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SYSTEMATIC REVIEW

Systemic treatment of cutaneous leishmaniasis: A systematic review and meta-analysis

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Abstract

Background: Cutaneous leishmaniasis (CL) is increasingly reported in previously non-endemic European countries. Although often self-limiting or amenable to topical therapy, systemic treatment is indicated in specific situations. Evidence guiding systemic therapies remains limited and heterogeneous.

Objectives: This systematic review and meta-analysis aimed to synthesize available evidence on systemic treatment regimens for CL.

Methods: MEDLINE/PubMed and Embase were searched for clinically and/or parasitologically confirmed CL receiving systemic monotherapy with meglumine antimoniate (MA), miltefosine, azoles, pentamidine, or liposomal amphotericin B (L-AmB) until February 2026. Primary outcome was clinical cure assessed 2–7.5 months after treatment initiation. Pooled cure rates were estimated using random-effects meta-analysis. Subgroup analyses were performed for Old World (OWCL) and New World (NWCL) CL, and by *Leishmania* species.

Results: Eighty-three studies comprising 96 treatment arms and 4603 patients with OWCL and NWCL were included. Overall, study quality was moderate (per JBI checklist). MA, long regarded as standard of care in many countries, had a pooled cure rate of 59% (95% CI 52%–66%). Higher rates were observed with L-AmB (77%; 95% CI 56%–90%), followed by miltefosine (75%; 95% CI 69%–81%), itraconazole (70%; 95% CI 65%–76%), and fluconazole (62%; 95% CI 16%–93%). Lower rates were obtained with pentamidine (55%; 95% CI 42%–67%) and ketoconazole (36%; 95% CI 7%–82%). Species- and region-specific sub-analyses indicated miltefosine highly effective for OWCL (particularly *L. major*) and NWCL (*L. braziliensis*, *L. guyanensis*, *L. panamensis*). Head-to-head comparisons of miltefosine and MA showed no statistically significant difference. L-AmB was similarly effective in NWCL (particularly *L. braziliensis*), with lack of evidence for other species.

Conclusions: Systemic treatment options for CL show variable efficacy. Despite the promising cure rates for miltefosine and L-AmB, comparative evidence remains insufficient to support therapy recommendations. Confirmation in adequately powered, high-quality RCTs, ideally stratified by species, is warranted to strengthen the evidence base.

PROSPERO registration number: CRD420261292193.

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KEYWORDS
azoles, cutaneous leishmaniasis, liposomal amphotericin B, meglumine antimoniate, miltefosine, pentamidine

INTRODUCTION

Leishmaniasis comprises a spectrum of vector-borne diseases caused by protists of the genus *Leishmania* and is classified as a neglected tropical disease by the WHO.[1] The main phenotypic forms are cutaneous (CL), visceral (VL), and mucocutaneous/mucosal leishmaniasis (MCL/ML).[2,3] CL is the most common form, endemic in over 100 countries, with an estimated 0.7–1 million cases annually and 350 million people at risk of infection.[1,4] Although traditionally endemic in North Africa, Central Asia, Middle East, Latin America, and Southern Europe, CL is becoming increasingly relevant in Central and Northern Europe[5,6] due to growing international travel activities, forced migration, and climate-driven acceleration of parasite development and northward expansion of sandfly vectors.[7–10]

More than 20 *Leishmania* species can infect humans, having historically been classified into Old World (OW) or New World (NW) species. While OWCL is mostly caused by *L. major*, *L. tropica*, *L. aethiopica* and increasingly *L. infantum*, the main causative agents of NWCL are *L. mexicana*, *L. amazonensis* and members of the subgenus *Viannia*, including *L. braziliensis*, *L. guyanensis* and *L. panamensis*.[2,3] CL may resolve spontaneously or be manageable with topical therapeutics, but systemic treatment is indicated for complex CL (i.e., ≥4 lesions, lesion(s) ≥5 cm, lesions located at functionally/cosmetically sensitive sites, immunocompromised hosts, diffuse, disseminated and therapy-refractory forms) and in cases involving *Viannia* or other species associated with MCL/ML.[3,11–13] Although rarely life-threatening, CL can cause morbidity, functional impairment and psychosocial distress.[2,14,15]

Several systemic agents are available, including pentavalent antimonials, miltefosine, azoles, pentamidine, and liposomal amphotericin B (L-AmB). Although antimonials – with meglumine antimoniate (MA) the most widely used drug globally[16] – have been the traditional mainstay in the treatment of leishmaniasis since the 1940s in many countries, no standardized regimen has been established, and no single drug is equally effective against all *Leishmania* species. Moreover, heterogeneous study designs and a paucity of high-quality randomized controlled trials (RCTs) limit the strength of treatment recommendations. Meta-analyses are scarce and complicated by variable treatment regimens and outcome measures. This poses a substantial challenge for clinicians, who are often compelled to rely on expert opinion or experience-based evidence. This systematic review and meta-analysis aimed to synthesize the available data on systemic treatments for CL to inform clinical practice, facilitate future guideline development, and support public health policy decisions.

Why was the study undertaken?

Cutaneous leishmaniasis (CL) is endemic in parts of Southern Europe and is increasingly being reported in formerly non-endemic regions of Central Europe. Several systemic treatments for CL exist, with pentavalent antimonials (e.g., meglumine antimoniate (MA)) having been used as standard care for many decades despite limited evidence. This study was undertaken to systematically synthesize and compare the efficacy of currently used systemic monotherapies for CL.

What does this study add?

This systematic review and meta-analysis comprising 83 studies and 96 intervention arms revealed marked variations in pooled cure rates across the systemic antileishmanial agents. MA showed only moderate efficacy, whereas miltefosine and liposomal amphotericin B (L-AmB) were associated with relatively high pooled cure rates. Subgroup analyses also highlighted important regional and species-specific differences in treatment response, with miltefosine demonstrating the most consistent evidence across different settings. Head-to-head comparisons were performed for agents with sufficient study evidence.

What are the implications of this study for disease understanding and/or clinical care?

These findings call into question the contemporary role of MA as the standard of care for CL and underscore that systemic treatment should be guided by region and, where possible, the infecting *Leishmania* species. Miltefosine and L-AmB demonstrate high efficacy along with advantages in toxicity profile and/or modality of administration; however, current comparative evidence is insufficient to establish valid therapy recommendations. Adequately powered, standardized comparative trials are required before treatment guidelines can be revised confidently.

METHODS

Reporting guidelines and protocol registration

This systematic literature review was prepared according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2020,[17] following an a priori defined protocol (PROSPERO: CRD420261292193).

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TABLE 1 Eligible systemic therapy regimens.

Therapy	Dose	Administration route	Duration
Meglumine antimoniate	20 mg/kg (15 mg/kg if age < 12 years)	intravenous/intramuscular	20–21 days
Miltefosine	1.5–2.5 mg/kg	oral	21–28 days
Azoles	200–800 mg/day[b]	oral	4–8 weeks
Pentamidine	4 mg/kg[a]	intravenous/intramuscular	2–4 doses
Liposomal Amphotericin B	3–4 mg/kg	intravenous	5–6 doses

[a]One study using pentamidine 2 mg/kg for 7 doses was included, because the cumulative total dose was considered comparable to the prespecified regimen.[24]
[b]Studies evaluating itraconazole and fluconazole were restricted to a total daily dose of ≤450 mg. For ketoconazole, due to limited evidence, studies using doses up to 800 mg/day were included.

