



WHO guidelines on leishmaniases

Treatment of visceral leishmaniasis and
post-kala-azar dermal leishmaniasis
in eastern Africa and South-East Asia



World Health
Organization

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WHO guidelines on leishmaniasis: treatment of visceral leishmaniasis and post-kala-azar dermal leishmaniasis in eastern Africa and South-East Asia

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Declarations of conflicts of interest

In accordance with WHO policy, all members of the GDG, the external review group, the systematic review team and the guideline writer declared their interests. The names and brief biographies of individuals considered for participation in developing the guidelines, with a description of the objectives of relevant meetings, were published online before the GDG meeting to allow sufficient time for public notice and comment.

The steering group assessed the submitted declarations and consulted the Office of Compliance, Risk Management and Ethics for five GDG members whose interests appeared to conflict with one or more PICO questions. To maintain the transparency of the process, three GDG members did not participate in the PICO for PKDL in South-East Asia, one did not participate in the PICO for PKDL in eastern Africa and one did not participate in the PICO for VL treatment in eastern Africa. Additionally, the Guideline Review Committee secretariat was invited to explain the guideline development process at the inaugural GDG meeting and at every meeting held online, each participant verbally disclosed any change in their interests.

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Abbreviations

ABLC	amphotericin B lipid complex
AE	adverse event
AmB	amphotericin B
BID	twice daily
CI	confidence interval
ECG	electrocardiogram
GDG	Guidelines Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
IM	intramuscularly
IQR	interquartile range
ITT	intention-to-treat
IV	intravenously
LAmB	liposomal amphotericin B
MSF	Médecins sans Frontières
NTD	neglected tropical disease
PCR	polymerase chain reaction
PICO	population, intervention, comparator and outcomes
PKDL	post-kala-azar dermal leishmaniasis
PM	paromomycin
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SSG	sodium stibogluconate
VL	visceral leishmaniasis
WHO	World Health Organization

Notes on terminology

All evidence on PKDL in South-East Asia and PICO 4 (VL relapse in South-East Asia) in these guidelines refers to work from the Indian subcontinent (Bangladesh, India and Nepal); however, the guidelines are applicable to all countries of the WHO Region of South-East Asia that are endemic for *Leishmania donovani*.

The term “eastern Africa” is used operationally to designate the shared epidemiology, burden of disease, risk factors for transmission and endemic occurrence of VL in Chad, Djibouti, Eritrea, Ethiopia, Kenya, Somalia, South Sudan, Sudan and Uganda. Given the potential occurrence and notification of VL in other countries, the term may be used in future to include other countries on the African continent with a similar epidemiological pattern. These recommendations also apply to areas such as in Yemen, where the causative parasite species for visceral leishmaniasis (VL) is *L. donovani*.



Leishmaniasis in humans are poverty-related vector-borne neglected diseases (NTDs) caused by infection with a protozoan parasite of one of over 20 pathogenic *Leishmania* species. An estimated 31 species of *Phlebotomus* and 47 species of *Lutzomyia* are proven vectors of human leishmaniasis (1). The three main clinical forms of the disease are VL, also known as kala-azar, which is a fatal disease if not treated rapidly; cutaneous leishmaniasis, which is the most common form that causes skin lesions, mainly ulcers on the exposed parts of the body; and mucocutaneous leishmaniasis, which involves the mucosa of the nose, mouth and/or throat.

The leishmaniasis can also be classified into two broad categories according to the source of human infection: zoonotic leishmaniasis, in which the reservoir hosts are animals, and anthroponotic leishmaniasis, in which the reservoir host is humans.

VL is caused by parasites of the *L. donovani*-*L. infantum* complex. Epidemics are characteristic of VL. In 2023, 73% of VL cases were reported from nine countries of eastern Africa (Chad, Djibouti, Eritrea, Ethiopia, Kenya, Somalia, South Sudan, Sudan and Uganda (2). In the past four decades, more than 10 000 deaths due to VL have occurred in this subregion, illustrating the devastating impact of this disease (3,4).

Post-kala-azar dermal leishmaniasis (PKDL) is a skin NTD (5). PKDL occurs in all areas endemic for *L. donovani* but is most common in eastern Africa (mainly in Sudan) and on the Indian subcontinent, where up to 50% and 17% of patients with kala-azar, respectively, develop the condition (6–8). PKDL is uncommon in areas endemic for *L. infantum*, except among HIV co-infected patients. Almost 90% of PKDL cases reported to WHO since 2011 have been on the Indian subcontinent. Such cases rarely heal spontaneously, whereas self-healing is the rule in 85% of PKDL patients in eastern Africa (1,2).

These guidelines update the previous treatment recommendations (1) by including new evidence from multicentric clinical trials for VL in eastern Africa and for PKDL in South-East Asia (11,12) and a phase II, open label, randomized trial for PKDL in eastern Africa (13).

Target readership

These guidelines are intended primarily for managers of national leishmaniasis control or NTD programmes. They will also be of interest to policy-makers in health ministries, subnational NTD programme managers, clinicians, other health service providers, front-line and public health workers, nongovernmental organizations and other implementing partners, patient groups, international and bilateral agencies and organizations that provide financial and technical support to leishmaniasis programmes in the relevant regions. They will also be useful for national drug regulatory authorities and pharmacovigilance and antimicrobial resistance programmes.

Guideline development

These guidelines were developed with the methods described in the WHO Handbook for guideline development, 2nd edition (14). A WHO steering committee consisting of WHO staff at the regional offices and headquarters defined the scope of the guidelines and formulated the questions to be addressed, in the PICO format. All PICO questions, critical and important outcomes were finalized in consultation with the GDG members, the methodologists and the Cochrane team. A specialized Cochrane team was commissioned to conduct systematic reviews of the literature and to assess the certainty of the evidence according to the GRADE method. Evidence-to-decision tools were based on the following elements: balance between desirable and undesirable effects, certainty of evidence, values, resource implications, equity, acceptability and feasibility.

WHO also conducted a mixed-methods study to generate qualitative evidence on the equity, accessibility, feasibility, affordability and rating of the outcomes. The protocol was approved by the WHO ethics board. The GDG consisted of experts with relevant knowledge and experience and were selected to ensure appropriate geographical and gender representation. An in-person meeting of the GDG was convened on 28–30 November 2023, which was followed by three online sessions.

What's new in these guidelines?

These guidelines provide updates on the safety profile of miltefosine and on the reasonable possibility of a causal relationship with ocular adverse events. They include risk mitigation measures suggested by the WHO Advisory Committee on the Safety of Medicinal Products (15) (Annex 1). In addition, they cover new treatment regimens for PKDL in eastern Africa and South-East Asia and alternative treatment options for primary VL patients in eastern Africa. They also cover VL relapse management in South-East Asia. All the recommendations made in these guidelines pertain to HIV-negative patients. Recommendations for HIV-co-infected VL patients have been published (9).

The guidelines include weight-band-based allometric dosing for miltefosine (Annex 2) and new recommendations on indicators to be monitored.

Recommendations

1. VL in eastern Africa

What are the efficacy and safety of different pharmacological treatments for the management of VL patients in eastern Africa?

Recommendations

- 1.1 A combination of paromomycin plus miltefosine^a is suggested rather than a combination of sodium stibogluconate (SSG) plus paromomycin^b.
(**Conditional** recommendation, **low-certainty** evidence)
^a Doses when given in combination: paromomycin sulfate (20 mg/kg [equivalent to 15 mg/kg paromomycin base] per day intramuscularly [IM] once a day for 14 days) plus miltefosine (allometric doses, orally twice a day [BID] for 14 days)
^b Doses when given in combination: SSG (20 mg/kg per day intravenously [IV] or IM once a day for 17 days) plus paromomycin sulfate (15 mg/kg [equivalent to 11 mg/kg paromomycin base] per day IM once a day for 17 days)
- 1.2 A combination of SSG plus paromomycin^a is suggested rather than SSG^b monotherapy in patients for whom paromomycin plus miltefosine is excluded.
(**Conditional** recommendation, **low-certainty** evidence)
^a Doses when given in combination: pentavalent antimonial (20 mg/kg per day IV or IM once a day for 17 days) plus paromomycin sulfate (15 mg/kg per day [equivalent to 11 mg/kg paromomycin base] IM once a day for 17 days)
^b SSG (20 mg/kg per day IV or IM once a day for 30 days)
- 1.3 Liposomal amphotericin B (LAmB)^a is suggested in patients in whom paromomycin plus miltefosine^b and/or SSG plus paromomycin^c is excluded.
(**Conditional** recommendation, **very low-certainty** evidence)
^a Doses of liposomal amphotericin B (LAmB) 3–5 mg/kg per daily dose by infusion given over 6–10 days up to a total dose of 30 mg/kg
^{b,c} Doses as above

Remarks

1. Exclusion criteria used in the paromomycin plus miltefosine trial and other excluded conditions
- patient's age < 4 years and > 50 years; pregnant or lactating women; female patients of childbearing potential who do not agree to a pregnancy test at screening for VL and/or who do not agree to use contraception from the treatment period until 5 months after treatment; VL relapse; severe malnutrition; haemoglobin < 5 g/dL; severe VL according to the physician's judgement of clinical manifestations (e.g. jaundice, bleeding, oedema) and significant abnormalities in laboratory parameters (e.g. haemoglobin, white blood cells, platelets, liver enzymes [alanine and aspartate transaminases], total bilirubin and creatinine); history of hypersensitivity to drugs or known drug class allergies; pre-existing hearing loss; underlying comorbid conditions (e.g. cardiac, renal or hepatic); concomitant infections such as pneumonia, tuberculosis, schistosomiasis, HIV infection or any other immunosuppressive condition; and
 - inability to comply with the planned study visits and regimen (e.g. unable to swallow miltefosine capsules, treatment failure, severe side-effects or drug intolerance).

2. Mitefosine is to be provided in allometric doses, particularly for patients weighing <30 kg (see Annex 2).
3. Mitefosine is potentially teratogenic. Its use in pregnancy is contraindicated. It should not be used in women of childbearing potential for whom pregnancy cannot be ruled out and adequate contraception cannot be assured for the duration of treatment and for 2 months (for shorter miltefosine regimens, e.g. 5, 7 or 10 days) or 5 months (for miltefosine regimens ≥ 28 days) after treatment (67).
4. Availability and acceptability of contraception (oral versus injectable) should be taken into account before prescription.
5. Supportive treatment is important; patients should be properly hydrated and given nutritional supplements. Severe anaemia should be corrected with blood transfusions, and concomitant infections should be treated with appropriate anti-infective agents.

Implementation considerations : please refer to [section 5.1](#) for full details

2. VL relapse in South-East Asia

What are the efficacy and safety of different pharmacological treatments for the management of VL relapse in South-East Asia?

Recommendations

- 2.1 In settings in which primary VL in immunocompetent patients was treated with single-dose LAmB (10 mg/kg by infusion over 2 h), a parasitologically confirmed case of relapse should not be treated with a single dose of LAmB (10 mg/kg by infusion over 2 h).

(**Conditional** recommendation based on expert opinion, **very low-certainty** evidence)

- 2.2 When available, a combination of drugs (co-administered) can be used to treat relapse cases.

- miltefosine^a plus paromomycin^b, both daily for 10 days
- LAmB (5 mg/kg by infusion, single dose) plus miltefosine^a (daily for 7 days)
- LAmB (5 mg/kg by infusion, single dose) plus paromomycin^b (daily for 10 days)

^a allometric doses of miltefosine (see Annex 2)

^b paromomycin sulfate 15 mg (11 mg base) per kg/body weight per day intramuscularly

(**Conditional** recommendation based on expert opinion, **very low-certainty** evidence)

- 2.3 For relapse cases that are not eligible for combination regimens, higher doses of LAmB up to a total dose of 15–20 mg/kg by infusion should be administered in three or four administrations.

