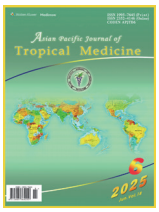

Systematic Review

Asian Pacific Journal of Tropical Medicine

apjtm.org

doi: 10.4103/apjtm.apjtm_685_24

Therapeutic efficacy and safety of antileishmanial agents for visceral leishmaniasis in children: A systematic review

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ABSTRACT

Objective: To evaluate the dosing, efficacy and safety of the main antileishmanial agents amphotericin B (conventional or liposomal), pentavalent antimonials, miltefosine and paromomycin recommended for the treatment of visceral leishmaniasis in children.

Methods: The efficacy and safety of visceral leishmaniasis treatments in children were systematically reviewed using literature from PubMed, Cochrane, clinicaltrials.gov, and Google Scholar, focusing on randomised trials with separate pediatric data (published from 2000-2024). The risk of bias of selected trials was assessed using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2). Reporting was done per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 checklist.

Results: Of 1 186 records, only 7 were eligible for qualitative synthesis. Three trials exclusively included children. The treatment regimens studied showed high heterogeneity and lacked sufficient data for a meta-analysis. Most trial arms reported efficacies over 94% for children across different regimens. Miltefosine monotherapy showed the highest rate of late treatment failures, highlighting that allometric dosing is crucial to ensure proper drug exposure in children. Safety data for children were available in only three studies with varied reporting systems of adverse events. Although regimens in this review were generally considered to be safe in children, antimonial-related cardiac toxicity remains a threat.

Conclusions: This review highlights the need for pediatric-specific trials, clear presentation of pediatric data, and systematic documentation of adverse events to enhance evidence for policy-making and pediatric guideline development.

KEYWORDS: Visceral leishmaniasis; Children; Treatments; Efficacy; Safety; Systematic review

1. Introduction

Visceral leishmaniasis (VL) is a neglected tropical disease caused by flagellated protozoan parasites of the genus *Leishmania*[1,2],

Summary

Question: What are the dosing, efficacy, and safety of antileishmanial agents (conventional and liposomal amphotericin B, antimonials, miltefosine, paromomycin) for treating visceral leishmaniasis in children?

Findings: The systematic review found only 7 of 1 186 studies eligible for analysis, with three on children only and most regimens showed over 94% efficacy in children. Miltefosine had the highest failure rate, highlighting the need for allometric dosing while safety data were limited, and antimonial-related cardiac toxicity remained a concern.

Meaning: Paediatric trials, segregated paediatric data, and systematic safety reporting are critical for high-level evidence-based guidelines.

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How to cite this article: De Silva NL, Hettiarachchi M, Ranasinghe CS, Yahathugoda TC, Ranasinghe S. Therapeutic efficacy and safety of antileishmanial agents for visceral leishmaniasis in children: A systematic review. Asian Pac J Trop Med 2025; 18(6): 243-251.

Article history: Received 15 November 2024 Revision 10 June 2025
Accepted 21 June 2025 Available online 27 June 2025

a vector-borne disease that occurs through the bites of infected female sandflies in the genera of *Phlebotomus* and *Lutzomyia*. VL disproportionately affects economically disadvantaged populations and can be fatal if untreated. Other clinical forms of leishmaniasis include cutaneous and mucosal forms. Although annual VL estimates suggest 50 000 to 90 000 new cases, underreporting is likely. The disease burden is concentrated in Brazil, East Africa, and India. Encouragingly, the Kala-azar elimination programme in Southeast Asia (SEAR) has significantly lowered case numbers[2], reducing the global burden, with Africa and the Eastern Mediterranean now carrying 63% of the burden as of 2020[3]. The World Health Organisation (WHO) identifies VL as an neglected tropical disease requiring innovative and intensified management approaches[2].

Chemotherapy remains central to VL management but regrettably, the therapeutic options remain limited to a few drugs, *viz*. antimonials (sodium stibogluconate-SSG and meglumine antimoniate-MA), amphotericin B (in both amphotericin B deoxycholate-AMB-and liposomal amphotericin B-L-AMB), parenteral paromomycin (PM) and miltefosine (MF). Challenges such as prolonged treatment courses, toxicity, high costs, resistance and the rising immunosuppressed and HIV-co-infected populations have further complicated the management of VL. Drug discovery for VL has been neglected, evident in the scarcity of novel therapeutics[4]. In the Indian subcontinent, over 60% of patients were resistant to pentavalent antimonials, prompting changes in the first-line treatment in the Kala-azar elimination programme[5,6]. Combination regimens have been tested to preserve efficacy and reduce treatment time, toxicity, and costs[7,8]. Geographic differences in drug efficacy due to parasite or host genetic variations further complicate VL management[9,10].

Global statistics on VL demonstrate that a substantial proportion of those afflicted are children, especially in endemic regions where the disease causes significant morbidity and mortality. Between 2015 and 2020, 40%-50% of yearly new cases in high-burden countries occurred in children under 14[3]. Their vulnerability is heightened by immature and developing immune systems, lack of acquired immunity and malnutrition, making them particularly susceptible to the disease[9,11].

In agreement with the aphorism that children are not miniature adults, the pharmacokinetics of drugs are influenced by growth and development leading to differences in drug responses compared to adults. Moreover, these responses may vary across childhood stages such as the neonatal period, infancy, or adolescence[12,13]. A well-recognized challenge is the limited number of randomised clinical trials on the paediatric population. This results in a lack of high-level evidence regarding drugs, dosing regimens and efficacy tailor-made for children[13]. Instead, data from adults are often extrapolated for paediatric dosing. Given the substantial number of VL-infected children, health implications, drug-related risks and the evident knowledge gap about children, this review aimed to assess the dosing, efficacy, and safety of VL drugs in children.

2. Methods

2.1. Study design and review question

A systematic review and meta-analysis were conducted to assess the therapeutic efficacy and safety of the treatments for VL in children (review protocol available as Protocol in Supplementary File 1). Our reporting adheres to the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 checklist[14]. The eligibility of studies was determined based on PICO (Population, Intervention, Comparison and Outcome) components[15].

Population: children with VL-a child defined as an individual less than 18 years of age as defined in the Convention of the Rights of the Child[16,17];

Intervention: four main drugs: amphotericin B (conventional-AMB or liposomal-L-AMB), pentavalent antimonials (sodium stibogluconate-SSG and meglumine antimoniate-MA), miltefosine (MF) and paromomycin (PM);

Comparison: against standard treatment or placebo;

Outcomes: drug efficacy, treatment failures, safety, relapses or deaths. A relapse was defined as the reappearance of parasites after initial cure, usually within 6 months of follow-up[18,19]. Therefore, at least a 6-month follow-up was deemed necessary to evaluate treatment efficacy.

2.2. Eligibility criteria

We included randomised clinical and interventional trials on VL treatments, focusing on specified drugs with freely accessible full-text reports in English, published from 2000 to 2024 (We focused on studies from this period to ensure the evidence reflects current research standards, methodologies, and clinical practices). VL was defined by a comparable clinical presentation along with parasite/DNA demonstration or positive serology. Studies on other forms of leishmaniasis (cutaneous, mucosal, post-Kala-azar dermal leishmaniasis), those without separate paediatric data, other study designs (case reports or series, non-interventional studies, reviews, meta-analyses), animal studies, experimental or *in-vitro* studies, non-English publications, papers without freely available full text and those limited to abstracts including conference/symposium

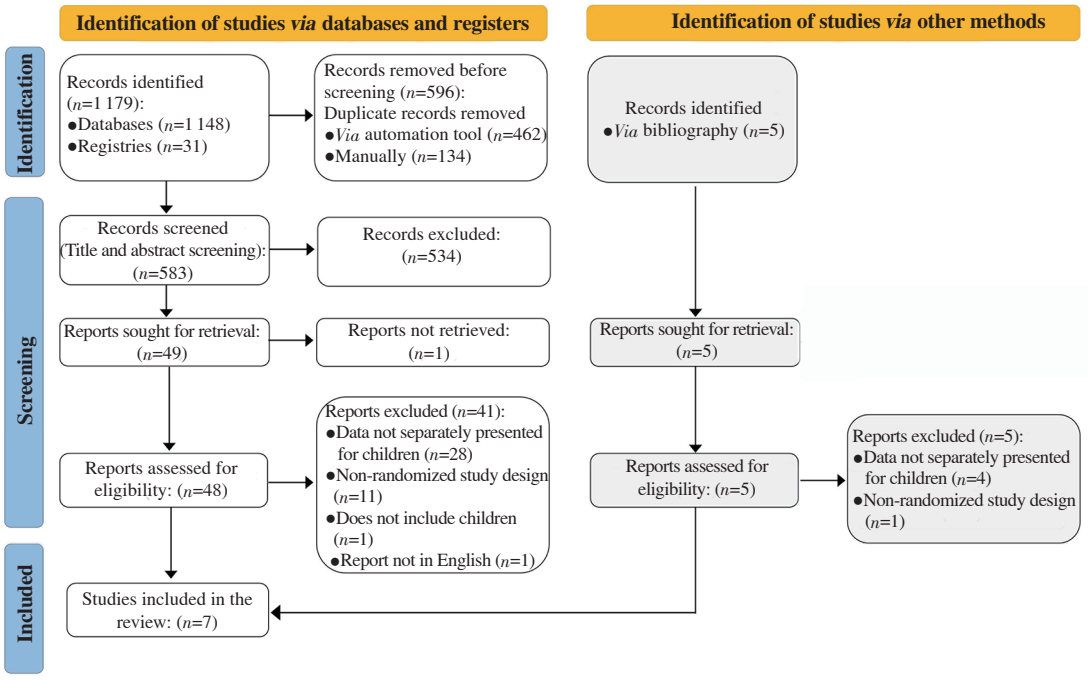

Figure 1. PRISMA flow diagram of study selection.

abstracts were excluded from the study. Publications for which full-text access could not be obtained through any means were also excluded.