Eligibility criteria

The criteria were pre-specified according to PICOS. Individuals of any age with clinically and/or parasitologically confirmed CL (P) were included if they received the following interventions (I): systemic monotherapy with MA, miltefosine, azoles (i.e., itraconazole, fluconazole, ketoconazole), pentamidine or L-AmB, at pre-defined dosing regimens (Table 1) based on the German guideline for CL.[11] Only studies reporting sufficient dosing information (i.e., dose, duration, administration route) were included. Studies combining systemic treatment with topical placebo were included to retain several high-quality RCTs.[18–23] Studies with and without a comparison (C) group were eligible. The outcome (O) was the clinical cure rate assessed 2–7.5 months after treatment initiation. The primary outcome was cure, defined as complete re-epithelialization of lesion(s), complete healing, scarring or clinical cure of all lesions. Only studies reporting the total number of patients prior to treatment and the number of patients achieving clinical cure were included. Eligible study designs (S) included RCTs, non-randomized clinical trials, observational studies and case series. Case reports, reviews, meta-analyses, editorials, comments and conference abstracts were excluded.

Search strategy and data collection

MEDLINE/PubMed and Embase were searched from inception to February 17, 2026, without language or geographical restrictions (Appendix A1). Non-English and non-German articles were translated using DeepL.[25] Spanish translations were reviewed by a native speaker (Am.H.); other translations were not independently verified.

Two authors independently screened titles/abstracts; two others independently assessed full texts for eligibility, resolving discrepancies by consensus or, if needed, a third reviewer as arbitrator. Two authors independently extracted data on *Leishmania* species, study region, number of enrolled and cured patients, diagnostic methods, treatment, and participant/lesion characteristics.

Data synthesis

Pooled cure rates for each systemic regimen were calculated using a random-effects generalized linear mixed model (GLMM) with logit link in R 4.4.1 ("meta" package[26]), accounting for the anticipated between-study variability in true effect sizes. Results are presented as pooled estimates with Hartung-Knapp-adjusted 95% confidence intervals (CIs). Statistical heterogeneity was assessed using I^2.

Subgroup analyses stratified outcomes by region (OWCL vs. NWCL) or the most likely causative *Leishmania* species. Species assignment was based on molecular identification or, when unavailable, the predominant species reported in the study region.

Head-to-head comparisons were performed when at least two comparative studies were available. Random-effects meta-analyses of risk ratios (RRs) were calculated in R using the "meta" package, based on the total number of treated patients and cured cases.

Study quality assessment

Methodological quality was assessed using the appropriate revised Joanna Briggs Institute (JBI) Critical Appraisal tool.[27] Two authors independently evaluated each study; discrepancies were resolved by consensus. The proportion of criteria met was determined to classify the risk of bias (RoB) as high (<50%), moderate (50–69%), or low (>70%). Publication and small study bias were assessed using Egger's test and funnel plot asymmetry for meta-analyses including ≥10 study arms. The quality of evidence from the comparative meta-analyses was evaluated using GRADE.[28]

RESULTS

Identification of relevant literature

The search identified 2945 records (MEDLINE/PubMed $n = 1286$; Embase $n = 1659$). After removal of 833 duplicates, 2112 records were screened and 425 full texts assessed. Of

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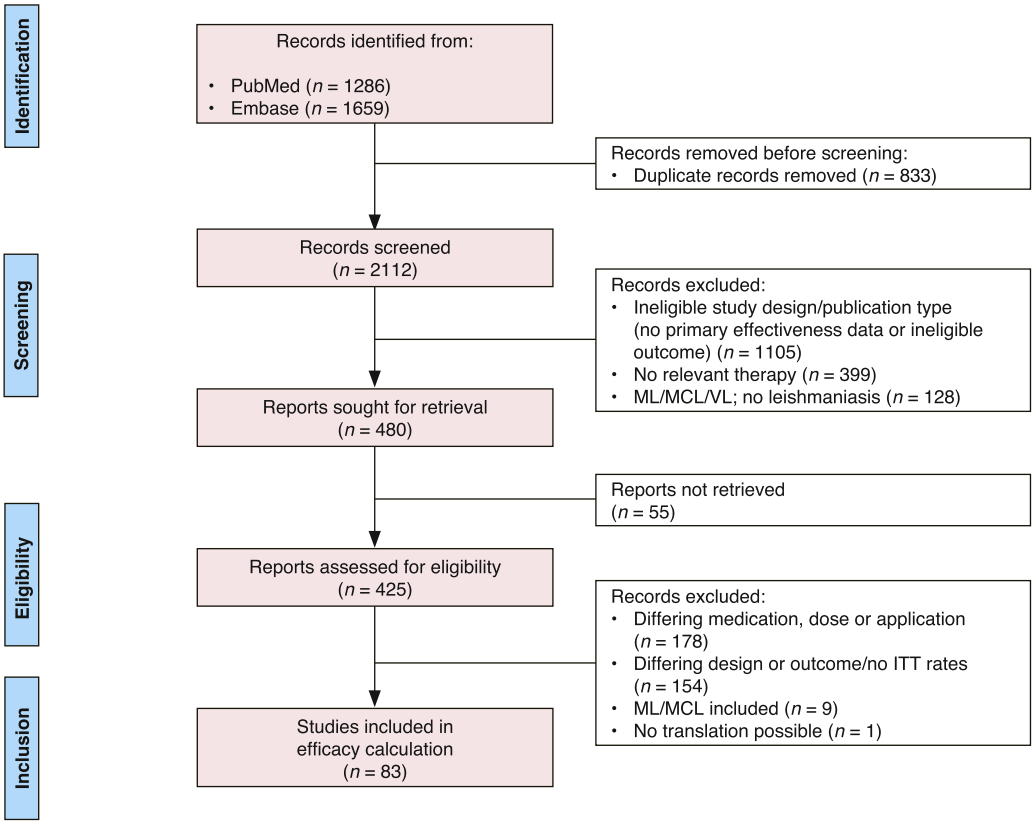


FIGURE 1 PRISMA flow-diagram for study identification and selection. The search strings are detailed in Appendix A1. ITT, intention-to-treat; MCL, mucocutaneous leishmaniasis; ML, mucosal leishmaniasis; VL, visceral leishmaniasis.

43 non-English full texts, 42 were translated (French $n = 19$, Portuguese $n = 14$, Spanish $n = 6$, Farsi $n = 2$, Turkish $n = 1$); one non-extractable article was excluded. Overall, 342 full texts were excluded, leaving 83 studies with 96 study arms for inclusion (Figure 1, Appendix B1).

Study characteristics

The full characteristics, including RoB, are provided in Appendix C1. 14 studies were classified as high RoB, mainly due to limited internal validity and high loss to follow-up, 37 as moderate and 32 as low. 49 study arms were RCT-derived, 24 from prospective non-randomized trials, 11 from prospective observational studies, 5 from retrospective studies, and 7 from case series (Table 2). 27 study arms involved OWCL, mainly from Iran ($n = 9$) and Pakistan ($n = 6$), whereas 68 focused on NWCL, predominantly from Brazil ($n = 24$) and Colombia ($n = 14$). One arm included imported cases from both regions.[29]

In total, 4603 patients with confirmed diagnoses of CL were included. Five study arms enrolled exclusively children. Across the 96 study arms, 41 reported treatment interventions with MA, 17 with miltefosine, nine with itraconazole, six with fluconazole, seven with ketoconazole, 11 with pentamidine, and five with L-AmB. Fifteen included patients with prior anti-leishmanial therapy. Three studies exclusively enrolled pre-treated populations: two miltefosine studies included MA-resistant disease and one MA study patients with prior miltefosine failure.[30–32] 60 study arms defined cure as complete re-epithelialization/epithelialization, 23 as complete healing, scarring or clinical cure of all lesions. Thirteen study arms used alternative definitions: three defined cure as absence of therapeutic failure[32] or lesion size reduction of ≥80%,[33] but were retained because of high overall quality. In nine, cure was based on clinico-parasitological resolution; in one solely on negative parasitology.