(**Conditional** recommendation based on expert opinion, **very low-certainty** evidence)

Remarks

- Relapse patients should be diagnosed parasitologically.
- The choice of drugs should include consideration of availability, feasibility and cost.
- Mitefosine should be administered by allometric dosing, particularly for patients weighing <30 kg.

Implementation considerations : please refer to [section 5.1](#) for full details

3. PKDL in eastern Africa

What are the efficacy and safety of different pharmacological treatments for the management of PKDL in eastern Africa?

Recommendations

- 3.1 A combination of paromomycin plus miltefosine^a is suggested rather than a combination of LAmB plus miltefosine^b

^a Dose of paromomycin sulfate (20 mg/kg [equivalent to 15 mg/kg paromomycin base] once a day IM for 14 days) and miltefosine (allometric dose orally BID for 42 days)

^b Dose of LAmB 5 mg/kg per day IV on days 1, 3, 5, and 7 (total dose, 20 mg/kg) and miltefosine (allometric dose orally BID for 28 days)

Conditional recommendation, **low-certainty** evidence

Remarks

- PKDL cases are reservoirs of infection. Although most cases heal spontaneously, the GDG considered that, when possible, every patient should be offered treatment according to the VL elimination initiative in eastern Africa.
- Patients should be counselled about the disease, the benefits and risks of treatment and available alternatives that are in accordance with the national patient safety policies and strategies of countries.
- Miltefosine is potentially teratogenic. Its use in pregnancy is contraindicated. It should not be used in women of childbearing potential for whom pregnancy cannot be ruled out and adequate contraception cannot be assured for the duration of treatment and 2 months (for shorter miltefosine regimens, e.g. 5, 7 or 10 days) or 5 months (for 28-day or longer miltefosine regimens) post-treatment.
- The availability and acceptability of contraception (oral versus injectable) should be taken into account before prescription.
- **Children:** As monitoring of ocular side-effects might be particularly difficult in children, the shorter (LAmB plus miltefosine) regimen is preferred.
- **Severely malnourished patients:** LAmB plus miltefosine might be preferred to paromomycin plus miltefosine because of its shorter treatment regimen and its safety profile in such patients. In addition, lack of food with miltefosine intake might increase gastrointestinal side-effects and reduce compliance with therapy.
- Improvement of skin lesions before the end of treatment might reduce adherence, especially to the longer (paromomycin plus miltefosine) regimen. Patient education will therefore be important.

Implementation considerations : please refer to [section 5.1](#) for full details

4. PKDL in South-East Asia

What are the efficacy and safety of different pharmacological treatments for the management of PKDL in South-East Asia?

Recommendations

- 4.1 LAmB (total dose, 30 mg/kg administered in six doses of 5 mg/kg, twice a week for 3 weeks) is suggested rather than miltefosine (2.5 mg/kg to children aged 2-11 years or 100 mg/day orally for 12 weeks in divided doses).

Conditional recommendation, **low-certainty** evidence

- 4.2 A combination of LAmB (total dose, 20 mg/kg administered on days 1, 4, 8, 11 and 15) plus miltefosine (allometric dose orally BID for 21 days) or LAmB monotherapy (total dose, 20 mg/kg administered on days 1, 4, 8, 11 and 15) is suggested to treat PKDL.

Conditional recommendation, **very low-certainty** evidence

- 4.3 A combination of LAmB (total, 15 mg/kg on days 1, 8 and 15) plus miltefosine (100 mg/day orally after the first dose of LAmB and continued daily until the end of 45 days) is suggested rather than miltefosine monotherapy (100 mg/day orally for 90 days).

Conditional recommendation, **very low-certainty** evidence

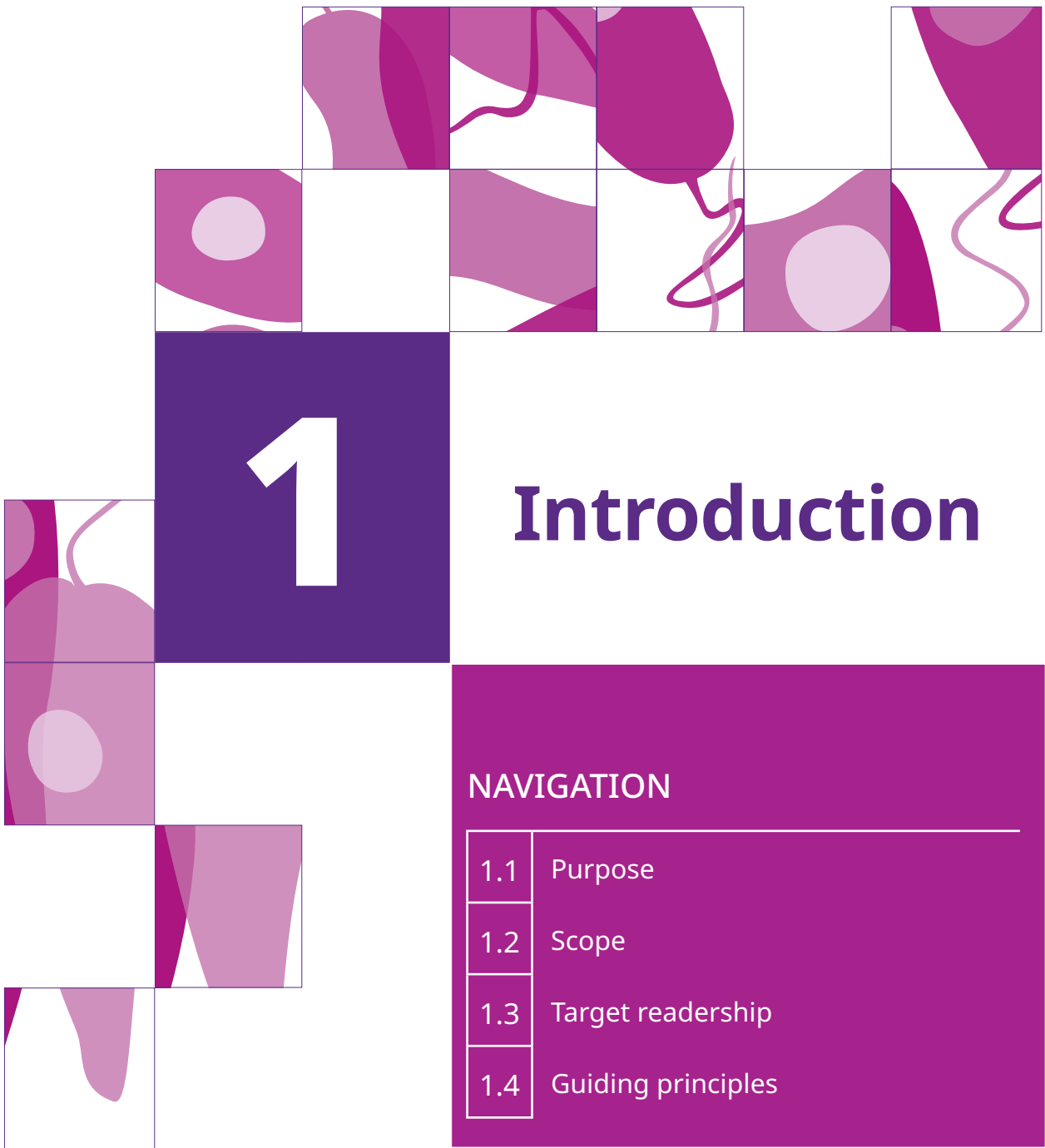
Remarks

Because of the lack of a common comparator of the studies, heterogeneity in regimens and study designs and insufficient direct comparisons, a network meta-analysis could not be conducted. Therefore, all the regimens used in the reported studies were assessed and compared. Contexts in which each of these recommendations can be implemented are indicated.

Selection of regimen: In selecting a regimen, consider the national context, such as health system architecture, social and cultural practices, health workforce density per population, laboratory capacity, monitoring and reporting pathways, referral network, availability of pregnancy tests, contraception advice, logistics and supply chain, pharmacovigilance and antimicrobial programmes.

- PKDL cases are potential reservoirs. Cases of PKDL in South-East Asia rarely self-heal; therefore, treat every patient in the VL elimination programme when possible.
- Patients should be counselled about the disease, the benefits and risks of treatment and available alternatives, which should adhere to the national patient safety policies and strategies.
- Miltefosine is potentially teratogenic. Its use in pregnancy is contraindicated. It should not be used in women of childbearing potential for whom pregnancy cannot be ruled out and adequate contraception cannot be assured for the duration of treatment and for 2 months (for shorter miltefosine regimens, e.g. 5, 7 or 10 days) or 5 months (for ≥ 28 -day miltefosine regimens) post-treatment.
- The availability and acceptability of contraception (oral versus injectable) should be taken into account before prescription.
- **Children:** As monitoring of ocular side-effects might be particularly difficult in children, a non-miltefosine regimen or a miltefosine regimen of shorter duration could be considered.
- **Severely malnourished patients:** A shorter regimen may be preferred for such patients. In addition, lack of food with miltefosine intake might increase gastrointestinal side-effects, which could reduce compliance with therapy.
- Hypokalemia is a very common side-effect of LAmB, leading to tiredness, confusion, muscle weakness or cramps. This may be more prominent and dose-related in regimens of cumulative high-dose administration, e.g. 30 mg/kg of LAmB. Monitor serum potassium, other electrolytes and renal function during treatment. Proper hydration, a potassium-rich diet and potassium supplementation are important to prevent such side-effects.
- High cumulative doses of LAmB should be administered only in centres with the capacity to monitor serum potassium, renal function, and manage electrolyte abnormalities.
- If miltefosine is refused, unavailable or contraindicated, consider alternative treatment with LAmB.
- Improvement in skin lesions before the end of treatment might compromise adherence, especially to the longer regimen. Patient education is therefore important.

Implementation considerations : please refer to [section 5.1](#) for full details