2.3. Sources of information and literature search

An electronic search was conducted starting September 2023 across several databases, registries, and search engines including PubMed, Cochrane Library, clinicaltrials.gov and Google Scholar. Search strategies were tailored for each repository using key concepts: visceral leishmaniasis, children, anti-leishmanial drugs, efficacy, and safety. Multiple strategies were employed in each repository to broaden the search, and results were combined. Detailed information about the literature search is available in the supporting information file (Supplementary File 2). Additionally, the bibliography of five systematic reviews related to the therapeutic management of VL was reviewed for relevant references[20–24]. The systematic literature search was updated before the initiation of data analysis in July 2024 using the same search strategies.

2.4. Article selection, data extraction and synthesis

The EndNote™ reference management tool facilitated the initial screening process. Imported references from different search strategies for each repository and then different repositories were combined and duplicates were removed using the 'find and remove duplicates' feature. After title and abstract screening, the remaining studies were selected for full-text review. Data extraction was performed using a modified Cochrane data extraction form for RCTs only[15]. A qualitative summary of the evidence was synthesized. A meta-analysis was not conducted due to the high heterogeneity of the trial arms of the selected randomised trials.

2.5. Risk of bias assessment

Each study was assessed for risk of bias using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2) version of 22 August 2019[25]. The RoB2 evaluates the risk of bias in randomised trials using a series of signalling questions based on five key domains: the randomisation process, deviations from the intended interventions (the effect of assignment of interventions), missing outcome data, measurement of the outcome and selection of the reported result. Each domain was judged separately, and the overall risk of bias was determined as low, with some concerns or high risk of bias (according to the guidelines provided by the Cochrane training). Each included study was independently assessed for the risk of bias by two authors, with any disagreements resolved through discussion.

Table 1. Characteristics of the included studies.

Citation	Study ID (author, year)	Geographical region	Study design	Total number of subjects randomised	Number of children, *n* (%)	Age of the children	Sex
[26]	Sundar S *et al*, 2007	India (SEAR)	Randomised controlled Parallel design (phase Ⅲ)	667	252 (37.7)	5-14 years	NR separately for children
[27]	Singh UK *et al*, 2010	India (SEAR)	Randomised parallel (phase not mentioned)	605	605 (100)	1-14 years	NR
[28]	Wasunna M *et al*, 2016	Sudan (EMR) and Kenya (African)	Randomised Non-comparative sequential (phase Ⅱ)	151	107 (70.8)	7-17 years	NR separately for children
[29]	Alborzi A *et al*, 2017	Iran (EMR)	Randomised Non-inferiority (phase not mentioned)	75	75 (100)	2-156 months	NR
[30]	Borges MM *et al*, 2017	Brazil (Americas)	Randomised controlled Parallel design (phase Ⅳ)	101	101 (100)	6-143 months	Males=55% Females=45%
[31]	Rahman R *et al*, 2017	Bangladesh (SEAR)	Randomised controlled Parallel design (phase Ⅲ)	602	297 (49.33)	Not mentioned	NR separately for children
[32]	Musa AM *et al*, 2023	Eastern Africa (African)	Randomised controlled (phase Ⅲ)	341 (excluding the discontinued arm)	208 (61%)	4-12 years	Males=65.4% Females=34.6%
Total				2 542	1 645 (64.7)		

EMR: Eastern Mediterranean Region; SEAR: Southeast Asia Region; NR: Not reported.

3. Results

3.1. Study selection

The databases and registry search identified 1 179 records: 848 from databases, 31 from registries, and 300 from Google Scholar. Seven additional records were found through the bibliographies of other review articles, totalling 1 186. The selection process according to the PRISMA guidelines is shown in Figure 1[14].

3.2. Characteristics of the included studies

Seven randomised trials (Table 1) published between 2007 and 2023 (conducted 2006-2020) across three WHO regions were included[26-32]. All were randomised trials ranging from phase Ⅱ to Ⅳ. These trials took place in South-East Asia (India[26,27], Bangladesh[31]), the Eastern Mediterranean region (Iran[29]) and the Americas (Brazil[30]). One study was conducted in both Sudan (Eastern Mediterranean) and Kenya (Africa)[28]. The trial in Eastern Africa[32] was a multi-country trial involving Kenya, Uganda, Sudan and Ethiopia.

Three studies included only children[27,29,30] while the rest had mixed populations[26,28,31,32]. Out of 2 542 randomised patients, 1 645 (64.7%) were children. The randomised trial by Musa *et al*., discontinued one arm halfway through recruitment, hence those children were excluded. The South-East Asia region contributed the highest number of children (*n*=1 154; 70.15%). Age ranges varied from 6 months to 17 years, but some studies didn't specify ages[29,31]. Two studies provided sex data for children[30,32], both included higher percentages of male children than female (55% *vs*. 45%[30] and 65.4% *vs*. 34.6%[32]).

All trials involved WHO-defined VL patients[18] confirmed *via* parasitological or serological tests. Samples included bone marrow, spleen, lymph node aspirates and serum while techniques were microscopy for Leishman-Donovan bodies, PCR, rK39 rapid test, and indirect fluorescent antibody test. All trials required parasitological confirmation, except one which allowed either method[29]. Mixed population studies excluded women of childbearing age (or offered contraception), pregnant or lactating women, previously treated VL patients, and those with organ dysfunction, co-infections, or severe malnutrition (detailed inclusion, exclusion and diagnostic criteria are provided in the Supplementary File 3).

Treatment outcomes varied, with cure defined by clinical or parasitological criteria or both. Four studies used clinical criteria[29-32] while others used parasitological tests of cure[26-28]. Follow-up was typically six months with some extending to 210 days[28,32]. Treatment failures included lack of initial cure, no response, death, or relapse. The *Leishmania* species in all reported studies are considered as the endemic species of the region and it was considered when interpreting the efficacy data. Only two studies[28,29] mentioned the relevant endemic species causing VL in the reports.

The seven trials studied 18 treatment groups (Table 2) with different drugs and combinations.

Table 2. Drugs and regimens studied.

Drug	Groups	Number of studies
AMB	4	3 [26,27,30]
L-AMB	1	1 [31]
MA	4	2 [29,30]
L-AMB+MF	2	2 [28,31]
PM	1	1 [26]
MF	1	1 [28]
AMB+PM	1	1 [31]
L-AMB+SSG	1	1 [28]
PM+MF	2	2 [31,32]
SSG+PM	1	1 [32]
Total	18	7

AMB: Amphotericin B; L: AmB-Liposomal Amphotericin B; SSG: Sodium stibogluconate; MA: Meglumine antimoniate; PM: paromomycin; MF: Miltefosine.

Most trials had a low risk of bias (Supplementary File 4) except one[27] due to concerns in three domains. Two others had concerns about randomisation[26,29]. All trials were judged to have a low risk of bias for the measurement of the outcome and selection of the reported results.

3.3. Efficacy of individual VL drugs at the end of follow–up among children

Dosing regimens tested among children with VL and their efficacy at the end of treatment and end of follow-up is shown in Table 3.

•AMB: Across two trials[27,30], 352 children received daily AMB regimen, achieving 98.3% efficacy (346/352). The alternate-day

Table 3. Dosing regimens tested among children with VL and their efficacy at the end of treatment and end of follow-up.

Study	Study ID (author, year)	Treatment arms and dosages	Efficacy: End of treatment	Efficacy: End of follow-up	95% *CI*
[26]	Sundar S *et al*, 2007	PM 11 mg/kg deep IM daily×21 days	NRSC	181/188 (96.3%)	92.4-98.4
		AMB 1 mg/kg iv EOD×30 days (a total of 15 infusions)	NRSC	63/64 (98.4%)	91.6-99.9
[27]	Singh UK *et al*, 2010	AMB 1 mg/kg/day IV×15 days (cumulative dose: 15 mg/kg)	300/302 (99.3%)	299/302 (99.0%)	97.1-99.7
		AMB 1 mg/kg/day IV EOD×30 days (cumulative dose: 15 mg/kg)	270/303 (89.1%)	267/303 (88.1%)	83.9-91.5
[28]	Wasunna M *et al*, 2016	L-AMB 10 mg/kg single dose (IV) on day 1 +SSG (IM) 20 mg/kg from day 2-11	NRSC	22/25 (88.0%)	68.7-97.4
		L-AMB 10 mg/kg single dose (IV) on day 1 +MF 2.5 mg/kg/ day (oral) from day 2-11 (up to a maximum dose of 150 mg)	NRSC	20/27 (74.1%)	53.7-88.8
		MF 2.5 mg/kg/day (oral) from day 1-28 (up to a maximum dose of 150 mg)	NRSC	13/22 (59.1%)	36.3-79.2
[29]	Alborzi A *et al*, 2017	MA 20 mg/kg/day deep IM×1/52 after fever subsides	25/25 (100%)	24/25 (96.0%)	79.6-99.9
		MA 20 mg/kg/day deep IM×2/52 after fever subsides	25/25 (100%)	25/25 (100%)	86.2-100
		MA 20 mg/kg/day deep IM×3/52 after fever subsides	25/25 (100%)	25/25 (100%)	86.2-100
[30]	Borges MM *et al*, 2017	AMB 1 mg/kg/daily IV×14 days	NR	47/50 (94.0%)	83.4-98.7
		MA 20 mg/kg/day IV×20 days		48/51 (94.1%)	83.7-98.7
[31]	Rahman R *et al*, 2017	L-AMB 5 mg/kg on day 1+MF×7 days >12 y & <25 kg: 50 mg/daily, >12 y & >25 kg: 50 mg twice daily; <12 y: 2.5 mg/kg/day in 2 divided doses	59/60 (98.33%)	59/60 (98.33%)	91.0-99.9
		L-AMB 5 mg/kg on day 1+PM 11 mg/kg/day deep IM×10 days	83/83 (100%)	83/83 (100%)	95.6-100
		PM 11 mg/kg/day deep IM+MF >12 y & <25 kg: 50 mg/daily, >12 y & >25 kg: 50 mg twice daily; <12 y: 2.5 mg/kg/day in 2 divided doses. Daily dose for 10 days	73/75 (97.33%)	73/75 (97.33%)	90.7-99.6
		L-AMB 15 mg/kg in doses of 5 mg/kg, days 1, 3, 5	78/79 (98.73%)	78/79 (98.73%)	93.1-99.9
[32]	Musa AM *et al*, 2023	PM 20 mg/kg deep IM daily×14 days+ MF (oral) according to body weight twice daily for 14 days	NRSC	97/103 (94.1%)	87.7-97.8
		SSG 20 mg/kg/day IM/IV+PM 15 mg/kg/day IM for 17 days	NRSC	100/105 (95.2%)	89.2-98.4

MA: Meglumine antimoniate; AMB: Amphotericin B; L-AmB: Liposomal Amphotericin B; SSG: Sodium stibogluconate; PM; Paromomycin; IM: Intramuscular; IV: Intravenous; EOD: Every other day; NR: Not reported; NRSC: Not reported separately for children. y: Years. Criteria of efficacy for individual studies: [26]: Clinical & parasitological cure, [27]: Parasitological cure, [28]: Clinical cure with no requirement for rescue treatment, [29]: Clinical cure with no relapse for 6 months, [30]: Clinical cure with remission for three months after completion of treatment, [31]: Initial clinical cure (day 45) and remission for 6 months, [32]: Clinical cure with no requirement for rescue treatment.

regimen in 367 children across two studies[26,27], showed 89.9% efficacy (330/367). The majority represented VL due to *Leishmania* (*L.*) *donovani* in SEAR. A minority (14.2%, 50/352) in the daily regimen represented *L. infantum* in EMR.