Synthesis of the results

In the overall analysis (Figure 2), MA had a pooled cure rate of 59% (95% CI 52%–66%). Higher pooled cure rates were observed with L-AmB at 77% (95% CI 56%–90%), followed by miltefosine at 75% (95% CI 69%–81%) and the triazole compounds itraconazole at 70% (95% CI 65%–76%) and fluconazole at 62% (95% CI 16%–93%). The pooled cure rates were lower with pentamidine at 55% (95% CI 42%–67%) and ketoconazole at 36% (95% CI 7%–82%). All agents showed substantial heterogeneity with $I^2 > 70\%$, except for itraconazole ($I^2 = 0.0\%$) and L-AmB ($I^2 = 37.7\%$).

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TABLE 2 Characteristics of the included study arms according to treatment.

Characteristics	MA	Miltefosine	Itraconazole	Fluconazole	Ketoconazole	Pentamidine	L-AmB	Total
Study arms, *n*	41	17	9	6	7	11	5	96
Study design								
Randomized controlled trial	24	10	5	2	3	4	1	49
Non-randomized trial	8	4	4	2	1	3	2	24
Prospective observational study	7	1	0	0	0	3	0	11
Retrospective study	2	1	0	0	0	1	1	5
Case series	0	1	0	2	3	0	1	7
Region								
Old World	6	5	7	5	3	0	1	27
New World	35	12	1	1	4	11	4	68
Not segregated	0	0	1	0	0	0	0	1
Timepoint of reported cure								
2–3 months	16	3	2	2	4	4	3	34
4–5 months	9	2	4	3	1	2	0	21
6–7.5 months	16	12	3	1	2	5	2	41
Species[a]								
L. major	3	1	2	1	1	0	0	8
L. tropica	3	2	1	0	1	0	1	8
L. braziliensis	18	3	0	0	1	2	3	27
L. guyanensis	6	2	1	1	2	4	0	16
L. panamensis	4	3	0	0	0	1	0	8
L. mexicana	0	1	0	0	0	0	0	1
L. amazonensis	1	0	0	0	0	0	0	1

Abbreviations: L-AmB, liposomal amphotericin B; MA, meglumine antimoniate; n, number.

[a]Either identified by molecular techniques or reported as predominant in the respective study region.

In the sensitivity analysis restricted to the 49 RCT-derived study arms, pooled effects were consistent with the overall cure rates, except for fluconazole (72% vs. 62%) and L-AmB (44% vs. 77%). However, these estimates should be interpreted cautiously due to the limited number of available study arms ($n = 2$ and $n = 1$, respectively). Two additional sensitivity analyses, one excluding studies at high RoB and one restricted to the 83 study arms meeting the predefined cure criterion, yielded results consistent with the primary analysis (Appendix D1).

Subgroup analyses

For the subgroup analysis stratified by OWCL and NWCL (Figure 3, Appendix E1), one study was excluded because it included cases in both settings.[29] In OWCL, MA displayed a low pooled cure rate of 43% (95% CI 28%–60%). Higher rates were observed with miltefosine (80%; 95% CI 52%–93%), followed by fluconazole (73%; 95% CI 34%–93%) and itraconazole (70%; 95% CI 63%–76%). Evidence for L-AmB was limited to a single study with a cure rate of 85%. Ketoconazole (27%; 95% CI 0%–100%) demonstrated highly heterogeneous results, including one study reporting complete treatment failure.[33] In NWCL, MA showed a higher pooled cure rate than in OWCL (62%; 95% CI 54%–70%). However, the cure rates for miltefosine and L-AmB reached 74% (95% CI 67%–79%) and 75% (95% CI 43%–92%), respectively, although one of the four L-AmB studies reported a low rate of 44%.[34] Pentamidine, evaluated exclusively in NWCL, yielded a pooled estimate identical to the overall analysis. Interpretations for azoles were hampered, as evidence for itraconazole and fluconazole in NWCL was limited to a single study arm each (cure of 73% and 5%, respectively), and ketoconazole demonstrated substantial heterogeneity (37%; 95% CI 6%–84%).

Overall, 69 study arms identified the causative *Leishmania* species by molecular methods ($n = 39$) and/or stated the species predominant in the study region ($n = 32$) (Figure 4, Appendix F1). For OWCL-associated *L. major* and *L. tropica*, MA appeared low-to-moderate effective, with pooled cure rates of 49% (95% CI 34%–65%) and 38% (95% CI 24%–55%), respectively. Miltefosine showed relative moderate-to-high effectiveness of 81% (95% CI 64%–91%) and 55% (95% CI 46%–65%), respectively. L-AmB was only assessed in one *L. tropica study* with a cure rate of 85%. For *L. major*, the three azoles showed comparable effectiveness from 59%–65%. However, in the single *L. tropica study*, ketoconazole completely failed

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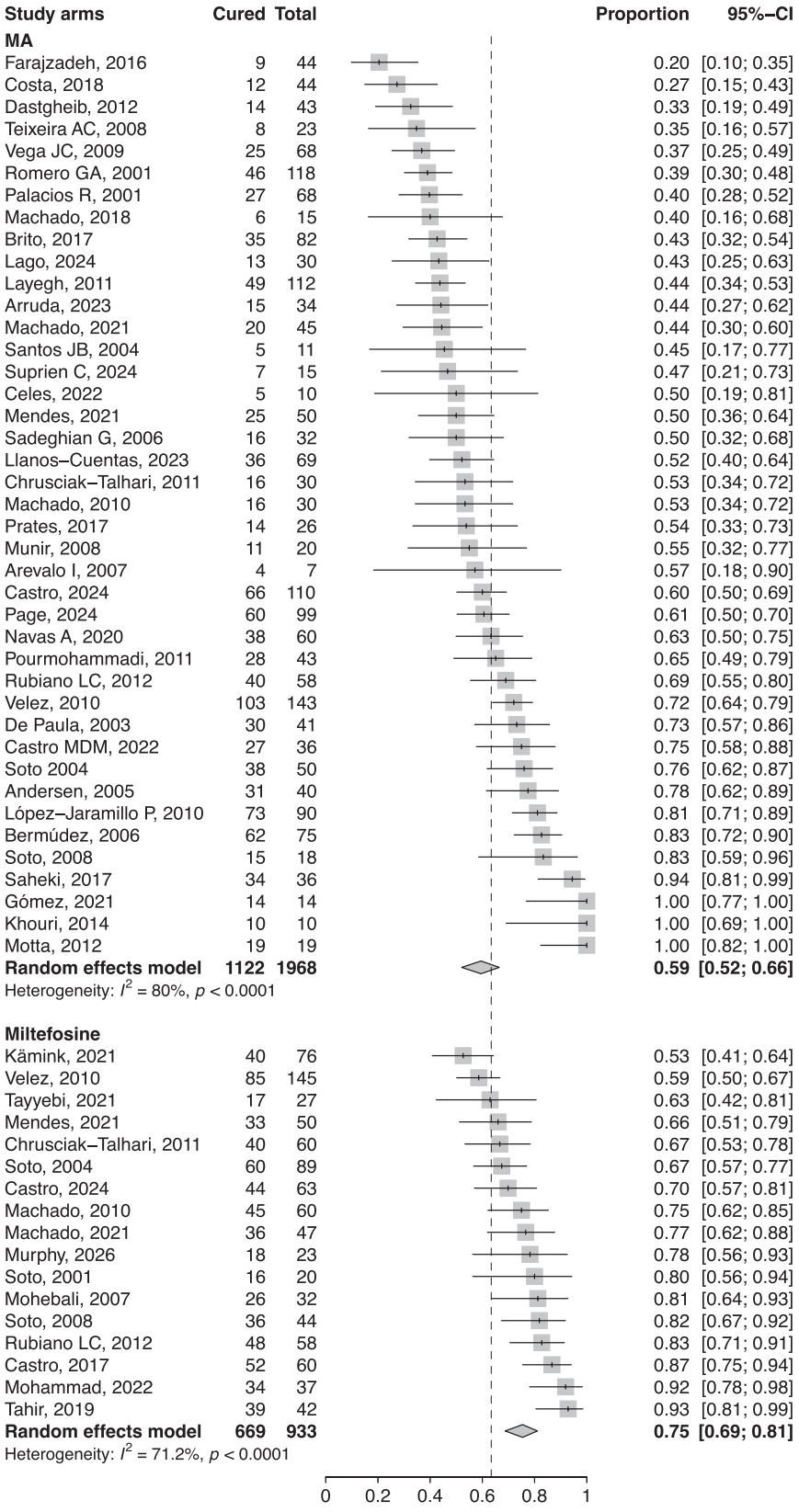


FIGURE 2 Forest plots of the pooled final cure rates of (a) meglumine antimoniate (MA), (b) miltefosine, (c) itraconazole, (d) fluconazole, (e) ketoconazole, (f) pentamidine, and (g) liposomal amphotericin B (L-AmB). Calculation of the pooled cure rates with 95% confidence intervals (CI) for the different systemic treatment regimens was performed with the random-effects generalized linear mixed model.

