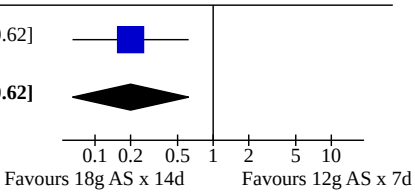
Heterogeneity: Not applicable
Test for overall effect: Z = 2.50 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 31.2. Comparison 31: Different regimens of IM Aminosidine in *L. panamensis*; FU: 1 year, Outcome 2: Complete cure; AS 12-g base x 7d *versus* AS 18-g base for 14 d

Study or Subgroup	12g AS x 7d Events	Total	18g AS x 14d Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Soto 1994a	3	30	15	30	100.0%	0.20 [0.06 , 0.62]
Total (95% CI)		**30**		**30**	**100.0%**	**0.20 [0.06 , 0.62]**
Total events:	3		15			

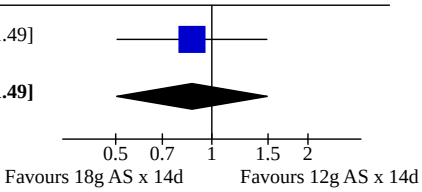
Heterogeneity: Not applicable
Test for overall effect: Z = 2.79 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 31.3. Comparison 31: Different regimens of IM Aminosidine in *L. panamensis*; FU: 1 year, Outcome 3: Complete cure; AS 12-g base x 14 d *versus* AS 18-g base x 14 d

Study or Subgroup	12g AS x 14d Events	Total	18g AS x 14d Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Soto 1994a	13	30	15	30	100.0%	0.87 [0.50 , 1.49]
Total (95% CI)		**30**		**30**	**100.0%**	**0.87 [0.50 , 1.49]**
Total events:	13		15			

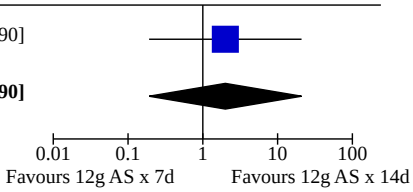
Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.61)
Test for subgroup differences: Not applicable



Analysis 31.4. Comparison 31: Different regimens of IM Aminosidine in *L. panamensis*; FU: 1 year, Outcome 4: Adverse effects: AST level 50% higher that normal

Study or Subgroup	12g AS x 7d Events	12g AS x 7d Total	12g AS x 14d Events	12g AS x 14d Total	Weight	Risk Ratio M-H, Random, 95% CI
Soto 1994a	2	30	1	30	100.0%	2.00 [0.19 , 20.90]
Total (95% CI)		**30**		**30**	**100.0%**	**2.00 [0.19 , 20.90]**
Total events:	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



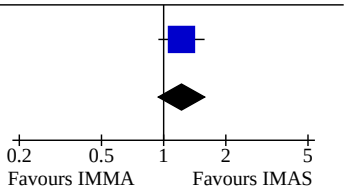
Comparison 32. IM Aminosidine 20mg/kg/day for 20 days *vs* IM Meglumine Antimoniate 10mg/kg/day for 20 days in *L. braziliensis*; FU: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
32.1 Complete cure	1	31	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.94, 1.58]
32.2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
32.2.1 Myalgias	1	31	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.07, 1.06]
32.2.2 Anorexia	1	31	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.44, 2.59]
32.2.3 Asthenia	1	31	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.25, 2.03]
32.2.4 Arthralgias	1	31	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 1.61]

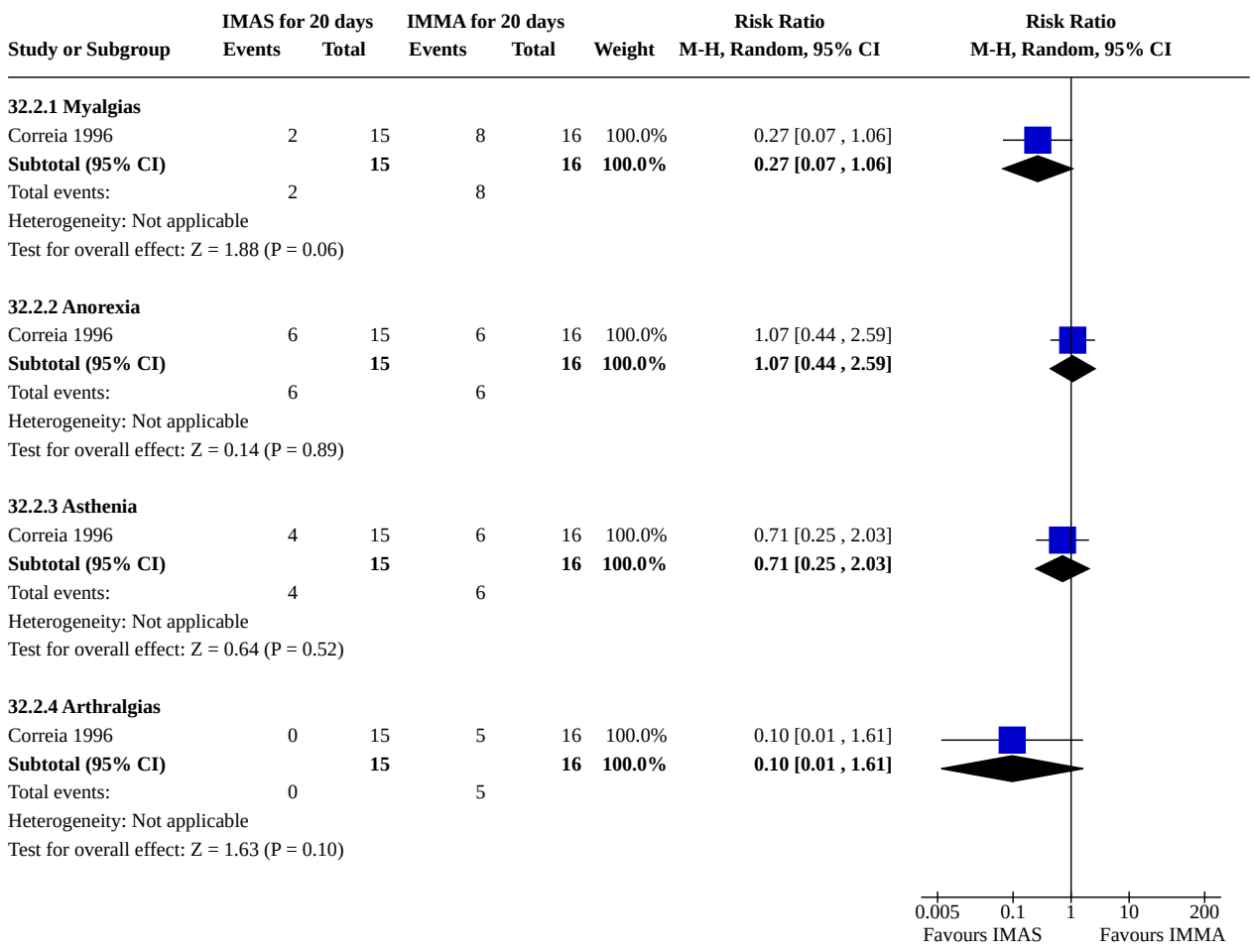
Analysis 32.1. Comparison 32: IM Aminosidine 20mg/kg/day for 20 days *vs* IM Meglumine Antimoniate 10mg/kg/day for 20 days in *L. braziliensis*; FU: 1 year, Outcome 1: Complete cure

Study or Subgroup	IMAS for 20 days Events	IMAS for 20 days Total	IMMA for 20 days Events	IMMA for 20 days Total	Weight	Risk Ratio M-H, Random, 95% CI
Correia 1996	15	15	13	16	100.0%	1.22 [0.94 , 1.58]
Total (95% CI)		**15**		**16**	**100.0%**	**1.22 [0.94 , 1.58]**
Total events:	15		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 32.2. Comparison 32: IM Aminosidine 20mg/kg/day for 20 days *vs* IM Meglumine Antimoniate 10mg/kg/day for 20 days in *L. braziliensis*; FU: 1 year, Outcome 2: Adverse effects



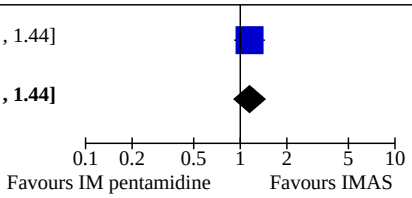
Comparison 33. IM Aminosidine for 20 days *vs* IM Pentamidine Isethionate x 8 applications in *L. braziliensis*; FU: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
33.1 Complete cure	1	30	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.91, 1.44]
33.2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
33.2.1 Myalgias	1	30	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.39]
33.2.2 Anorexia	1	30	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.38, 1.95]
33.2.3 Asthenia	1	30	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.27, 2.41]
33.2.4 Arthralgias	1	30	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 3.85]

Analysis 33.1. Comparison 33: IM Aminosidine for 20 days *vs* IM Pentamidine Isethionate x 8 applications in *L. braziliensis*; FU: 1 year, Outcome 1: Complete cure

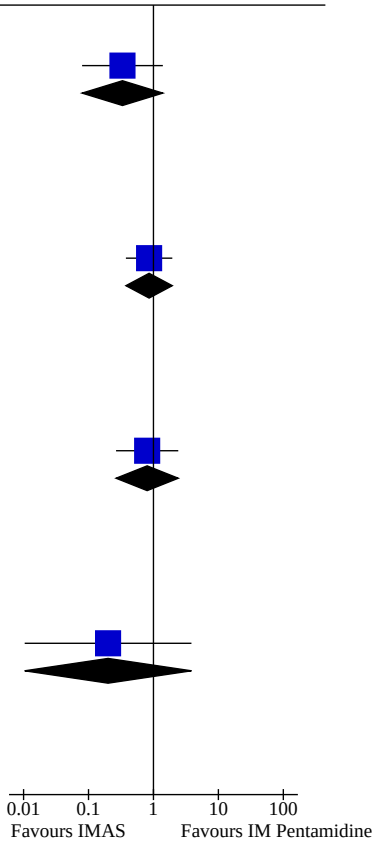
Study or Subgroup	IMAS Events	IMAS Total	IM pentamidine Events	IM pentamidine Total	Weight	Risk Ratio M-H, Random, 95% CI
Correia 1996	15	15	13	15	100.0%	1.15 [0.91 , 1.44]
Total (95% CI)		**15**		**15**	**100.0%**	**1.15 [0.91 , 1.44]**
Total events:	15		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.24)
Test for subgroup differences: Not applicable



Analysis 33.2. Comparison 33: IM Aminosidine for 20 days *vs* IM Pentamidine Isethionate x 8 applications in *L. braziliensis*; FU: 1 year, Outcome 2: Adverse effects

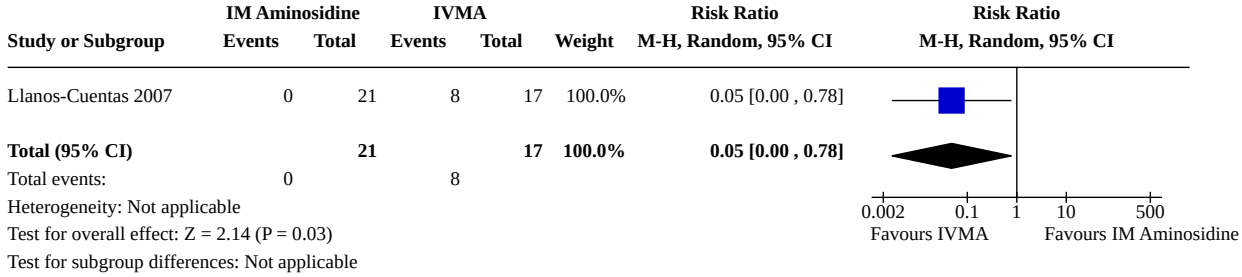
Study or Subgroup	IMAS for 20 days Events	IMAS for 20 days Total	IM Pentamidine Events	IM Pentamidine Total	Weight	Risk Ratio M-H, Random, 95% CI
33.2.1 Myalgias						
Correia 1996	2	15	6	15	100.0%	0.33 [0.08 , 1.39]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**0.33 [0.08 , 1.39]**
Total events:	2		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
33.2.2 Anorexia						
Correia 1996	6	15	7	15	100.0%	0.86 [0.38 , 1.95]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**0.86 [0.38 , 1.95]**
Total events:	6		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
33.2.3 Asthenia						
Correia 1996	4	15	5	15	100.0%	0.80 [0.27 , 2.41]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**0.80 [0.27 , 2.41]**
Total events:	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
33.2.4 Arthralgias						
Correia 1996	0	15	2	15	100.0%	0.20 [0.01 , 3.85]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**0.20 [0.01 , 3.85]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.29)						



Comparison 34. IM Aminosidine 20 mg/kg/d for 28 d *vs* IV Meglumine Antimoniate 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
34.1 Complete cure	1	38	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.78]

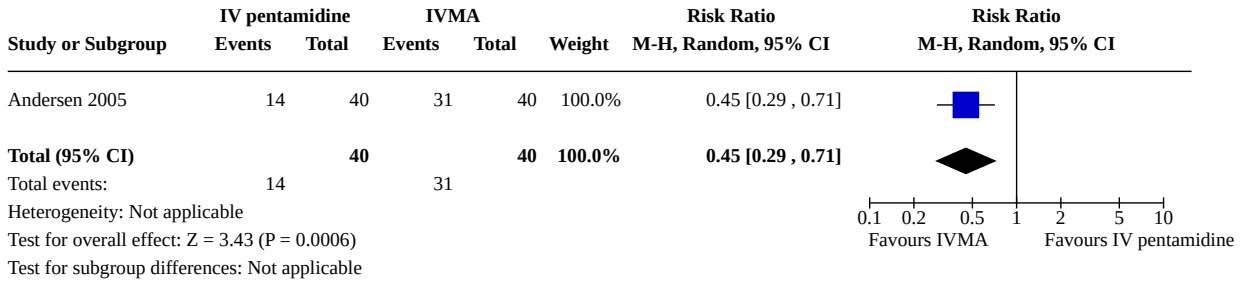
Analysis 34.1. Comparison 34: IM Aminosidine 20 mg/kg/d for 28 d *vs* IV Meglumine Antimoniate 20 mg/kg for 28 d; *L. braziliensis*; FU: 1 year, Outcome 1: Complete cure



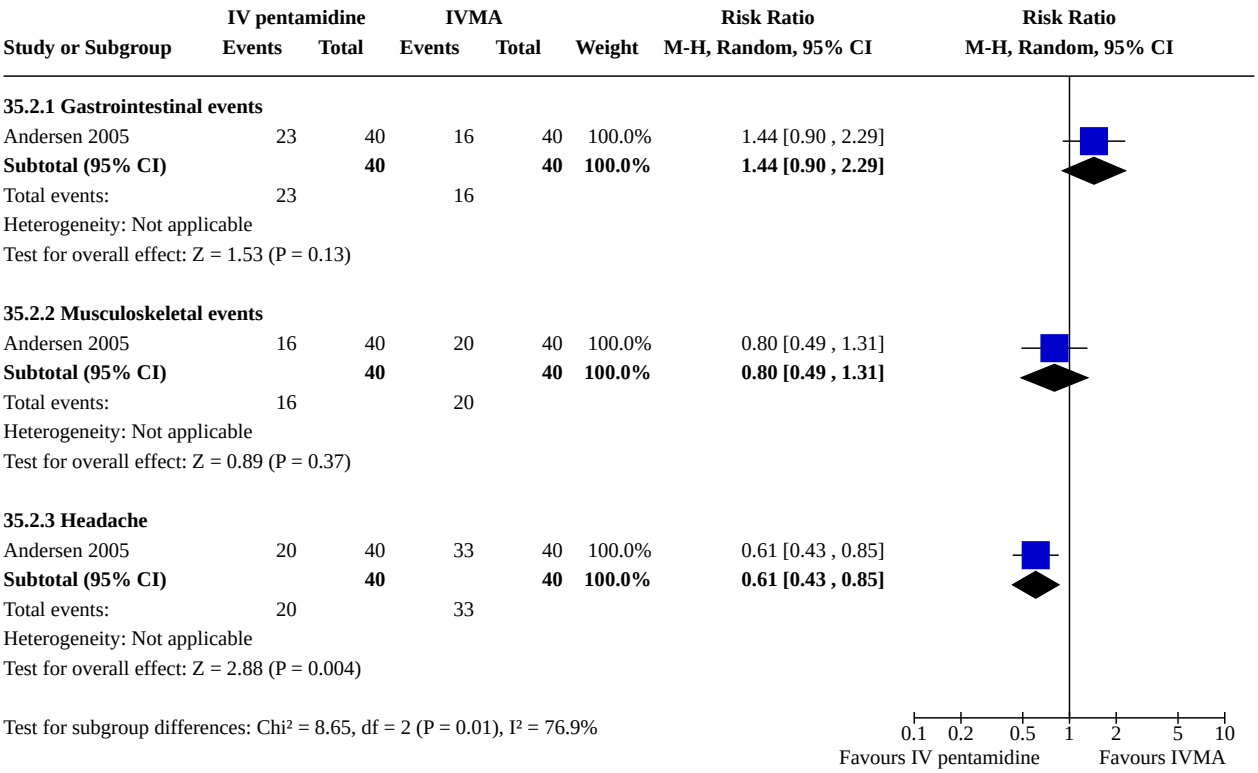
Comparison 35. IV Pentamidine (2mg/kg) seven doses *vs* IV Meglumine Antimoniate (20 mg/kg) for 20 days in *L. braziliensis*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
35.1 Complete cure	1	80	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.29, 0.71]
35.2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
35.2.1 Gastrointestinal events	1	80	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.90, 2.29]
35.2.2 Musculoskeletal events	1	80	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.49, 1.31]
35.2.3 Headache	1	80	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.43, 0.85]