•L-AMB: Only one trial arm in the SEAR[31] comprising 79 children received L-AMB monotherapy. The species represented was *L. donovani* and the efficacy was 98.7%.

•MA: MA was administered for up to 1, 2 or 3 weeks after defervescence[29] and for 20 days[30] to 126 children across two trials. An overall efficacy of 96.8% (122/126) was reported and the involved species was *L. infantum* in EMR and the Americas.

•PM: PM monotherapy (21 days) was administered to 188 children in SEAR[26]. The represented species was *L. donovani* and an efficacy of 96.2% (181/188) was reported.

•MF: A trial conducted in Sudan (EMR) and Kenya (African) provided data for 22 children (<12 years) who were given MF monotherapy (for 28 days[28]. The efficacy was 59.1% (13/22). The same study reported 86.2% (25/29) efficacy for the 12-60 year group. Both countries in this trial are endemic for *L. donovani*.

•Combination regimens: Two trials involving SEAR, EMR and Africa[28,31] investigated L-AMB and MF combination using slightly different dosing regimens, in 87 children (Table 3) reporting an overall efficacy of 90.8% (79/87). Interestingly, the SEAR trial arm demonstrated a high efficacy of 98.3% in children, while Sudan and Kenya reported a lower efficacy of 74%[28], reducing the overall efficacy. Wasunna *et al*[28] reported efficacy below 90% for all tested combination regimens in Sudan and Kenya for children but higher efficacy for all regimens in those over 12 years. The combination of L-AmB (5 mg/kg on day 1) with PM (11 mg/kg/day for 10 days) reported the highest efficacy (100%)[31] among all combination regimens, in 83 children in the SEAR. The PM-MF combination tested in two trial arms in the SEAR and Eastern Africa showed an overall efficacy of 95.5% (170/178) with SEAR exhibiting a slightly superior efficacy (97.3 *vs*. 94.1%).

3.4. Efficacy at the end of treatment

Only 3 out of 7 studies reported efficacy at the end of treatment for children[27,29,31] (Table 3). All treatment arms reported efficacies beyond 97% except for one trial arm reported by Singh *et al* in 2010, in which the efficacy was 89.1% (30 alternate-day AMB regimens where many participants did not complete treatment) (Table 3).

3.5. VL treatment failures, relapses and deaths among children

3.5.1. Early treatment failure

Four studies reported 9 events among 1 078 participants[27,29–31]. Among them, treatment failures occurred in only two studies-Borges *et al*.[30], and Rahman *et al*.[31], while the other 2 reported none. Borges *et al*[30] reported that early therapeutic failure occurred due to drug toxicities with 3 events linked to MA and two events to AMB. Rahman *et al*.[31] studied combination regimens and reported 1 failure for AMB+MF, 2 for PM+MF and 1 for AMB likely related to drug toxicities rather than poor response. However, all regimens in children achieved over 95% initial cure rates (Supplementary File 5).

3.5.2. Late treatment failure

Late treatment failures were reported/extractable in 6/7 studies. The heterogeneity was high (Table 2) with only a few trial arms using the same drug in the same regimen, allowing to determine a combined treatment failure rate. Only single-drug regimens showed sufficient similarity for merging in this review (Figure 2). For combination regimens, high heterogeneity remained, with variations in dosing even when the same drug combinations were used, hence this data was excluded from Figure 2. Overall, 38 late treatment failures were reported among 1 437 children (2.6%) in the 6 studies. Only two relapses were reported among the 7 studies (classified as treatment failures), with no deaths.

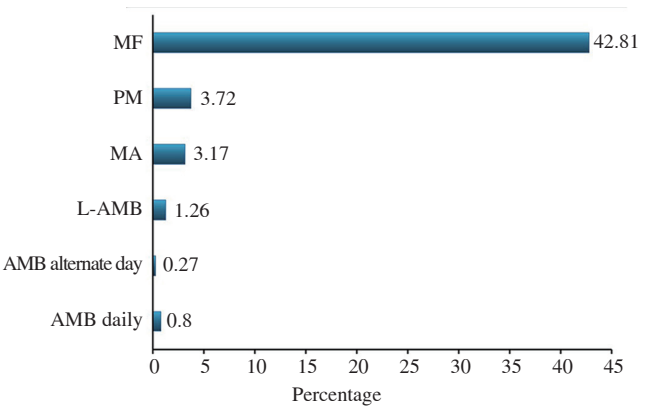

Figure 2. Late treatment failures for the single-drug regimens (MF: miltefosine, PM: paromomycin, MA: meglumine antimoniate, L-AMB: liposomal amphotericin B, AMB: conventional amphotericin B).

The highest late failure rate was observed for MF monotherapy (42.8%)[28], while the lowest was for the alternate-day AMB regimen (0.27%). However, this figure excludes patients from Singh *et al*.[27] who left the trial, as their outcomes were unknown and not necessarily classified as treatment failures. The L-AMB monotherapy with 79 children had a 1.26% failure rate. MA and PM had failure rates of 3.17% and 3.72%, respectively. Among combination therapies, L-AMB+MF in Wasunna *et al*.[28] had the highest failure rate (25.9%), followed by L-AMB+SSG (12.0%). However, L-AMB+MF in the trial by Rahman *et al*.[31] showed only 1.66% failure. The lowest failure rate among combinations was L-AMB+PM at 0%[31].

3.6. Safety of anti–leishmanial drugs/adverse drug reactions

Reporting of adverse events (AE), reporting systems and monitoring durations varied across studies. AEs were reported in three out of the seven studies[27,28,30] (Supplementary File 6). Three studies reported AEs in common for adults and children[26,31,32] while one didn't report AEs[29]. Grading of AEs were varied across studies: the Division of AIDS Table, and MedDRA version 2.0 coding system were used in two studies. Singh *et al*.[27] did not report a grading system and reported a limited array of events than the other two studies (Supplementary File 6). Due to the heterogeneity of the interventions, outcome definitions, and the duration of monitoring, a summary effect of the AEs was not assessed in this review.

Borges *et al*[30] reported that children in the antimonial group experienced a higher frequency of serious AEs, leading to their withdrawal. Moderate to severe liver enzyme abnormalities, myalgia, anaemia, and hypomagnesaemia were the common AEs observed. As opposed to the AMB group, the antimonial group also experienced cardiac arrhythmias (sinus arrhythmia and right branch conduction disturbance). Additionally, liver enzyme derangements were notably higher in the antimonial group. The AMB group experienced severe anaemia and hypomagnesaemia. Except for shivering, which occurred more frequently in the AMB group, the overall frequency of AEs was similar between the two groups. Singh *et al*[27] also reported a higher occurrence of infusion-related shivering, rigors and fever with both daily and alternate-day AMB. This study further documented elevated creatinine levels in 5% of children on the daily regimen and 4% on the alternate-day regimen. However, this particular AE was not observed among the children who received the daily AMB regimen in the study by Borges *et al*[30]. In the combination regimens by Wasunna *et al*[28], treatment arms involving SSG and L-AMB as well as L-AMB and MF showed sinus arrhythmia rates of 4% and 13% respectively in children <12 years of age. Infusion-related AE was reported in 20% of those receiving L-AMB. Vomiting emerged as the most frequently reported AE for MF. Overall, no major safety concerns were identified for the tested treatment regimens across studies. However, antimony-related toxicities continue to pose a challenge in ensuring the successful completion of treatment.

4. Discussion

This study systematically reviewed randomised trials from 2000 to 2023 on the efficacy and safety of VL treatments in children. The main reason for excluding studies (60.3%) was the lack of separate paediatric data, despite children representing a significant burden of VL in endemic regions. This review highlights the need for more paediatric-specific trials and better reporting of child-related data, particularly regarding safety. It also found a scarcity of randomised trials exclusively for children, with many combining adult and paediatric data.

In evaluating the potential bias of the selected studies, missing allocation concealment details led to 'some concerns' on the potential bias which affect the study's quality and intervention effects estimates[33]. The risk of bias assessment primarily focused on the main outcome-treatment efficacy. Performance bias and detection bias were not judged as high risk of bias by default for open-label trials. However, measurable clinical outcomes are less prone to bias[34]. The efficacy outcomes in these trials were objective, minimizing bias.