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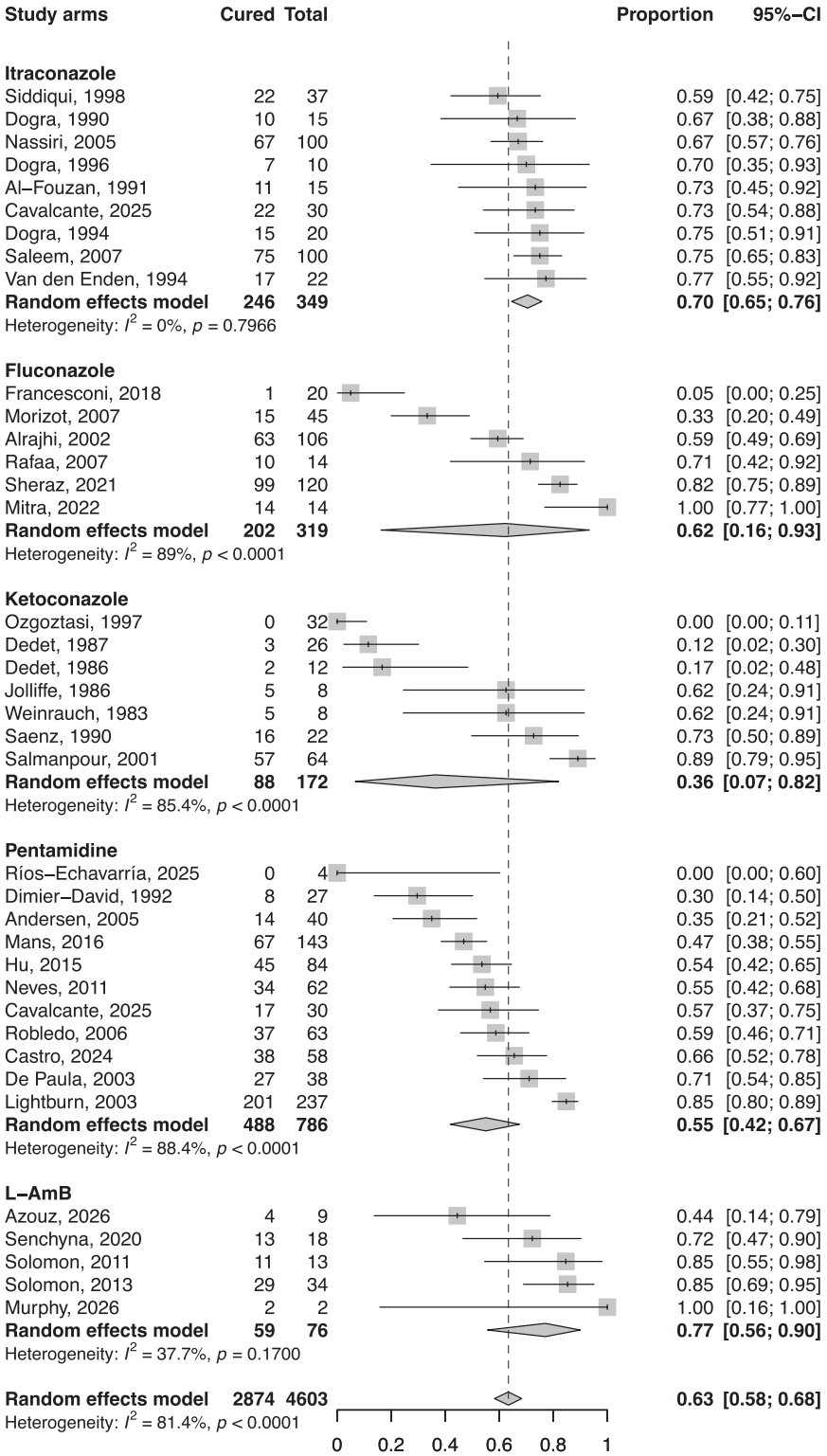


FIGURE 2 (Continued)

to cure. In NWCL-associated species, the pooled cure rates of MA ranged from 55%–62% for *L. braziliensis*, *L. guyanensis* and *L. panamensis*, whereas all patients were cured in the single *L. amazonensis study*. Miltefosine showed consistently high pooled cure rates from 66%–80%. Studies involving L-AmB were confined to *L. braziliensis*, where cure rates

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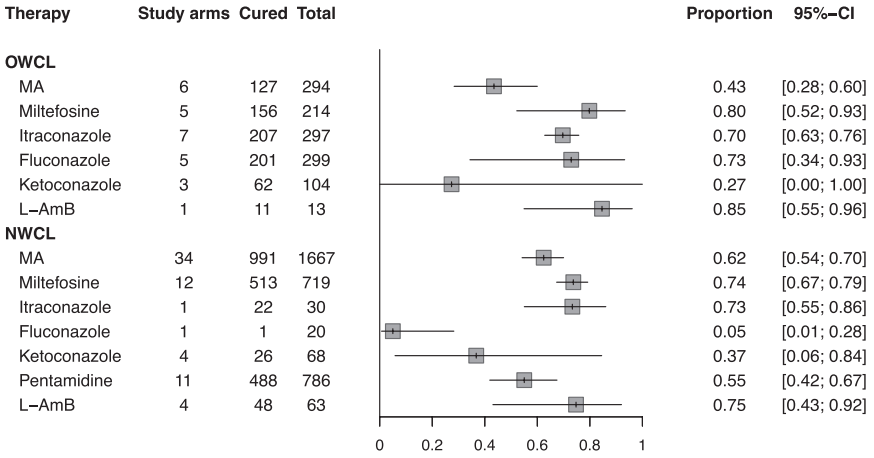


FIGURE 3 Subgroup analysis forest plot of pooled cure rates for each systemic therapy, stratified according to Old World (OWCL) and New World (NWCL) cutaneous leishmaniasis. Effect sizes are presented with corresponding 95% confidence intervals (CI). L-AmB, liposomal amphotericin B; MA, meglumine antimoniate.