Analysis 35.1. Comparison 35: IV Pentamidine (2mg/kg) seven doses *vs* IV Meglumine Antimoniate (20 mg/kg) for 20 days in *L. braziliensis*; FU: 6 months, Outcome 1: Complete cure



Analysis 35.2. Comparison 35: IV Pentamidine (2mg/kg) seven doses *vs* IV Meglumine Antimoniate (20 mg/kg) for 20 days in *L. braziliensis*; FU: 6 months, Outcome 2: Adverse effects



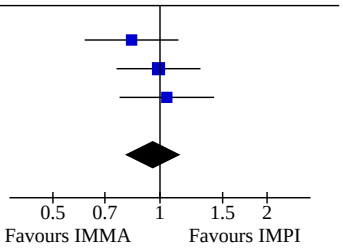
Comparison 36. IM Pentamidine *vs* IM Meglumine Antimoniate for 20 days in *L. braziliensis*; FU: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36.1 Complete cure	3	226	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.81, 1.13]
36.2 Adverse effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
36.2.1 Myalgias	2	156	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.35, 1.53]
36.2.2 Anorexia	1	31	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.54, 2.86]
36.2.3 Asthenia	2	155	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.34, 1.76]
36.2.4 Arthralgias	2	156	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.11, 0.69]
36.2.5 Pain at the injection site	1	125	Risk Ratio (M-H, Random, 95% CI)	53.84 [3.35, 864.51]
36.2.6 Induration	1	125	Risk Ratio (M-H, Random, 95% CI)	17.27 [1.02, 292.90]

Analysis 36.1. Comparison 36: IM Pentamidine *vs* IM Meglumine Antimoniate for 20 days in *L. braziliensis*; FU: 1 year, Outcome 1: Complete cure

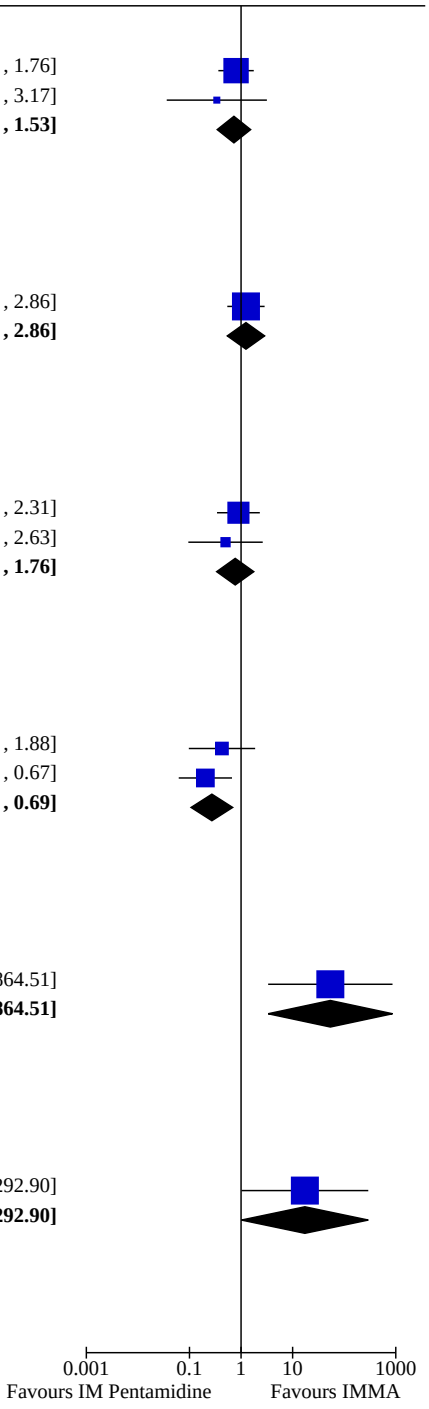
Study or Subgroup	IM pentamidine (PI) Events	Total	IMMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Alves 2016	22	34	28	36	30.9%	0.83 [0.61 , 1.13]
Correia 1996	13	15	14	16	38.6%	0.99 [0.75 , 1.30]
Neves 2011	36	62	35	63	30.4%	1.05 [0.77 , 1.42]
Total (95% CI)		**111**		**115**	**100.0%**	**0.95 [0.81 , 1.13]**
Total events:	71		77			

Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable



Analysis 36.2. Comparison 36: IM Pentamidine *vs* IM Meglumine Antimoniate for 20 days in *L. braziliensis*; FU: 1 year, Outcome 2: Adverse effects

Study or Subgroup	IM Pentamidine Events	IM Pentamidine Total	IMMA Events	IMMA Total	Weight	Risk Ratio M-H, Random, 95% CI
36.2.1 Myalgias						
Correia 1996	6	15	8	16	88.9%	0.80 [0.36 , 1.76]
Neves 2011	1	62	3	63	11.1%	0.34 [0.04 , 3.17]
Subtotal (95% CI)		**77**		**79**	**100.0%**	**0.73 [0.35 , 1.53]**
Total events:	7		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
36.2.2 Anorexia						
Correia 1996	7	15	6	16	100.0%	1.24 [0.54 , 2.86]
Subtotal (95% CI)		**15**		**16**	**100.0%**	**1.24 [0.54 , 2.86]**
Total events:	7		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
36.2.3 Asthenia						
Correia 1996	5	15	6	16	75.1%	0.89 [0.34 , 2.31]
Neves 2011	2	62	4	62	24.9%	0.50 [0.10 , 2.63]
Subtotal (95% CI)		**77**		**78**	**100.0%**	**0.77 [0.34 , 1.76]**
Total events:	7		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.62 (P = 0.54)						
36.2.4 Arthralgias						
Correia 1996	2	15	5	16	39.2%	0.43 [0.10 , 1.88]
Neves 2011	3	62	15	63	60.8%	0.20 [0.06 , 0.67]
Subtotal (95% CI)		**77**		**79**	**100.0%**	**0.27 [0.11 , 0.69]**
Total events:	5		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.75 (P = 0.006)						
36.2.5 Pain at the injection site						
Neves 2011	26	62	0	63	100.0%	53.84 [3.35 , 864.51]
Subtotal (95% CI)		**62**		**63**	**100.0%**	**53.84 [3.35 , 864.51]**
Total events:	26		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.81 (P = 0.005)						
36.2.6 Induration						
Neves 2011	8	62	0	63	100.0%	17.27 [1.02 , 292.90]
Subtotal (95% CI)		**62**		**63**	**100.0%**	**17.27 [1.02 , 292.90]**
Total events:	8		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						



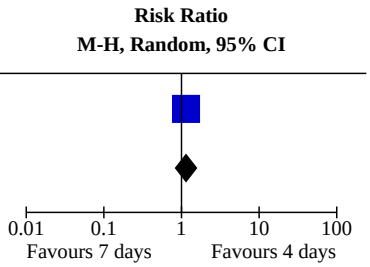
Comparison 37. Pentamidine Isethionate 7 mg/Kg 4 days *vs* Pentamidine Isethionate 4 mg/kg 7 days; FU: 12 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
37.1 Complete cure	1	163	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.84, 1.56]

Analysis 37.1. Comparison 37: Pentamidine Isethionate 7 mg/Kg 4 days *vs* Pentamidine Isethionate 4 mg/kg 7 days; FU: 12 weeks, Outcome 1: Complete cure

Study or Subgroup	4 days Events	4 days Total	7 days Events	7 days Total	Weight	Risk Ratio M-H, Random, 95% CI
Hu 2015	45	84	37	79	100.0%	1.14 [0.84 , 1.56]
Total (95% CI)		**84**		**79**	**100.0%**	**1.14 [0.84 , 1.56]**
Total events:	45		37			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable

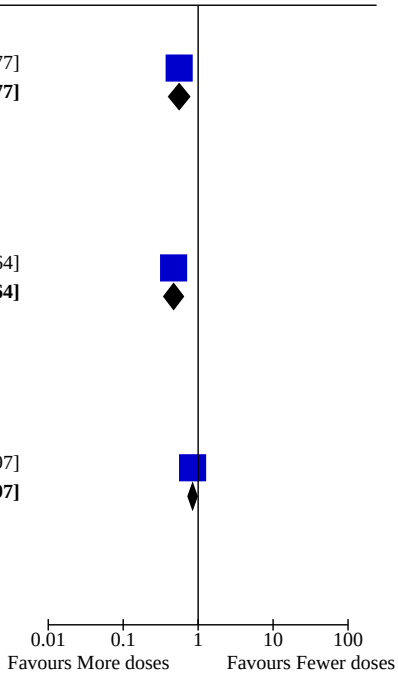


Comparison 38. Pentamidine Isethionate (7mg/kg): single dose *versus* two doses *versus* three doses in *L. guyanensis*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
38.1 Complete cure at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
38.1.1 Single dose *versus* two doses	1	106	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.40, 0.77]
38.1.2 Single dose *versus* three doses	1	106	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.35, 0.64]
38.1.3 Two doses *versus* three doses	1	106	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.73, 0.97]

Analysis 38.1. Comparison 38: Pentamidine Isethionate (7mg/kg): single dose *versus* two doses *versus* three doses in *L. guyanensis*; FU: 6 months, Outcome 1: Complete cure at 6 months

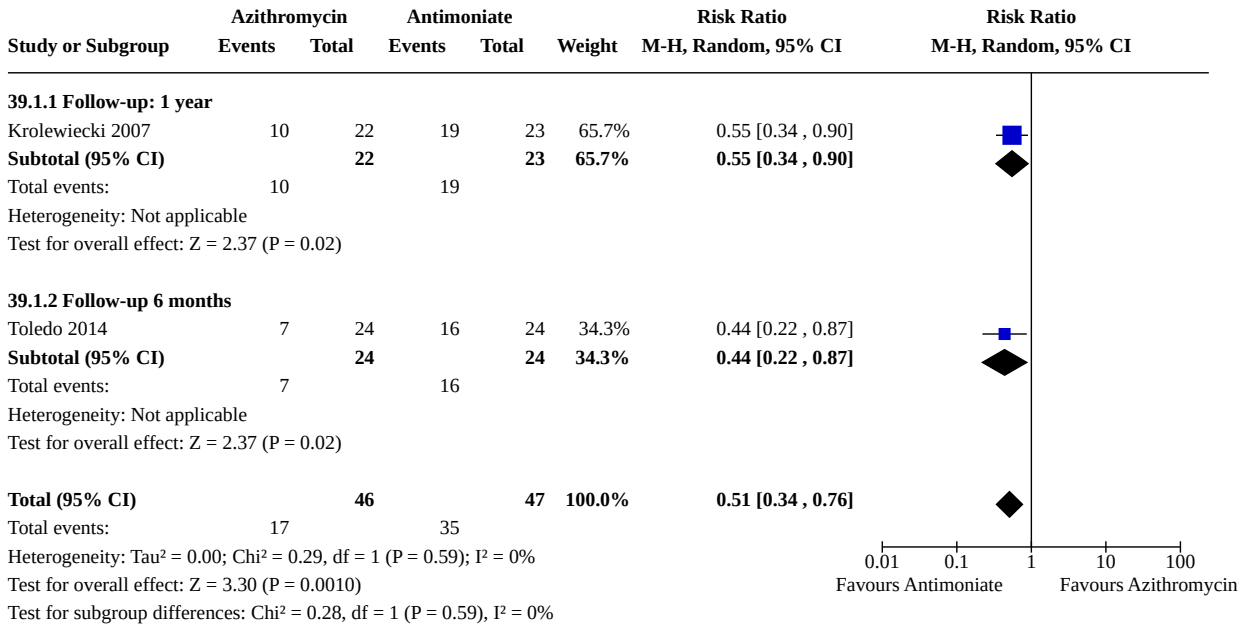
Study or Subgroup	Less doses Events	Total	More doses Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
38.1.1 Single dose *versus* two doses						
Gadelha 2018	24	53	43	53	100.0%	0.56 [0.40 , 0.77]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**0.56 [0.40 , 0.77]**
Total events:	24		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.54 (P = 0.0004)						
38.1.2 Single dose *versus* three doses						
Gadelha 2018	24	53	51	53	100.0%	0.47 [0.35 , 0.64]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**0.47 [0.35 , 0.64]**
Total events:	24		51			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.91 (P < 0.00001)						
38.1.3 Two doses *versus* three doses						
Gadelha 2018	43	53	51	53	100.0%	0.84 [0.73 , 0.97]
Subtotal (95% CI)		**53**		**53**	**100.0%**	**0.84 [0.73 , 0.97]**
Total events:	43		51			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.38 (P = 0.02)						
Test for subgroup differences: Chi² = 14.89, df = 2 (P = 0.0006), I² = 86.6%						



Comparison 39. 500 mg oral Azithromycin *vs* 1.5 g parenteral Meglumine Antimoniate in *L. braziliensis*; FU: 6-12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
39.1 Complete cure	2	93	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.34, 0.76]
39.1.1 Follow-up: 1 year	1	45	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.34, 0.90]
39.1.2 Follow-up 6 months	1	48	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.22, 0.87]

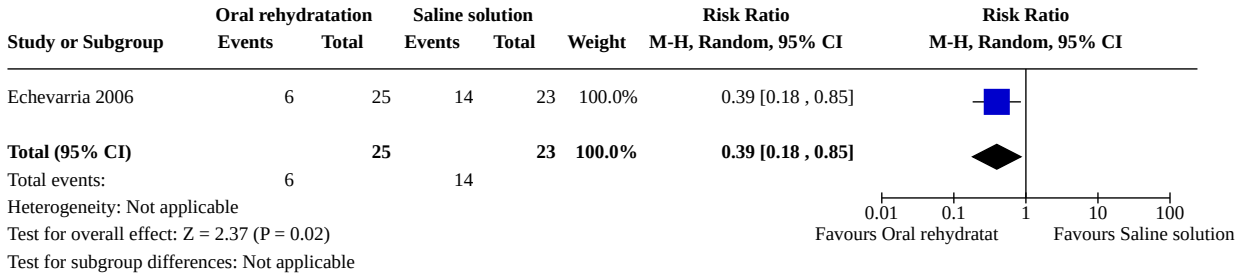
Analysis 39.1. Comparison 39: 500 mg oral Azithromycin *vs* 1.5 g parenteral Meglumine Antimoniate in *L. braziliensis*; FU: 6-12 months, Outcome 1: Complete cure



Comparison 40. Oral rehydration solution vs intravenous saline solution for patients treated with amphotericine B in *L. braziliensis*; FU: 42 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
40.1 Adverse effects: hypokaliemia	1	48	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.18, 0.85]

Analysis 40.1. Comparison 40: Oral rehydration solution vs intravenous saline solution for patients treated with amphotericine B in *L. braziliensis*; FU: 42 days, Outcome 1: Adverse effects: hypokaliemia