1

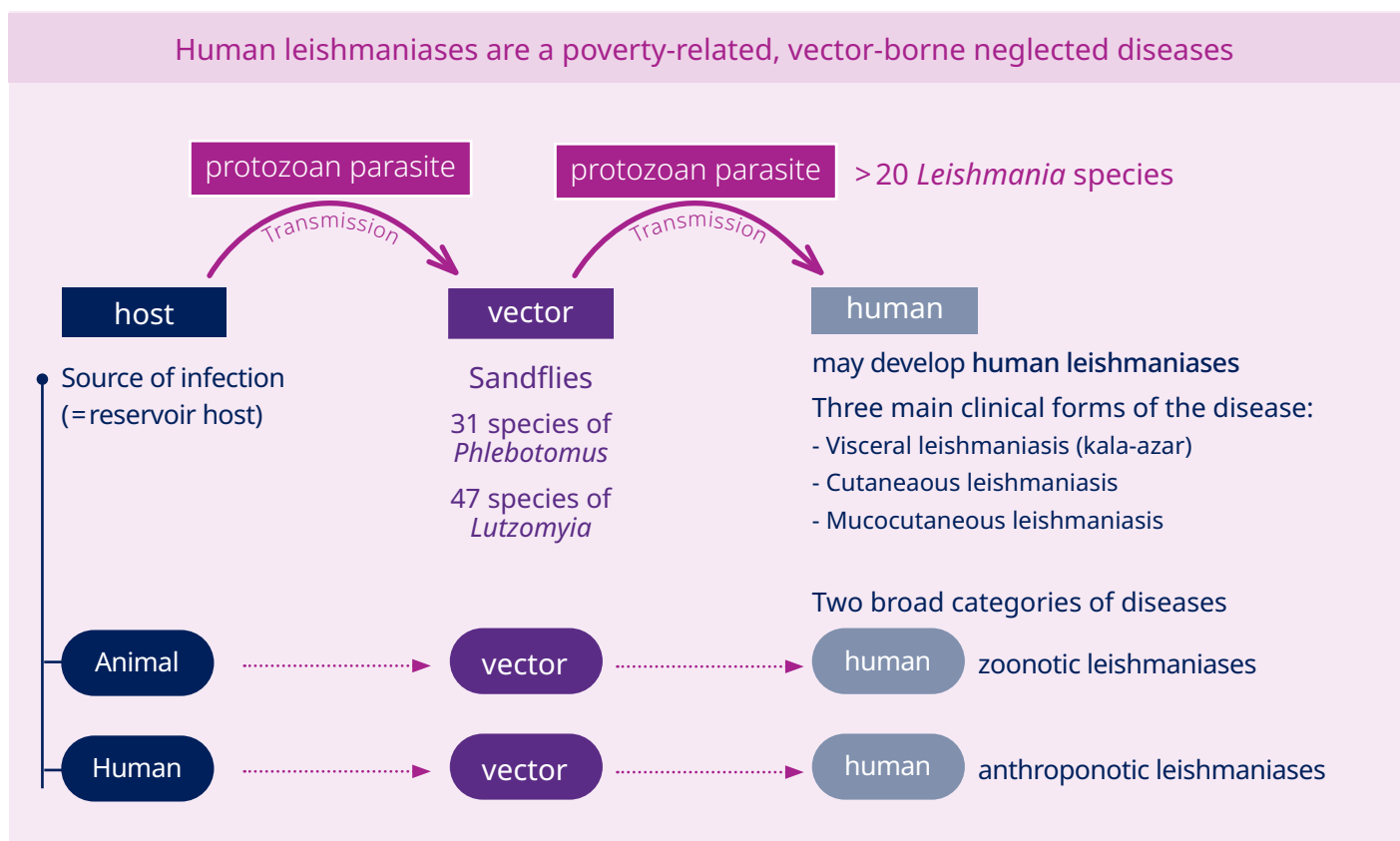
Introduction

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| 1.2 | Scope |
| 1.3 | Target readership |
| 1.4 | Guiding principles |

Leishmaniases in humans are poverty-related, vector-borne neglected diseases caused by infection with a protozoan parasite transmitted by over 20 *Leishmania* species. An estimated 31 species of *Phlebotomus* and 47 species of *Lutzomyia* are proven vectors of human leishmaniases (1). The three main clinical forms of the disease are VL, also known as kala-azar, which is a fatal disease if not treated rapidly; cutaneous leishmaniasis, the most common form, which causes skin lesions, mainly ulcers, on exposed parts of the body; and mucocutaneous leishmaniasis, which involves the mucosa of the nose, mouth and throat.

The leishmaniases can also be classified into two broad categories according to the source of human infection: zoonotic leishmaniases, in which the reservoir hosts are animals, and anthroponotic leishmaniases, in which the reservoir host is human.



The leishmaniases are widely distributed. Although *Leishmania* is transmitted to humans on five continents, the human disease burden is concentrated in a few major foci. VL is caused by parasites of the *L. donovani*–*L. infantum* complex. The largest focus of anthroponotic *L. donovani* transmission is eastern African, with the highest incidence in Sudan; the second largest focus is the Indian subcontinent. The other two important foci, both due to zoonotic *L. infantum*, are the region composed of the Mediterranean Basin, the Middle East and western Asia and the New World, predominantly Brazil.

VL is an outbreak-prone, fatal disease if not treated rapidly. Most *Leishmania* infections, however, remain asymptomatic, and only a minority of infected individuals eventually develop clinical disease. Malnutrition and immune suppression, notably tuberculosis and HIV infection, predispose to progression from (asymptomatic) infection to clinical disease. In endemic areas of eastern Africa and the Indian subcontinent, the highest incidence of VL is reported in children and young adults. In many countries, more male than female cases are reported.

The most common symptoms of VL are fever, malaise, shivering or chills, weight loss, anorexia and discomfort in the left hypochondrium. Common clinical signs are non-tender splenomegaly with or without hepatomegaly and wasting and pallor of the mucous membranes. Lymphadenopathy may be

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present and may be the only clinical manifestation. In Sudan and, rarely, in other endemic countries of eastern Africa, a cutaneous nodule or ulcer or a mucosal lesion may be present, containing *Leishmania* parasites. Signs of malnutrition (oedema, skin and hair changes) develop as the disease progresses. Intercurrent infections are common (1).

In 2023, 73% of VL cases were reported from nine countries in eastern Africa (Chad, Djibouti, Eritrea, Ethiopia, Kenya, Somalia, South Sudan, Sudan and Uganda (2). In the past four decades, more than 10 000 case fatalities attributable to VL have occurred in this subregion, demonstrating the devastating impact of this chronic illness (3,4).

PKDL is a skin NTD (5). It occurs in all areas endemic for *L. donovani* but is most common in eastern Africa (mainly Sudan) and on the Indian subcontinent, where up to 50% and 17% of patients with kala-azar, respectively, develop the condition (6–8). PKDL usually appears 6 months to ≥ 1 years after apparent cure of VL but may occur earlier or even concurrently with VL. In a minority of patients, PKDL appears without previous VL. Hypopigmented or erythematous macules on any part of the body, especially on the face, may later become papular or nodular and infiltrative. PKDL may also affect the buccal and genital mucosa and the conjunctiva. PKDL heals spontaneously in a proportion of cases in Africa but rarely, if ever, in patients on the Indian subcontinent (1).

Since 2011, a total of 13 515 PKDL cases has been reported, mainly from the Indian subcontinent (90%). In 2023, 483 PKDL cases were reported, 67% of which were in India, 17% in Bangladesh, 10% in Sudan, 2% in South Sudan, 1% in Nepal, and < 1% each in Ethiopia and Kenya (2).

In 2022, WHO published guidelines for the treatment of VL in HIV-co-infected patients in East Africa and South-East Asia (9) and guidelines for the treatment of leishmaniasis in the Americas (10).

The current guidelines update the treatment recommendations according to new evidence from multicentric clinical trials for VL in eastern Africa and for PKDL in South-East Asia (11,12) and a phase II, open-label, randomized trial for PKDL in eastern Africa (13).

1.1 Purpose

The purpose of these guidelines is to provide evidence-informed treatment recommendations to Member States in eastern Africa and South-East Asia for the management of VL and its complications and PKDL.

1.2 Scope

The treatment of VL and PKDL depends on many factors, such as parasite species, concomitant pathologies, the patient's immune status and the efficacy of treatment, which differs by nosogeographical entity. These are presented, ranked by preference, in the report of the WHO Expert Committee on the Control of the Leishmaniases (1).

In 2022, WHO updated its recommendations for the treatment of leishmaniasis in the Americas and in HIV co-infected patients in East Africa and South-East Asia (9,10). Subsequently, new clinical trial results became available on VL and PKDL treatment in eastern Africa and on PKDL on the Indian subcontinent,

necessitating an evidence review and updated recommendations for those regions. As no new evidence became available for the remaining endemic regions, these guidelines address only eastern Africa and South-East Asia.

1.3 Target readership

These guidelines are intended for use primarily by national leishmaniasis control programme managers. They will also be of interest to the following readers:

- policy-makers in ministries of health;
- national leishmaniasis control programme managers;
- national drug regulatory authorities, pharmacovigilance programmes and antimicrobial resistance programme managers;
- subnational programme managers;
- clinicians, other health service providers and front-line and public health workers;
- nongovernmental organizations and other implementing partners;
- relevant patient groups and population networks;
- international and bilateral agencies and organizations that provide financial and technical support to programmes on leishmaniasis and control in resource-limited settings;
- research organizations seeking guidance on investment in new treatments for VL and PKDL;
- funders of research; and
- manufacturers of the drugs used in the recommended treatments.

1.4 Guiding principles

The following principles were the basis for development of these guidelines and should guide implementation of the recommendations.

- The objective of WHO is attainment by all individuals of the highest possible level of health. The present guidelines have been developed in accordance with this principle and that of the United Nations Universal Declaration of Human Rights.
- Implementation of the guidelines should contribute towards the Sustainable Development Goals, WHO's Triple Billion targets (16) and the targets proposed for ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030 (17).
- Implementation of the guidelines should also contribute to the targets proposed in the Strategic framework for the elimination of VL as a public health problem in eastern Africa 2023–2030 (18) and the Regional strategic framework for accelerating and sustaining elimination of kala-azar in South-East Asia 2022–2026 (19). It should also promote the strategic framework for integrated control and management of skin-related NTDs (5).
- The guideline is based on a public health approach to scaling up management of VL and PKDL patients, including treatment of intercurrent infections, proper hydration, management of anaemia, screening for HIV and follow-up to the standard duration to assess treatment outcomes.
- The recommendations provided in these guidelines should also be used to strengthen broader health systems, especially primary and chronic care, and integrated approaches to detecting and managing cases.

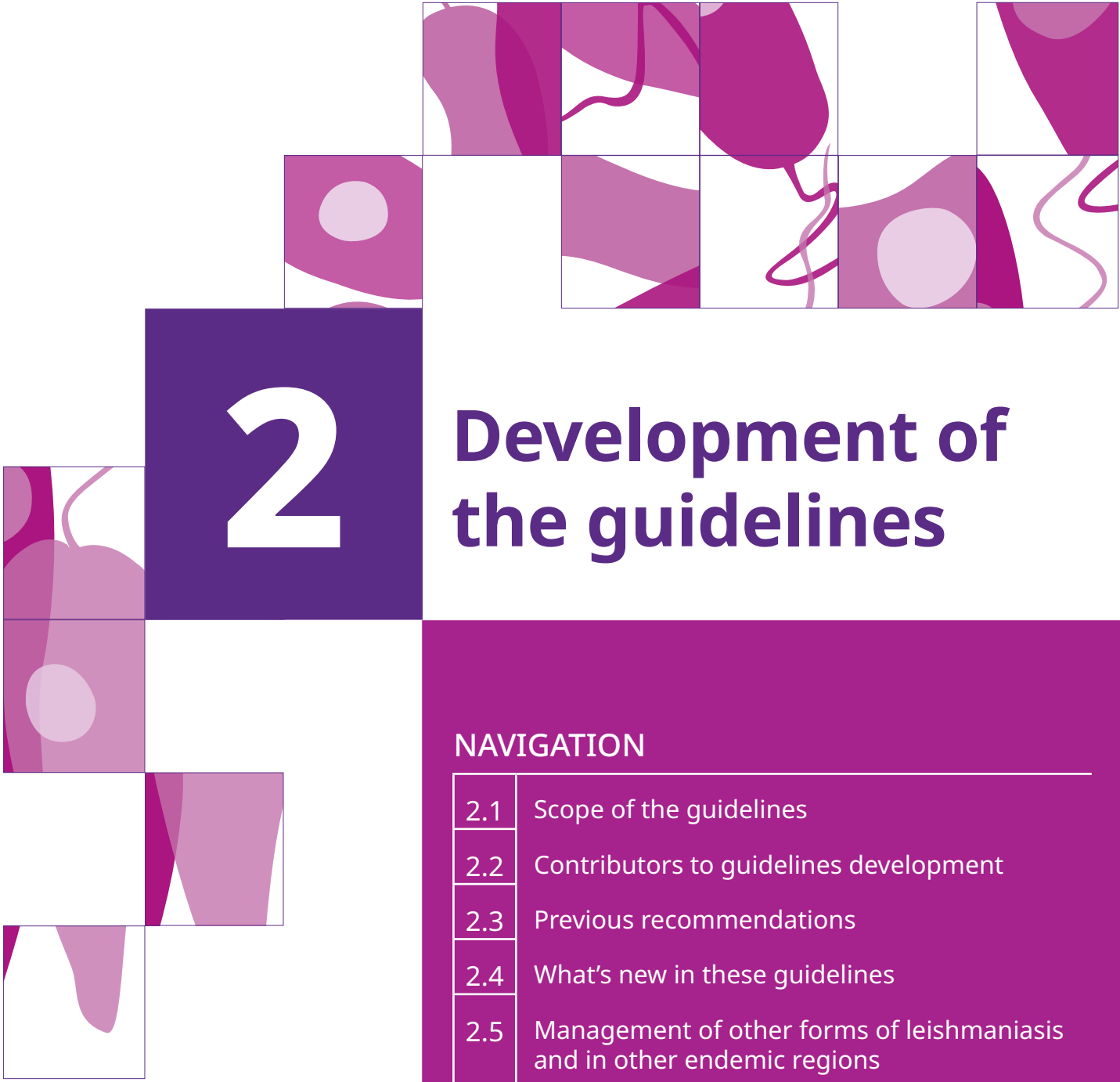
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- The recommendations in these guidelines should be implemented according to the local context, including the epidemiology of leishmaniasis, the feasibility of implementation, the availability of resources, the organization and capacity of the health system and anticipated cost-effectiveness.
- Most patients with VL or PKDL are usually in vulnerable or marginalized groups with poor access to health care, who face potential discrimination and stigmatization. Therefore, it is imperative that the guidelines and the policies derived from them include consideration of basic human rights and equity, including the right to confidentiality and informed decision-making about whether to be screened and treated for VL or PKDL. High-quality care and treatment for VL and PKDL patients require an uninterrupted supply of quality-assured medication and adequately trained staff to ensure complete, correct administration of the appropriate medicines. The fundamental ethical principles of good clinical practice (respect for presence, beneficence and justice) must be respected at all times by all health personnel caring for VL and PKDL patients.