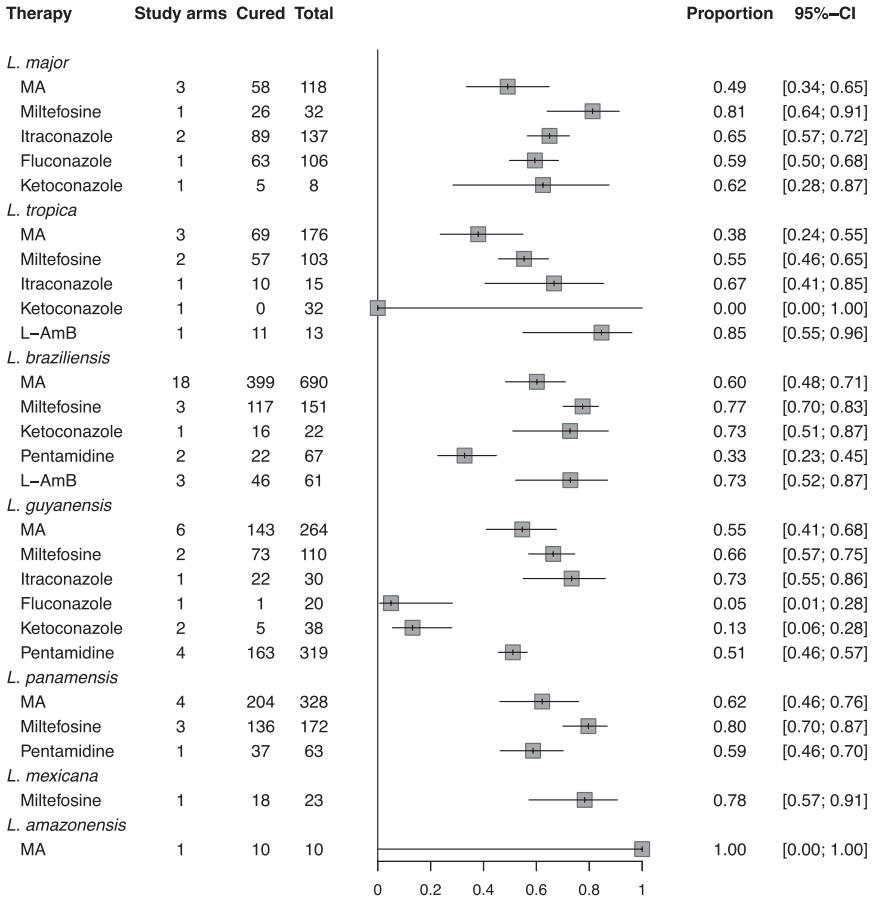


FIGURE 4 Subgroup analysis forest plot of pooled cure rates for each systemic therapy, according to species. Species assignment was based on the reported molecular identification or, when unavailable, on the species reported in the study as predominant in the respective geographic region. Effect sizes are presented with corresponding conventional 95% confidence intervals (CI). L-AmB, liposomal amphotericin B; MA, meglumine antimoniate.

were high (73%; 95% CI 52%–87%). Pentamidine displayed moderate effectiveness for *L. guyanensis* and *L. panamensis* of 51% (95% CI 46%–57%) and 59% (95% CI 46%–70%), respectively, but only low rates of 33% (95% CI 23%–45%) for *L. braziliensis*. Evidence for azoles was limited and the outcomes highly inconsistent.

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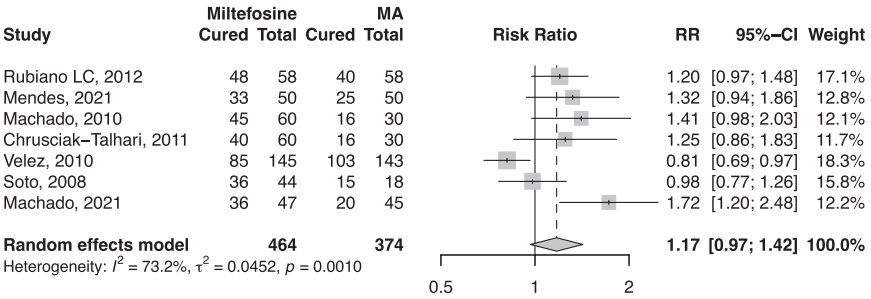


FIGURE 5 Forest plot showing head-to-head comparison of miltefosine and meglumine antimoniate (MA) in New World cutaneous leishmaniasis studies. The pooled risk ratio (RR) with 95% confidence intervals (CI) is calculated using a random-effects model, with the vertical line at RR = 1 indicating no difference between groups.

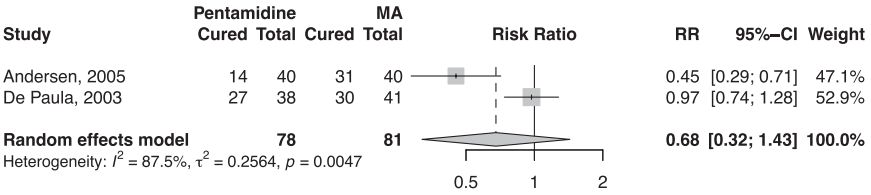


FIGURE 6 Forest plot of head-to-head comparison of pentamidine and meglumine antimoniate (MA) in studies on New World cutaneous leishmaniasis. The random-effects model was employed to calculate the pooled risk ratio (RR) with 95% confidence intervals (CI). The vertical line set at RR = 1 indicates no difference between groups.

Head-to-head comparisons

Only a limited number of comparative studies were available, all in NWCL, allowing for two head-to-head meta-analyses.

Seven RCTs directly compared MA and miltefosine, assessing final cure at 6–7 months using a uniform outcome of complete re-epithelialization of all lesions. Although the RRs favoured miltefosine, difference did not reach statistical significance (RR 1.17; 95% CI 0.97–1.42) (Figure 5). The certainty of evidence was rated as very low, due to the limited number of low RoB studies, imprecision (95% CI 0.97–1.42) and heterogeneity (I^2 = 73.2%). In a sub-analysis stratified by species, exclusion of studies reporting on *L. braziliensis* revealed miltefosine as statistically significantly superior to MA (RR 1.23; 95% CI 1.05–1.45) (Appendix G1).

Two studies, including one RCT, compared the cure rates of pentamidine with MA. Although pentamidine appeared less effective, the difference was not significant (RR 0.68; 95% CI 0.32–1.43) (Figure 6). The certainty of evidence was rated very low due to the substantial heterogeneity (I^2 = 87.5%) and imprecision (GRADE assessments detailed in Appendix H1).

Quality assessment

Since the formal assessment of publication bias was limited to the overall treatment-specific meta-analysis, only MA, miltefosine, and pentamidine were evaluated (Appendix I1). Egger's test did not indicate funnel plot asymmetry for MA (p = 0.186) or pentamidine (p = 0.286), whereas asymmetry was suggested for miltefosine (p < 0.001). Smaller miltefosine study arms (<50 participants) were more often conducted in OWCL (4/8 vs. 1/9) and less often RCT-derived (4/8 vs. 6/9).

DISCUSSION

This systematic review and meta-analysis synthesized 83 studies on systemic CL therapies. For decades, pentavalent antimonials have been used as first-line systemic CL treatment in many endemic regions. Herein, in OWCL, MA showed overall low-to-moderate efficacy with variable species-specific outcomes, likely reflecting inter-species differences in MA responsiveness and spontaneous resolution.[35,36] One high-efficacy *L. major* study was excluded due to short follow-up.[37] Efficacy was higher in NWCL, supporting its use in selected settings. The constraints of MA, including variable efficacies, rising local resistances[38,39] and notable nephro- and cardiotoxicity, however, question its role as standard care.

L-AmB is the treatment of choice for VL in many regions[16]; its use in CL is off-label and primarily extrapolated from VL. While our findings suggest potential efficacy, interpretation is hampered by the small number of dedicated CL studies. Nevertheless, our findings are broadly consistent with a previous meta-analysis,[40] which relied on case series and case reports (the latter not included herein) and investigated tegumentary leishmaniasis instead of CL. Although L-AmB may represent a promising alternative, its role remains controversial due to its toxicity, limited stability at

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temperatures >25°C, inconvenient administration route, and lack of data on skin penetration.[41] To strengthen evidence, more RCTs assessing its species-specific efficacy are urgently needed.