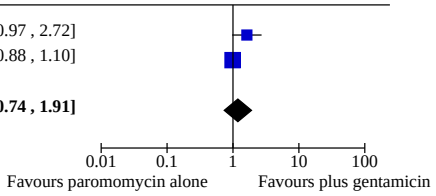
Comparison 41. Topical Paramomycin (15%) + gentamicin (0.5%) vs topical Paramomycin (15%) alone once daily in *L. panamensis*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
41.1 Complete cure	2	429	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.74, 1.91]
41.2 Complete cure in children	1	184	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.74, 1.33]
41.2.1 Children under 12 years	1	107	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.74, 1.01]
41.2.2 Children 12 to 17 years	1	77	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.95, 1.43]

Analysis 41.1. Comparison 41: Topical Paramomycin (15%) + gentamicin (0.5%) vs topical Paramomycin (15%) alone once daily in *L. panamensis*; FU: 6 months, Outcome 1: Complete cure

Study or Subgroup	Paromomycin+gentamicin Events	Total	Paramomycin alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Sosa 2013	13	15	8	15	37.1%	1.63 [0.97 , 2.72]
Sosa 2019	151	201	151	198	62.9%	0.99 [0.88 , 1.10]
Total (95% CI)		**216**		**213**	**100.0%**	**1.19 [0.74 , 1.91]**
Total events:	164		159			

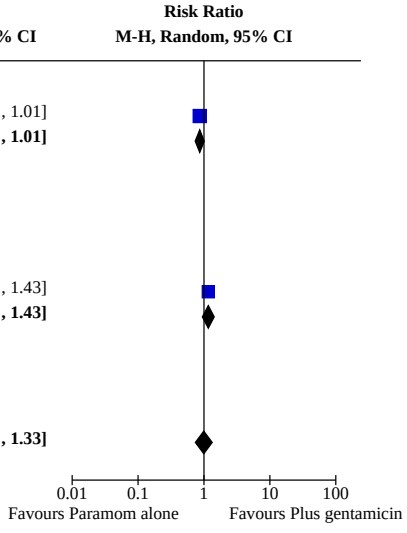
Heterogeneity: Tau² = 0.09; Chi² = 3.52, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 41.2. Comparison 41: Topical Paramomycin (15%) + gentamicin (0.5%) vs topical Paramomycin (15%) alone once daily in *L. panamensis*; FU: 6 months, Outcome 2: Complete cure in children

Study or Subgroup	Paromomycin+gentamicin Events	Total	Paramomycin alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
41.2.1 Children under 12 years						
Sosa 2019	48	61	42	46	52.6%	0.86 [0.74 , 1.01]
Subtotal (95% CI)		**61**		**46**	**52.6%**	**0.86 [0.74 , 1.01]**
Total events:	48		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.84 (P = 0.07)						
41.2.2 Children 12 to 17 years						
Sosa 2019	31	35	32	42	47.4%	1.16 [0.95 , 1.43]
Subtotal (95% CI)		**35**		**42**	**47.4%**	**1.16 [0.95 , 1.43]**
Total events:	31		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
Total (95% CI)		**96**		**88**	**100.0%**	**0.99 [0.74 , 1.33]**
Total events:	79		74			

Heterogeneity: Tau² = 0.04; Chi² = 5.12, df = 1 (P = 0.02); I² = 80%
Test for overall effect: Z = 0.04 (P = 0.96)
Test for subgroup differences: Chi² = 5.08, df = 1 (P = 0.02), I² = 80.3%



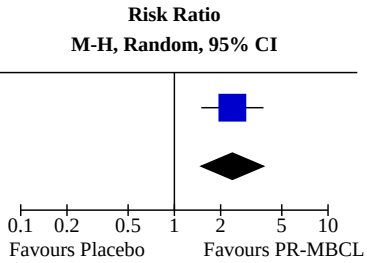
Comparison 42. Topical Paramomycin PR-MBCL TD for 20d *vs* placebo TD for 20d in *L. panamensis* and *L. mexicana*; FU: 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
42.1 Complete cure	1	76	Risk Ratio (M-H, Random, 95% CI)	2.38 [1.50, 3.80]

Analysis 42.1. Comparison 42: Topical Paramomycin PR-MBCL TD for 20d *vs* placebo TD for 20d in *L. panamensis* and *L. mexicana*; FU: 12 months, Outcome 1: Complete cure

Study or Subgroup	PR-MBCL Events	PR-MBCL Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Arana 2001	31	38	13	38	100.0%	2.38 [1.50 , 3.80]
Total (95% CI)		**38**		**38**	**100.0%**	**2.38 [1.50 , 3.80]**
Total events:	31		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.65 (P = 0.0003)
Test for subgroup differences: Not applicable

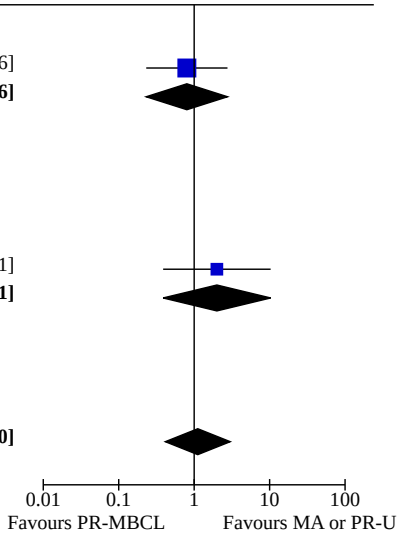


Comparison 43. Paromomycin 15% plus methylbenzonium chloride (PR–MBCL) 30 days versus meglumine antimoniate (MA) 20 mg/kg/day 10 days. FU: 3 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
43.1 Recurrence	1	160	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.42, 3.00]
43.1.1 PR-MBCL versus MA	1	80	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.23, 2.76]
43.1.2 PR-MBCL versus PR-U	1	80	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.39, 10.31]
43.2 Speed to healing	1	160	Mean Difference (IV, Random, 95% CI)	6.73 [-6.99, 20.44]
43.2.1 PR-MBCL versus MA	1	80	Mean Difference (IV, Random, 95% CI)	13.60 [7.75, 19.45]
43.2.2 PR-MBCL versus PR-U	1	80	Mean Difference (IV, Random, 95% CI)	-0.40 [-7.30, 6.50]

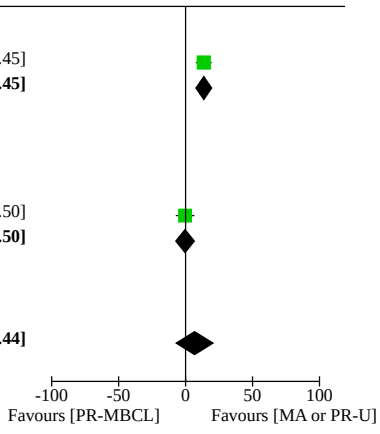
Analysis 43.1. Comparison 43: Paromomycin 15% plus methylbenzonium chloride (PR–MBCL) 30 days versus meglumine antimoniate (MA) 20 mg/kg/day 10 days. FU: 3 months, Outcome 1: Recurrence

Study or Subgroup	PR-MBCL Events	PR-MBCL Total	MA or PR-U Events	MA or PR-U Total	Weight	Risk Ratio M-H, Random, 95% CI
43.1.1 PR-MBCL versus MA						
Armijos 2004	4	40	5	40	63.6%	0.80 [0.23 , 2.76]
Subtotal (95% CI)		**40**		**40**	**63.6%**	**0.80 [0.23 , 2.76]**
Total events:	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.72)						
43.1.2 PR-MBCL versus PR-U						
Armijos 2004	4	40	2	40	36.4%	2.00 [0.39 , 10.31]
Subtotal (95% CI)		**40**		**40**	**36.4%**	**2.00 [0.39 , 10.31]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
Total (95% CI)		**80**		**80**	**100.0%**	**1.12 [0.42 , 3.00]**
Total events:	8		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.22 (P = 0.83)						
Test for subgroup differences: Chi² = 0.76, df = 1 (P = 0.38), I² = 0%						



Analysis 43.2. Comparison 43: Paromomycin 15% plus methylbenzonium chloride (PR–MBCL) 30 days versus meglumine antimoniate (MA) 20 mg/kg/day 10 days. FU: 3 months, Outcome 2: Speed to healing

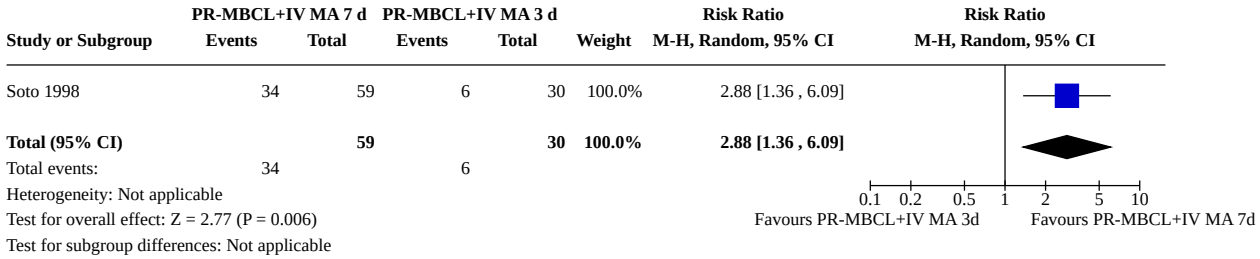
Study or Subgroup	PR-MBCL Mean	PR-MBCL SD	PR-MBCL Total	MA or PR-U Mean	MA or PR-U SD	MA or PR-U Total	Weight	Mean Difference IV, Random, 95% CI
43.2.1 PR-MBCL versus MA								
Armijos 2004	43.1	14.4	40	29.5	12.2	40	50.9%	13.60 [7.75 , 19.45]
Subtotal (95% CI)			**40**			**40**	**50.9%**	**13.60 [7.75 , 19.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.56 (P < 0.00001)								
43.2.2 PR-MBCL versus PR-U								
Armijos 2004	43.1	14.4	40	43.5	17	40	49.1%	-0.40 [-7.30 , 6.50]
Subtotal (95% CI)			**40**			**40**	**49.1%**	**-0.40 [-7.30 , 6.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.11 (P = 0.91)								
Total (95% CI)			**80**			**80**	**100.0%**	**6.73 [-6.99 , 20.44]**
Heterogeneity: Tau² = 87.34; Chi² = 9.20, df = 1 (P = 0.002); I² = 89%								
Test for overall effect: Z = 0.96 (P = 0.34)								
Test for subgroup differences: Chi² = 9.20, df = 1 (P = 0.002), I² = 89.1%								



Comparison 44. Topical Paromomycin PR-MBCL (TD x 10d) + IV Meglumine Antimoniate x 7 d *vs* Paromomycin PR-MBCL + IV Meglumine Antimoniate 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
44.1 Complete cure	1	89	Risk Ratio (M-H, Random, 95% CI)	2.88 [1.36, 6.09]

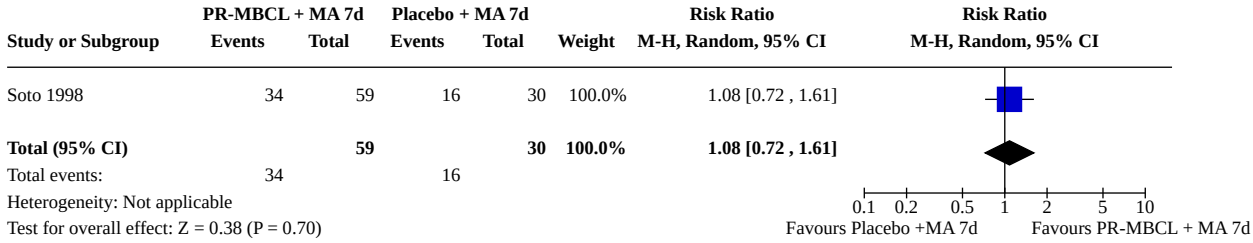
Analysis 44.1. Comparison 44: Topical Paromomycin PR-MBCL (TD x 10d) + IV Meglumine Antimoniate x 7 d *vs* Paromomycin PR-MBCL + IV Meglumine Antimoniate x 3 d in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 1: Complete cure



Comparison 45. Topical Paromomycin PR-MBCL (TD x 10d) + IV Meglumine Antimoniate x 7 d *vs* Placebo + IV Meglumine Antimoniate 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
45.1 Complete cure	1	89	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.72, 1.61]

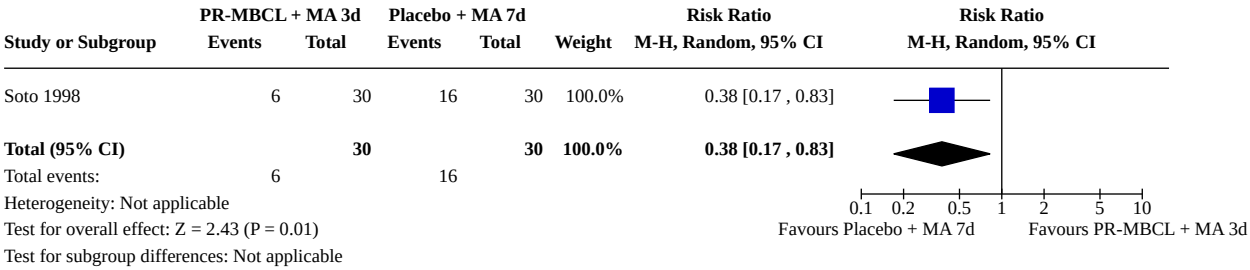
Analysis 45.1. Comparison 45: Topical Paromomycin PR-MBCL (TD x 10d) + IV Meglumine Antimoniate x 7 d *vs* Placebo + IV Meglumine Antimoniate x 7 d in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 1: Complete cure



Comparison 46. Topical Paromomycin PR-MBCL (TD x 10d) + IV Meglumine Antimoniate x 3 d *vs* Placebo + IV Meglumine Antimoniate 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
46.1 Complete cure	1	60	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.17, 0.83]

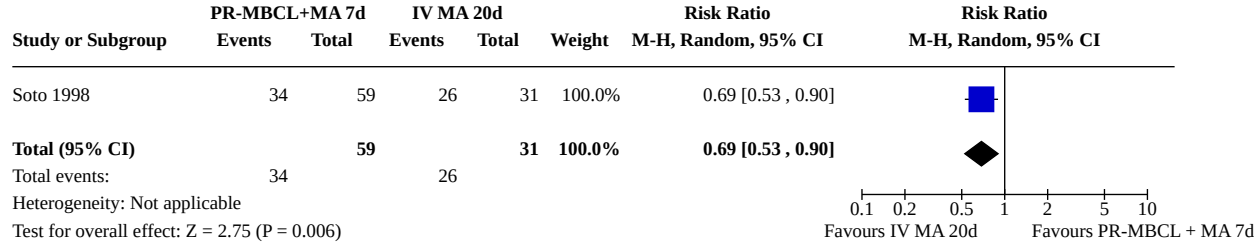
Analysis 46.1. Comparison 46: Topical Paromomycin PR-MBCL (TD x 10d) + IV Meglumine Antimoniate x 3 d *vs* Placebo + IV Meglumine Antimoniate x 7 d in *L. braziliensis* and *L. panamensis;* FU: 1 year, Outcome 1: Complete cure



Comparison 47. Topical Paromomycin PR-MBCL (TD x 10d) + IV Meglumine Antimoniate x 7 d *vs* IV Meglumine Antimoniate 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
47.1 Complete cure	1	90	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.53, 0.90]

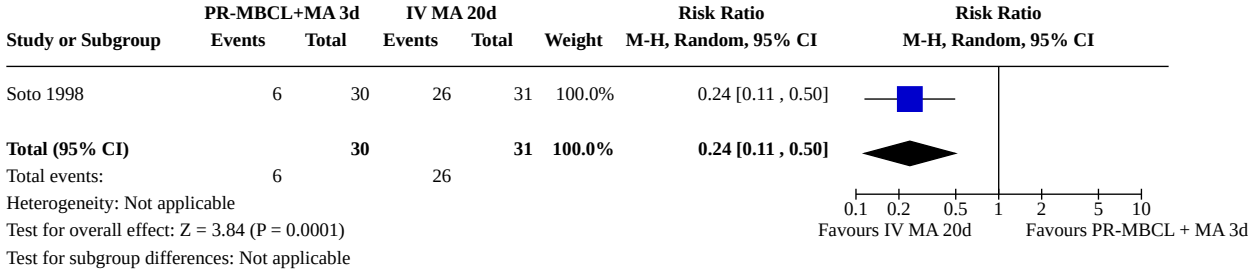
Analysis 47.1. Comparison 47: Topical Paromomycin PR-MBCL (TD x 10d) + IV Meglumine Antimoniate x 7 d *vs* IV Meglumine Antimoniate for 20 d in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 1: Complete cure