WHO and the Ministry of Health team visiting the Jinka Hospital, Ethiopia (2023)

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2

Development of the guidelines

NAVIGATION

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| 2.2 | Contributors to guidelines development |
| 2.3 | Previous recommendations |
| 2.4 | What's new in these guidelines |
| 2.5 | Management of other forms of leishmaniasis and in other endemic regions |

The WHO guidelines for treatment of VL and PKDL in eastern Africa and South-East Asia were developed according to the WHO handbook for guideline development (2nd edition, 2014) (14). The main steps in development of WHO guidelines are 1) identification of the general scope of the guideline and development of the key questions and a detailed work plan; 2) identification of contributors to the guidelines; 3) assessment of declarations of interest and management of any conflicts of interest for all contributors; 4) systematic reviews of the evidence to address the key questions; 5) assessment of the certainty (quality) of the body of evidence for critical and important outcomes; 6) formulation of recommendations; 7) drafting of the guideline document for review and approval by the GDG, followed by targeted peer review; 8) review and approval by WHO's quality assurance body; and 9) publication and dissemination.

2.1 Scope of the guidelines

In 2022, results from new clinical trials on VL in eastern Africa were published. Furthermore, the results of clinical trials on PKDL in eastern Africa and South-East Asia became available. In 2022, following reports of ocular adverse events in PKDL patients treated with miltefosine, mainly in South-East Asia, the WHO Advisory Committee on the Safety of Medicinal Products advised constitution of a multidisciplinary technical advisory group to investigate and provide advice on causality, risk characteristics and frequency, risk minimization measures, risk communication, remaining uncertainties and further studies that would be required. In 2023, the WHO Advisory Committee on the Safety of Medicinal Products acknowledged the statement of the advisory group that a causal relationship between ocular adverse events and exposure to miltefosine is at least a reasonable possibility. (See also Annex 1.)

In 2022, the WHO Regional Technical Advisory Group on Kala-azar of South-East Asia noted increasing numbers of reports of VL relapses in countries of the Indian subcontinent and asked for guidance on treatment and management of such cases (20).

A draft of the proposed scope of the guidelines, with potential priority topics, was then discussed by the WHO guideline steering group, and PICO questions and critical and important outcomes were finalized.

2.2 Contributors to guideline development

(See also Acknowledgements.)

2.2.1 WHO guideline steering group

A steering group was constituted, comprising WHO staff from the Global Neglected Tropical Disease Programme, the Department of Regulation and Prequalification and the Special Programme for Research and Training in Tropical Diseases at headquarters and the regional offices for Africa, South-East Asia and the Eastern Mediterranean. The head of the Prevention, Treatment and Care unit of the Global Neglected Tropical Diseases Programme chaired the steering group.

2.2.2 GDG

The steering group identified 20 people with the necessary expertise, who assisted the steering group in finalizing the questions in PICO format, ranked outcomes by priority; reviewed the results of systematic reviews for any deficiency and completeness; examined the recommendations for GRADE evidence profiles and assessments of the quality of the evidence; interpreted the evidence, with explicit consideration of the overall balance of benefits and harms; formulated recommendations, taking into account benefits, harms, values, preferences, feasibility, equity, acceptability, resource requirements and implementation factors; and reviewed and approved the final guideline document before submission to the Guideline Review Committee (21).

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2.2.3 External review group

The draft guidelines were circulated for review to members of the GDG and an external review group. The WHO steering group reviewed their comments and included them in the final document.

2.2.4 Systematic review team

Systematic reviews were commissioned to address the PICO questions. The criteria for inclusion and exclusion of studies (e.g. study design, sample size, duration of follow-up) were those for the evidence required to answer the PICO questions. The search strategies and summaries of evidence are reported in Annexes 7, 8 and in Web annexes A–D. The GRADE method was used to assess the certainty of evidence, which was categorized per outcome and per PICO question as high, moderate, low or very low according to the risks of bias, indirectness, imprecision, inconsistency and publication bias.

Then, for each PICO question, the GDG reviewed the evidence and judged each of the following aspects: desirable effects, undesirable effects, certainty of evidence, values, balance of effects, cost-effectiveness and resources required, impact on equity, acceptability and feasibility. The GDG then decided the direction (for or against) and the strength (strong or conditional) of the recommendation. The discussion was guided by GRADE “evidence-to-decision” tables (Web annex E). The GDG also used the tables to record additional information, as available, on justification, subgroup considerations, monitoring, evaluation and research priorities. All the systematic reviews were conducted according to the PRISMA guidelines (22,23). Single-arm observational studies were excluded from the analysis.

The Cochrane Collaboration was engaged to conduct the systematic reviews.

2.2.5 External experts who attended the meeting

A guideline methodologist was hired, who acted as a co-chair and conducted the proceedings of the meeting in consultation with the steering group and subject expert chair and the other co-chair of the meeting. Subject experts were invited to provide additional information and/or clarification to the GDG when requested by the Chair or a Co-Chair. Experts from the WHO Collaborating Centre and the Infectious Disease Data Observatory were observers.

A guideline writer was hired, who was rapporteur of the meeting.

No attendees other than the GDG participated in voting or decision-making.

2.2.6 Synthesis of qualitative evidence

To obtain detailed evidence on the equity, feasibility, affordability and acceptability of the outcome, WHO conducted a mixed-methods study (24). Ethical approval was obtained from the Research Ethics Review Committee at WHO and the local institutional review boards at the Armauer Hansen Research Institute in Ethiopia, the Indian Council of Medical Research–Rajendra Memorial Research Institute of Medical Sciences in India, and Blue Nile University, Sudan. The Sudan research arm could not complete its work owing to compromised internal security. The summary results are presented in Annex 4.

2.2.7 Decision-making by the GDG

The methodologist (Co-Chair) familiarized the GDG with the GRADE method, process, voting and consensus building.

PKDL cases are potential reservoirs of the causative agent; however, in some areas in which it occurs, such as South-East Asia, it may not affect the daily lives of some patients. Patients may therefore play an important role in maintaining transmission if they do not seek health services for their skin lesions. The GDG deliberated on the individual and public health aspects of the recommendations and agreed to prioritize the public health importance but to give equal attention to the benefits for individual patients. It decided to adopt the same approach for the remaining PICO questions. The GDG used the available evidence to draft recommendations. The final recommendations were fully agreed by all members. When consensus was not reached, the GDG used anonymous voting through polls on Zoom and/or www.menti.com directly into the GRADEpro Guideline Development Tool, and the methodologist, Chair, and Co-Chair reinitiated discussions to reach a consensus. Relevant discrepancies were noted in the evidence-to-decision tables. A recommendation was made when all the GDG members agreed upon the group decisions.

The first guideline meeting was held in person on 28–30 November 2023. Three further sessions were held online in January, March and May 2024.

2.2.8 Evidence assessment and interpretation of the strength of recommendations

If randomized controlled trials (RCTs) were available, they were the preferred source of evidence for the effects of interventions. For the potential harms of an intervention, feasibility of implementation or for other contextual factors, nonrandomized trials and observational studies were also included.

Evidence-to-recommendation tables were formulated to show how the factors that determine the direction and strength of a recommendation were used in developing it. The strength of a recommendation expresses the degree to which the GDG is confident in the balance between the desirable and undesirable consequences of implementing the recommendation. Table 1 shows how the strength of a recommendation can be interpreted.

Each recommendation includes remarks and considerations for implementation.

Remarks in these guidelines provide clarifying information, context or additional explanations for interpreting a recommendation. For a conditional recommendation, they clarify scientific nuances, qualifying conditions or contextual points related to the recommendation. They may include exceptions, patient populations or interpretive notes.

Implementation considerations describe steps, resources, potential barriers or facilitators that should be taken into account in operationalizing a recommendation. They address feasibility, local adaptation, monitoring and evaluation strategies and factors that affect the success of guideline adoption in various contexts.

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Table 1. Interpretation of strong and conditional recommendations for an intervention

User	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would Prefer the recommended course of action; only a small proportion would not. Formal decision aides are unlikely to be required to help an individual in making a decision according to their values and preferences.	Most individuals in this situation would prefer the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to the recommendation could be used as a criterion of quality or a performance indicator.	Different choices will be appropriate for different patients, who will require assistance in arriving at a management decision consistent with his or her values and preferences. Decision aides may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy-makers	The recommendation can be adopted as policy for most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

2.3 Previous recommendations

Previous recommendations on treatment of VL and PKDL are included in the Expert Committee report on the control of leishmaniases (1). Treatment regimens are ranked by preference (Table 2).

Table 2. Previous recommendations for treatment of VL and PKDL

Recommended treatment regimes for VL ranked by preference ^a
VL caused by <i>L. donovani</i> in Eastern Africa and Yemen: 1. Combination: pentavalent antimonials (20 mg/kg antimony per day IM or IV) plus paromomycin (15 mg [11 mg base] per kg body weight per day IM) for 17 days (A) 2. Pentavalent antimonials: 20 mg/kg antimony per day IM or IV for 30 days (A) 3. LAmB: 3–5 mg/kg per daily by infusion over 6–10 days to a total dose of 30 mg/kg (B) 4. Amphotericin B deoxycholate: 0.75–1 mg/kg per day by infusion, daily or on alternate days, for 15–20 doses (A) 5. Miltefosine orally for 28 days at dosage as above (A)

Rescue treatment in case of non-response: Conventional amphotericin B deoxycholate or LAmB at higher doses

PKDL

Eastern Africa

1. Pentavalent antimonials: 20 mg/kg antimony per day IM or IV for 30–60 days, when indicated (C)
2. LAmB: 2.5 mg/kg per day by infusion for 20 days, when indicated (C)

Bangladesh, India, Nepal

1. Amphotericin B deoxycholate: 1 mg/kg per day by infusion, up to 60–80 doses over 4 months (C)
2. Miltefosine orally for 12 weeks at dosage as above (A)

^a Antileishmanial medicines and treatment regimens are qualified by grade of evidence (adapted from Cochrane reviews), as follows: (A) evidence from at least one properly designed RCT; (B) evidence from well-designed trials without randomization; (C) opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees; and (D) expert opinion in the absence of consistent or conclusive studies

2.4 What's new in these guidelines

These guidelines update the safety profile of miltefosine and the reasonable possibility of a causal relationship between miltefosine and ocular adverse events; they propose risk mitigation measures based on the suggestions of the WHO Advisory Committee on the Safety of Medicinal Products (15). In addition, they include new treatment regimens for PKDL in eastern Africa and South-East Asia and alternative treatment options for primary VL patients in eastern Africa. They also address VL relapse in South-East Asia. The guidelines describe weight-band-based allometric dosing with miltefosine (Annex 2) and indicators for monitoring implementation of the new recommendations.