Miltefosine, approved by the FDA for *L. donovani*-associated VL, *L. braziliensis*–/*L. guyanensis*–/*L. panamensis*-associated CL, and *L. braziliensis*-associated ML,[42] showed the most consistent efficacy in this analysis, with stable pooled cure rates across OWCL and NWCL and a relatively large evidence base. This is important, as treatment decisions often rely on the predominant regional species rather than species confirmation. Miltefosine's good efficacy for OWCL appeared attenuated in *L. tropica* studies. Even though biologic characteristics may contribute to this finding, this should be interpreted cautiously, as two available studies investigated exclusively or partially MA-resistant cases,[31,43] indicative of inherently more difficult-to-treat lesions. No head-to-head comparisons between miltefosine and antimonials were available in OWCL, highlighting a key research gap. For NWCL, head-to-head comparisons revealed no significant difference between miltefosine and MA, supported by previous meta-analyses demonstrating miltefosine's non-inferiority.[44,45] Although in vitro data suggested reduced susceptibility of *L. braziliensis* due to decreased expression of the miltefosine transport complex,[46] the cure rates in this study indicate non-negligible efficacy even against this species. Thus, miltefosine appears to be a promising option with broad efficacy across different CL settings, supported by a favourable safety profile and oral administration.[47,48] However, Egger's test ($p < 0.001$) indicated small-study effects, which may reflect publication bias and potential overestimation of pooled efficacy due to the preferential publication of favourable outcomes in smaller studies. At the same time, differences in study region and design also suggest true between-study heterogeneity. These results should therefore be interpreted with appropriate caution.

Azoles can be used as salvage therapies for selected OWCL and NWCL species,[11,13] although evidence is fragmented. The most robust data were available for itraconazole and fluconazole in OWCL. In NWCL, one study reported near-complete failure of fluconazole against *L. guyanensis*,[49] whereas itraconazole achieved a cure rate of 73% in another study.[50] This difference may potentially reflect the more favourable tissue and intracellular distribution of itraconazole.[39,51] Although a previous meta-analysis reported comparable, albeit modest, pooled efficacies for the three azoles,[52] this was not confirmed here for ketoconazole, possibly reflecting differences in study inclusions and/or substantial heterogeneity across studies investigating ketoconazole. Notably, itraconazole showed near-zero between-study heterogeneity, suggesting consistent efficacy estimates, likely reflecting the limited clinical diversity of the evidence with one study arm in NWCL- and all others in OWCL-settings. The favourable safety profile and oral administration represent major advantages that may offset the longer treatment duration, suggesting that azoles may become a pragmatic alternative in selected settings once efficacy has been unequivocally established.

Evidence for pentamidine is confined to NWCL. Piccica et al. reported cure rates comparable to MA,[53] mirrored in our head-to-head analysis. The substantial study heterogeneity and the potential risk of irreversible toxicity, however, limit the compound's therapeutic reliability. Consequently, its use may best be reserved for selected situations, such as prior failure of other treatment options.

Although this meta-analysis focused on treatment efficacy, clinical decision-making should also consider factors beyond efficacy, toxicity, and route of administration. The considerations of regulatory approval, availability, and treatment costs are particularly relevant in resource-limited endemic settings, where MA remains widely used because of its low cost and broad availability. In contrast, the use of miltefosine and L-AmB is often constrained by high acquisition costs and restricted access. Improving equitable access to quality-assured medicines for CL will require better global procurement coordination and supply planning.[16]

The main limitations of this study are the scarcity of high-quality (randomized) comparative studies and the substantial heterogeneity observed for most agents ($I^2 > 70\%$). This heterogeneity is likely multifactorial, reflecting differences in outcome reporting, intra-drug specific formulations and biological factors. Generic formulation-related variability may be particularly relevant for L-AmB, as differences in particle size, drug-lipid association and tissue distribution can influence the drug's pharmacokinetics and efficacy.[54] Although efforts to harmonize CL trial methodology are ongoing,[55,56] implementation of standardized study designs remains necessary. To strengthen validity, here only studies reporting both the number of treated and cured patients were included, while avoiding mixing of per-protocol and intention-to-treat outcomes as in previous meta-analyses. Additionally, excluding outcomes assessed before 2 and after 7.5 months post-treatment initiation improved comparability by accounting for differences in CL self-healing. Remaining heterogeneity may further reflect species-specific effects and substance-, host- and lesion-related characteristics (e.g., skin permeability, innate immunity, microbial burden, *Leishmania* RNA virus).[57–62]

In conclusion, this systematic review and meta-analysis suggests that systemic treatments for CL show variable efficacy, with miltefosine supported by the most consistent estimates. Despite the promising cure rates observed for miltefosine and potentially, L-AmB in OWCL and NWCL, adequately powered, standardized RCTs, ideally stratified by *Leishmania* species, are warranted to delineate the comparative evidence.

AUTHOR CONTRIBUTIONS

M. Egg: conceptualization, data acquisition, analysis, interpretation, writing – original draft, review & editing; D. Wienand: conceptualization, methodology, writing – review &

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editing; L. Harpain: data acquisition, analysis, writing – review & editing; M-L. Brunner-Kovarik: data acquisition, analysis, writing – review & editing; J. Walochnik: conceptualization, methodology, writing – review & editing; M. Wiesmueller: data acquisition, analysis, interpretation, writing – review & editing; A. Hampel: data acquisition, interpretation, writing – review & editing; T. Spath: analysis, writing – review & editing; L. Trnka: data acquisition, interpretation, writing – review & editing; J. Simon: conceptualization, methodology, writing – review & editing; A. Handisurya: conceptualization, data acquisition, interpretation, writing – original draft, review & editing. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All study-related data and statistical code are stored at the Medical University of Vienna, Department of Dermatology and are available upon reasonable request.

ETHICS STATEMENT

This study is a systematic review and meta-analysis of previously published literature and does not involve the collection of primary data from human participants or animals.