The heterogeneity of the trial arms and varying dosing regimens precluded conducting a meta-analysis of the data and the authors confined their reporting to a systematic review. One trial by Singh *et al*.[27] skewed results slightly in favour of control regimens due to high bias risk and issues with patients leaving against medical advice (LAMA). Re-analysis excluding this study showed a marginally favourable effect for experimental regimens, though not statistically significant. The said trial by Sing *et al*.[27], explored daily *vs*. alternate-day AMB therapy and many patients in the alternate-day arm LAMA due to extended hospital stays and costs, creating an imbalance between groups. Additionally, the report lacked details on the imputation method for missing data, with LAMA patients considered not cured for analysis purposes. Outcome data was missing for these patients. This further limited the availability of robust data. Considering the reasons for dropout, we refrained from classifying the missing data as treatment failures for this review. In the trial by Sundar *et al*.[26], the same regimen showed a high efficacy at 98.4% without similar dropouts.

The daily AMB regimen demonstrated high efficacy (98.3%), but

the alternate-day regimen was less effective (89.9%) (Singh *et al*[27]). In Sundar *et al*'s study[26] where data for all alternate-day regimen patients were available, efficacy was high at 98.4%. However, the alternate-day regimen requires prolonged hospitalisation, necessitating the presence of a parent/family member with increased meal and travel costs, loss of income, disruptions to siblings' lives, and a greater financial burden on the family, contributing to LAMA and subsequent treatment failure. Thus, the alternate-day regimen does not appear encouraging for children.

A trial arm receiving the L-AMB formulation in the SEAR (Bangladesh) showed a high efficacy of 98.7% (Rahman *et al*.[31]), underscoring the regimen's success as a first-line drug in the Kala-azar elimination program in the Indian subcontinent[35]. Although the efficacies are comparable for AMB and L-AMB, L-AMB has the advantages of a short regimen, lower toxicity, improved compliance, and minimal interference with daily life and the economy. The trial by Rahman *et al*.,[31], tested 15 mg/kg body weight administered in three 5 mg/kg doses, which exhibited high efficacy in Bangladesh. However, in the Kala-azar elimination programme, Bangladesh has opted for the single dose regimen of 10 mg/kg for L-AMB[35]. Therefore, this review could not comment on the efficacy of this regimen in children.

The PM and MF combination, recommended as second-line therapy in the Indian subcontinent, showed high efficacy (97.33%) in children[31] and was non-inferior to L-AMB monotherapy. This combination is promising due to fewer toxicities and painful injections compared to SSG+PM, making it more suitable for children in regions like Africa where SSG+PM is the first-line regimen[36]. Musa *et al*. found it to be equally effective as SSG+PM with a lower risk of post-Kala-azar dermal leishmaniasis[32].

MA demonstrated high efficacy (96.8%) in the EMR and the Americas but with more AEs leading to participant withdrawals (Borges *et al*.)[30]. In contrast, Alborzi *et al*.[29], found a shorter MA regimen to be non-inferior in efficacy to the standard 28-day regimen with benefits like lesser painful intramuscular injections, reduced hospital stays and costs and fewer AEs. Higher relapse rates were noted with shorter regimens (8.3% *vs*. 5.0%)[29] but within an acceptable range for a control programme.

This review included only one trial from Africa on MF monotherapy in children, which showed low efficacy (59.1%)[28]. Poor outcomes in children have demonstrated that MF in children compared to adults in equivalent weight-adjusted doses with higher treatment failure rates[37]. Poor outcomes were linked to insufficient MF exposure in children compared to adults, highlighting the need for allometric dosing to improve efficacy[38,39]. Supporting this fact, Musa *et al*.'s trial demonstrated similar MF exposure in both children and adults using allometric dosing[32]. However, compliance with the 28-day MF treatment remained challenging due to gastrointestinal side effects. Geographic variations in parasite strains and host genetics further complicated achieving high cure rates[5]. Trials in Africa and Brazil also reported late treatment failures, especially with MF monotherapy and combinations with L-AMB[28,30].

Borges *et al*.,[30] in Brazil while showing comparable efficacies for MA and AMB, reported the next highest rate of late treatment failures for daily AMB during the period when antimonials and AMB were the recommended treatment in the Americas. However, since 2022, The Pan American Health Organisation now recommends L-AMB as the first-line therapy in the Americas due to concerns over antimonial toxicity[40].

The efficacy of PM monotherapy in India (96.3%) was promising[26] although it has consistently displayed suboptimal efficacy in African patients, thought to be due to host genetics, virulence variations or resistance[20]. This review lacked RCT data for PM monotherapy in the African region, hence we are unable to comment on it. In the Indian subcontinent, PM can serve as an alternative[26].

Reporting of AEs varied across studies, with many not specifying those affecting children. Although regimens in this review were generally considered to be safe in children, antimonial-related cardiac toxicity remains a threat[30]. The gastrointestinal side effects, particularly vomiting, which was frequently reported following MF[28], remain a concern because of the potential to impact compliance, drug exposure and efficacy. Through this review, we encourage authors to systematically evaluate and report safety data for children and to present this data separately in their manuscripts, because safety data is underreported.

The protocol for this review was not registered in a public registry due to time constraints (conducted within a limited timeframe); however, methodological rigour was ensured by adhering to established systematic review guidelines. One potentially relevant non-English article was excluded because Google Translate™ did not provide a sufficiently reliable translation for valid data extraction. Another potential article could not be retrieved in full text despite multiple attempts. The limited availability of RCTs for children resulted in a scarcity of robust data for this population. The included studies exhibited significant heterogeneity in drug regimens, including different medications, combinations, and dosing, hindering performing a meta-analysis while one study showed a high risk of bias. Despite these limitations, the review provides a comprehensive synthesis of the existing evidence and highlights key gaps that future research should address.

5. Conclusions

This study revealed a significant lack of segregated paediatric data in randomised trials, despite frequent inclusion of children. Few trials specifically target children, and treatment arm heterogeneity posed challenges in consolidating data. L-AMB monotherapy showed high efficacy for VL in SEAR, while SSG+PM remains effective in Africa. However, the PM+MF regimen offers a promising alternative with fewer injections and no antimony-related toxicity. Proper allometric dosing of MF is essential for optimal efficacy in children. There was also a notable underreporting of safety data. This study underscores the need for more paediatric-specific trials, clearer reporting of paediatric data, and systematic documentation of adverse events to better inform policy and guidelines for treating children with VL.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Funding

The authors received no extramural funding for the study.

Authors' contributions

Concept, design and protocol development was by all authors; Literature search, article selection, and data acquisition was by NLDS and CSR; Independent data extraction was by NLDS and SR; Data analysis and Risk of bias assessment was by NLDS; Manuscript preparation by NLDS; Review of selected articles, editing and reviewing of the manuscript and resolving disagreements in the risk of bias judgement was by SR, MH and TCY. All authors read and approved the final manuscript.

References

[1] World Health Organisation. *Leishmaniasis fact sheets. 2023;* [Online]. Available from: https://www.who.int/news-room/fact-sheets/detail/leishmaniasis. [Accessed on 12 January 2023].

[2] World Health Organisation. *FOURTH WHO report on neglected tropical diseases. Apr 2017.* [Online]. Available from: https://www.who.int/publications/i/item/9789241565448. [Accessed on 12 January 2023].

[3] Ruiz-Postigo JA, Jain S, Mikhailov A, Maia-Elkhoury AN, Valadas S, Warusavithana S, et al. Global leishmaniasis surveillance: 2019-2020, a baseline for the 2030 roadmap/surveillance mondiale de la leishmaniose: 2019-2020, une periode de reference pour la feuille de route a l'horizon 2030. *Weekly Epidemiol Record* 2021; **96**(35): 401-420.

[4] Freitas-Junior LH, Chatelain E, Kim HA, Siqueira-Neto JL. Visceral leishmaniasis treatment: What do we have, what do we need and how to we deliver it? *Int J Parasitol Drugs Drug Resist* 2012; **2:** 11-19.

[5] Ponte-Sucre A, Gamarro F, Dujardin JC, Barrett MP, López-Vélez R, García-Hernández R, et al. Drug resistance and treatment failure in leishmaniasis: A 21st century challenge. *PLoS Negl Trop Dis* 2017; **11**(12): e0006052.

[6] Mohapatra S. Drug resistance in leishmaniasis: Newer developments. *Trop Parasitol* 2014; **4**(1): 4.

[7] Alves F, Bilbe G, Blesson S, Goyal V, Monnerat S, Mowbray C, et al. Recent development of visceral leishmaniasis treatments: Successes, pitfalls, and perspectives. *CMR* 2018; **31**(4). doi: 10.1128/cmr. 00048-18.

[8] Van Griensven J, Dorlo TP, Diro E, Costa C, Burza S. The status of combination therapy for visceral leishmaniasis: An updated review. *Lancet Infect Dis* 2024; **24**(1): e36-e46.

[9] Scarpini S, Dondi A, Totaro C, Biagi C, Melchionda F, Zama D, et al. Visceral leishmaniasis: Epidemiology, diagnosis, and treatment regimens in different geographical areas with a focus on paediatrics. *Microorganisms* 2022; **10**(10): 1887.

[10]Verrest L, Wasunna M, Kokwaro G, Aman R, Musa AM, Khalil EA, et al. Geographical variability in paromomycin pharmacokinetics does not explain efficacy differences between eastern African and Indian visceral leishmaniasis patients. *Clin Pharmacokinet* 2021; **60**: 1463-1473.

[11]Bhattacharya SK, Choudhury TK. Visceral leishmaniasis in children. *APCC* 2020; **8**(4): 1183.

[12]Stephenson T. How children's responses to drugs differ from adults. *Br J Clin Pharmacol* 2005; **59**(6): 670-673.

[13]O'Hara K. Paediatric pharmacokinetics and drug doses. *Aust Prescr* 2016; **39**(6): 208.

[14]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; **88**: 105906.

[15]Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: A new edition of the cochrane handbook for systematic reviews of interventions. *Cochrane Database Syst Rev* 2019; **10**(10): ED000142.

[16]UNICEF. *Convention on the Rights of the Child. 1989.* [Online]. Available from: https://www.unicef.org/child-rights-convention/convention-text. [Accessed on 12 January 2023].

[17]Assembly UGJUN, treaty series. *Convention on the rights of the child. 1989.* [Online]. Available from: https://www.un.org/en/development/desa/population/migration/generalassembly/docs/globalcompact/A_

RES_44_25.pdf. [Accessed on 12 January 2023].