2.5 Management of other forms of leishmaniasis and in other endemic regions

WHO guidelines for treatment of VL in HIV co-infected patients in East Africa and South-East Asia and guidelines for the treatment of leishmaniasis in the Americas were published in 2022 (9,10). The guidance of the WHO Expert Committee Report on the control of leishmaniases in 2010 (1) remains valid for other clinical forms and epidemiological regions, as does that for the European Region (25).



3

Background

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| 3.2 | VL relapse in South-East Asia |
| 3.3 | PKDL |

3.1 VL in eastern Africa

Eastern Africa is the ecoepidemiological subregion most severely affected by VL, accounting for 73% of cases globally that were reported to WHO in 2023 (2). VL is considered endemic in Chad, Djibouti, Eritrea, Ethiopia, Kenya, Somalia, South Sudan, Sudan and Uganda, where it is caused by infection with *L. donovani*. The disease is generally considered anthroponotic, although indications of zoonotic reservoirs exist.

In eastern Africa, VL occurs in two distinct ecological settings. The first is the savannah regions in the north, where the vegetation consists primarily of *Acacia seyal* and/or *Balanites aegyptiaca* trees, and *Ph. orientalis* (in north Ethiopia, northern South Sudan and Sudan) is the major vector. These sandflies breed inside the cracks of black cotton soil and rarely enter houses but bite humans in peridomestic habitats, such as courtyards. They show marked seasonality, with peak abundance in the dry season (March–June), thus with corresponding annual falls and rises in the caseload of VL.

The second ecological setting is the savannah and forest areas of the south, where *Ph. martini* and *Ph. celiae* are the predominant vectors. The setting includes Kenya, Somalia, Uganda, the south of Ethiopia and southern foci in South Sudan. Although both *Ph. martini* and *Ph. celiae* live mainly inside old *Macrotermes* termite hills in red-soil areas, their habitats do not geographically overlap.

VL affects the poorest populations living in remote locations, such as low-income households in rural villages, semi-nomadic pastoralists, seasonal agricultural workers and displaced populations. HIV and other comorbidities or co-infections are substantial risk factors for developing clinical disease, as is malnutrition. Spending time outdoors during the hot, dry season in proximity to *Balanites* or *Acacia* trees (or, in the southern foci, near termite mounds) increases the risk of infection.



Acacia savannah in West Pokot County, Kenya—an environment where *Phlebotomus* sand flies thrive and sustain VL transmission (2023)

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Specific risk factors include the presence of cattle and the person's age and genetic background. Sleeping outside under *Acacia* trees and living in houses constructed of grassy material appear to increase the risk for the disease. In areas where *Ph. martini* and *Ph. celiae* are the predominant vectors, the proximity of human dwellings to termite mounds increases the risk of infection.

Large outbreaks occur regularly in endemic areas where *Ph. orientalis* is the vector but are less frequent in endemic areas where *Ph. martini* is the vector. Population movements and climate change influence the epidemiology of VL. Outbreaks often occur when the parasite is introduced into new foci. Such outbreaks can initially be mistaken for those of malaria or other acute febrile illnesses. They can spread rapidly and cause large numbers of cases. During outbreaks, individuals of all ages and of both sexes are roughly equally affected, whereas in longstanding endemic foci 60% of cases occur in children aged < 15 years; except in Ethiopia, where seasonal migrant labourers travelling to endemic zones to plant and harvest cash crops are at highest risk and contribute 80% of cases in people aged ≥ 15 years (26).

Large outbreaks with high case fatality rates have been reported in the past, such as those that occurred during the civil war in southern Sudan in the 1980s and 1990s. They are considered to be due to anthroponotic transmission under conditions of massive population displacement, destruction of health-care infrastructure and increased incidences of other diseases. Seasonal movement for labour may also spread the disease, when migrants return to nonendemic areas, as appears to have occurred in the highlands of Ethiopia in the 2000s.

Sporadic sylvatic zoonotic VL transmission is recognized (27–31). Although *L. donovani* infection has been found in dogs in several foci, their importance in the transmission cycle is uncertain.

3.2 VL relapse in South-East Asia

Ideally, treatment for VL cures patients, reduces the risk of relapse, reduces the risk for PKDL, reduces transmission and prevents the emergence of resistant parasites. Successful therapy improves the patient's general condition, resolves fever, causes regression of splenomegaly and recovers blood counts to normal.

An initial cure can be declared if a patient is afebrile, their spleen size is reduced, the patient has gained weight and has increased haemoglobin and an improved general appearance by the end of treatment or within 2–4 weeks of completion of treatment for shorter-duration therapy. Complete regression of splenomegaly can take several months. A good indicator of definitive (or final) cure is the absence of clinical relapse at 6 months, relapse being the recurrence of signs and symptoms of VL any time after initial cure that is confirmed parasitologically.

In an observational retrospective cohort study in Bihar, India (32), 8749 patients were administered LAmB (AmBisome®) by infusion in four doses of 5 mg/kg (for a total dose of 20 mg/kg) over 4–10 days. Of 8588 patients who were HIV-negative, 8537 (99.4%) achieved initial cure, 24 (0.3%) defaulted, and 27 (0.3%) died during or immediately after treatment. In total, 114 (1.4%) of the initially cured patients developed parasitologically confirmed VL relapse, within a median time to relapse of 10.1 months. Male sex, age < 5 years and ≥ 45 years, a decreased spleen size at the time of discharge of ≤ 0.5 cm/day and a shorter duration of symptoms before seeking treatment were significantly associated with relapse. In another follow-up assessment of VL-treated cases and the impact of coronavirus disease in 2019 on the

VL control services in Nepal (33), eight of 112 VL-treated cases (7.14%) followed up to 12 months had relapsed, and two (1.8%) had developed PKDL. Risk factors for relapse were not reported.

In an observational retrospective study in Bangladesh (34), the analysis included 1521 patients who were treated with AmBisome® at 15 mg/kg in three equal doses of 5 mg/kg and were initially cured, of whom 1278 (84%) and 1179 (77.5%) were followed-up at 6 and 12 months, when the cure rates were 98.7% (1262/1278) and 96.4% (1137/1179), respectively. Of the 39 relapses (39/1179, 3.3%) that occurred within 12 months, 29 were parasitologically confirmed. Most relapses (26/39) occurred between 6 and 12 months after treatment. The odds for relapse at 12 months were highest for the youngest and oldest age groups. There was some evidence that spleen size measured on discharge (1 month after initiation of treatment) was associated with risk of relapse: odds ratio = 1.25 (95% confidence interval [CI]: 1.01; 1.55) per cm below the lower costal margin ($P=0.04$).

In a meta-analysis in a systematic review of studies on the Indian subcontinent, in which 0.6% of patients relapsed after 6 months, the proportion of relapse at 6 months was 4.5% after single-dose LAmB and 1.5% after LAmB in combination therapy with miltefosine and paromomycin. It was estimated that 27.6% of relapses would have been missed at a 6-month follow-up, indicating that the follow-up period should be extended to at least 12 months (35).

Earlier clinical relapses after miltefosine treatment have been reported to be due to low or non-response to drugs, possibly due to inadequate drug exposure of tissues, particularly in children aged < 12 years. In a cohort study, 120 miltefosine-treated VL patients in Nepal were monitored for up to 12 months for treatment outcomes; 10.8% of patients relapsed within 6 months and 20% within 12 months. No significant clinical risk factors of relapse were found, apart from age < 12 years. The pre- and post-treatment parasite isolates from definitive cures and relapses suggested no significant difference in drug susceptibility; however, more drug-tolerant strains were observed in relapse cases (36).

Limited data are available on VL relapse in patients, and the risk factors appear to differ from country to country.

3.3 PKDL

PKDL occurs in all areas endemic for *L. donovani* but is most common in eastern Africa (mainly Sudan) and on the Indian subcontinent (Bangladesh, India and Nepal). Almost 90% of PKDL cases reported to WHO since 2011 were reported from South-East Asia (2). PKDL may also occur sporadically in areas endemic for *L. infantum*, such as Mediterranean countries and Latin America, especially in patients with concurrent HIV infection (37). PKDL is considered to be triggered immunologically and usually appears 6 months to ≥ 1 years after apparent cure of VL, although it may occur earlier or even concurrently with VL in Sudan. The different features of PKDL in eastern Africa and the Indian subcontinent are summarized in Table 3.

PKDL is characterized by the occurrence of a skin rash; the interval after a preceding VL episode depends on the endemic area. The rash usually starts on the face, from which it may spread to other parts of the body. Lesions can involve the buccal mucosa, nose, and genital mucosa. Ocular lesions, may include eyelids, conjunctiva, cornea, and uveal tract, are also not uncommon. These conditions are often not recognized and may lead to blindness if parasites persist in the eyes, and the developing immune response can cause inflammation and destruction. Ocular involvement due to PKDL on the Indian subcontinent has been reported less frequently than in eastern Africa (41–45,72).

In contrast to VL, PKDL is not directly life-threatening; however, severity, clinical course, and management differ by region, and some cases can be severe and disfiguring. The risk factors for PKDL are not well known; previous treatment of VL with an inadequate dosage of drug and the type of antileishmanial drug used may play a role, as may malnutrition, HIV infection, male gender, young age and genetic and parasite-related factors (40).

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Table 3. Distinct features of PKDL in Sudan and on the Indian subcontinent

	Eastern Africa	Indian subcontinent
Epidemiology		
Highest rate reported in a field study	4.8/100	4.8/1 000
Maximum reported PKDL rate after VL	recent data 3-20% (6-months follow-up)	2–17%
Interval after VL (majority cases)	0–6 months	2-3 years
Most vulnerable age at presentation	Childhood	All ages
Clinical presentation		
Most common presentation	Polymorphic, papular	Polymorphic, papulonodular, macular
Typical distribution: Face-arms/chest-legs	Yes	Face and body, face nearly always
Sun-exposed areas	Yes	Yes
Spontaneous cure	Yes	No
May occur with visceral disease	Yes	Uncommon
May occur without previous VL	Yes	Yes
May occur while on treatment for VL	Yes	No
May have other kala-azar manifestations (uveitis, conjunctivitis)	Yes	Yes
Genital lesions	Uncommon	Common (India), uncommon (Bangladesh)
Mucosal lesions	Rare	Not uncommon

Sources: adapted from Zijlstra et al. (38); WHO (39); Zijlstra (40); Zijlstra et al. (8)

The importance of PKDL is both clinical and epidemiological. Clinically, patients develop a skin rash that may last for weeks, months or years. The rash may become generalized, with severe mucosal lesions, or may mimic other diseases such as vitiligo, fungal infections or leprosy. PKDL can cause stigmatisation, especially in young and unmarried patients and when there are polymorphic lesions (46,47).

The epidemiological significance of PKDL is that PKDL patients play an important role in transmission (anthroponotic transmission). Smears or biopsies taken from the lesions may show *Leishmania* parasites, and xenodiagnostic studies have confirmed that sand flies feeding on PKDL patients can become infectious (48,49). It has been postulated that chronic PKDL cases may maintain the cycle of transmission during the low inter-epidemic transmission period and can thus give rise to new outbreaks years after

the last VL patient was seen (50,51). Thus, PKDL patients who harbour parasites may play an important role in subsequent upsurges in VL cases. Except in severe cases, PKDL patients generally do not seek medical care; cases should therefore be actively sought and treated.