Comparison 48. Topical Paromomycin PR-MBCL (TD x 10d) + IV Meglumine Antimoniate x 3 d *vs* IV Meglumine Antimoniate 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
48.1 Complete cure	1	61	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.11, 0.50]

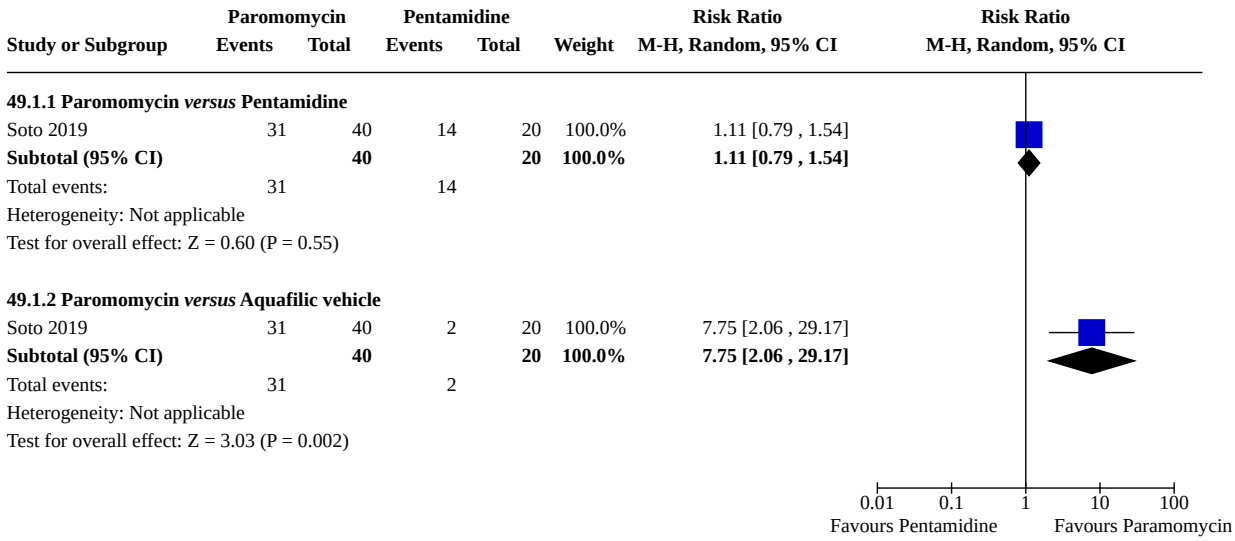
Analysis 48.1. Comparison 48: Topical Paromomycin PR-MBCL (TD x 10d) + IV Meglumine Antimoniate x 3 d *vs* IV Meglumine Antimoniate for 20 d in *L. braziliensis* and *L. panamensis*; FU: 1 year, Outcome 1: Complete cure



Comparison 49. Paromomycin (15%) in Aquaphilic *versus* intralesional pentamidine (30 mg/ ml) *versus* Aquaphilic vehicle in *L. braziliensis*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
49.1 Complete cure at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
49.1.1 Paromomycin *versus* Pentamidine	1	60	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.79, 1.54]
49.1.2 Paromomycin *versus* Aquafilic vehicle	1	60	Risk Ratio (M-H, Random, 95% CI)	7.75 [2.06, 29.17]

Analysis 49.1. Comparison 49: Paromomycin (15%) in Aquaphilic *versus* intralesional pentamidine (30 mg/ ml) *versus* Aquaphilic vehicle in *L. braziliensis*; FU: 6 months, Outcome 1: Complete cure at 6 months



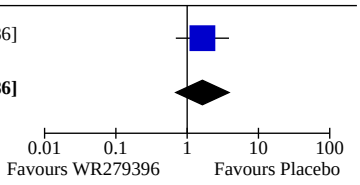
Comparison 50. Topical Aminoglycoside WR279396 *versus* placebo in *L. panamensis*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
50.1 Adverse effects: mild side effects	1	45	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.69, 3.86]
50.2 Speed to healing	1	45	Mean Difference (IV, Random, 95% CI)	-21.00 [-38.39, -3.61]

Analysis 50.1. Comparison 50: Topical Aminoglycoside WR279396 *versus* placebo in *L. panamensis*; FU: 6 months, Outcome 1: Adverse effects: mild side effects

Study or Subgroup	Aminoglycoside WR279396 Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Soto 2002	18	33	4	12	100.0%	1.64 [0.69 , 3.86]
Total (95% CI)		**33**		**12**	**100.0%**	**1.64 [0.69 , 3.86]**
Total events:	18		4			

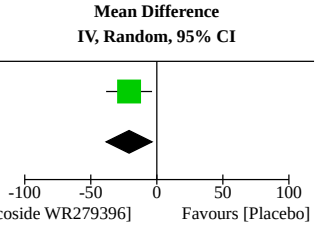
Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 50.2. Comparison 50: Topical Aminoglycoside WR279396 *versus* placebo in *L. panamensis*; FU: 6 months, Outcome 2: Speed to healing

Study or Subgroup	Aminoglycoside WR279396 Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Soto 2002	35	21	33	56	28	12	100.0%	-21.00 [-38.39 , -3.61]
Total (95% CI)			**33**			**12**	**100.0%**	**-21.00 [-38.39 , -3.61]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.37 (P = 0.02)
Test for subgroup differences: Not applicable



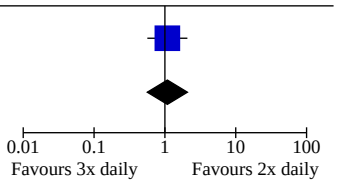
Comparison 51. Topical 3% amphotericin B cream twice a day versus three times a day in *L . panamensis* and *L. braziliensis*; FU: 6 months.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
51.1 Complete cure at 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.57, 2.08]
51.2 Complete cure at 6 months	1	67	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.60, 2.08]

Analysis 51.1. Comparison 51: Topical 3% amphotericin B cream twice a day versus three times a day in *L . panamensis* and *L. braziliensis*; FU: 6 months., Outcome 1: Complete cure at 3 months

Study or Subgroup	Amphotericin 2x daily Events	Total	Amphotericin 3x daily Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
López 2018	13	40	12	40	100.0%	1.08 [0.57 , 2.08]
Total (95% CI)		**40**		**40**	**100.0%**	**1.08 [0.57 , 2.08]**
Total events:	13		12			

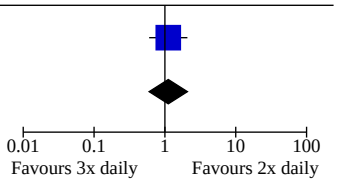
Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



Analysis 51.2. Comparison 51: Topical 3% amphotericin B cream twice a day versus three times a day in *L . panamensis* and *L. braziliensis*; FU: 6 months., Outcome 2: Complete cure at 6 months

Study or Subgroup	Amphotericin 2x daily Events	Total	Amphotericin 3x daily Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
López 2018	13	33	12	34	100.0%	1.12 [0.60 , 2.08]
Total (95% CI)		**33**		**34**	**100.0%**	**1.12 [0.60 , 2.08]**
Total events:	13		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable



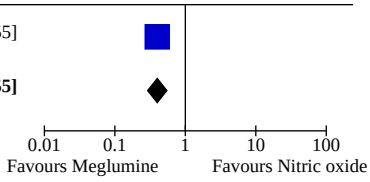
Comparison 52. Nitric oxide patch (≈3.5 µmol NO/cm2 /day, NOP) + IM placebo *vs* IM Meglumine Antimoniate (20 mg/kg/day) + placebo patch

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
52.1 Complete cure	1	143	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.29, 0.55]

Analysis 52.1. Comparison 52: Nitric oxide patch (≈3.5 µmol NO/cm2 /day, NOP) + IM placebo *vs* IM Meglumine Antimoniate (20 mg/kg/day) + placebo patch, Outcome 1: Complete cure

Study or Subgroup	Nitric oxide Events	Total	Meglumine antimoniate Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lopez-Jaramillo 2010	25	66	73	77	100.0%	0.40 [0.29 , 0.55]
Total (95% CI)		**66**		**77**	**100.0%**	**0.40 [0.29 , 0.55]**
Total events:	25		73			

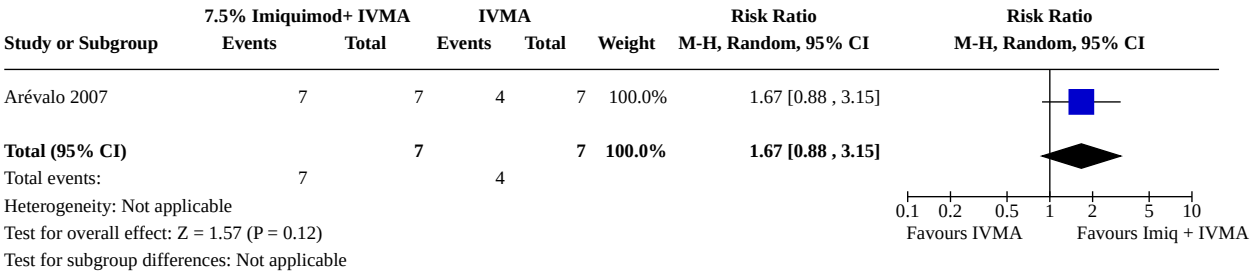
Heterogeneity: Not applicable
Test for overall effect: Z = 5.74 (P < 0.00001)
Test for subgroup differences: Not applicable



Comparison 53. 7.5% Imiquimod cream x 20 days + IV Meglumine Antimoniate for 20 days *vs* IV Meglumine Antimoniate 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
53.1 Complete cure	1	14	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.88, 3.15]

Analysis 53.1. Comparison 53: 7.5% Imiquimod cream x 20 days + IV Meglumine Antimoniate for 20 days *vs* IV Meglumine Antimoniate x 20 days in *L. braziliensis*, *L. peruviana*, *L. mexicana* and *L. amazonensis*; FU: 3 months, Outcome 1: Complete cure

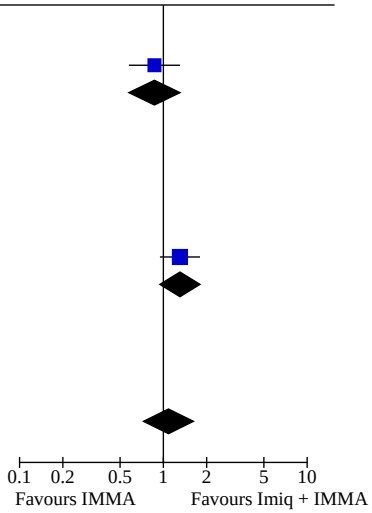


Comparison 54. Topical Imiquimod 5% + IV Meglumine Antimoniate *vs* placebo + IM/IV Meglumine Antimoniate in *L. braziliensis*, *L. guyanensis* and *L. peruviana*; FU: 1 year

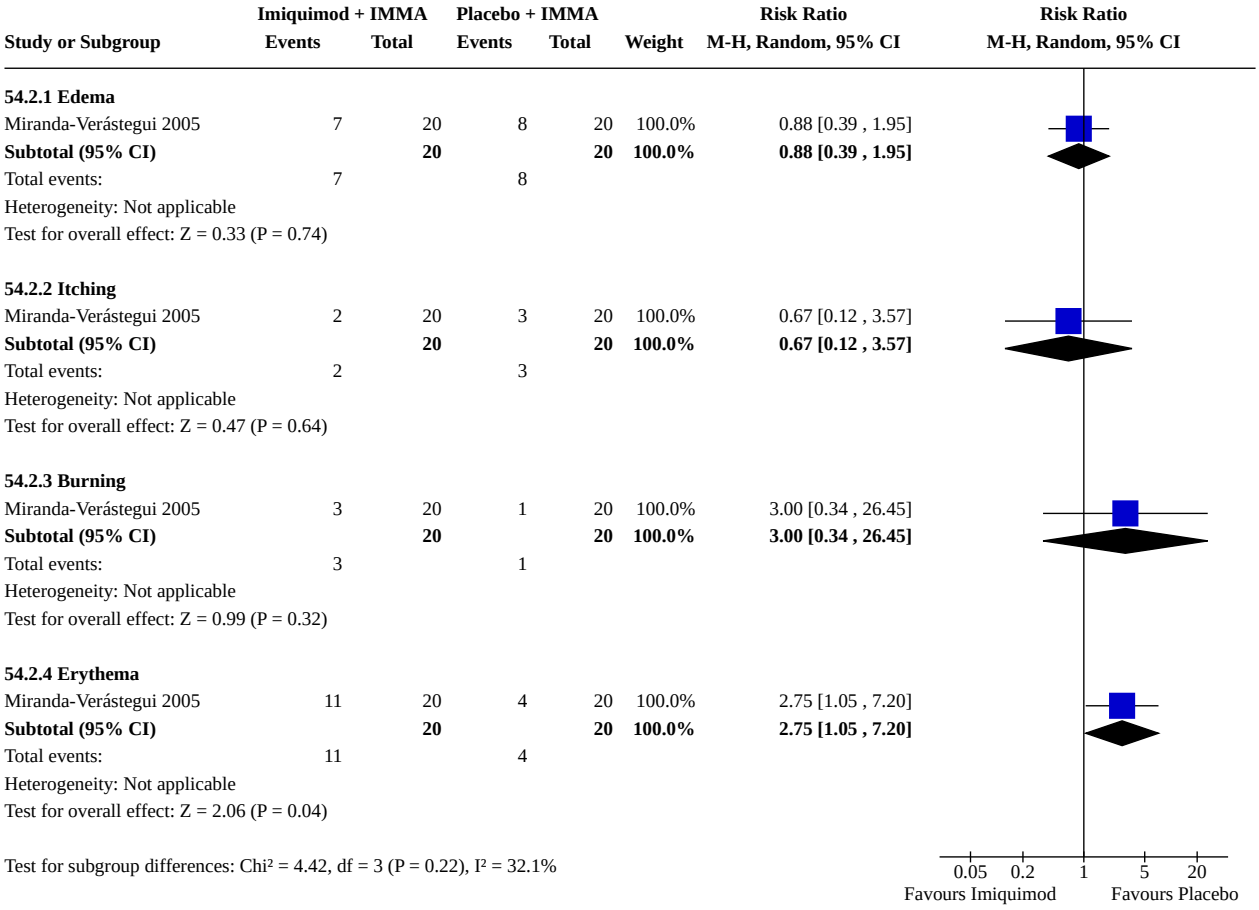
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
54.1 Complete cure	2	120	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.73, 1.62]
54.1.1 Patients with previous treatment failure	1	40	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.58, 1.30]
54.1.2 Previously untreated patients	1	80	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.95, 1.80]
54.2 Adverse effects in patients in which previous treatment failed	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
54.2.1 Edema	1	40	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.39, 1.95]
54.2.2 Itching	1	40	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.12, 3.57]
54.2.3 Burning	1	40	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.34, 26.45]
54.2.4 Erythema	1	40	Risk Ratio (M-H, Random, 95% CI)	2.75 [1.05, 7.20]

Analysis 54.1. Comparison 54: Topical Imiquimod 5% + IV Meglumine Antimoniate *vs* placebo + IM/IV Meglumine Antimoniate in *L. braziliensis, L. guyanensis* and *L. peruviana*; FU: 1 year, Outcome 1: Complete cure

Study or Subgroup	Imiquimod+MA Events	Total	IMMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
54.1.1 Patients with previous treatment failure						
Miranda-Verástegui 2005	13	20	15	20	45.0%	0.87 [0.58 , 1.30]
Subtotal (95% CI)		**20**		**20**	**45.0%**	**0.87 [0.58 , 1.30]**
Total events:	13		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
54.1.2 Previously untreated patients						
Miranda-Verástegui 2009	30	40	23	40	55.0%	1.30 [0.95 , 1.80]
Subtotal (95% CI)		**40**		**40**	**55.0%**	**1.30 [0.95 , 1.80]**
Total events:	30		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.62 (P = 0.10)						
Total (95% CI)		**60**		**60**	**100.0%**	**1.09 [0.73 , 1.62]**
Total events:	43		38			
Heterogeneity: Tau² = 0.05; Chi² = 2.38, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 0.40 (P = 0.69)						
Test for subgroup differences: Chi² = 2.37, df = 1 (P = 0.12), I² = 57.9%						