[18]WHO technical series. *Report of a meeting of the WHO expert committee on the control of leishmaniases, Geneva, Switzerland, 22–26 March 2010*. [Online]. Available from: https://iris.who.int/bitstream/handle/10665/44412/WHO_TRS_949_eng.pdf;sequence=1. [Accessed on 12 January 2023].

[19]Noiri E, Jha T. *Kala Azar in South Asia*. Berlin: Springer; 2017.

[20]da Silva CG, Sobreira AC, Macedo FB, Junior AG, Lopes VH, dos Santos MD, et al. Therapeutic management of visceral leishmaniasis in children: A systematic review. *HealthMed* 2015; **9**(3): 87-89.

[21]Pokharel P, Ghimire R, Lamichhane P. Efficacy and safety of paromomycin for visceral leishmaniasis: A systematic review. *J Trop Med* 2021; **2021**: 8629039.

[22]Bush JT, Wasunna M, Alves F, Alvar J, Olliaro PL, Otieno M, et al. A systematic review of clinical trials assessing the therapeutic efficacy of visceral leishmaniasis treatments: A first step to assess the feasibility of establishing an individual patient data sharing platform. *PLoS Negl Trop Dis* 2017; **11**(9): e0005781.

[23]Gebreyohannes EA, Bhagvathula AS, Abegaz TM, Seid MA. Treatment outcomes of visceral leishmaniasis in Ethiopia from 2001 to 2017: A systematic review and meta-analysis. *Infect Dis Poverty* 2018; **7**(1): 108.

[24]Rodrigo C, Weeratunga P, Fernando SD, Rajapakse S. Amphotericin B for treatment of visceral leishmaniasis: Systematic review and meta-analysis of prospective comparative clinical studies including dose-ranging studies. *Clin Microbiol Infect* 2018; **24**(6): 591-598.

[25]Sterne JA, Savovi J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing the risk of bias in randomised trials. *BMJ* 2019; **366**: l4898. doi: 10.1136/bmj.l4898.

[26]Sundar S, Jha T, Thakur CP, Sinha PK, Bhattacharya SK. Injectable paromomycin for visceral leishmaniasis in India. *NEJM* 2007; **356**(25): 2571-2581.

[27]Singh UK, Prasad R, Jaiswal BP, Singh PK, Thakur CJ. Amphotericin B therapy in children with visceral leishmaniasis: Daily *vs*. alternate day, a randomised trial. *J Trop Pediatr* 2010; **56**(5): 321-324.

[28]Wasunna M, Njenga S, Balasegaram M, Alexander N, Omollo R, Edwards T, et al. Efficacy and safety of AmBisome in combination with sodium stibogluconate or miltefosine and miltefosine monotherapy for African visceral leishmaniasis: Phase][randomised trial. *PLoS Negl Trop Dis* 2016; **10**(9): e0004880.

[29]Alborzi A, Pouladfar G, Attar A, Falahi F, Jafarpour Z, Karimi A, et al. Effectiveness of short-course meglumine antimoniate (Glucantime®) for treatment of visceral leishmaniasis: A 13-year, multistage, non-inferiority study in Iran. *Am J Trop Med Hyg* 2017; **96**(1): 182-189.

[30]Borges MM, Pranchevicius MC, Noronha EF, Romero GA, Carranza-Tamayo CO. Efficacy and safety of amphotericin B deoxycholate versus *N*-methylglucamine antimoniate in pediatric visceral leishmaniasis: An open-label, randomised, and controlled pilot trial in Brazil. *Rev Soc Bras Med Trop* 2017; **50**(1): 67-74.

[31]Rahman R, Goyal V, Haque R, Jamil K, Faiz A, Samad R, et al. Safety and efficacy of short course combination regimens with AmBisome, miltefosine and paromomycin for the treatment of visceral leishmaniasis (VL) in Bangladesh. *PLoS Negl Trop Dis* 2017; **11**(5): e0005635.

[32]Musa AM, Mbui J, Mohammed R, Olobo J, Ritmeijer K, Alcoba G, et al. Paromomycin and miltefosine combination as an alternative to treat patients with visceral leishmaniasis in eastern Africa: A randomised, controlled, multicountry trial. *Clin Infect Dis* 2023; **76**(3): e1177-e85.

[33]Page MJ, Higgins JP, Clayton G, Sterne JA, Hróbjartsson A, Savovi JJPo. Empirical evidence of study design biases in randomised trials: Systematic review of meta-epidemiological studies. *PLoS One* 2016; **11**(7): e0159267.

[34]Gluud LL. Bias in clinical intervention research. *Am J Epidemiol* 2006; **163**(6): 493-501.

[35]World Health Organization. *Kala–Azar elimination programme: Report of a WHO consultation of partners, Geneva, Switzerland, 10–11 February 2015: WHO; 2015*. [Online]. Available from: https://www.who.int/publications/i/item/9789241509497. [Accessed on 12 January 2023].

[36]World Health Organisation. *WHO guideline for the treatment of visceral leishmaniasis in HIV co–infected patients in East Africa and South–East Asia: WHO; 2022*. [Online]. Available from: https://www.who.int/publications/i/item/9789240048294. [Accessed on 12 January 2023].

[37]Dorlo TP, Rijal S, Ostyn B, de Vries PJ, Singh R, Bhattarai N, et al. Failure of miltefosine in visceral leishmaniasis is associated with low drug exposure. *J Infect Dis* 2014; **210**(1): 146-153.

[38]Dorlo TP, Huitema AD, Beijnen JH, de Vries PJ. Optimal dosing of miltefosine in children and adults with visceral leishmaniasis. *Antimicrob Agents Chemother* 2012; **56**(7): 3864-3872.

[39]Kelleci K, Allahverdiyev A, Bağırova M, Ihlamur M, Şefik Abamor E. Immunomodulatory activity of polycaprolactone nanoparticles with calcium phosphate salts against Leishmania infantum infection. *Asian Pac J Trop Biomed* 2024; **14**(8): 359-368.

[40]Pan Americal Health Organization. *Guideline for the treatment of leishmaniasis in the Americas. Washington DC 2022*. [Online]. Available from: https://api.pageplace.de/preview/DT0400.9789275125038_A47717409/preview-9789275125038_A47717409.pdf. [Accessed on 12 January 2023].

Publisher's note

The Publisher of the *Journal* remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Edited by Pan Y, Lei Y, Zhang Q

Protocol for a systematic review and meta-analysis on the therapeutic efficacy and safety of treatment of visceral leishmaniasis in children

Description of the PICO-S criteria used to define the research question

Parameter	Description
Population	Children with visceral leishmaniasis <18 years of age
Intervention	Drug treatment of VL – Amphotericin B (conventional or liposomal), Pentavalent antimonials, Miltefosine and Paromomycin
Comparison	Standard treatment or placebo
Outcome	Outcomes of treatment – drug efficacy/cure, treatment failure, safety (adverse events), relapse, death
Setting	**Randomized** clinical trials
Time	Manuscripts published after year 2000
Research question	What are the outcomes of drug management of visceral leishmaniasis in children?
Study title	A systematic review and meta-analysis on the therapeutic efficacy and safety of treatment of visceral leishmaniasis in children
Objectives	**General objective:** To evaluate the efficacy and safety of the main antileishmanial agents (Amphotericin B (conventional or liposomal), Pentavalent antimonials, Miltefosine and Paromomycin) recommended for the treatment visceral leishmaniasis in children.

	Specific objectives 1. To review the dosing regimens of antileishmanial drugs in children studied in interventional trials. 2. To evaluate the efficacy of the antileishmanial drugs in children by assessing outcome measures; cure rate/failure rate/mortality rate 3. To review the safety (by reported adverse events) of antileishmanial drugs in children
Main concepts	Visceral leishmaniasis, antileishmanial agents, drug treatment (Amphotericin B (conventional or liposomal), Pentavalent antimonials, Miltefosine and Paromomycin), efficacy of drugs, safety of drugs, children
Inclusion criteria	Randomized clinical trials/interventional trials evaluating treatment of VL in children or including children, clinical trials that assess treatment efficacy at $\geq$ 6 months, papers written in English, full text available, any country, gender or race
Exclusion criteria	Other types of leishmaniasis, studies where data are not separately presented for children, other types of study designs including case reports/series/non-interventional studies, animal studies, experimental/in-vitro studies, papers in languages other than English, free full text not available, abstract only papers- Conference / symposium abstracts, articles not presenting interventional studies like reviews, meta-analysis, etc

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Databases, registries and web search engines for the literature search

- PubMed
- Cochrane Reviews
- Google scholar
- Clinical trials.gov

Main concepts

Visceral leishmaniasis	children	Antileishmanial drugs	Efficacy	Safety
Kala-azar	Paediatic/Pediatric – wildcard characters	Amphotericin B	Effectiveness	Tolerability
	infant	Ambisome		
		Pentavalent antimonial		
		Sodium stibogluconate		
		Meglumine		
		Miltefosine		
		Paromomycin		

Outcomes

Justification – Randomized trials that assess treatment efficacy/cure at minimum of 6 months and beyond will be considered for this study. A relapse is reappearance of parasites after initial cure, usually within 6 months of follow-up. As per this general definition trials that assess efficacy at least for 6 months is necessary to assess efficacy.