3.3.1 PKDL in eastern Africa

In eastern Africa, South Sudan and Sudan have the highest burdens of PKDL (2), which is unique and different from PKDL on the Indian subcontinent (Table 3). PKDL is much less common in Ethiopia, Kenya and Uganda, for unclear reasons; differences in the parasite or the genetic background of the population may be involved (39). Earlier studies when VL patients were treated mainly with antimonials, showed a PKDL rate of 50–60% (after 12 months of follow-up). However, 6-month follow-up data from RCTs suggest a lower PKDL rate of 3–20% with majority of VL patients treated with combination therapies (6,40). In Sudan, the majority of patients usually present within 6 months after treatment for VL but sometimes present as soon as 2 weeks after or, in 15%, present concomitantly with VL (6); alternatively, 10% present with PKDL without a history of previous VL (52).

In Ethiopia, PKDL occurs at low rates in different endemic regions and populations of patients. The true number of cases is unknown for several reasons. PKDL cases often do not seek medical care, mild PKDL lesions are easily missed, many mild cases when diagnosed will not be treated, and VL patients are inadequately followed-up after treatment. Consequently, many PKDL cases are not identified or reported. There are also differences within the country. For example, PKDL is more common in northern than southern Ethiopia, and the rate of PKDL is particularly high in HIV-co-infected patients, who may have atypical presentations. The prevalence of PKDL appears to be lower in southern Ethiopia, but no published information includes active follow-up of cases. Limited unpublished data indicate differences between the parasites in the northern and southern foci.

In eastern Africa, PKDL is often described in three grades of severity according to the density and spread of lesions (Table 4)

Table 4. Grading system for PKDL in eastern Africa

Clinical presentation	
Grade I	Scattered maculopapular or nodular rash on the face with or without lesions on the upper chest or arms
Grade II	Dense maculopapular or nodular rash covering most of the face and extending to the chest, back, upper arms and legs, with only scattered lesions on the forearms and legs
Grade III	Dense maculopapular or nodular rash covering most of the body, including the hands and feet; the mucosa of the lip and palate may be involved.

In eastern Africa, PKDL is not routinely treated, as the majority of cases (85%) heal spontaneously within 1 year (53). Only patients with severe (grade III) or disfiguring disease, those with lesions that have persisted for >6 months, those with concomitant anterior uveitis and young children with oral lesions that interfere with feeding are treated, with either SSG (20 mg/kg pentavalent antimony per day) for up to 2 months or a 20-day course of LAmB at 2.5 mg/kg per day. In Sudan, the end-point is flattening of lesions and improvement of dyschromia (1).

The Strategic framework for the elimination of VL as a public health problem in eastern Africa 2023–2030 (18) recommends treatment of all PKDL cases, as they are potential reservoirs and contribute to maintaining transmission.

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3.3.2 PKDL on the Indian subcontinent

In the Indian subcontinent, up to 17% of apparently cured VL patients develop PKDL (7,8). It can occur at any age and rarely heals spontaneously. The majority of PKDL patients in Bangladesh present with macular lesions, whereas, in India, polymorphic lesions are observed most often. The polymorphic form may show hypopigmented or erythematous macules in combination with papules and/or nodules.

It would be difficult to provide a general description of the clinical picture of PKDL on the Indian subcontinent, as most field studies were conducted in Bangladesh. In India, data from hospital-based studies show various presentations. It is not clear whether the differences are due to differences in delays in patient presentation, diagnosis or reporting or to the parasite involved, the genetic background of patients, treatment received or other factors.

On the Indian subcontinent, PKDL cases are generally treated as chronic cases, because they do not heal spontaneously and because their role in transmission is especially relevant in view of ongoing VL elimination programmes. There is no standard grading system for the severity of PKDL on the Indian subcontinent. After treatment, the skin returns to normal, but re-pigmentation may occur over time and is therefore not a good indicator of cure.



Technical Officer Kinyeru Esther conducts a home examination of a kala-azar patient during a joint Ministry of Health and the three levels of WHO mission on kala-azar outbreak response in Wajir County in Kenya (2025)



4

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4.1 VL in eastern Africa

Efficacy and safety of different pharmacological treatments for the management of VL patients in eastern Africa

Recommendations

- 4.1.1 Use of a combination of paromomycin plus miltefosine^a is suggested rather than a combination of SSG plus paromomycin^b

(**Conditional** recommendation, **low-certainty** evidence)

^a Doses when given in combination: paromomycin sulfate (20 mg/kg [equivalent to 15 mg/kg/day paromomycin base] per day IM once a day for 14 days) plus miltefosine (allometric doses, orally BID for 14 days)

^b Doses when given in combination: SSG (20 mg/kg per day IV or IM once a day for 17 days) plus paromomycin sulfate (15 mg/kg [equivalent to 11 mg/kg/day paromomycin base] per day IM once a day for 17 days)

- 4.1.2 Use of a combination of SSG plus paromomycin^a is suggested rather than SSG^b monotherapy in patients in whom paromomycin plus miltefosine is excluded .

(**Conditional** recommendation, **low-certainty** evidence)

^a Doses when given in combination: pentavalent antimonial (20 mg/kg per day IV or IM once a day for 17 days) plus paromomycin sulfate (15 mg/kg [equivalent to 11 mg/kg/day paromomycin base] per day IM once a day for 17 days)

^b Doses of SSG (20 mg/kg per day IV or IM once a day for 30 days)

- 4.1.3 Use of LAmB^a is suggested in patients in whom paromomycin plus miltefosine and/or pentavalent antimonial plus paromomycin is excluded

(**Conditional** recommendation, **very low-certainty** evidence)

^a Doses of LAmB (3–5 mg/kg per day by infusion given over 6–10 days up to a total dose of 30 mg/kg)

Remarks

1. The following are the exclusion criteria in the paromomycin plus miltefosine trial and other excluded conditions.

- patient's age <4 years and >50 years; pregnant or lactating women; female patients of childbearing potential who do not agree to a pregnancy test at screening for VL and/or to use contraception from the treatment period until 5 months after treatment; VL relapse; severe malnutrition; VL concurrent with PKDL; haemoglobin <5 g/dL; severe VL according to the physician's judgement based on clinical manifestations (e.g. jaundice, bleeding, oedema) and significant abnormalities in laboratory parameters (e.g. haemoglobin, white blood cells, platelets, liver enzymes [alanine and aspartate transaminases], total bilirubin and creatinine); history of hypersensitivity to drugs or known drug class allergies; pre-existing hearing loss; underlying comorbid conditions (e.g. cardiac, renal or hepatic); concomitant infections such as pneumonia, tuberculosis, schistosomiasis, HIV infection or any other immunosuppressive condition; and
- unable to comply with the planned study visits and regimen (e.g. unable to swallow miltefosine capsules, severe side-effects or drug intolerance).

2. Miltefosine is to be provided in allometric doses, particularly for patients weighing <30 kg (see Annex 2).

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3. Miltefosine is potentially teratogenic. Its use in pregnancy is contraindicated. It should not be used in women of childbearing potential for whom pregnancy cannot be ruled out and adequate contraception cannot be assured for the duration of treatment and 2 months (for shorter miltefosine regimens, e.g. 5, 7 or 10 days) or 5 months (for 28-day or longer miltefosine regimens) post-treatment.

4. The availability and acceptability of contraception (oral versus injectable) should be taken into account before prescription.

5. Supportive treatment is important; patients should be properly hydrated and given nutritional supplements. Severe anaemia should be corrected with blood transfusions, and concomitant infections should be treated with appropriate anti-infective agents.

Implementation considerations : please refer to [section 5.1](#) for full details

4.1.1 Use of a combination of paromomycin (20 mg [15 mg base]/kg per day IM once a day for 14 days) plus miltefosine (allometric dose, orally BID for 14 days) is suggested as an alternative to a combination of SSG (20 mg/kg per day IM/IV) plus paromomycin (15 mg [11 mg base]/kg per day IM for 17 days).

Conditional recommendation, **low-certainty** evidence

Rationale

The WHO expert committee report published in 2010 (1) and Musa et al. (54) recommended combination treatment with SSG plus paromomycin as the first-line regimen for primary VL rather than 30-day monotherapy with SSG. The combination had an overall efficacy of 91.4% at 6 months post-treatment. The safety and efficacy of the combination treatment and SSG monotherapy were similar; however, SSG administration requires hospitalization, with painful daily injections of both SSG and paromomycin for 17 days and potentially life-threatening antimony-associated toxicity such as cardiotoxicity, hepatotoxicity and pancreatitis.

In a more recent randomized, controlled, multicountry trial in eastern Africa, a combination of paromomycin plus miltefosine for 14 days achieved a cure rate of 91% (11). This exceeds the cure rates with miltefosine monotherapy (72%), AmBisome® and SSG (87%) and AmBisome® and miltefosine (77%) combination therapies. Paromomycin plus miltefosine was better tolerated than SSG plus paromomycin, with expected adverse drug reactions as per the drug safety profiles and removal of the risk of SSG-associated life-threatening cardiotoxicity. Paromomycin plus miltefosine treatment and duration of hospitalization are 3 days shorter, with one fewer painful injection daily.

Summary of data on efficacy and safety to support the recommendation

In an open-label, phase 3, randomized, controlled, multicentre, noninferiority trial in adult and paediatric patients at seven sites in Ethiopia, Kenya, Sudan and Uganda (11), a combination of paromomycin (20 mg/kg per day IM once a day for 14 days) plus miltefosine (allometric doses, orally BID for 14 days) was compared with the standard of care, SSG (20 mg/kg per day IV or IM once a day for 17 days) plus paromomycin (15 mg/kg per day IM once a day for 17 days). An intervention arm of paromomycin for 14 days and

miltefosine for 28 days was discontinued, as the combination of paromomycin plus miltefosine for 14 days was shorter, allowing complete administration during hospitalization, and was less costly. No concern about efficacy or safety was noted for early termination. Patients aged 4 to $\leq$ 50 years with signs and symptoms of VL and parasitological diagnosis were included; exclusions were relapse cases; people with severe malnutrition, severe VL, a positive HIV diagnosis or a concomitant severe infection; and women of childbearing potential who were unwilling to use contraception until 5 months after the end of treatment. The primary end-point was definitive cure after 6 months. Of 439 participants with primary VL, 424 completed the trial. The rate of definitive cure at 6 months in a primary efficacy modified intention-to-treat analysis was 91.2% (155 of 170) in the paromomycin plus miltefosine arm and 91.8% (156 of 170) in the SSG plus paromomycin arm (difference, 0.6%; 97.5% confidence interval [CI], -6.2; 7.4), with the noninferiority margin of 7%. In the per-protocol analysis, efficacy was 92% (149 of 162) and 91.7% (155 of 169) for the paromomycin plus miltefosine and SSG plus paromomycin arms (difference, -0.3%; 97.5% CI, -7.0; 6.5), demonstrating noninferiority.

The results of the systematic review show little or no difference in the number of deaths (relative risk [RR] 0.33, 95% CI 0.04; 3.17; low-certainty evidence), initial cure (RR 1.00, 95% CI 0.98; 1.02; moderate-certainty evidence) and definitive clinical cure (RR 1.00, 95% CI 0.98; 1.03; low-certainty evidence). Paromomycin plus miltefosine may result in fewer cases of PKDL (RR 0.22, 95% CI 0.08; 0.56; low-certainty evidence) but may result in more serious adverse events (SAEs) (RR 1.67, 95% CI 0.40; 6.86; low-certainty evidence). The known side-effects of miltefosine are, however, manageable. The regime may also result in little or no difference in adverse events (RR 1.02, 95% CI 0.83; 1.26; low-certainty evidence) or in withdrawals (RR 0.20, 95% CI 0.01; 4.14; low-certainty evidence).