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REFERENCES

1. World Health Organization (WHO). The Global health observatory. leishmaniasis. https://www.who.int/data/gho/data/themes/topics/gho-ntd-leishmaniasis
2. Pareyn M, Alves F, Burza S, Chakravarty J, Alvar J, Diro E, et al. Leishmaniasis. Nat Rev Dis Primers. 2025;11(1):81. https://doi.org/10.1038/s41572-025-00663-w
3. Mann S, Frasca K, Scherrer S, Henao-Martínez AF, Newman S, Ramanan P, et al. A review of Leishmaniasis: current knowledge and future directions. Curr Trop Med Rep. 2021;8(2):121–32. https://doi.org/10.1007/s40475-021-00232-7
4. De Vries HJC, Schallig HD. Cutaneous Leishmaniasis: a 2022 updated narrative review into diagnosis and management developments. Am J Clin Dermatol. 2022;23(6):823–40. https://doi.org/10.1007/s40257-022-00726-8
5. European Centre for Disease Prevention and Control (ECDC). Surveillance, prevention and control of leishmaniases in the European Union and its neighbouring countries. 2022. https://www.ecdc.europa.eu/en/publications-data/surveillance-prevention-control-leishmaniases-European-Union-and-neighbouring-countries
6. Van Der Auwera G, Davidsson L, Buffet P, Ruf MT, Gramiccia M, Varani S, et al. Surveillance of leishmaniasis cases from 15 European centres, 2014 to 2019: a retrospective analysis. Euro Surveill. 2022;27(4):2002028. https://doi.org/10.2807/1560-7917.ES.2022.27.4.2002028
7. Aagaard-Hansen J, Nombela N, Alvar J. Population movement: a key factor in the epidemiology of neglected tropical diseases: population movement and neglected tropical diseases. Trop Med Int Health. 2010;15(11):1281–8. https://doi.org/10.1111/j.1365-3156.2010.02629.x
8. Berry I, Berrang-Ford L. Leishmaniasis, conflict, and political terror: a spatio-temporal analysis. Soc Sci Med. 2016;167:140–9. https://doi.org/10.1016/j.socscimed.2016.04.038
9. Koch LK, Kochmann J, Klimpel S, Cunze S. Modeling the climatic suitability of leishmaniasis vector species in Europe. Sci Rep. 2017;7(1):13325. https://doi.org/10.1038/s41598-017-13822-1
10. Carvalho BM, Maia C, Courtenay O, Llabrés-Brustenga A, Lotto Batista M, Moirano G, et al. A climatic suitability indicator to support Leishmania infantum surveillance in Europe: a modelling study. Lancet Reg Health - Eur. 2024;43:100971. https://doi.org/10.1016/j.lanepe.2024.100971
11. AWMF. Diagnostik und therapie der kutanen und mukokutanen Leishmaniasis in Deutschland. https://www.dtg.org/images/Leitlinien_DTG/Leitlinie_Kutane_Leishmaniasis.pdf
12. Blum J, Buffet P, Visser L, Harms G, Bailey MS, Caumes E, et al. LeishMan recommendations for treatment of cutaneous and mucosal leishmaniasis in travelers, 2014. J Travel Med. 2014;21(2):116–29. https://doi.org/10.1111/jtm.12089
13. 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). Clin Infect Dis. 2016;63(12):e202–e264. https://doi.org/10.1093/cid/ciw670
14. Institute for Health Metrics and Evaluation. Global Burden of Disease Collaborative Network. Global burden of disease study 2023 (GBD 2023) results. 2023. https://ghdx.healthdata.org/gbd-2023
15. Bailey F, Mondragon-Shem K, Haines LR, Olabi A, Alorfi A, Ruiz-Postigo JA, et al. Cutaneous leishmaniasis and co-morbid major depressive disorder: a systematic review with burden estimates. PLoS Negl Trop Dis. 2019;13(2):e0007092. https://doi.org/10.1371/journal.pntd.0007092
16. Choi HL, Jain S, Ruiz Postigo JA, Borisch B, Dagne DA. The global procurement landscape of leishmaniasis medicines. PLoS Negl Trop Dis. 2021;15(2):e0009181. https://doi.org/10.1371/journal.pntd.0009181
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
18. Brito G, Dourado M, Guimarães LH, Meireles E, Schriefer A, de Carvalho EM, et al. Oral Pentoxifylline associated with pentavalent antimony: a randomized trial for cutaneous Leishmaniasis. Am J Trop Med Hyg. 2017;96(5):1155–9. https://doi.org/10.4269/ajtmh.16-0435
19. Santos JB, de Jesus AR, Machado PR, Magalhães A, Salgado K, Carvalho EM, et al. Antimony plus recombinant human granulocyte-macrophage colony-stimulating factor applied topically in low

14683083, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jdv.70711 by Haiti Hinari access, Wiley Online Library on [13/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

doses enhances healing of cutaneous Leishmaniasis ulcers: a randomized, double-blind, placebo-controlled study. J Infect Dis. 2004;190(10):1793–6. https://doi.org/10.1086/424848
20. Sadeghian G, Nilforoushzadeh MA. Effect of combination therapy with systemic glucantime and pentoxifylline in the treatment of cutaneous leishmaniasis. Int J Dermatol. 2006;45(7):819–21. https://doi.org/10.1111/j.1365-4632.2006.02867.x
21. Farajzadeh S, Heshmatkhah A, Vares B, Mohebbi E, Mohebbi A, Aflatoonian M, et al. Topical terbinafine in the treatment of cutaneous leishmaniasis: triple blind randomized clinical trial. J Parasit Dis. 2016;40(4):1159–64. https://doi.org/10.1007/s12639-014-0641-1
22. Mendes L, Guerra JO, Costa B, da Silva AS, Guerra M d GB, Ortiz J, et al. Association of miltefosine with granulocyte and macrophage colony-stimulating factor (GM-CSF) in the treatment of cutaneous leishmaniasis in the Amazon region: a randomized and controlled trial. Int J Infect Dis. 2021;103:358–63. https://doi.org/10.1016/j.ijid.2020.11.183
23. Machado PRL, Prates FVO, Boaventura V, Lago T, Guimarães LH, Schriefer A, et al. A double-blind, randomized trial to evaluate Miltefosine and topical granulocyte macrophage Colony-stimulating factor in the treatment of cutaneous Leishmaniasis caused by Leishmania braziliensis in Brazil. Clin Infect Dis. 2021;73(7):e2465–e2469. https://doi.org/10.1093/cid/ciaa1337
24. Andersen EM, Cruz-Saldarriaga M, Llanos-Cuentas A, Luz-Cjuno M, Echevarria J, Miranda-Verastegui C, et al. Comparison of MEGLUMINE ANTIMONIATE and PENTAMIDINE for PERUVIAN cutaneous LEISHMANIASIS. Am J Trop Med Hyg. 2005;72(2):133–7. https://doi.org/10.4269/ajtmh.2005.72.133
25. DeepL translator. https://www.deepl.com/en/translator
26. Schwarzer G, Carpenter JR, Rücker G. Meta-analysis with R. Cham: Springer International Publishing; 2015. https://doi.org/10.1007/978-3-319-21416-0
27. Hilton M. JBI critical appraisal checklist for systematic reviews and research syntheses (product review). J Can Health Libr Assoc. 2024;45(3):180–3. https://doi.org/10.29173/jchla29801
28. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401–6. https://doi.org/10.1016/j.jclinepi.2010.07.015
29. Van Den Enden E, Van Compel A, Stevens A, Vandeghinste N, Le Ray D, Gigase P, et al. Treatment of cutaneous LEISHMANIASIS with oral ITRACONAZOLE. Int J Dermatol. 1994;33(4):285–6. https://doi.org/10.1111/j.1365-4362.1994.tb01049.x
30. Tahir M, Bashir U, Hafeez J, Ghafoor R. Safety and efficacy of miltefosine in cutaneous leishmaniasis: an open label, non-comparative study from Balochistan. Pak J Med Sci. 2019;35(2):495–9. https://doi.org/10.12669/pjms.35.2.54
31. Tayyebi M, Darchini-Maragheh E, Layegh P, Kiafar B, Goyonlo VM. The effect of oral miltefosine in treatment of antimoniate resistant anthroponotic cutaneous leishmaniasis: an uncontrolled clinical trial. PLoS Negl Trop Dis. 2021;15(3):e0009241. https://doi.org/10.1371/journal.pntd.0009241
32. Soto J, Rea J, Balderrama M, Toledo J, Soto P, Valda L, et al. Efficacy of miltefosine for Bolivian cutaneous leishmaniasis. Am J Trop Med Hyg. 2008;78(2):210–1.
33. Ozgoztasi O, Baydar I. A randomized clinical trial of topical paromomycin versus oral ketoconazole for treating cutaneous leishmaniasis in Turkey. Int J Dermatol. 1997;36(1):61–3. https://doi.org/10.1046/j.1365-4362.1997.00022.x
34. Azouz SF, Lago EL, Guimarães LH, Nolasco S, Suprien C, Carvalho EM, et al. Treatment of cutaneous Leishmaniasis with liposomal amphotericin B in the elderly: a randomized clinical trial. Am J Trop Med Hyg. 2026;114(1):105–7. https://doi.org/10.4269/ajtmh.24-0812
35. Hadighi R, Mohebali M, Boucher P, Hajjaran H, Khamesipour A, Ouellette M. Unresponsiveness to Glucantime treatment in Iranian cutaneous leishmaniasis due to drug-resistant Leishmania tropica parasites. PLoS Med. 2006;3(5):e162. https://doi.org/10.1371/journal.pmed.0030162
36. Sezavar M, Sharifi I, Ghasemi Nejad Almani P, Kazemi B, Davoudi N, Salari S, et al. The potential therapeutic role of PTR1 gene in non-healing anthroponotic cutaneous leishmaniasis due to Leishmania tropica. J Clin Lab Anal. 2021;35(3):e23670. https://doi.org/10.1002/jcla.23670
37. Firdous R, Yasinzai M, Ranja K. Efficacy of glucantime in the treatment of Old World cutaneous leishmaniasis. Int J Dermatol. 2009;48(7):758–62. https://doi.org/10.1111/j.1365-4632.2009.04072.x
38. Croft SL, Sundar S, Fairlamb AH. Drug resistance in Leishmaniasis. Clin Microbiol Rev. 2006;19(1):111–26. https://doi.org/10.1128/CMR.19.1.111-126.2006
39. Fernández OL, Rosales-Chilama M, Quintero N, Travi BL, Wetzel DM, Gómez MA, et al. Potency and preclinical evidence of synergy of Oral azole drugs and Miltefosine in an ex vivo model of Leishmania (Viannia) panamensis infection. Antimicrob Agents Chemother. 2022;66(1):e0142521. https://doi.org/10.1128/AAC.01425-21
40. Chivinski J, Nathan K, Naeem F, Ekmekjian T, Libman MD, Barkati S. Intravenous liposomal amphotericin B efficacy and safety for cutaneous and mucosal Leishmaniasis: a systematic review and meta-analysis. Open Forum Infect Dis. 2023;10(7):ofad348. https://doi.org/10.1093/ofid/ofad348
41. Frézard F, Aguiar MMG, Ferreira LAM, Ramos GS, Santos TT, Borges GSM, et al. Liposomal amphotericin B for treatment of Leishmaniasis: from the identification of critical physicochemical attributes to the Design of Effective Topical and Oral Formulations. Pharmaceutics. 2022;15(1):99. https://doi.org/10.3390/pharmaceutics15010099
42. U.S. Food and Drug Administration (FDA). Impavido (miltefosine) capsules: prescribing information. 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/204684s007s008lbl.pdf
43. Kämink S, Masih B, Ali N, Ullah A, Khan SJ, Ashraf S, et al. Effectiveness of miltefosine in cutaneous leishmaniasis caused by Leishmania tropica in Pakistan after antimonial treatment failure or contraindications to first line therapy-a retrospective analysis. PLoS Negl Trop Dis. 2021;15(1):e0008988. https://doi.org/10.1371/journal.pntd.0008988
44. Iranpour S, Hosseinzadeh A, Alipour A. Efficacy of miltefosine compared with glucantime for the treatment of cutaneous leishmaniasis: a systematic review and meta-analysis. Epidemiol Health. 2019;41:e2019011. https://doi.org/10.4178/epih.e2019011
45. Vieira ACP, Lins FC, Baquião AC. Comparison of meglumine antimoniate versus miltefosine in the treatment of new world cutaneous leishmaniasis: a systematic review and meta-analysis. An Bras Dermatol. 2026;101(1):501253. https://doi.org/10.1016/j.abd.2025.501253
46. Sánchez-Cañete MP, Carvalho L, Pérez-Victoria FJ, Gamarro F, Castanys S. Low plasma membrane expression of the miltefosine transport complex renders Leishmania braziliensis refractory to the drug. Antimicrob Agents Chemother. 2009;53(4):1305–13. https://doi.org/10.1128/AAC.01694-08
47. Zhang H, Yan R, Liu Y, Yu M, He Z, Xiao J, et al. Progress in antileishmanial drugs: mechanisms, challenges, and prospects. PLoS Negl Trop Dis. 2025;19(1):e0012735. https://doi.org/10.1371/journal.pntd.0012735
48. Fan Y, Gu Y, Tong X, He Y, Li Q, Chen K, et al. Efficacy and safety of different drugs for the treatment of leishmaniasis: a systematic review and network meta-analysis. Front Cell Infect Microbiol. 2025;15:1717863. https://doi.org/10.3389/fcimb.2025.1717863
49. Francesconi VA, Francesconi F, Ramasawmy R, Romero GAS, Alecrim M d GC. Failure of fluconazole in treating cutaneous leishmaniasis caused by Leishmania guyanensis in the Brazilian Amazon: an open, nonrandomized phase 2 trial. PLoS Negl Trop Dis. 2018;12(2):e0006225. https://doi.org/10.1371/journal.pntd.0006225
50. Cavalcante MDSM, Da Silva LIO, Ortiz JV, De Morais RF, Da Silva E Silva MRH, Pennini SN, et al. Evaluation of itraconazole monotherapy versus its combination with a single dose of pentamidine for treating cutaneous leishmaniasis caused by *Leishmania (Viannia) guyanensis* in Amazonas state, western Brazilian Amazon. Trop Med Int Health. 2025;30(9):954–65. https://doi.org/10.1111/tmi.70008