Efficacy/cure/ treatment failure

- Visceral leishmaniasis - comparable clinical picture combined with demonstration of parasites/DNA or positive serology
- Initial response to treatment and at the end of 6 months post treatment – efficacy assessed at the end of therapy in those who complete treatment and defined as clinical improvement +/- parasitological cure
- Treatment failure - lack of clinical improvement or parasitological improvement after completion of treatment (or within a defined time period after completion of treatment)

Treatment failure can manifest as initial treatment failure (failure to clear parasites at the end of the treatment course) or relapse (reappearance of parasites after initial cure, usually within 6 months of follow-up) (Ref: Kala-azar in South Asia - Eisei Noiri ·T.K. Jha / Control of the leishmaniases Report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22–26 March 2010-technical report series)

Mortality/ death

- At the end of treatment or at ≥6 months post treatment among those who completed treatment for VL

Safety (adverse events)

- Reported adverse events - either systematically (collecting adverse events in the same manner for each participant using defined methods such as a questionnaire or a laboratory test) or non-systematically (refers to collection of information on adverse events using methods such as open-ended questions (e.g. 'Have you noticed any symptoms since your last visit?'), or reported by participants spontaneously)

- Despite of the collection method the data on AE events will be recorded - Coding systems or standard terminology used, name of AE, Intensity (mild, mod, severe), whether AE was identified as related to the intervention, time point, reporting methods (eg. only report AE that occurred in 5% of the participants)

Risk of bias assessment (quality of the studies)

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) will be used to assess the risk of bias in each selected study. The domains of risk of bias including those arising from the randomization process, deviations from the intended intervention, missing data, measurement of the outcome and reporting are covered.

Data extraction

Data extraction will be performed using a modified version of the Cochrane data extraction form for RCTs only. Extractable data specific to the paediatric will be recorded.

Qualitative synthesis and meta-analysis

If the selected studies include trials with multiple treatment arms (more than two), they will be included in the meta analysis after included in the meta-analysis after they are suitably combined using the ‘combination of groups to create a single pair-wise comparison’ approach (Cochrane Handbook guiding systematic reviews). Random effects model meta-analysis using Review Manager 5.4 software will be performed. Dichotomous data will be combined to calculate pooled risk ratios (RR) and 95% confidence intervals (CI). Heterogeneity will be assessed with the I2 statistic and funnel plots. Subgroup meta-analysis and descriptive analysis will be performed if appropriate data is available for different VL treatments, age categories, gender etc. Results will be presented as forest and funnels plots, tables, figures and text descriptions.

Search strategies

Database	Search link
PubMed	1. ((((("visceral leishmaniasis"[All Fields]) OR ("kala azar"[All Fields])) AND (((((((("amphotericin b"[All Fields]) OR ("ambisome"[All Fields])) OR ("pentavalent antimonial"[All Fields])) OR ("pentavalent antimonial"[All Fields])) OR ("sodium stibogluconate"[All Fields])) OR ("meglumine antimoniate"[All Fields])) OR ("paromomycin"[All Fields])) OR ("miltefosine"[All Fields]))) AND (((((child*) OR ("infant"[All Fields])) OR ("adolescent"[All Fields])) OR ("pediatric"[All Fields])) OR ("paediatric"[All Fields]))) AND ((((("efficacy"[All Fields]) OR ("effectiveness"[All Fields])) OR ("safety"[All Fields])) OR ("tolerability"[All Fields])) Filters: clinical trials, 2000-2024 kala-azar
	2. (("visceral leishmaniasis"[All Fields]) OR ("kala azar"[All Fields])) AND (((((((("amphotericin b"[All Fields]) OR ("ambisome"[All Fields])) OR ("pentavalent antimonial"[All Fields])) OR ("pentavalent antimonial"[All Fields])) OR ("sodium stibogluconate"[All Fields])) OR ("meglumine antimoniate"[All Fields])) OR ("paromomycin"[All Fields])) OR ("miltefosine"[All Fields])) Filters: clinical trials, 2000-2024
	3.("visceral leishmaniasis"[All Fields]) OR ("kala azar"[All Fields]) Filters clinical trial and 2000-2024
	All 1,2,3 combined and duplicates removed
Cochrane (CENTRAL)	1. "visceral leishmaniasis" in All Text - (Word variations have been searched)
	Filter: Trials, 2000 – 2024
	1. "kala azar" OR “Kala-azar” in All Text - (Word variations have been searched)

	Filter: Trials, 2000 – 2024
	("kala-azar") OR (kala azar) OR ("visceral leishmaniasis") AND (Child") OR (infant) OR (paediatric) OR (pediatric) AND amphotericin B") OR ("AmBisome") OR (sodium stibogluconate) OR (miltefosine) OR (paromomycin) OR (pentavalent antimonial) OR (meglumine antimoniate) :ti,ab,kw Filter: 2000 – 2024 adolescent / how this search line was taken
Google scholar	1. **allintitle**: "visceral leishmaniasis" **with at least one of the words:** children OR infant OR paediatric OR pediatric OR sodium OR stibogluconate OR meglumine OR antimoniate OR amphotericin OR ambisome OR paromomycin OR pentavalent OR antimonials OR miltefosine OR safety OR **t**olerability OR efficacy OR effectiveness Without the words - cutaneous mucosal mucocutaneous case series reports murine mice dogs canine vitro animal vector
	2. allintitle: miltefosine visceral OR leishmaniasis OR kala OR azar OR efficacy OR safety OR effectiveness OR tolerability -cutaneous -mucosal -mucocutaneous -case -series -reports -murine -mice -dogs -canine -vitro -animal -vector
	3. allintitle: amphotericin visceral OR leishmaniasis OR kala OR azar OR ambisome OR safety OR efficacy OR effectiveness OR tolerability -cutaneous -mucosal -mucocutaneous -case -series -reports -murine -mice -dogs -canine -vitro -animal -vector
	4. allintitle: stibogluconate visceral OR leishmaniasis OR kala OR azar OR pentavalent OR meglumine OR effectiveness OR efficacy OR safety OR tolerability

	5. allintitle: paromomycin visceral OR leishmaniasis OR kala OR azar OR efficacy OR safety OR effectiveness OR tolerability -cutaneous -mucosal -mucocutaneous -case -series -reports -murine -mice -dogs -canine -vitro -animal -vector
Clinical trials.gov https://clinicaltrials.gov/	1. Disease – visceral leishmaniasis (Kala-azar and synonyms are automatically searched) Other terms – amphotericin b
	2. Disease – visceral leishmaniasis Other terms – Miltefosine
	3. Disease – visceral leishmaniasis Other terms – paromomycin
	4. Disease – visceral leishmaniasis Other terms – stibogluconate
	5. Disease – visceral leishmaniasis Other terms – meglumine

Characteristics of the included studies

Citation	Study ID (author, year)	Trial Design	Study Label	Trial phase	Participant allocation	Blinding	Unit of allocation	Start date	End date
[26]	Sundar, S. et al 2007	Prallel	Open-label	Phase III	Randomized controlled	No	Individuals (block randomization)	Jun-03	Nov-14
[27]	Singh, U. K. et al 2010	parallel	Open-label	Not mentioned	Randomized	No	individuals		
[28]	Wasunna, M. et al 2016	Non-comparative sequential	Open-label	Phase II	Randomized	No	individuals (block randomization startified by site)	May-10	Oct-12
[29]	Alborzi A et al, 2017	Non-inferiority	Open-label	Not mentioned	Randomized	No	Individuals	Not reported	Not reported
[30]	Borges, M. M et al 2017	Prallel	Open-label	Phase IV (but with features of a phase III pilot)	Randomized controlled	No	Individuals	Jan-06	Jan-09
[31]	Rahman, R et al 2017	Parallel	Open-label	Phase III	Randomized controlled	No	Individuals	Jul-10	Mar-14
[32]	Musa A.M. et al 2023	Non-inferiority	open-label	Phase III	Randomized controlled	No	Individuals	Jan-18	May-20

Study participants

Citation	Study ID (author, year)	Diagnostic criteria at entry (Inclusion)	Total number enrolled	Number Randomized	Number of children	No. in the treatment arm	No. in comparator arm	Age range	Male %	Female%	HIV status	Other co-morbidities
[26]	Sundar, S. et al 2007	Parasitologically positive splenic or bone marrow smear	667	667	252	(1)Paromomycin - 188	(2)Amphotericin - 64	5-14 years	NR separately for children	NR	Neg	NR
[27]	Singh, U. K. et al 2010	Compatible clinical features and presencne of L.donovani bodies in bone marrow aspirates	605	605	605	(1)Group A - 302	(2)Group B - 303	(1)8.62 ±3.4 (2)8.56 ±3.62	NR	NR	Neg	NR
[28]	Wasunna, M. et al 2016	Parasitlogical confirmation: lymphnode, spleen or bone	151	151	107	(1)Amb+SSG - 35 (2)Amb+Milt-35 (3)Milt-37	Non-comparative	7-17 years	NR separately for children	NR	Neg	Excluded

		marrow samples for microscopy										
[29]	Alborzi A et al, 2017	Signs of infection (fever, splenomegaly, etc), Positive serology IFA titer 1/128 or rK39 strip test, and/or positive bone marrow microscopy for Leishman bodies	75		75	(1)Group I - 25 (2)Group 2 - 25 (3)Group 3 - 25		(1) 28.16 (months) (2) 27.44 (3)29.32	NR	NR	NM	Underweight Short stature

[30]	Borges, M. M et al 2017	Clinical - fever for at least two weeks associated with splenomegaly Lab – Blood and bone marrow samples were collected for VL diagnosis. Indirect immunofluorescence test (IFAT), rapid immunoassay (Kala-azar Detect®), and standard PCR for Leishmania spp. detection in	135	101	101	(1)methylglucamine antimoniate 51	(2)Ampho B - 50	(1)52.65 mon (2)52.37 mon	(1) 49% (2) 62%		Neg	Excluded

		the blood were performed. Bone marrow samples were obtained for direct microscopic examination to detect amastigotes of Leishmania spp., culture of Leishmania spp. in a biphasic medium, and PCR (120bp kDNA)										
[31]	Rahman, R et al 2017	Primary VL with positive rK39 ICT and	673 (screened)	602	297	(2) AMB+PM - 83 (3)AMB+Mil	(1)AMB - 79	<12 years <18 years	NM separately for		Neg	Excluded

		parasitologically confirmed via bone marrow or spleen aspirates (only at CBMC-ie, one of the treatment centers in this study)				t - 60 (4)PM+Milt - 75			childr en			
[32]	Musa A.M. et al 2023	Symptoms of VL with parasitological confirmation	341	341	208	(1) PM+MF - 103	(2)SSG+ PM - 105	4-<50 years	65.40 %	34.60 %	Ne g	Exclud ed