Analysis 54.2. Comparison 54: Topical Imiquimod 5% + IV Meglumine Antimoniate *vs* placebo + IM/IV Meglumine Antimoniate in *L. braziliensis*, *L. guyanensis* and *L. peruviana*; FU: 1 year, Outcome 2: Adverse effects in patients in which previous treatment failed



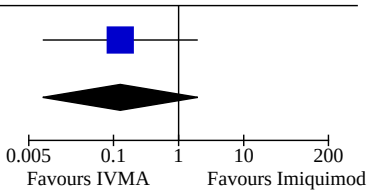
Comparison 55. 7.5% Imiquimod cream x 20 days *vs* IV Meglumine Antimoniate x 20 days in *L. braziliensis*, *L. peruviana*, *L. mexicana* and *L. amazonensis*; FU: 3 months

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
55.1 Complete cure	1	13	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 1.97]

Analysis 55.1. Comparison 55: 7.5% Imiquimod cream x 20 days *vs* IV Meglumine Antimoniate x 20 days in *L. braziliensis*, *L. peruviana*, *L. mexicana* and *L. amazonensis*; FU: 3 months, Outcome 1: Complete cure

Study or Subgroup	Imiquimod 7.5% Events	Total	IVMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Arévalo 2007	0	6	4	7	100.0%	0.13 [0.01 , 1.97]
Total (95% CI)		**6**		**7**	**100.0%**	**0.13 [0.01 , 1.97]**
Total events:	0		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable



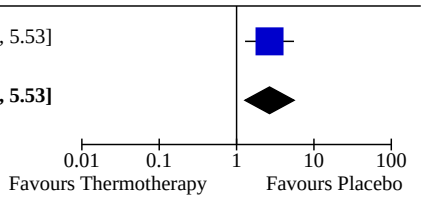
Comparison 56. Thermotherapy *versus* placebo in *L.braziliensis* and *L. mexicana. FU: 13 weeks.*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
56.1 Microbiological or histopathological cure of skin lesions at 13 weeks	1	44	Risk Ratio (M-H, Random, 95% CI)	2.67 [1.29, 5.53]

Analysis 56.1. Comparison 56: Thermotherapy *versus* placebo in *L.braziliensis* and *L. mexicana. FU: 13 weeks.*, Outcome 1: Microbiological or histopathological cure of skin lesions at 13 weeks

Study or Subgroup	Thermotherapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Navin 1990	16	22	6	22	100.0%	2.67 [1.29 , 5.53]
Total (95% CI)		**22**		**22**	**100.0%**	**2.67 [1.29 , 5.53]**
Total events:	16		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.64 (P = 0.008)
Test for subgroup differences: Not applicable



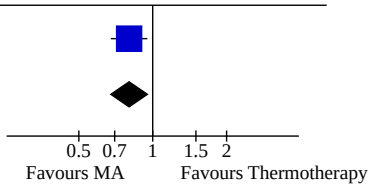
Comparison 57. Thermotherapy (at 50º for 30 seconds) *vs* Meglumine Antimoniate (20 mg Sb5/kg/day) in *L. panamensis* and *L. braziliensis*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
57.1 Complete cure	1	292	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.68, 0.95]
57.2 Microbiological or histopathological cure of skin lesions	1	44	Risk Ratio (M-H, Random, 95% CI)	2.67 [1.29, 5.53]

Analysis 57.1. Comparison 57: Thermotherapy (at 50° for 30 seconds) *vs* Meglumine Antimoniate (20 mg Sb5/kg/day) in *L. panamensis* and *L. braziliensis*; FU: 6 months, Outcome 1: Complete cure

Study or Subgroup	Thermotherapy Events	Total	MA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Vélez 2010	86	149	103	143	100.0%	0.80 [0.68 , 0.95]
Total (95% CI)		**149**		**143**	**100.0%**	**0.80 [0.68 , 0.95]**
Total events:	86		103			

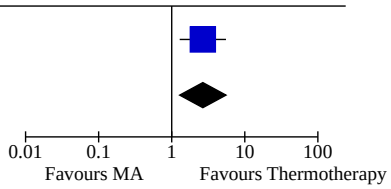
Heterogeneity: Not applicable
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 57.2. Comparison 57: Thermotherapy (at 50° for 30 seconds) *vs* Meglumine Antimoniate (20 mg Sb5/kg/day) in *L. panamensis* and *L. braziliensis*; FU: 6 months, Outcome 2: Microbiological or histopathological cure of skin lesions

Study or Subgroup	Thermotherapy Events	Total	MA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Navin 1990	16	22	6	22	100.0%	2.67 [1.29 , 5.53]
Total (95% CI)		**22**		**22**	**100.0%**	**2.67 [1.29 , 5.53]**
Total events:	16		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.64 (P = 0.008)
Test for subgroup differences: Not applicable



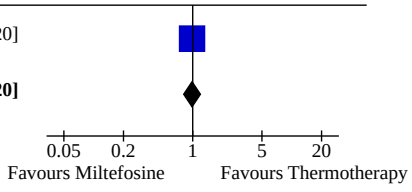
Comparison 58. Thermotherapy (at 50° for 30 seconds) *vs* oral Miltefosine (total dose of 4,200 mg) in *L. panamensis* and *L. brazililensis*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
58.1 Complete cure	1	294	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.81, 1.20]

Analysis 58.1. Comparison 58: Thermotherapy (at 50° for 30 seconds) *vs* oral Miltefosine (total dose of 4,200 mg) in *L. panamensis* and *L. brazililensis*; FU: 6 months, Outcome 1: Complete cure

Study or Subgroup	Thermotherapy Events	Total	Miltefosine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Vélez 2010	86	149	85	145	100.0%	0.98 [0.81 , 1.20]
Total (95% CI)		**149**		**145**	**100.0%**	**0.98 [0.81 , 1.20]**
Total events:	86		85			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.88)
Test for subgroup differences: Not applicable



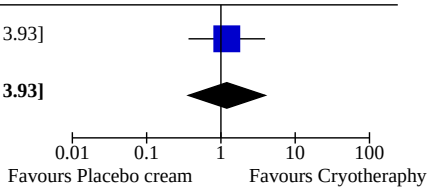
Comparison 59. Cryotherapy (5–20 seconds) *vs* placebo cream in *L. braziliensis*, *L. amazonensis*, *L. guyanensis* and *L. lainsoni*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
59.1 Complete cure	1	50	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.37, 3.93]

Analysis 59.1. Comparison 59: Cryotherapy (5–20 seconds) *vs* placebo cream in *L. braziliensis*, *L. amazonensis*, *L. guyanensis* and *L. lainsoni*; FU: 6 months, Outcome 1: Complete cure

Study or Subgroup	Cryotherapy Events	Cryotherapy Total	Placebo cream Events	Placebo cream Total	Weight	Risk Ratio M-H, Random, 95% CI
Soto 2013	4	20	5	30	100.0%	1.20 [0.37 , 3.93]
Total (95% CI)		**20**		**30**	**100.0%**	**1.20 [0.37 , 3.93]**
Total events:	4		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable



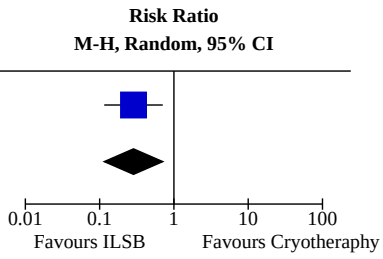
Comparison 60. Cryotherapy (5–20 seconds) *vs* IL SB (0.008 µL)/mm2 in *L. braziliensis*, *L. amazonensis*, *L. guyanensis* and *L. lainsoni*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
60.1 Complete cure	1	50	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.12, 0.71]

Analysis 60.1. Comparison 60: Cryotherapy (5–20 seconds) *vs* IL SB (0.008 µL)/mm2 in *L. braziliensis*, *L. amazonensis*, *L. guyanensis* and *L. lainsoni*; FU: 6 months, Outcome 1: Complete cure

Study or Subgroup	Cryotherapy Events	Cryotherapy Total	ILSB Events	ILSB Total	Weight	Risk Ratio M-H, Random, 95% CI
Soto 2013	4	20	21	30	100.0%	0.29 [0.12 , 0.71]
Total (95% CI)		**20**		**30**	**100.0%**	**0.29 [0.12 , 0.71]**
Total events:	4		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.71 (P = 0.007)
Test for subgroup differences: Not applicable



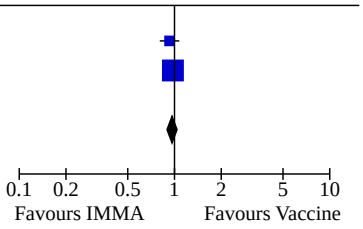
Comparison 61. Vaccine three doses *vs* IM Meglumine Antimoniate (50 mg/kg in 2-3 series of 20 daily injections) in *L. braziliensis*; FU: 6 months

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

Analysis 61.1. Comparison 61: Vaccine three doses *vs* IM Meglumine Antimoniate (50 mg/kg in 2-3 series of 20 daily injections) in *L. braziliensis*; FU: 6 months, Outcome 1: Complete cure

	Vaccine		IMMA			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Convit 1987	49	58	40	44	26.2%	0.93 [0.80 , 1.07]	
Convit 1989	114	124	48	51	73.8%	0.98 [0.90 , 1.06]	
Total (95% CI)		**182**		**95**	**100.0%**	**0.96 [0.90 , 1.04]**	
Total events:	163		88				

Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



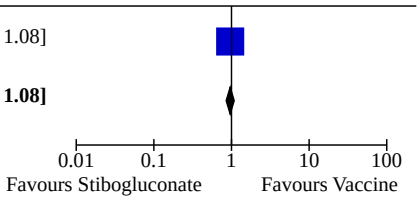
Comparison 62. Intradermal vaccine of biological LEISH-F2 + MPL-SE *versus* sodium stibogluconate in *L. Peruvian*. FU: up to 335 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
62.1 Adverse effects not serious	1	45	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.08]

Analysis 62.1. Comparison 62: Intradermal vaccine of biological LEISH-F2 + MPL-SE *versus* sodium stibogluconate in *L. Peruvian*. FU: up to 335 days, Outcome 1: Adverse effects not serious

	Vaccine		Stibogluconate			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
NCT01011309	23	24	21	21	100.0%	0.96 [0.86 , 1.08]	
Total (95% CI)		**24**		**21**	**100.0%**	**0.96 [0.86 , 1.08]**	
Total events:	23		21				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable



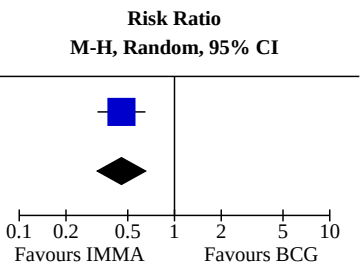
Comparison 63. BCG (three doses) *vs* IM Meglumine Antimoniate (50 mg/kg /day 40-60 injections) in *L. braziliensis*; FU: 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
63.1 Complete cure	1	93	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.32, 0.65]

Analysis 63.1. Comparison 63: BCG (three doses) *vs* IM Meglumine Antimoniate (50 mg/kg /day 40-60 injections) in *L. braziliensis*; FU: 6 months, Outcome 1: Complete cure

Study or Subgroup	BCG Events	BCG Total	IMMA Events	IMMA Total	Weight	Risk Ratio M-H, Random, 95% CI
Convit 1989	18	42	48	51	100.0%	0.46 [0.32 , 0.65]
Total (95% CI)		**42**		**51**	**100.0%**	**0.46 [0.32 , 0.65]**
Total events:	18		48			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.33 (P < 0.0001)
Test for subgroup differences: Not applicable



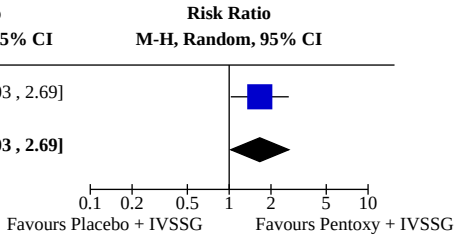
Comparison 64. Oral pentoxifylline 400 mg 3 times daily for 30d + IV Sodium Stibogluconate 20 mg/kg /d *vs* placebo + IV Sodium Stibogluconate in *L. braziliensis*; FU: 4 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
64.1 Complete cure	1	23	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.03, 2.69]
64.2 Speed to healing	1	23	Mean Difference (IV, Random, 95% CI)	-62.00 [-121.92, -2.08]

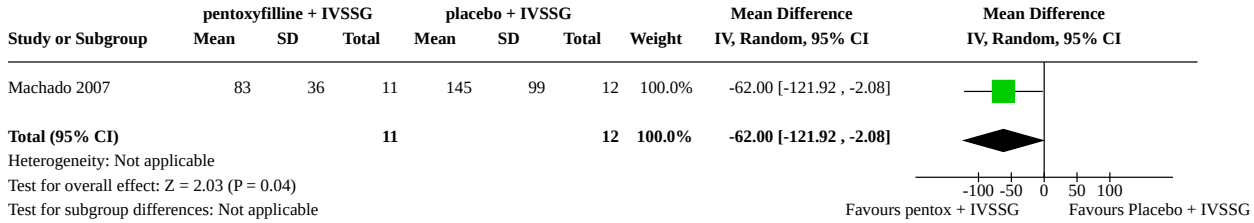
Analysis 64.1. Comparison 64: Oral pentoxifylline 400 mg 3 times daily for 30d + IV Sodium Stibogluconate 20 mg/kg /d *vs* placebo + IV Sodium Stibogluconate in *L. braziliensis*; FU: 4 months, Outcome 1: Complete cure

Study or Subgroup	pentoxyfilline + IVSSG Events	pentoxyfilline + IVSSG Total	placebo + IVSSG Events	placebo + IVSSG Total	Weight	Risk Ratio M-H, Random, 95% CI
Machado 2007	11	11	7	12	100.0%	1.66 [1.03 , 2.69]
Total (95% CI)		**11**		**12**	**100.0%**	**1.66 [1.03 , 2.69]**
Total events:	11		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.07 (P = 0.04)
Test for subgroup differences: Not applicable



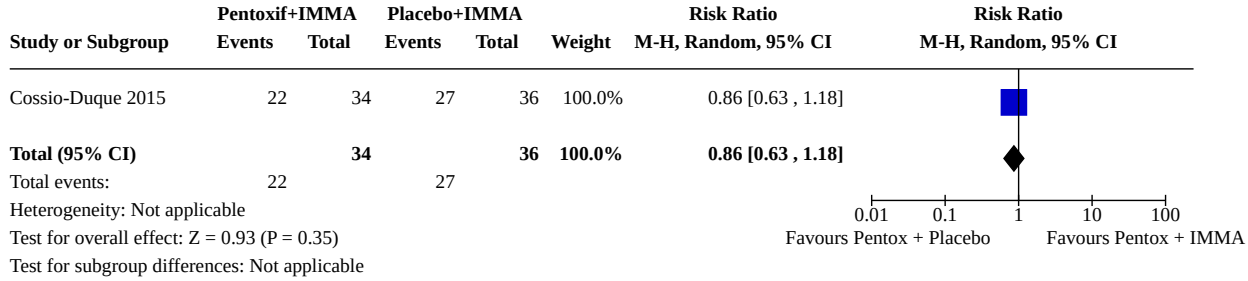
Analysis 64.2. Comparison 64: Oral pentoxifylline 400 mg 3 times daily for 30d + IV Sodium Stibogluconate 20 mg/kg /d *vs* placebo + IV Sodium Stibogluconate in *L. braziliensis*; FU: 4 months, Outcome 2: Speed to healing



Comparison 65. Oral Pentoxifylline (1200 mg/day) + IM Meglumine Antimoniate (20 mg/ kg /day) *vs* IM Meglumine Antimoniate + placebo; FU: 26 weeks

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
65.1 Complete cure	1	70	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.63, 1.18]

Analysis 65.1. Comparison 65: Oral Pentoxifylline (1200 mg/day) + IM Meglumine Antimoniate (20 mg/ kg /day) *vs* IM Meglumine Antimoniate + placebo; FU: 26 weeks, Outcome 1: Complete cure



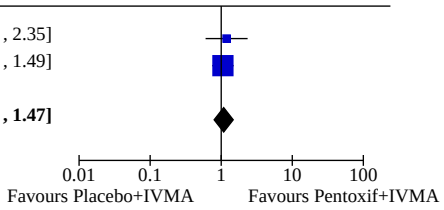
Comparison 66. Oral Pentoxifylline (1200 mg) + IM Meglumine Antimoniate (20mg/kg) *vs* IM Meglumine Antimoniate (20mg/kg) + placebo *L. braziliensis*; FU: 90-180 days