Summary of contextual factors

Acceptability and feasibility

The acceptability of the paromomycin plus miltefosine regimen may depend on the context. The life-threatening SSG-related toxicity may be less acceptable than mortality from VL or comorbid conditions. In some settings, however, injectable treatments such as SSG are perceived to be more effective than oral therapies. This may require sensitization of communities and health-care personnel about the drugs, their administration and their toxicity. Cultural and social views on contraception may affect the acceptability of miltefosine, particularly in populations where contraceptive use is limited or stigmatized. Similarly, miltefosine may be less acceptable for use in very young, malnourished children because of their difficulty in swallowing the capsules.

The results of a mixed-methods study in non-patient stakeholders (Annex 4) showed a preference for treatment regimens that are of overall shorter duration and include at least one orally administered drug. In view of the life-threatening nature of VL, the most critical considerations are drug effectiveness, fewer side-effects, lower cost and a shorter regimen with one oral drug.

Resource use

No studies on cost-effectiveness were available, and no formal costing studies were available for either treatment regimen. The direct drug costs are similar, but paromomycin plus miltefosine is associated with lower indirect costs (hospitalization, transport, income loss) as it can be administered to outpatients.

Equity

The requirements associated with miltefosine (contraception, monitoring) may be disadvantages for women of childbearing age, children and malnourished patients. Conversely, decentralization and reduced out-of-pocket costs improve access for vulnerable populations, including mobile and displaced groups.

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Key research gaps

- Children, pregnant women, severely malnourished patients, people with concomitant severe comorbidities and patients with severe VL were excluded from one study (11). Severely malnourished patients might, however, represent the majority of patients in some settings.
- No data on PKDL rates beyond 6 months post-treatment are available; the difference in PKDL rates between the two study regimens should therefore be interpreted with care (11).
- One report did not include treatment adherence, the workload of health-care staff or patient satisfaction (11).

4.1.2 Use of a combination of SSG (20 mg/kg per day IM or IV for 17 days) plus paromomycin (15 mg [11 mg base]/kg per day IM for 17 days) is suggested rather than SSG monotherapy (20 mg/kg per day for 30 days) in patients for whom paromomycin plus miltefosine is excluded.

Conditional recommendation, **low-certainty** evidence

Rationale

The GDG suggests use of a combination of SSG (20 mg/kg per day IM or IV for 17 days) plus paromomycin (15 mg [11 mg base]/kg per day IM for 17 days) rather than SSG monotherapy (20 mg/kg per day for 30 days) in patients for whom the paromomycin plus miltefosine regimen is contraindicated or excluded. This recommendation is based on a systematic review of five studies – two RCTs and three non-randomized studies comprising 5404 participants with primary VL (54–58), which suggest that the combination regimen may reduce mortality (RR 0.50, 95% CI 0.17; 1.44; low-certainty) and probably reduce the risk of PKDL (RR 0.49, 95% CI 0.30; 0.78; moderate certainty). It may result in little or no difference in initial clinical cure (RR 0.98, 95% CI 0.95; 1.02; moderate certainty) and in little or no difference in definitive clinical cure (RR 0.97, 95% CI 0.93; 1.01; low-certainty). The combination regimen may also result in little or no difference in severe adverse events (SAEs), overall adverse events, treatment adherence and withdrawals, although the certainty of evidence for these outcomes is low to very low.

The GDG considered that the results of the mixed-method study of non-patient stakeholders indicate that a combination regimen results in a shorter treatment duration, thereby increasing compliance; reduces the overall dose of medicines, thereby reducing their toxic effects; and reduces the probability of selection of drug-resistant parasites, thereby prolonging the effective life of the medicines. The shorter regimen also reduces hospitalization time and the associated indirect costs such as transport, accommodation and lost wages. From an equity perspective, although no formal cost-effectiveness studies are available, the combination regimen is estimated to require moderately fewer resources due to lower drug costs and shorter hospitalization.

Summary of contextual factors

Non-patient stakeholders indicated that treatment regimens with several drugs are generally more acceptable when the overall duration is shorter. Given the life-threatening nature of VL, however, effectiveness and safety are the most critical considerations, as experience indicates that SSG is effective. The shorter SSG plus paromomycin regimen reduces hospitalization time, lowering patient

costs for transport and lost income. From an equity perspective, shorter hospital stays free hospital beds, improve access for vulnerable populations and reduce the burden on caregivers and the health system associated with accommodation, food and wage loss.

Resources required

- No studies on cost-effectiveness were available.
- No formal costing studies were available. SSG plus paromomycin is cheaper than SSG monotherapy. Also, it requires shorter hospitalization. The overall resources required are therefore estimated to be moderately lower for the SSG plus paromomycin regimen.

Equity

- Shorter hospitalization benefits more patients and may increase equity.
- Shorter hospital stays may increase bed availability and reduce caregiver burden, especially in resource-limited settings.

Acceptability and feasibility

- Shorter hospitalization might be more acceptable to patients and health-care providers.
- The combination regimen is probably more feasible to implement than the monotherapy regime because of the shorter hospitalization.

Key research gap

The reports did not include relapse, workload of health-care staff or patient satisfaction.

4.1.3 Use of LAmB (3–5 mg/kg per daily dose by infusion given over 6–10 days up to a total dose of 30 mg/kg) is suggested for patients in whom paromomycin plus miltefosine and/or pentavalent antimonial plus paromomycin is excluded

Conditional recommendation, **very low-certainty** evidence

Groups of interest

- Patients with therapeutic failure or relapse after miltefosine + paromomycin and/or SSG + paromomycin
- Pregnant and lactating (for < 6 months) women
- Severely ill patients at increased risk of death
- Patients with known cardiac, liver or kidney disease or elevated liver enzyme activity (e.g. five times normal) or elevated creatinine level during treatment with SSG + paromomycin
- In the case of any other contraindication for miltefosine, paromomycin or SSG
- Children with severe acute malnutrition according to WHO Child Growth Standards. These children are very ill and often have impaired liver and kidney function (MSF experience)
- Adults with a BMI < 14. This was shown to be an independent risk factor for death (98).

Rationale

LAmB is generally used as a rescue drug in clinical trials. The clinical trial data on LAmB in eastern Africa is sparse. Organizations such as Médecins sans Frontières (MSF) have extensive clinical experience in the treatment of VL in emergencies (59,60,61), and the recommendation is based mainly on observational studies. Patients constitute a widely heterogeneous group who are often excluded from clinical trials, and the benefits may vary because of the heterogeneity of the groups. For example, it is likely that certain

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groups will experience more desirable effects (greater safety) than others (e.g. pregnant women) (61,62). The data on safety were extrapolated from studies in South-East Asia, where LAmB is the first-line treatment; they are identified as indirect evidence.

In an open-label dose-finding study in Kenya (62), 20% of cases were cured with a 6 mg/kg total dose, 90% of cases with a 10 mg/kg total dose (9/10 patients) and 100% with a 14 mg/kg total dose (10/10 patients). In an open trial of LAmB for the treatment of complicated VL cases in Sudan, a 50% cure rate was observed with a total dose of 9–15 mg/kg in 12 cases and an 88% cure rate with a total dose of 18–30 mg/kg in 16 cases (all were severely ill patients) (63). In a retrospective analysis of all pregnant VL patients treated by MSF in Sudan (61), 23 of 39 pregnant women were treated with SSG, 4 with LAmB and SSG and 12 with LAmB alone. Spontaneous abortions occurred in 13 women (57%) who received SSG monotherapy and none in either of the other two groups. All spontaneous abortions occurred in the first two trimesters. All patients were cured, except for one defaulter treated with SSG. In a systematic review of studies on VL in pregnancy and vertical transmission, LAmB was administered to 202 of 344 mothers (58.7%) and pentavalent antimony to 92 (26.7%). The outcomes of 176 mothers treated with LAmB included four (2.3%) maternal deaths, five (2.8%) miscarriages and two (1.1%) fetal deaths or stillbirths. For pentavalent antimony, outcomes were reported for 87 mothers, of whom 4 (4.6%) died, 24 (27.6%) had spontaneous abortions and 2 (2.3%) had miscarriages (64).

The GDG also took into account a summary presentation of the current treatment protocols in high-burden eastern African countries, with conditions in which LAmB is indicated, e.g. guidelines for diagnosis, treatment and prevention of leishmaniasis in Ethiopia (65). The following conditions were identified:

- acute pancreatitis with abdominal pain and vomiting;
- jaundice developing while on treatment;
- elevated liver function enzymes (five times the normal values);
- elevated creatinine;
- evidence of cardio-toxicity;
- severe, uninterrupted vomiting;
- decreasing haematological parameters; and
- failure to respond to treatment after 2 weeks of drug treatment.

Summary of contextual factors

The GDG considered contextual factors in formulating its recommendation. Stakeholders noted that LAmB is often used in emergencies and for patients excluded from standard regimens due to extremes of age, relapses, severity of illness, severe malnutrition, pregnancy, toxicity or other contraindications. The shorter treatment duration may reduce hospitalization costs and caregiver burden, particularly in resource-limited settings. The regimen may also improve equity by freeing hospital beds, thus giving access for vulnerable populations. Despite limited trial data, experiential evidence from humanitarian organizations supports its use in complex cases, including in pregnant women, for whom advantages have been observed in respect of safety.

4.2 VL relapse in South-East Asia

What are the efficacy and safety of different pharmacological treatments for the management of VL relapse in South-East Asia?

Recommendations

4.2.1 In settings in which primary VL in immunocompetent patients was treated with single-dose LAmB (10 mg/kg by infusion over 2 h), a parasitologically confirmed case of relapse should not be treated with a single dose of LAmB (10 mg/kg by infusion over 2 h).

(**Conditional** recommendation based on expert opinion, **very low-certainty evidence**)

4.2.2 When available, a combination of drugs (co-administered) can be used to treat relapse cases.

- miltefosine^a plus paromomycin^b, both daily for 10 days
- LAmB (5 mg/kg by infusion, single dose) plus miltefosine^a (daily for 7 days)
- LAmB (5 mg/kg by infusion, single dose) plus paromomycin^b (daily for 10 days)

^a allometric doses of miltefosine

^b paromomycin sulfate 15 mg (11 mg base) per kg/body weight per day intramuscularly

(**Conditional** recommendation based on expert opinion, **very low-certainty evidence**)

4.2.3 For relapse cases that are not eligible for combination regimens, higher doses of LAmB up to a total dose of 15–20 mg/kg should be administered in three or four administrations.

(**Conditional** recommendation based on expert opinion, **very low-certainty evidence**)

Remarks

- Relapse patients should be diagnosed parasitologically.
- The choice of drugs should include consideration of availability, feasibility and cost.
- Miltefosine should be administered by allometric dosing, particularly for patients weighing < 30 kg.

Implementation considerations : please refer to [section 5.1](#) for full details

Diagnosis of VL relapse requires parasitological confirmation, as serological tests remain positive for several years after cure due to the persistence of antibodies, and the tests cannot reliably distinguish between active and past infection. Polymerase chain reaction (PCR) testing for parasite DNA in blood or bone-marrow aspirates is substantially more sensitive than microscopy, but its use is currently limited to referral hospitals and research centres.

In the future, quantitative PCR techniques may be more specific for clinical disease, although proper standardization of PCR techniques and evaluation of their diagnostic accuracy in representative clinical settings are necessary. Until new tests for confirmation of cure are available, diagnosis of relapse cases will require parasitological confirmation.