Intervention groups

Trial No.	Study ID (author, year)	Groups	Drug	Dose, frequency, route, duration	Total randomized	Patients per arm
[26]	Sundar, S. et al 2007	(1)Paromomycin	Paromomycin	Paromomycin solution, 375 mg per milliliter (500 mg per millilitre as paromomycin sulfate) deep gluteal intramuscular injection, 11 mg/kg (15 mg/kg as the sulfate) daily for 21 days	252	(1)Paromomycin - 188
		(2)Amphotericin	Amphotericin B	Diluted in water and 5% dextrose and, after an initial dose (to test for an allergic response), 1 mg/kg iv infusion over 6 hours EOD for 30 days (a total of 15 infusions)		(2)Amphotericin - 64
[27]	Singh, U. K. et al 2010	(1)Group A	Daily Amphotericin B	(1)daily amphotericin B at a dose of 1 mg/kg /day as infusion in 5% dextrose over 6 h after hypersensitivity testing for 15 days (cumulative dose: 15 mg/kg)	605	(1)Group A - 302
		(2)Group B	Alternate day Amphotericin B	(2)alternate day amphotericin B at a dose of 1 mg/kg/day as infusion in 5% dextrose over 6 h after hypersensitivity testing for 30 days (cumulative dose: 15 mg kg1).		(2)Group B - 303
[28]	Wasunna, M.	(1)Amb+SSG	Ambisome and sodium stibogluconate	AmBisome 10 mg/kg single dose (IV) on day 1 followed by 10 days of SSG (IM) 20 mg/kg from day 2–11.	107	(1)Amb+SSG - 35

	et al 2016	(2)Amb+Milt	Ambisome and miltefosine	AmBisome 10 mg/kg single dose (IV) on day 1 followed by 10 days of miltefosine 2.5mg/kg/ day (oral) from day 2–11 (up to a maximum dose of 150mg)		(2)Amb+Milt -35
		(3)Milt	Miltefosine	Miltefosine 2.5 mg/kg/day (oral) from day 1–28 (up to a maximum dose of 150mg).		(3)Milt-37
[29]	Alborzi A et al, 2017	(1)Group I	Meglumine antimoniate	(1)20 mg/kg daily deep IM 1 week after fever subsides	75	25
		(2)Group II		(2)20 mg/kg daily deep IM 2 week after fever subsides		
		(3)Group III		(3)20 mg/kg daily deep IM 3 week after fever subsides		
[30]	Borges, M. M et al 2017	(1)Antimonial group	Meglumine antimoniate	(1) 20mg/kg daily IV for 20 days	101	51
		(2)ABD group	Amphotericin B deoxycholate	(2) 1mg/kg/daily IV in 5% dextrose over 6 hours 14 days		50
[31]	Rahman, R et al 2017	(1) AMB (ref)	Ambisome (liposomal) standard dose	(1)15 mg/kg , 5 mg/kg, days 1,3,5, infused over 2 hours in 5% dextrose solution, three doses on days 1,3,5		(1)AMB - 79
		(2)AMB+PM	Ambisome + Paromomycin	(2)5 mg/kg AmBisome on day 1, followed by 7 days of Miltefosine. >12 years at a dose of 50 mg once daily if < 25 kg bodyweight, 50 mg twice daily if > 25 kg bodyweight; or 2.5 mg/kg/day divided into 2 doses for children younger than 12 years.	297	(2) AMB+PM - 83

		(3)AMB+Milt	Ambisome + Miltefosine	(3)5 mg/kg AmBisome on day 1, followed by 10 days of paromomycin 11 mg/kg/day (base) equivalent to 15 mg/kg/day (sulphate salt), given by deep IM injection		(3)AMB+Milt - 60
		(4)PM+Milt	Paromomycin + Miltefosine	(4)Paromomycin paromomycin 11 mg/kg/day (base) equivalent to 15 mg/kg/day (sulphate salt), given by deep IM injection and miltefosine >12 years at a dose of 50 mg once daily if < 25 kg bodyweight, 50 mg twice daily if > 25 kg bodyweight; or 2.5 mg/kg/day divided into 2 doses for children younger than 12 years. Daily dose for 10 days		(4)PM+Milt - 75
[32]	Musa A.M. et al 2023	(1) PM+MF	Paromomycin and Miltefosine	PM 20mg/Kg deep IM daily x 14 days + MF (oral) according to body weight twice daily for 14 days	341	(1) 103
		(2) PM+SSG	Paromomycin and sodium stibigluconate	SSG 20 mg/kg/day IM/IV + PM 15 mg/kg/day IM for 17 days		(2) 105

Study outcomes

Citation	Study ID (author, year)	Inclusion	Exclusion	Diagnostic criteria	outcome definition	test of cure	Time points measured	Time points reported
[26]	Sundar, S. et al 2007	parasitologically positive splenic or bone marrow smear; negative serologic testing for the human immunodeficiency virus (HIV); hemoglobin level of at least 5.0 g per deciliter; white blood count greater than or equal to	Exclusion criteria were treatment for visceral leishmaniasis during the 2 weeks before enrollment, a hearing loss of 75 dB in frequencies 1 through 8 kHz, a history of vestibular or auditory dysfunction, prior treatment with amphotericin without response, allergy	parasitologically positive splenic or bone marrow smear	**Final cure** was defined as an initial cure (clinical improvement with no parasites at the end of treatment or parasite density of 1 at the end of treatment with no parasites on repeated smear 1 month after the end of	Splenic or bone marrow aspiration	At recruitment to confirm the diagnosis End of treatment At 4 weeks follow up in patients who had few residual parasite	Baseline and 6 months

		1×109 per liter; platelet count greater than or equal to 50×109 per liter; levels of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase less than or equal to three times the upper limit of the normal range; prothrombin time less than or equal to 5 seconds greater than that among control subjects; and serum creatinine and	or hypersensitivity to aminoglycosides, significant proteinuria (≥2+ on strip testing), significant coexisting diseases possibly affecting the response to the study treatment response, and pregnancy or lactation.		treatment) and no relapse during follow-up. **Relapse** was defined as suspected visceral leishmaniasis after an initial cure, followed by a positive result on analysis of a specimen obtained by splenic or bone marrow aspiration. **Treatment failure** was defined as lack of an initial cure or		s at the end of treatment In those who had relapse during 6 months follow up	

		potassium levels within the normal limits.			occurrence of relapse.			
[27]	Singh, U. K. et al 2010	Children aged 1–14 years of VL, who was diagnosed based on compatible clinical features and presence of L. donovani bodies in bone marrow aspirates	Children with bleeding diathesis, liver disorder [alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >3 times, serum bilirubin >2 times of normal], renal dysfunction [Blood urea nitrogen (BUN) and serum creatinine, 1.5	Bone marrow aspirates for LD bodies	**The cure was** defined as an absence of parasites at the end of therapy and no relapse during 6 months of follow-up. **Relapse** was defined by appearance of symptoms	Absence of parasites in bone marrow	Bone marrow was tested at completion of treatment, one month and at 6 months	Completion of treatment, then 1 and 6 months

			times of normal], co-existing malaria or HIV, neutrophil count		and signs suggestive of leishmaniasis with demonstrable L. donovani (LD) bodies in bone marrow aspirates after initial cure. **Treatment failure** was defined as either the lack of initial cure or relapse.			

[28]	Wasunna, M. et al 2016	HIV negative, and aged between 7 and 60 years with parasitologically confirmed VL who signed an informed consent (if aged 18y and over) or whom the parent or legal guardian consented to participate in the study (if under 18y). The target population was primary cases	known relapse cases, or receipt of any anti-leishmanial drugs in the previous 6 months, was an exclusion criterion. Other exclusion criteria were: severe protein and/or caloric malnutrition defined as kwashiorkor or marasmus in children and BMI <15 in adults; previous history of hypersensitivity reaction to SSG or amphotericin B; concomitant severe infection such as TB or other serious underlying	Lymph node, spleen or bone marrow samples for microscopy	**primary endpoint: parasitological cure at Day 28 (initial cure)** - absence of parasites on microscopy. This was used for interim analysis decisions. Initial treatment failures: Patients who died or required rescue before study treatment could be completed were considered.	Parasitological assessment by microscopy was done on lymph node aspirates (Dooka, Kassab), spleen aspirates (Kimalel) or bone marrow samples (all sites).	Day 28, Day 210 D56 for slow responders	D28 and D210 for all Only D210 for children

			disease which would preclude evaluation of patients response to the study medication; other conditions associated with splenomegaly such as schistosomiasis; previous history of cardiac arrhythmia or an abnormal ECG; Hb < 5 g/dL; WBC < 103 /mm3 ; platelets 40,000/mm3 , abnormal liver function tests (ALT and AST) of more than three times the upper limit of the normal range, serum creatinine outside the		**The secondary endpoint: Final (or definitive) cure** was assessed at Day 210 (six months post end of treatment). This was defined as lack of VL signs and symptoms, and no requirement for rescue treatment during the trial. **Slow responders :** patients who had not cleared parasites at			

			normal range for age and gender, and major surgical intervention within two weeks prior to enrolment. Due to the potential teratogenicity of miltefosine, females of child bearing age were also excluded.		Day 28 (D28), but who were clinically well, did not require rescue treatment at D28 and remained clinically well throughout follow-up. **Safety outcomes:** The number (%) of patient experiencing a serious adverse event at any time, frequency of adverse event within 60 days of			

					treatment onset and an adverse drug reaction (ADR) within 60 days.			
[29]	Alborzi A et al, 2017	Signs of infection (fever, splenomegaly, etc.), positive serology IFA titer 1/128 or rk39 strip test, and/or positive bone marrow	Clinically obvious jaundice, DIC, and/or shock	Clinical and positive serology IFA titer 1/128 or rk39 strip test, and/or positive bone marrow microscopy for Leishman bodies Defervescence	**Initial cure** defined as defervescence with starting treatment **Final cure** defined as no relapse during at least 6-	Defervescence	After treatment – initial cure Followed up for 6 months but time points not	Initial cure and end of 6 months

		microscopy for Leishman bodies		was used as a marker of response (Phase I pilot study tested and found a correlation between defervescence and significant drop of Leishman bodies in the spleen)	months follow up (relapse = persistent fever>10 days and significant splenomegaly with a positive serology IFA titer 1/128 or rK39 strip test and/or parasitological confirmation) **Treatment failure** – death, relapse, lack of initial cure		mentioned – final cure	