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
66.1 Complete cure	2	197	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.80, 1.47]

Analysis 66.1. Comparison 66: Oral Pentoxifylline (1200 mg) + IM Meglumine Antimoniate (20mg/kg) *vs* IM Meglumine Antimoniate (20mg/kg) + placebo *L. braziliensis*; FU: 90-180 days, Outcome 1: Complete cure

Study or Subgroup	Pentoxifylline+IMMA Events	Total	Placebo+IMMA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brito 2014	10	18	7	15	20.6%	1.19 [0.60 , 2.35]
Brito 2017a	37	82	35	82	79.4%	1.06 [0.75 , 1.49]
Total (95% CI)		**100**		**97**	**100.0%**	**1.08 [0.80 , 1.47]**
Total events:	47		42			

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)
Test for subgroup differences: Not applicable



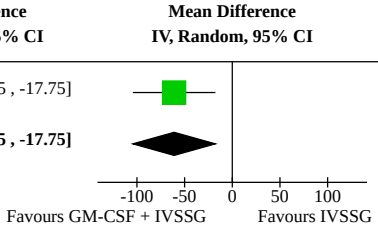
Comparison 67. GM-CSF combined with IV sodium stibogluconate *versus* IV sodium stibogluconate in *L. braziliensis*. FU 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
67.1 Speed to healing	1	20	Mean Difference (IV, Random, 95% CI)	-61.00 [-104.25, -17.75]

Analysis 67.1. Comparison 67: GM-CSF combined with IV sodium stibogluconate *versus* IV sodium stibogluconate in *L. braziliensis*. FU 6 months, Outcome 1: Speed to healing

Study or Subgroup	GM-CSF + IVSSG Mean	SD	Total	IVSSG Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Almeida 1999	49	32.8	10	110	61.6	10	100.0%	-61.00 [-104.25 , -17.75]
Total (95% CI)			**10**			**10**	**100.0%**	**-61.00 [-104.25 , -17.75]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.76 (P = 0.006)
Test for subgroup differences: Not applicable

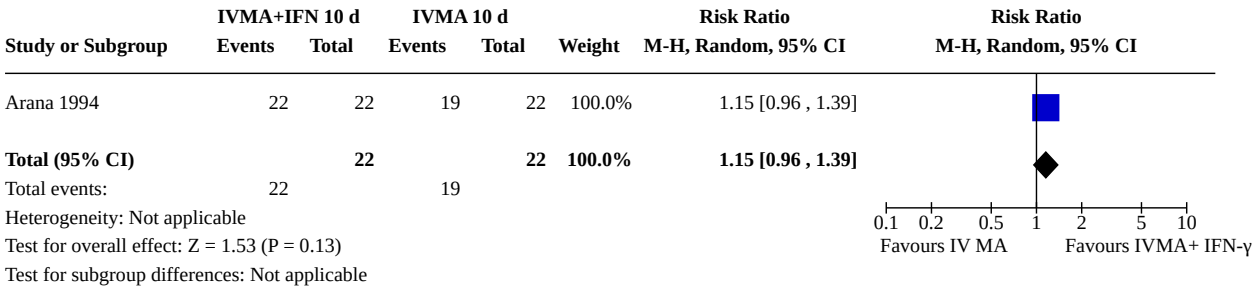


Comparison 68. Subcutaneous interferon-Gamma plus IV MA versus IVMA alone in *L. braziliensis* and *L. mexicana*; FU: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
68.1 Complete cure; 10-day IV MA+10-day IFN-γ *versus* 10-day IV MA+10-day placebo	1	44	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.99, 1.50]
68.2 Complete cure; 10-day IV MA+ 10-day IFN-γ *versus* 20-day IV MA	1	44	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.96, 1.39]

Analysis 68.1. Comparison 68: Subcutaneous interferon-Gamma plus IV MA versus IVMA alone in *L. braziliensis* and *L. mexicana*; FU: 1 year, Outcome 1: Complete cure; 10-day IV MA+10-day IFN-γ *versus* 10-day IV MA+10-day placebo

Analysis 68.2. Comparison 68: Subcutaneous interferon-Gamma plus IV MA versus IVMA alone in *L. braziliensis* and *L. mexicana*; FU: 1 year, Outcome 2: Complete cure; 10-day IV MA+ 10-day IFN-γ *versus* 20-day IV MA



ADDITIONAL TABLES

Table 1. Glossary

Term	Definition
Aminoglycoside	antibiotic composed of an amino sugar structure with antimicrobial effect through the inhibition of protein synthesis
Anfotericin B	polyene antibiotic used for treatment of severe fungal infections and some protozoal infections such as leishmaniasis
Antigenic	a molecule that is capable of binding to an antibody or to an antigen receptor on a cell of the immune system, especially one that induces an immune response
Anthropic interventions	environmental modifications due to human activities such as deforestation, etc
Antimonials	medications composed of antimony salts for intravenous, intramuscular or subcutaneous application
Azalide	antibiotic composed of a macrolide ring containing nitrogen that inhibits microorganism growth through the inhibition of protein synthesis
Cryotherapy	local use of low temperature (freezing) for treating cutaneous lesions
Larynx	the hollow muscular organ forming an air passage from the pharynx to the trachea and holding the vocal cords in humans and other mammals

Table 1. Glossary *(Continued)*

Lymph node	a small organ of the lymphatic system characterised by lymphoid tissue surrounded by a capsule of connective tissue with the function of antigen processing and presenting to organise the adaptive immune response
Miltefosine	alkyl-phosphocholine compound medication used as oral treatment for leishmaniasis
Parenteral	route of administering medications other than the digestive tract
Paromomycin	an aminoglycoside with antiprotozoal activity
Pentamidine	a synthetic amidine derivative medication with antiprotozoal and antifungal agent used as intravenous or intramuscular treatment for leishmaniasis
Pentavalent antimony	the pentavalent form of antimony salts used for intravenous, intramuscular or subcutaneous application
Pentoxifylline	a methylxanthine derivative compound medication use for treatment of vascular disorders and as an adjuvant for treatment of leishmaniasis due to its capacity of modulate the immune response
Pharynx	the membrane-lined cavity behind the nose and mouth, connecting them to the oesophagus
Photodynamic therapies	is a treatment that uses a drug, called a photosensitiser or photosensitising agent, and a particular type of light. When photosensitisers are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells
Purine analogue	medication that mimics purine bases essential for DNA synthesis
Reservoir	an organism (a vertebrate in the case of leishmaniasis) where an infectious agent lives and multiplies
Sympatric circulation	used to refer to the concomitant transmission of more than one parasite species in the same geographical area
Ulceration	the process of ulcer formation
Vector	is an organism (an arthropod – Diptera, Psycodidade – in the case of leishmaniasis) that does not cause disease itself but which spreads infection by conveying pathogens from one host to another
Zoonotic	a disease that can spread from animals to humans

Table 2. Interventions for American cutaneous and mucocutaneous leishmaniasis

Type of interventions	Pharmacological class of interventions	Intervention	Current clinical applicability	Administration route	Main toxicity	Pregnancy safety	Key references
1. Antimonials	Pentavalent antimonial	N-methyl glucamine antimoniate (MA)	CL, MCL	IV; IM; IL	Common: QT prolongation, abnormal liver and pancreatic enzymes, myalgias and infusion-related fever. Rare: severe pancreatitis and hepatic failure	Possible harm to the fetus; insufficient controlled studies in humans and animals. Experimental studies with pentavalents antimonials in pregnant rats showed an increase in fetal skeletal malformations. May be toxic to the embryo even in the absence of signs of maternal toxicity	(Oliveira 2011; Soto 2013; Fontenele e Silva 2013)
		Sodium stibogluconate (SSG)	CL, ML	IV; IM	Common: QT prolongation, abnormal liver and pancreatic enzymes, myalgias and infusion related fever. Rare: severe pancreatitis and hepatic failure.		(Oliveira 2011; Fontenele e Silva 2013)
2. Non-antimonial systemic treatments	Antifungals: Macrolide polyene antibiotic	Amphotericin B	CL, ML	IV	Common: infusion-related fever and phlebitis, hypokalaemia, renal dysfunction and anaemia	Remote possibility of fetal harm; animal studies showed no risk to the fetus. Studies in people with visceral leishmaniasis show no adverse effects on the fetus or abortions when it was used during the first trimester of pregnancy	(Mishra 2007; Gallis 1990; Fontenele e Silva 2013)
		Liposomal amphotericin B	CL, ML	IV	Common: fever, nausea, phlebitis, dorsal pain, vomiting, headache and mild renal toxicity		(Wortmann 2010; Fontenele e Silva 2013; Machado 2015).
	Antifungals: Azoles	Ketoconazole	CL	Oral	Common: nausea, abdominal pain, headache, fever, dizziness, abnormal liver enzymes, rash. Rare: severe liver injury and adrenal gland dysfunction	Ketoconazole can compromise early pregnancy due to inhibiting progesterone synthesis in the ovary	(Saenz 1990; Navin 1992; Cummings 1997; FDA 2013)
		Itraconazole	CL	Oral	Common: nausea, headache and abnormal liver enzymes Rare: severe hepatitis	Animal reproduction studies have shown an adverse effect on the fetus, but there are no adequate and well-controlled studies in humans	(Consigli 2006; FDA 2014)

Table 2. Interventions for American cutaneous and mucocutaneous leishmaniasis *(Continued)*

		Fluconazole	CL	Oral	Common: headache; abnormal liver enzymes. Rare: severe neurologic toxicity.	High-dose fluconazole (400-800 mg/day) during most or all of the first trimester has been associated to birth defects in infants.	(Sousa 2011; Neto 2006; Alves Noroes 2015; FDA 2011; FDA 2016)
	Purine analogue	Allopurinol	CL	Oral	Common: headache and epigastric pain Rare: rash and haematologic abnormalities	Caution recommendation in the first trimester. Possible teratogenicity	(Vélez 1997; Hoeltzenbein 2013)
	Alkylphosphocholine analogue	Miltefosine	CL, ML	Oral	Common: reversible gastrointestinal disturbances, renal toxicity.	Teratogenic, contraindicated in pregnancy	(Sundar 2006; Fontenele e Silva 2013).
	Aromatic diamidine	Pentamidine isethionate	CL; ML	IV; IM	Common: pain at the site of injection, nausea, vomiting, headache, burning sensation and hypotension Rare: skin eruptions, abnormal liver enzymes, renal dysfunction, hypoglycaemia and diabetes mellitus	Possible harm to the fetus; insufficient controlled studies in humans and animals	(Sands 1985; Neves 2011; Fontenele e Silva 2013).
	Aminoglycosides	Aminosidine sulphate	CL; ML	IV	Ototoxicity and renal dysfunction	As for all the aminoglycosides there is evidence of human fetal risk.	(Kim 2009)
3. Non-antimonial topical or intralesional therapies	Aminoglycosides	Paromomycin sulphate	CL	Topical	Common: local pain, burning sensation and pruritus. Very rare: ototoxicity	As for all the aminoglycosides there is evidence of human fetal risk.	(Kim 2009)
4. Physical therapies	Physical therapies	Thermotherapy	CL	Local	Common: moderate to severe local cellulites and burns; pain at the lesion area 4 days after the initiation of treatment	Safe	(Lobo 2006; Lopez 2012)
		Photodynamic therapy	CL	Local	Common: Local pain	Studies in diseases other than leishmaniasis indicate that this lo-	(Enk 2015; Yang 2012)

Table 2. Interventions for American cutaneous and mucocutaneous leishmaniasis *(Continued)*

						cal therapy could be safe during pregnancy	
5. Immuno-chemotherapy	Immunomodulatory agent: methyl xanthine derivative	Pentoxifylline	CL; ML	Oral	Common: nausea, arthralgia, dizziness, abdominal pain and diarrhoea	There are no adequate and well-controlled studies in pregnant women. Pentoxifylline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus	(Machado 2007)
	Immunomodulatory agent: TLR stimulator	Imiquimod	CL	Topical	Common: Moderate pruritus and burning sensation, erythema	Studies in diseases other than leishmaniasis have reported no adverse local effect nor adverse fetal outcomes or fetal and neonatal abnormalities	(Edwards 2000; Miranda-Verástegui 2005; Arevalo 2007)
	Immunomodulatory agent: cytokine	Granulocyte-macrophage colony-stimulating factor (GM-CSF)	CL	Topical	In 1 study no systemic side effects or contact allergic reactions were reported	No data available	(Almeida 2005)

CL: cutaneous; MCL: mucocutaneous; IV: intravenous; IM: intramuscular; IL: intralesional.

Table 3. Geographic distribution of *Leishmania*

Study reference	Country	Form of *Leishmania*	Type of parasite	Interventions
Garcia 2014 (New)	Argentina	MCL	*L. braziliensis; L. amazonensis* (confirmed in only 3 participants)	T1: Oral miltefosine, 2.5 to 3.3 mg/kg/day (maximum dose 150 mg/day) for 28 - 35 days; T2: IMMA 10 to 20 mg/kg/day (maximum dose 850 mg/day) for 28 - 35 days
Krolewiecki 2007 (New)	Argentina	CL	*L. braziliensis* (confirmed)	T1: Oral AZ 500-mg tablets at a dose of two tablets on the first day, followed by one tablet every 24 hours for another 27 days; T2: IM or IVMA (5-mL vials containing 1.5 g of antimony, corresponding to 425 mg of pentavalent Sb) for 28 days
Hepburn 1994	Belize	CL	*L. braziliensis; L. mexicana* (confirmed)	T1: IVAS 14 mg/kg/day; T2: IVSSG 20 mg/kg/day for 20 days
Soto 2004a	Bolivia & Colombia	CL	*L. panamensis* (confirmed)	T1: IMSSG 20 mg/Kg/day; T2: IMMA 20 mg/Kg/day for 20 days
Guzman-Rivero 2014 (New)	Bolivia	CL	*L. braziliensis* (endemic)	T1: IMMA 20 mg/kg/day for 20 days + zinc capsule contained 315 mg of zinc gluconate (45 mg zinc) for 60 days; T2: IMMA 20 mg/kg/day for 20 days + placebo capsule contained 315 mg of corn starch for 60 days
Soto 2013 (New)	Bolivia	CL	*L. braziliensis; L. amazonensis; L. guyanensis; L. lainsoni* (confirmed)	T1: ILSSG 15% (81 mg/mL) was administered on each of days 1, 3, and 5; T2: Cryotherapy on days 1 and 14; T3: topical placebo for 20 days
Soto 2008 (New)	Bolivia	CL	*L. braziliensis* (endemic)	T1: Oral miltefosine (2.5 mg/kg/d) for 28 days; T2: IMMA 20 mg/kg/d for 20 days
Soto 2016a (New)	Bolivia	CL	*L. braziliensis*; *L. amazonensis*; *L. guyanensis*; *L. lainsoni* (confirmed)	T1: ILSb (N-methylglucamine (Glucantime®; 81 mg Sb/mL) was administered on each of days 1, 3, and 5 (ILSb-3 injections); T2: ILSb (N-methylglucamine on each of days 1, 3, 5, 8, and 11 (ILSb-5 injections) at a dose of 650 µg Sb (8 µL)/mm2 of lesion area per day; T3: IL pentamidine (30 mg/mL; Pentacarinat®) was administered at a dose of 120 µg (4 µL)/mm^2 of lesion area (ILpenta-120-3 injections) or 240 µg (8 µL)/mm^2 of lesion area (ILpenta-240-3 injections) on each of days 1, 3, and 5
Soto 2016b (New)	Bolivia	CL	*L. braziliensis*; *Leishmania sp* (confirmed)	T1: ILSb (N-methylglucamine on each of days 1, 3, 5, 8, and 11 (ILSb-5 injections) at a dose of 650 µg Sb (8 µL)/mm2 of lesion area per day; T2: IL pen-