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51. Perfect JR, Savani DV, Durack DT. Uptake of itraconazole by alveolar macrophages. Antimicrob Agents Chemother. 1993;37(4):903–4. https://doi.org/10.1128/AAC.37.4.903
52. 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. https://doi.org/10.1371/journal.pone.0186117
53. Piccica M, Lagi F, Bartoloni A, Zammarchi L. Efficacy and safety of pentamidine isethionate for tegumentary and visceral human leishmaniasis: a systematic review. J Travel Med. 2021;28(6):taab065. https://doi.org/10.1093/jtm/taab065
54. Dorlo TPC, Balasegaram M. Different liposomal amphotericin B formulations for visceral leishmaniasis. Lancet Glob Health. 2014;2(8):e449. https://doi.org/10.1016/S2214-109X(14)70252-9
55. 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 Negl Trop Dis. 2018;12(1):e0006141. https://doi.org/10.1371/journal.pntd.0006141
56. 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. Clin Infect Dis. 2010;51(4):409–19. https://doi.org/10.1086/655134
57. Singh TP, Farias Amorim C, Lovins VM, Bradley CW, Carvalho LP, Carvalho EM, et al. Regulatory T cells control *Staphylococcus aureus* and disease severity of cutaneous leishmaniasis. J Exp Med. 2023;220(12):e20230558. https://doi.org/10.1084/jem.20230558
58. Farias Amorim C, Lovins VM, Singh TP, Novais FO, Harris JC, Lago AS, et al. Multiomic profiling of cutaneous leishmaniasis infections reveals microbiota-driven mechanisms underlying disease severity. Sci Transl Med. 2023;15(718):eadh1469. https://doi.org/10.1126/scitranslmed.adh1469
59. Bourreau E, Ginouves M, Prévot G, Hartley MA, Gangneux JP, Robert-Gangneux F, et al. Presence of *Leishmania* RNA virus 1 in *Leishmania guyanensis* increases the risk of first-line treatment failure and symptomatic relapse. J Infect Dis. 2016;213(1):105–11. https://doi.org/10.1093/infdis/jiv355
60. Adaui V, Lye LF, Akopyants NS, Zimic M, Llanos-Cuentas A, Garcia L, et al. Association of the Endobiont Double-Stranded RNA virus LRV1 with treatment failure for human Leishmaniasis caused by *Leishmania braziliensis* in Peru and Bolivia. J Infect Dis. 2016;213(1):112–21. https://doi.org/10.1093/infdis/jiv354
61. Ginouvès M, Couppié P, Simon S, Bourreau E, Rogier S, Brousse P, et al. Leishmaniavirus genetic diversity is not related to leishmaniasis treatment failure. Clin Microbiol Infect. 2021;27(2):286.e1–286.e5. https://doi.org/10.1016/j.cmi.2020.04.037
62. Gómez MA, Belew AT, Vargas DA, Giraldo-Parra L, Alexander N, Rebellón-Sánchez DE, et al. Innate biosignature of treatment failure in human cutaneous leishmaniasis. Nat Commun. 2025;16(1):3235. https://doi.org/10.1038/s41467-025-58330-3

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