[30]	Borges, M. M et al 2017	presence of fever for at least two weeks associated with splenomegaly plus diagnosis confirmed by visualization of Leishmania spp. amastigotes in direct bone marrow microscopic examination or parasitic DNA by PCR	patients who underwent previous treatment with leishmanicidal drugs, clinically evident jaundice (total bilirubin > 2.5mg/dL), hemorrhages with coagulation disorders, generalized edema, signs of toxemia, severe malnutrition according to Gómez criteria, presence of comorbidities or immunosuppressive conditions, and lack of informed consent	Clinical - fever for at least two weeks associated with splenomegaly Lab – Blood and bone marrow samples were collected for VL diagnosis. Indirect immunofluorescence test (IFAT), rapid immunoassay (Kala-azar Detect®), and standard PCR for Leishmania spp. detection in the blood were performed. Bone marrow samples were obtained for direct microscopic examination to detect	**Clinical cure** = complete remission of clinical signs and symptoms up to three months after treatment completion, normalization of hematological changes, and no recurrence of VL until the sixth month of follow-up. **Recurrence** = resurgence or reappearance of VL signs or symptoms	Clinical cure	Clinical and laboratory evaluation on days 0, 3, 7, 14, 21, 28, 60, 90, 120, 150, and 180	6 months

				amastigotes of Leishmania spp., culture of Leishmania spp. in a biphasic medium, and PCR (120bp kDNA	after an improvement period or after clinical cure during the 6-month follow-up. **Therapeutic failure** = any outcome different from cure (interruption due to severe toxicity or drug intolerance, in the definition of therapeutic failure. In these cases, MA or ABD were replaced by liposomal			

					amphotericin B)			
[31]	Rahman, R et al 2017	HIV negative primary VL patients between 5 and 60 years, positive rK39 ICT and parasitologically confirmed via bone marrow or spleen aspirates (only at CBMC)	women of childbearing age who were not using an assured method of contraception for the duration of treatment and three months afterwards were excluded, unless they agreed to receive an injection of medroxyprogesterone acetate. hepatitis B,	positive rK39 ICT parasitologically confirmed by bone marrow or spleen aspirates (only at CBMC)	**Main outcome – final cure** , defined as initial cure at day 45 and absence of VL signs and symptoms during the follow-up period of 6 months. **The secondary outcome**	Clinical improvement and absence of symptoms by 6 months	45 days and 6 months	45 days and 6 months

			hepatitis C, or HIV, Hb < 5 g/dl, platelet count < 40,000/ mm3 (at CBMC only), a prothrombin time >5 seconds longer than the control (at CBMC only), severe malnutrition [for adults (> 18 years) defined as BMI < 18 years) defined as BMI for age z score < -3 in children measuring > 121.5cm; and weight for height less than 60% in children measuring <121.5 cm], known alcohol or drug abuse, use of any investigational (unlicensed) drug		**was initial cure**, defined as clinical improvement at day 45. In the CBMC hospital setting, initial cure was confirmed by the absence of parasites in splenic/bone marrow aspirates at day 15. In cases of 1+ parasite at day 15, patients were retested at day 45			

			within the last 3 months, and severe concurrent illnesses (TB, malaria) or chronic conditions (diabetes, hypertension). Pregnant and breast-feeding women, and patients with known hypersensitivity to the study drugs were also excluded.					
[32]	Musa A.M. et al 2023	Patients aged 4 to ≤50 years with VL symptoms and parasitological diagnosis were included	relapse, severe malnutrition, severe VL, positive human immunodeficiency virus (HIV) diagnosis or a concomitant severe infection,	inclusion criteria, bonemarrow and spleen microscopy	**definitive cure at 6 months follow-up:** defined as absence of clinical signs and symptoms	absence of clinical signs and symptoms of VL at day 210 and no rescue treatment	End of followup/ 6 months and End of treatment	End of followup/ 6 months End of treatment - not reported separate

			or were women of childbearing potential unwilling to use contraception until 5 months after the end of treatment		of VL at day 210 and no rescue treatment during the trial. **A secondary efficacy endpoint: initial cure** at EOT (resolution of clinical signs and symptoms, negative microscopy [spleen or bone marrow], and no rescue treatment). **Safety endpoints:** defined but not mentioned	during the trial.		ly for children

					separately for children			

	Randomization process	Effect of assignment	Missing outcome data	Outcome measure	Selective reporting	**Overall risk of bias**
Sundar et al. 2007 [26]	C	L	L	L	L	C
Singh et al. 2010 [27]	C	C	C	L	L	H
Alborzi et al. 2017 [28]	C	L	L	L	L	C
Borges et al. 2017 [29]	L	L	L	L	L	L
Wasunna et al. 2016 [30]	L	L	L	L	L	L
Rahman et al. 2017 [31]	L	L	L	L	L	L
Musa et al. 2023 [32]	L	L	L	L	L	L

Supporting information 5 (S5 Table): Data on treatment failures, relapses and deaths

Citation	Study ID (author, year)	Early treatment failure	Late treatment failure	Relapse	Death-end of treatment	Death-End of follow up
26	Sundar, S. et al 2007	NR separately for children	PM: 7/188 (3.72%) AMB: 1/64 (1.5%)	NR separately for children	NR separately for children	NR separately for children
27	Singh, U. K et al 2010	AMB daliy: 0/302 AMB alt day - 0/303	AMB daliy: 0/302 (0%) AMB alt day: 0/303 (0%)	0	0	0
28	Wasunna, M. et al 2016	NR separately for children	L-AMB+SSG: 3/25 (12%) L-AMB+Milt: 7/27(25.9%) MF: 9/22 (42.8%)	no data	NR separately for children	NR separately for children
29	Alborzi A et al, 2017	MA_G1: 0/25 (0%) MA_G2: 0/25 (0%) MA_G3: 0/25 (0%)	MA_G1: 1/25 (4%) MA_G2: 0/25 (0%) MA_G3: 0/25 (0%)	G1: 1 (4%) G2: 0 (0%) G3: 0 (0%)	0	0
30	Borges, M. M et al 2017	ABD: 2/50 (4%) MA: 3/51 (5.88%)	ABD: 3/50 (6%) MA: 3/51 (5.88%)	ABD: 1/50 (2%) MA: 0/51 (0%)	0	0
31	Rahman, R et al 2017	L-AMB+PM: 0/83 (0%) L-AMB+MF: 1/60 (1.66%) PM+MF: 2/75 (2.66%) L-AMB: 1/79 (1.26%)	L-AMB+PM: 0/83 (0%) L-AMB+MF: 1/60 (1.66%) PM+MF: 2/75 (2.66%) L-AMB: 1/79 (1.26%)	0 (reported for the entire population)	NR separately for children	NR separately for children
32	Musa, A.M. et al 2023	NR separately for children	NR separately for children	NR separately for children	NR separately for children	NR separatelyfor children

NR-not reported; G-group; AMB-Amphotericin B, L-AMB; Liposomal amphotericin B, PM-paromomycin, MF; miltefosine, SSG-sodium stobogluconate; MA-meglumine antimoniate

Treatment arms and citation	Dalily Amphotericin-[27]		Alternate day Amphotericin-[27]		Amb+SSG -[28]		Amb+Milt-[28]		Miltefosine -[28]		MA-[30]						Dalily Amphotericin-[30]					
											Moderate		Severe		Total		Moderate		Severe		Total	
	No	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Clinical adverse events																						
Abdominal pain											2	3.9					5	10				
Constipation											1	1.9					nil					
Diarrhoea											2	3.9					2	4				
Myalgia/arthralgia											37	72.5					35	70				
Nausea/vomiting					0	0%	8	33%	6	30%	29	56.9					35	70				
Plebitis											1	1.9					3	6				
Shivers											1	1.9					10	20				
Shivering, rigor and fever	500/4810		577/4500																			
Severe reactions	1		3																			
Pyrexia					8	35%	3	13%	3	15%												
Epistaxis					5	22%	1	4%	2	10%												
Blood and lymphatic system																						
Anaemia					2	9	4	17	5	25	13	25.5	37	73	50	98	10	20	37	74	47	94
Thrombocytopenia											24	47.1	2	3.9	26	51	23	46	2	4	25	50
Altered blood biochemistry																						
Alkaline phosphatase					4	17	4	17	3	15	2	3.9			2	3.92	3	6			3	6
ALT					3	13	1	4	4	20	14	27.5	16	31	30	58.8	8	16	10	20	18	36
AST					6	26	5	21	6	30	20	39.2	8	16	28	54.9	10	20	6	12	16	32
gamma glutamyl transpeptisdase											8	15.6	3	5.8	11	21.6	2	4	2	4	4	8
Total bilirubin											1	1.9			1	1.96	1	2			1	2
Hypocalcaemia											8	15.6	2	3.9	10	19.6	6	12	2	4	8	16
Hypokalaemia					1	4	2	8	0	0	11	21.6	1	1.9	12	23.5	11	22			11	22
Hypomagnesaemia					4	17	7	29	5	25	15	29.4	24	47	39	76.5	19	38	20	40	39	78
Hyponatraemia					2	9	3	13	3	15	25	49			25	49	25	50			25	50
Creatinine					1	4	1	4	1	5												
Blood uria					4	17	3	13	1	5												
Cardiac disorders																						
Supraventricular arrhythmia					0	0	0	0	0	0												
Sinus arrhythmia					1	4	3	13	0	0												
Sinus bradycardia					0	0	0	0	0	0												
ECG abnormalities					0	0	1	4	0	0												
Renal disorders																						
Renal impairment					0	0	1	4	0	0												
renal failure					0	0	0	0	0	0												