Table 3. Geographic distribution of *Leishmania* *(Continued)*

				tamidine 240 µg (8 µL)/mm2 of lesion area (ILpenta-240-3 injections) on days 1, 3, and 5.
Soto 2019 (New)	Bolivia	CL	*L. braziliensis* (endemic), although 5 patients had it confirmed	T1: 15% paromomycin in aquafilm base twice a day for 20 consecutive days; T2: IL Pentamidine (30 mg/mL; Pentacarinat Sanofi-Aventis, Bogota, Colombia) was administered intralesionally at a dose of 120 µg (4 µL)/mm2 of the lesion area on days 1, 3, and 5; T3: 10% Urea in parafilm cream, twice a day for 20 days
Almeida 1999	Brazil	CL	*L. braziliensis* (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
Alves 2016 (New)	Brazil	CL	*L. braziliensis* (confirmed)	T1: IM pentamidine 3 doses, 4 mg/kg/per day each 3 days for 20 days; T2: IVMA 20 mg SbV/kg/per day for 20 days.
Alves Noroes 2015 (New)	Brazil	CL	*L. braziliensis* (confirmed)	T1: Capsules of 126 or 168 Fluconazol ® at a concentration of 150 mg/capsule, respectively, having to eat 2 or 3 capsules at once in the morning; T2: intravenous glucantime® at a dose of 20 mg/kg/day
Correia 1996	Brazil	CL	*L. braziliensis* (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
D'Oliveira 1997	Brazil	CL	*L. braziliensis* (confirmed)	T1: Oral allopurinol 20 mg/kg 3 times/day for 20 days; T2: IVMA 10 mg/kg OD 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	*L. braziliensis* (endemic)	T1: Single session heat therapy; T2: IVMA 20 mg/kg/d for 20 days
Machado 2007	Brazil	MCL	*L. braziliensis* (endemic)	T1: Oral pentoxifylline 400 mg 3 times/day for 30 days + IVSSG 20 mg/kg/d; T2: Oral placebo + IVSSG 20 mg/kg/day
Oliveira-Neto 1997	Brazil	CL	*L. braziliensis* (confirmed)	T1: IVMA 5 mg/kg/day; T2: IVMA 20 mg/kg/day *for 30 days
Santos 2004	Brazil	CL	*L. braziliensis* (endemic)	T1: GM-CSF+ IV MA 20 mg/kg/d for 20 days;

Table 3. Geographic distribution of *Leishmania* *(Continued)*

				T2: Placebo + IVMA 20 mg/kg/d for 20 days
Machado-Pinto 2002	Brazil	CL	*L. braziliensis* (endemic)	T1: Subcutaneous injection of *L. amazonensis* strain vaccine (0.5 ml) daily + IMMA; T2: Subcutaneous injection of placebo daily+ IMMA *(8.5 mg/kg) for 10 days and 10 days of rest
Brito 2014 (New)	Brazil	CL	*L. braziliensis* (confirmed)	T1: Pentavalent antimony (Sbv) 20 mg/kg a day + oral pentoxifylline (400 mg); T2: pentavalent antimony (Sbv) 20 mg/kg a day + oral placebo 3 times a day)
Brito 2017a (New)	Brazil	CL	*L. braziliensis* (confirmed)	T1: VMA 20 mg Sbv/Kg/day for 20 consecutive days (maximum daily dose of 1215 mg) and simultaneously pentoxifylline (400 mg) 3 times daily for 20 days; T2: IVMA 20 mg Sbv/Kg/day (maximum daily dose of 1215 mg) day for 20 days and inert pills (3 times daily for 20 days)
Chrusciak-Talhari 2011 (New)	Brazil	CL	*L. braziliensis; L. guyanensis; L. lainsoni* (confirmed)	T1: Oral miltefosine total target daily dosage of 2.5 mg/kg of body weight (maximum daily dose of 150 mg) for 28 days; T2: IVMA 20 mg/kg/day or 15 mg/kg/day (if aged < 12 years) for 20 days
Ferreira 2014 (New)	Brazil	MCL	*L. braziliensis* (endemic; although identification was claimed to have been done, no species were reported in results)	T1: SSG 20 mg Sb5+/kg/day for 30; T2: Sb5+ 5 mg/kg/day until cured or maximum of 120 days
Gadelha 2018 (New)	Brazil	CL	*L. guyanensis*, *L. naifi*, and *L. braziliensis* (confirmed)	T1: single intramuscular injection of 7 mg/kg pentamidine isethionate (PI) salt; T2: 2 intramuscular injections of 7 mg/kg within a 7-day interval; T3: 3 intramuscular injections of 7 mg/kg with a 7-day interval between each dose
Machado 2010 (New)	Brazil	CL	*L. braziliensis* (confirmed)	T1: Oral miltefosine for 28 days; T2: Sbv for 20 days
Machado 2018 (New)	Brazil	CL	*L. braziliensis* (confirmed)	T1: oral tamoxifen 20 mg/ day tamoxifen citrate every 12 h for 20 consecutive days plus SbV; T2: topical tamoxifen (a cream formulated in oil-free vehicle at 0.1% tamoxifen citrate twice a day for 20 day) plus SbV; T3: SbV monotherapy for 20 days

Table 3. Geographic distribution of *Leishmania* *(Continued)*

Neves 2011 (New)	Brazil	CL	*L. braziliensis; L. guyanensis* (confirmed)	T1: IV or IMMA 15 mg/kg/day for 20 days; T2: IM pentamidine 4 mg/kg were administered every 72 hours; T3: IV amphotericin B 1mg/kg/day for 20 days
Newlove 2011 (New)	Brazil	CL	*L. braziliensis* (endemic)	T1: Oral albendazole (400 mg), ivermectin (200 µg/kg), and praziquantel (50 mg/kg) on days 0 and 30 + placebo on day 60; T2: Placebo at Days 0 and 30
Prates 2017 (New)	Brazil	CL	*L. braziliensis* (confirmed)	T1: fluconazole administered orally in capsules containing 150 mg of the drug at a dosage of 6.5 – 8 mg/kg/d for 28 days; T2: Sbv (Glucantime), administered intravenously at a dosage of 20 mg/kg/d for 20 days
Saheki 2017 (New)	Brazil	CL	*L. braziliensis* (confirmed)	T1: 20 mg IL MA Sb5+/kg/day (high dose) for 20 days; T2: 5 mg IL MA Sb5+/kg/day (low dose) for 30 days
Sampaio 2019 (New)	Brazil	ML	*L. braziliensis* (confirmed)	T1: miltefosine 1.3 – 2 mg/kg/day (2 capsules) for 28 days; T2: intravenous 20 mg SbV/kg/day of meglumine antimoniate (N-MA) for 30 days
Souza 1998 (New)	Brazil	CL	NR	T1: Pentamidine injections 4 mg/kg/dose - 3 doses with 2 day interval; T2: glucantime injections 15 mg/kg/day for 20 days; T3: glucantime injections 7.5 mg/kg/day for 15 days
Toledo 2014 (New)	Brazil	CL	*L. braziliensis* (endemic)	T1: IV or IMMA 15 mg/kg/day (maximum daily dose of 1215 mg) for 20 days; T2: Oral AZ 500 mg a day for 20 days
Cossio-Duque 2015 (New)	Colombia	CL	NR	T1: IMMA (20 mg/ kg /day) for 20 days plus oral PTX 400 mg thrice daily; T2: MA plus placebo
Martínez 1992	Colombia	CL	*L. panamensis* (confirmed)	T1: Oral AL 20 mg/kg/day in 4 doses for 15 days; T2: IVMA 20 mg/kg/day for 15 days; T3: AL+ MA same doses; T4: no treatment
Martínez 1997	Colombia	CL	*L. braziliensis* (confirmed)	T1: Oral AL 20 mg/kg/day in 4 doses for 15 days+ IVSSG;

Table 3. Geographic distribution of *Leishmania* *(Continued)*

				T2: IVSSG *20 mg/kg/day for 15 days
Palacios 2001	Colombia	CL	*L. braziliensis; L. panamensis* (confirmed)	T1: IMMA 20 mg/kg/day once a day for 10 days; T2: IMMA 20 mg/kg/day once a day for 20 days
Soto 2002	Colombia	CL	*L. panamensis* (confirmed)	T1: Topical WR279396 TD for 20 days; T2: Topical placebo
Soto 1994a	Colombia	CL	*L. panamensis* (confirmed)	T1: AS 12 mg/Kg/day for 7 days; T2: AS 12 mg/Kg/day for 14 days; T3: AS 18 mg/Kg/day for 14 days
Soto 1998	Colombia	CL	*L. braziliensis; L. panamensis* (confirmed)	T1: Topical 15% PR sulphate 12% MBCL thrice daily for 10 days + IVMA for 7 days; T2: Topical placebo thrice daily for 10 days + IVMA for 7 days; T3: Topical 15% PR sulphate 12% MBCL thrice daily for 10 days+ IV MA for 3 days; T4: IVMA for 20 days
Vélez 1997	Colombia	CL	*L. braziliensis; L. panamensis* (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	*L. panamensis; L. braziliensis; L. mexicana* (confirmed)	T1: Oral miltefosine for 28 days; T2: Placebo
López 2018 (New)	Colombia	CL	*L. panamensis; L. braziliensis* (confirmed)	T1: Amphotericin B at 3% thrice daily for 28 days; T2: amphotericin B at 3% thrice daily for 28 days
Lopez-Jaramillo 2010 (New)	Colombia	CL	*L. panamensis* (caused but not clear if confirmed)	T1: IMMA 20 mg/kg/day plus a placebo patch for 20 days; T2: Intramuscular placebo (5 – 20 cc/day), and topical nanofiber nitric oxide (NO) releasing patch (≈ 3.5 µmol NO/cm 2 /day, NOP) for 20 days
Rubiano 2012 (New)	Colombia	CL	*L. panamensis; L. guyanensis; L. braziliensis* (confirmed)	T1: Oral miltefosine (10 mg miltefosine/capsule) at 1.5 – 2.5 mg/kg/d in 2 - 3 doses/day for 28 days; T2: IMMA 20 mg/kg/day for 20 days
Vélez 2010 (New)	Colombia	CL	*L. panamensis; L. braziliensis* (confirmed)	T1: Oral miltefosine (50 mg miltefosine/capsule) 3 times/day for 28 days; T2: Thermotherapy given as a single session followed by 10 days of antibiotic treatment; T3: IMMA 20 mg/kg/day for 20 days
Armijos 2004	Ecuador	CL	NR	T1: Topical PR 15% + 12% MBCL TD for 30 days;

Table 3. Geographic distribution of *Leishmania* *(Continued)*

				T2: Topical PR 15% + 10% urea thrice daily for 30 days; T3: IMMA 20 mg/kg/day for 10 days
Guderian 1991	Ecuador	CL	*L. panamensis; L. guyanensis; L. braziliensis; L. mexicana* (confirmed)	T1: Oral AL ribonucleoside (1500 mg 4 times a day) plus probenecid (500 mg 4 times a day) for 28 days; T2: IMSSG (20 mg/Kg/day) for 20 days; T3: no treatment
Chico 1995 (New)	Ecuador	CL	*L. braziliensis; L. mexicana; L. panamensis; L.guyanensis; L. amazonensis* (confirmed)	T1: Oral allopurinol riboside (1500 mg/6 h, four times per day) plus probenecid (500 mg/6 h, four times per day) for 28 days; T2: IMSSG 20 mg/kg/day for 20 days; T3: untreated
Arana 2001	Guatemala	CL	*L.braziliensis; L.mexicana* (previous studies)	T1: Topical 15% PR plus 12% MBCL; T2: Topical placebo *thrice daily for 20 days
Arana 1994	Guatemala	CL	*L. braziliensis; L. mexicana* (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-γ
Navin 1990	Guatemala	CL	*L. braziliensis; L. mexicana* (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	*L. braziliensis; L. mexicana* (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	*L. chagasi; L. mexicana* (confirmed)	T1: Topical 15% PR + 10% urea; T2: Topical placebo *3 times/day for 4 weeks
Saenz 1987	Panama	CL	*L. panamensis* (confirmed)	T1: IMSSG 20 mg/kg/d; T2: IMMA 20 mg/kg/d *for 20 days
Saenz 1990	Panama	CL	*L. panamensis; L. mexicana* (confirmed)	T1: Oral ketoconazole 3 (200 mg tablets) each day for 28 days; T2: IMMA 20 mg/Kg for 20 days; T3: Oral placebo 3 tablets for 28 days
Sosa 2019 (New)	Panama	CL	*L. panamensis; L.guyanensis;*	T1: WR 279,396 (15% paromomycin + 0.5% gentamicin topical cream) once daily for 20 days;

Table 3. Geographic distribution of *Leishmania* *(Continued)*

			L.braziliensis; L. naiffi (confirmed)	T2: paromomycin (15% paromomycin topical cream) once daily for 20 days
Ravis 2013 (New)	Panama	CL	NR	T1: Topical WR 279,396 (each gram of cream contains 150 mg (15% (wt/wt)) paromomycin USP base and 5 mg (0.5% (wt/wt)) gentamicin USP base) for 20 days; T2: Topical paromomycin alone (each gram of cream contains 150 mg (15% (wt/wt)) paromomycin USP base) for 20 days
Sosa 2013 (New)	Panama	CL	*L. panamensis* (confirmed)	T1: Topical WR 279,396 (15% paromomycin +0.5% gentamicin) for 20 days; T2: Topical paromomycin 15% for 20 days
Andersen 2005	Peru	CL	*L. braziliensis* (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	*L. braziliensis; L. peruviana; L. mexicana; L. amazonensis* (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
Franke 1994	Peru	MCL	*L. braziliensis* (confirmed)	T1: IVSSG 20 mg Sb/Kg/d for 28 days; T2: IVSSG 20 mg/Kg/d for 40 days
Llanos-Cuentas 2007	Peru	MCL	*L. braziliensis* (confirmed)	T1: IMAS 14 mg/kg once a day for 21 days; T2: IVMA 20 mg/kg once a day for 28 days
Llanos-Cuentas 1997	Peru	MCL	*L. braziliensis* (confirmed)	T1: IVSSG (20 mg/kg/d) + oral AL (20 mg/kg/d in 4 doses); T2: IVSSG (20 mg/kg/d) for 28 days
Miranda-Verástegui 2005	Peru	CL	*L. braziliensis; L. peruviana* (endemic)	T1: Topical imiquimod cream 5% every other day for 20 days + IMMA; T2: Topical placebo + IMMA as in T1
Echevarria 2006 (New)	Peru	MCL	*L. braziliensis* (endemic)	T1: IVSSG 1 L of the solution 60 minutes before starting the infusion of AB (sodium 153 mEq/l, chloride 153 mEq/L, osmolarity 306 mosm/L); T2: ORS 1 L of a solution containing: 90 mEq/L of sodium, 104 mEq/L of chloride, 22 mEq/L of bicarbonate, and 12 mEq/L of potassium, osmolarity 290 mosm/L, 60 minutes before starting the infusion of AB, and 2 L throughout the rest of the day, for a total of 3 L a day
Miranda-Verástegui 2009 (New)	Peru	CL	*L. braziliensis; L. peruviana; L. guyanensis* (confirmed)	T1: Pentavalent antimony + topical 5% imiquimod cream 3 times a week (total of 9 applications) for 20 days;

Table 3. Geographic distribution of *Leishmania* *(Continued)*

				T2: Pentavalent antimony + topical placebo cream 3 times a week (total of 9 applications) for 20 days
NCT01011309 (New)	Peru	CL	*L. peruviana* (confirmed)	T1: 10 mcg LEISH-F2 antigen + 25 mcg MPL-SE adjuvant given as 3 subcutaneous injections on days 0, 28, and 56; T2: 10 mcg LEISH-F2 antigen + 25 mcg MPL-SE adjuvant given as 3 subcutaneous injections on days 0, 14, and 28; T3: Sodium stibogluconate (SSG) given 20 mg/kg/day IV for 20 days
Hu 2015 (New)	Suriname	CL	*L. guyanensis* (endemic)	T1: 2 IM injections of pentamidine isethionate salt 7 mg/kg on days 1 and 3 (3-day regimen); T2: 3 IM injections of pentamidine isethionate 4 mg/kg on days 1, 4 and 7 (7-day regimen)
Ballou 1987	USA (mainly Panama)	CL	*L. panamensis; L. chagasi* (confirmed)	T1: IVSSG 10 mg/kg (P10); T2: IVSSG 20 mg/kg (P20) *once a day for 20 days
Oster 1985	USA (Panama or Brazil)	CL	*L. braziliensis; L. mexicana; L. chagasi* (confirmed)	T1: IVSSG 600 mg once a day 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	*L. braziliensis* (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	*L. braziliensis* (confirmed)	T1: Vaccine + BCG; T2: BCG alone intradermally in 2 sites, 3 doses at 6- to 8-week intervals; T2: IMMA 50 mg/kg/day in series of 20 daily injections with intervals of 15 days

*: dosage schedule for all groups; AL: allopurinol; AS: aminosidine sulphate; AZ: azithromycin; BCG: Bacillus Calmette-Guerin; CL: cutaneous leishmaniasis; GM-CSF: Granulocyte macrophage colony-stimulating factor; IL: intralesional; IM: intramuscular; IV: intravenous; MA: meglumine antimoniate; MCL: mucocutaneous leishmaniasis; MPL-SE: unknown but they claim this is an adjuvant; NOP: Nitric oxide patch; NR: not reported; PI: Pentamidine isethionate; PR: paromomycin; ORS: oral rehydration solution; SSG: Sodium stibogluconate; T1,2,3,4: Treatment groups; TD: twice a day.

Table 4. New comparisons identified in this update

Type of interventions	Intervention	Comparison
Antimonials	Meglumine antimoniate	Low doses of IVMA versus higher dose for 30 days (5 mg/kg/day versus 30 mg/kg/day) IL MA versus placebo Meglumine antimoniate plus tamoxifen versus meglumine antimoniate alone

Table 4. New comparisons identified in this update *(Continued)*

		Intravenous meglumine antimoniate (IVMA) plus antihelminthic treatment versus IVMA plus placebo
Non-antimonial systemic treatments	Fluconazole	Fluconazole versus IV MA
	Pentamidine isethionate	Pentamidine Isethionate 7 days versus pentamidine isethionate 4 days
	Azithromycin	Azithromycin versus IM MA
Non-antimonial topical or intralesional therapies	Paromomycin	Paromomycin plus gentamicin versus paromomycin alone Paromomycin versus intralesional pentamidine
	Amphotericin B	3% Amphotericin B cream twice a day for 4 weeks versus thrice a day for 4 weeks
	Pentamidine	Intralesional pentamidine versus Intralesional sodium stibogluconate Pentamidine isethionate: single dose versus 2 doses versus 3 doses
	Nitric oxide patch	Nitric oxide patch versus MA
Physical therapies	Cryotherapy	Cryotherapy versus placebo cream Cryotherapy versus local sodium stibogluconate
Immuno-chemotherapy	Pentoxifylline	Pentoxifylline combined with IMMA versus IMMA plus placebo Pentoxifylline combined with IVMA versus IVMA plus placebo
Vaccines	Biological LEISH-F2 + MPL-SE	Biological LEISH-F2 + MPL-SE versus sodium stibogluconate

IM: intramuscular; IV: intravenous; MA: meglumine antimoniate

APPENDICES

Appendix 1. Cochrane Skin Specialised Register (CRSW) search strategy

(Leish* and (mucocutan* or mucos* or american or new world or nose* or nariz or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or oreja* or orelha* or tegument*)) or espundia

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor: [Leishmaniasis, Mucocutaneous] explode all trees
#2 espundia:ti,ab,kw
#3 #1 or #2
#4 MeSH descriptor: [Leishmaniasis, Cutaneous] explode all trees
#5 leish*:ti,ab,kw
#6 #4 or #5
#7 (mucocutan* or mucos* or american or new world or nose* or nariz or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or oreja* or orelha* or tegument*):ti,ab,kw
#8 #6 and #7
#9 #3 or #8

Appendix 3. MEDLINE (Ovid) search strategy

1. exp Leishmaniasis, Mucocutaneous/

2. espundia.mp.
3. or/1-2
4. exp Leishmaniasis, Cutaneous/
5. leish$.mp.
6. 4 or 5
7. (mucocutan$ or mucos$ or american or new world or nose$ or nariz or naso$ or pharyn$ or faring$ or laring$ or laryn$ or paladar$ or palat$ or cartila$ or ear$ or oreja$ or orelha$ or tegument$).mp.
8. 6 and 7
9. 3 or 8
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. clinical trials as topic.sh.
15. randomly.ab.
16. trial.ti.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp animals/ not humans.sh.
19. 17 not 18
20. 9 and 19

[Lines 10-19: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format, from section 3.6.1 in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook]

Appendix 4. Embase (Ovid) search strategy

1. exp skin leishmaniasis/
2. leish$.mp.
3. 1 or 2
4. (mucocutan$ or mucos$ or american or new world or nose$ or nariz or naso$ or pharyn$ or faring$ or laring$ or laryn$ or paladar$ or palat$ or cartila$ or ear$ or oreja$ or orelha$ or tegument$).mp.
5. 3 and 4
6. espundia.mp.
7. 5 or 6
8. crossover procedure.sh.
9. double-blind procedure.sh.
10. single-blind procedure.sh.
11. (crossover$ or cross over$).tw.
12. placebo$.tw.
13. (doubl$ adj blind$).tw.
14. allocat$.tw.
15. trial.ti.
16. randomized controlled trial.sh.
17. random$.tw.
18. or/8-17
19. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
20. human/ or normal human/
21. 19 and 20
22. 19 not 21
23. 18 not 22
24. 7 and 23

[Lines 8-18: Based on terms suggested for identifying RCTs in Embase (section 3.6.2) in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook]

Appendix 5. CINAHL (EBSCO) search strategy

S1 TI espundia OR AB espundia

S2 TI mucocutaneous leishmaniasis or AB mucocutaneous leishmaniasis
S3 TI leish* OR AB leish*
S4 TI ((mucocutan* or mucos* or american or new world or nose* or nariz or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or oreja* or orelha* or tegument*)) OR AB ((mucocutan* or mucos* or american or new world or nose* or nariz or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or oreja* or orelha* or tegument*))
S5 (TI ((mucocutan* or mucos* or american or new world or nose* or nariz or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or oreja* or orelha* or tegument*)) OR AB ((mucocutan* or mucos* or american or new world or nose* or nariz or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or oreja* or orelha* or tegument*))) AND (S3 AND S4)
S6 ((TI ((mucocutan* or mucos* or american or new world or nose* or nariz or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or oreja* or orelha* or tegument*)) OR AB ((mucocutan* or mucos* or american or new world or nose* or nariz or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or oreja* or orelha* or tegument*))) AND (S3 AND S4)) AND (S1 OR S2 OR S5)
S7 (MH "Clinical Trials+")
S8 PT clinical trial
S9 TX (clinic* n1 trial*)
S10 (MH "Random Assignment")
S11 TX random* allocat*
S12 TX placebo*
S13 (MH "Placebos")
S14 (MH "Quantitative Studies")
S15 TX allocat* random*
S16 "randomi#ed control* trial*"
S17 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S18 S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17
S19 S6 AND S18

[Lines S7-S18 are an adaptatation of the SIGN filter for RCTs for CINAHL via EBSCO]

Appendix 6. LILACS search strategy

(Leish$ and (mucocutan$ or mucos$ or american or new world or nose$ or nariz or naso$ or pharyn$ or faring$ or laring$ or laryn$ or paladar$ or palat$ or cartila$ or ear$ or oreja$ or orelha$ or tegument$)) or espundia

These terms were combined with the Controlled clinical trials topic-specific query filter.

Appendix 7. MEDLINE (Ovid) Adverse effects search strategy

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.

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.
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.
48. imiquimod.mp.
49. IFN-gamma.mp.
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

WHAT'S NEW

Date	Event	Description
26 August 2020	New citation required and conclusions have changed	This update includes studies assessing new types of treatments including azithromycin, amphotericin B, nitric oxide patch, and cryotherapy. Miltefosine appears to be consolidated as a consistent alternative for treating cutaneous leishmaniasis cases associated with the most relevant parasite species (i.e. *L. braziliensis*, *L. guyanensis*, and *L. panamensis*) across South American countries, including Brazil, Colombia, and Bolivia. Finally, the emergence of topicals alone or combined with systemic (oral or parenteral) treatments seem to be the future developing trend for cutaneous leishmaniasis treatment.
26 August 2020	New search has been performed	A new search led to the addition of 37 new included studies, and we updated the review in line with GRADE and MECIR standards.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 2, 2009

Date	Event	Description
5 August 2015	Amended	Author information (affiliation) updated
16 May 2012	Amended	The lead author's contact details have been edited.
30 April 2008	Amended	Converted to new review format.
14 February 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

MP was the contact person with the editorial base and co-ordinated contributions from the co-authors.
MP, LR screened papers against eligibility criteria.
MP, LR obtained data on ongoing and unpublished studies.
VE, KO, CEP, MP, JRR appraised the quality of papers.
VE, KO, CEP, MP, JRR extracted data for the review and sought additional information about papers.
MP, JRR entered data into RevMan.
JRR analysed data.
MP, JRR, LR, GAR interpreted data.
MP, JRR worked on the Methods sections.
ANE, GAR drafted the clinical sections of the Background.
JT was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.
MP is the guarantor of the update.

Disclaimer

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Skin Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DECLARATIONS OF INTEREST

Mariona Pinart: none known.
José-Ramón Rueda: none known.
Gustavo AS Romero: author on included study Toledo 2014 but not involved in data extraction or assessment of risks of bias.
Carlos Eduardo Pinzón-Flórez: none known.
Luz Karime Osorio Arango: none known.
Ana Nilce Silveira Maia-Elkhoury: none known.
Ludovic Reveiz: none known. Ludovic Reveiz has contributed to this review in a personal capacity and during his spare time. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the organisation where he works.
Vanessa M Elias: none known.
John A Tweed: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support found, Germany

External sources

- The National Institute for Health Research (NIHR), UK

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the protocol and the current update

For differences between other published versions, please see the 'Differences between protocol and review section' within the original publications.

The protocol of this review was first entitled 'Interventions for mucocutaneous leishmaniasis' (González 2004). However, the clinical subject was split into two reviews, entitled 'Interventions for Old World cutaneous leishmaniasis' (Heras-Mosteiro 2017) and 'Interventions for American cutaneous and mucocutaneous leishmaniasis' (González 2009). As reported in the update of the former, this decision stemmed from the fact that the *Leishmania* species in the geographical areas involving the Old World differ from those affecting the New World (Heras-Mosteiro 2017). We adapted and updated the Background, and the Objectives of the present review are focused on the cutaneous and mucocutaneous forms of leishmaniasis (CL) in the New World.

Compared with the published protocol, there were some alterations in the tasks completed by review authors because none of the previous authors except for MP remain as authors of the updated version of this review.

Objectives: The original protocol focused on the mucocutaneous form of leishmaniasis. The objective had to be modified to include cutaneous leishmaniasis, as we included the cutaneous form. Because in the protocol only immuno-competent people who had the disease were included, we modified the objective accordingly. Given that few *Leishmania sp* can produce the mucosal form, causing destruction of the nasopharyngeal mucosa, we thought it appropriate to assess variations in response to treatment attributable to exposure to different species.

Type of participants: As we were including the cutaneous form of leishmaniasis, we extended the definition to 'All immuno-competent people who have cutaneous leishmaniasis or mucocutaneous leishmaniasis, or both'. We have also included parasite confirmation by smear tests.

Types of interventions: we added a list of interventions in response to referees' comments and to ease readability.

Types of outcome measures: We added the following sentence to justify that in the previous review, studies that did not report any of the outcomes of interest were excluded: "We included studies that reported at least one of the outcomes listed below. Studies that did not report any of the outcomes of interest were therefore excluded."

Types of outcome measures > Primary outcomes: The primary outcome originally stated in the protocol was the following "Percentage of participants 'cured' at three months after the end of treatment". For this updated review we included the term 'at least' to include cure at three months and beyond. We deemed as short-term those studies that assessed cure prior to three months after cessation of treatment, and we deemed long-term those studies assessing cure at three months and beyond. Studies reporting a cure within three months after the end of treatment (short-term) were considered for inclusion, and their results, although reported narratively, were excluded from any meta-analysis. We also moved adverse effects from a secondary to a primary outcome, following the MECIR C14 criterion.

Types of outcome measures > Tertiary outcomes: We added the term 'All-cause mortality' for clarification, since it was unclear whether we were assessing mortality attributable to Leishmaniasis or to any cause of death. We have also added a definition for 'speed of healing' for clarification, as suggest by one external referee. Speed of healing is now defined as the average time from start of treatment to cure. We added a new outcome 'Development of cell-mediated immunity', defined as any difference in the size of leishmanin skin test reaction.

Electronic searches: for this review update, we did not search the Cochrane Database of Abstracts of Reviews of Effectiveness (DARE) or MedCarib, as we replaced them with the following databases, which we considered relevant for the identification of ongoing trials.

- The ISRCTN registry (www.controlled-trials.com)
- The US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au)
- The World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/)
- The EU Clinical Trials Register (www.clinicaltrialsregister.eu/)

Searching other resources > Unpublished literature: We did not contact the following Tropical Medicine Centres, due to lack of resources: 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.

Searching other resources > Adverse effects: Although planned in the protocol, we did not conduct a search using the terms efeito $ colaterai$, efecto$ adverso$, adverse effect$, toxici$. The review team used the search strategy developed in Appendix 7, which was published in the previous review (González 2009), because it was more accurate.

Data collection and analysis: Since the protocol was published some time ago (2004), we have updated the methodology in line with Cochrane standards.

Measures of treatment effect: We planned in the protocol to express results as the number needed to treat for an additional beneficial outcome where appropriate, for a range of plausible control event rates. We did not do this, because the great variety found among different participant populations made it impossible to obtain a range of plausible control event rates. As the *Cochrane Handbook for Systematic Reviews of Interventions* says, "Risk ratios and relative risk reductions remain crucial because relative effect tends to be substantially more stable across risk groups than does absolute benefit" (Higgins 2011). We decided to describe hazard ratios (HRs) for time-to-event outcomes data when the studies did. We have followed the recommendation, "Conducting a meta-analysis using summary information from published papers or trial reports is often problematic, as the most appropriate summary statistics are typically not presented", and we have not calculated them because we did not have enough information from studies (Higgins 2011).

Assessment of heterogeneity: In the protocol, we had planned to explore reasons for heterogeneity using sensitivity or subgroup analyses, or both, but we did not do this because there were too few studies to perform a sensitivity or subgroup analysis. We had not planned how to assess clinical heterogeneity in the protocol, but we have covered this in the update.

Data synthesis: Although not planned in the protocol, we decided to only undertake data synthesis if we were able to identify two or more studies investigating similar treatments and reporting data that could be pooled. We did this because the previous systematic review chose this approach, and we consider that defining a minimum number of studies is necessary to be informative in the data synthesis phase. Where it was not possible to perform a meta-analysis, we summarised the data for each trial.

We decided not to meta-analyse studies when I^2 was above 75% and effect estimates crossed the no-effect line. However, we did meta-analyse studies with a high I^2 if none of the confidence intervals crossed the line of no effect, and we discuss the reasons for such significant heterogeneity.

Although not planned in the protocol, where an ITT approach was not stated, we used the numbers originally randomised to the groups in order to calculate effect estimates. We did this to avoid overestimating the effect of the intervention (to reduce attrition bias). For losses to follow-up, it was not always possible to determine within which arm the losses occurred, and therefore to perform ITT analyses.

Dealing with missing data: In the protocol, we did not specify how to deal with missing data; for this update, we therefore specified that we would treat missing data as treatment failures.

Reporting bias: In the protocol we did not specify if we would investigate reporting bias. In the review we planned to investigate it but were unable to do so, due to the low number of studies included in the meta-analyses.

Subgroup analysis: Following clinical recommendations from an external referee we aimed to consider the age of participants in a subgroup analysis; separately children under five years, and over five years of age. In particular the clinical reason was given as: "Therapeutic failure and relapses are frequent in children with cutaneous leishmaniasis, especially with pentavalent antimonials and this may be due to differences in pharmacokinetics. It is important to report results separately for children and adults as this variable may influence the results." However, it was not possible to carry out the subgroup analysis as too few studies reported separate data for these age categories.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Antiprotozoal Agents [administration & dosage] [adverse effects]; Azithromycin [administration & dosage] [adverse effects]; BCG Vaccine [therapeutic use]; Hyperthermia, Induced; Immunocompetence; Injections, Intramuscular; Injections, Intravenous; Interferon-gamma [therapeutic use]; Leishmaniasis Vaccines [therapeutic use]; Leishmaniasis, Cutaneous [*therapy]; Leishmaniasis, Mucocutaneous [therapy]; Meglumine Antimoniate [administration & dosage] [adverse effects]; Pentoxifylline [administration & dosage] [adverse effects]; Phosphorylcholine [administration & dosage] [adverse effects] [analogs & derivatives]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Male