Rationale

A total of 27 studies with 3557 participants with confirmed relapse of VL in Bangladesh and India were included for systematic review. Of those, five were comparative studies: four were RCTs, and one was a non-randomized trial; 22 were single-arm/non-comparative studies on safety outcomes. Of the latter, nine studies reported on amphotericin B (AmB) deoxycholate (one on LAmB therapy), three on pentamidine

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isethionate, one on pentamidine methane sulfonate after SSG relapse, three on SSG, one on allopurinol, one on miltefosine, one on ketoconazole, one on metronidazole and one on lipid formulations of AmB, miltefosine, paromomycin or combinations. None of the studies in the systematic review provided evidence of VL relapse in patients who had received a single dose of LAmB as primary VL treatment.

In the absence of relevant studies and data, current practices in the national VL programmes and referral centres in the region were assessed. Data from Nepal showed a total of 63 relapse cases between 2019 and 2023, of which only 31 were confirmed parasitologically. The information on treatment of relapses and cure was insufficient to draw any conclusion.

Data from referral centres in India showed that, between 2019 and 2023, of 191 parasitologically confirmed relapse patients, 146 (76%) were treated with a repeat dose of LAmB (10 mg/kg), of which 146 (100%) achieved initial cure (within 15–30 days of treatment), 133 (91%) achieved definitive cure at 6-month standard post-treatment, 11 (8%) relapsed again, and 2 died (1%).

Of the 36 patients who received a higher dose of LAmB (15–20 mg/kg), all (100%) achieved initial cure, 33 (87%) definitive cure and 3 (13%) re-relapsed. Nine patients received a combination of LAmB (5 mg/kg, single dose) plus miltefosine (orally, daily for 7 days), all of whom showed initial and definitive cure (100%).

The data suggest that repetition of a single dose of LAmB (10 mg/kg) can result in cure, although a proportion of patients (8%) may not respond to this dose and re-relapse. In addition, combination regimens might decrease the risk of selecting drug-resistant parasites in patients for whom LAmB monotherapy proved insufficient to achieve cure. Data on nine relapse patients treated with combination therapy showed no relapse. This observation is based on a very small number, but the treatment outcomes were similar to those of a study on the safety and efficacy of short-course combination regimens with AmBisome®, miltefosine and paromomycin for the treatment of primary VL in Bangladesh, in which no relapse and PKDL at 6-month follow-up were observed (66).

4.3 PKDL in eastern Africa

What are the efficacy and safety of different pharmacological treatments for the management of PKDL in Eastern Africa?

Recommendations

4.3.1

A combination of paromomycin plus miltefosine^a is suggested rather than a combination of LAmB and miltefosine.^b

^a Dose of paromomycin sulfate (20 mg/kg [equivalent to 15 mg/kg/day paromomycin base] once a day IM for 14 days) and miltefosine (allometric dose orally BID for 42 days)

^b Dose of LAmB 5 mg/kg per day IV on days 1, 3, 5, and 7 (total dose, 20 mg/kg) and miltefosine (allometric dose orally BID for 28 days)

Conditional recommendation, low-certainty evidence

Remarks

- PKDL cases are reservoirs of infection. Although the majority of cases heal spontaneously, the GDG considered that, whenever possible, every patient should be offered treatment, in line with the VL elimination initiative in eastern Africa.
- Patients should be counselled about the disease, the benefits and risks of treatment and available alternatives, which should adhere to the national patient safety policies and strategies of countries.
- Miltefosine is potentially teratogenic. Its use in pregnancy is contraindicated. It should not be used in women of childbearing potential for whom pregnancy cannot be ruled out, and adequate contraception cannot be assured for the duration of treatment and for 2 months (for shorter miltefosine regimens, e.g. 5, 7 or 10 days) or for 5 months (for 28-day or longer miltefosine regimens) post-treatment (67).
- The availability and the acceptability of contraception (oral versus injectable) should be taken into account before prescription. Miltefosine is potentially teratogenic. Its use in pregnancy is contraindicated.
- **Children:** Monitoring of ocular side-effects might be particularly difficult in children; therefore, the shorter (LAmB plus miltefosine) regimen is preferred.
- **Severely malnourished patients:** LAmB plus miltefosine might be preferred to paromomycin plus miltefosine due to the shorter treatment and the safety profile of LAmB plus miltefosine in such patients. In addition, the absence of food to accompany miltefosine intake might increase gastrointestinal side-effects, reducing compliance with therapy.
- Improvement in skin lesions before the end of treatment might compromise adherence, especially to the longer (paromomycin plus miltefosine) regimen. Patient education is therefore important.

Implementation considerations : please refer to [section 5.1](#) for full details

Rationale

Studies included in the systematic review

Nine studies with a total of 609 PKDL patients: two RCTs (68–70), one retrospective cohort study (71) and six single arm/non-comparative studies reporting on safety outcomes (73–77). Only two studies included a direct comparison with the currently recommended treatment regimen (SSG monotherapy) (68,71).

For this PICO, seven outcome results were presented (Web annex C). One RCT in which SSG plus a mixture of killed *L. major* adsorbed onto alum plus bacillus Calmette-Guérin (BCG) versus SSG plus placebo was tested was not assessed in depth by the GDG because of the very small sample size (n=30) (68). For the comparison between SSG plus paromomycin versus SSG monotherapy (71), the GDG decided that no meaningful recommendation could be formulated from a single retrospective cohort study.

The recommendation to use paromomycin plus miltefosine rather than LAmB plus miltefosine is based on findings from a single RCT involving 110 patients with PKDL in Sudan (70). Paromomycin plus miltefosine resulted in a higher cure rate and a lower incidence of adverse events than LAmB plus miltefosine. Additionally, the paromomycin plus miltefosine regimen offers programmatic advantages, including reduced hospitalization and lower toxicity than the current standard of care, such as SSG administered over 30–60 days.

Previous WHO recommendations based on expert opinion and descriptive studies (1) included pentavalent antimonials and LAmB. Because of the known toxicity of antimonials, however, they were excluded from the recent trial used to make this recommendation. While the overall certainty of the evidence remains low, the better safety profile, shorter treatment duration and operational feasibility of paromomycin plus miltefosine led to a conditional recommendation.

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Summary of data on efficacy and safety

Comparison of the combination of paromomycin and miltefosine with the combination of LAmB and miltefosine:

- may **increase** the rate of clinical cure over 12 months (RR 1.18, 95% CI 1.04; 1.34; low-certainty evidence);
- may result in little or no difference in the risk of relapse at 12 months (RR 0.09; 95% CI 0.00; 1.55; very low-certainty evidence);
- may result in little to no difference in treatment adherence (RR 2.89; 95% CI 0.31; 29.93; very low-certainty evidence); and
- may result in **fewer** adverse events (RR 0.69, 95% CI 0.49; 0.98; low-certainty evidence).

No deaths were reported during the 12-month study.

Acceptability

- The acceptability of miltefosine is mixed due to its ocular side-effects, particularly in the 42-day regimen (paromomycin plus miltefosine). This concern is less pronounced with the shorter LAmB plus miltefosine regimen.
- Health-care providers may prefer paromomycin plus miltefosine due to reduced hospitalization, although, in some settings, paromomycin administration still requires 2 weeks of inpatient care.
- Patients may favour shorter regimens, despite the requirement for hospitalization. Adherence to miltefosine may decrease as lesions heal, especially with longer regimens.
- Overall, paromomycin plus miltefosine is considered acceptable in most settings, although there is little tolerance for side-effects in view of the non-lethal nature of PKDL.

Feasibility

- Paromomycin plus miltefosine is generally more feasible than LAmB plus miltefosine because of the reduced cold-chain requirements and simpler administration.
- Safe delivery of LAmB requires trained staff and hospital infrastructure.
- Ocular monitoring is essential for miltefosine regimens; however, it may be a challenge, especially in children and resource-limited settings.

Resource use

- No formal studies of cost-effectiveness or costing were available.
- Paromomycin plus miltefosine probably results in moderate resource savings due to the feasibility of outpatient administration and therefore less hospitalization.
- The GDG estimates favours paromomycin plus miltefosine in view of the lower direct drug costs and requirements for a cold chain and inpatient care.

Equity

- Both regimens require miltefosine, posing similar risks for women of childbearing potential and requiring contraception and pregnancy testing.

- Paediatric and severely malnourished populations may be at a disadvantage with paromomycin plus miltefosine because of its greater toxicity and difficulty in reporting ocular symptoms in this population subgroup.
- Poorer populations may face barriers if LAmB becomes unavailable in the public sector, limiting access to the combination of LAmB plus miltefosine.

Implementation considerations

- A test dose of LAmB of 1 mg should be given by infusion, followed by a full dose.
- People with pre-existing ocular conditions should be excluded, and risk mitigation for miltefosine-related ocular adverse events is essential with both regimens. (Follow advice as described in Annex 1.)
- Regular eye examinations (every 2 weeks) should be conducted during and after treatment.
- Educate patients to recognize symptoms.

Key research gaps

- No children <6 years were included in the source study.
- Comorbidities: HIV and other co-morbidities were not included in the source study.
- Pregnancy was not considered in the source study.
- Data on patients' perspectives were not available at the time the recommendation was developed.

4.4 PKDL in South-East Asia

What are the efficacy and safety of different pharmacological treatments for the management of PKDL in South-East Asia?

Recommendations

4.4.1 LAmB (total dose, 30 mg/kg administered IV in six doses of 5 mg/kg twice a week for 3 weeks) is suggested rather than miltefosine (2.5 mg/kg to children between 2-11 years or 100 mg/day orally for 12 weeks in divided doses).

(Conditional recommendation, low-certainty evidence)

4.4.2 A combination of LAmB (total dose, 20 mg/kg administered IV on days 1, 4, 8, 11 and 15) plus miltefosine (allometric dose orally BID for 21 days) or LAmB monotherapy (total dose, 20 mg/kg administered IV on days 1, 4, 8, 11 and 15) is suggested for the treatment of PKDL.

Conditional recommendation, very low-certainty evidence

4.4.3 A combination of LAmB (total dose, 15 mg/kg administered IV on days 1, 8 and 15) plus miltefosine (100 mg/day orally after the first dose of LAmB and daily until the end of 45 days) is suggested rather than miltefosine monotherapy (100 mg/day orally for 90 days).

Conditional recommendation, very low-certainty evidence

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Remarks^a

In the absence of a common comparator of all studies, heterogeneous regimens and study designs and an insufficient number of direct comparisons, a network meta-analysis was not feasible. Therefore, a number of regimens were assessed and compared. The settings in which each recommendation can be implemented are indicated.

Selection of regimen

When selecting a regimen, consider the national context, such as the health system architecture, health workforce density per population, laboratory capacity, monitoring and reporting pathways, referral network, availability of pregnancy tests, contraception advice, logistics and supply chain, pharmacovigilance and antimicrobial programmes.

- PKDL cases are potential reservoirs. Cases of PKDL in South-East Asia rarely self-heal; therefore, treat every patient when possible in the VL elimination programme.
- Patients should be counselled about the disease, the benefits and risks of treatment and the available alternatives, which should adhere to national patient safety policies and strategies.
- Miltefosine is potentially teratogenic. Its use in pregnancy is contraindicated. It should not be used in women of childbearing potential for whom pregnancy cannot be ruled out and adequate contraception cannot be assured for the duration of treatment and 2 months (for shorter miltefosine regimens, e.g. 5, 7 or 10 days) or 5 months (for ≥ 28 -day miltefosine regimen) post-treatment (67).
- **Children:** Monitoring of ocular side effects might be particularly difficult in children; therefore, a non-miltefosine regimen or a miltefosine regimen of shorter duration can be considered.
- **Severely malnourished patients:** A shorter regimen may be preferred for such patients. In addition, lack of food to accompany miltefosine intake might increase gastrointestinal side-effects and reduce compliance with the therapy.
- Hypokalemia is a very common side-effect of LAmB, leading to tiredness, confusion, muscle weakness or cramps. This may be more prominent and dose-related in regimens of cumulative high-dose administration, e.g. 30 mg/kg of LAmB. Monitor serum potassium, other electrolytes and renal function during treatment. Proper hydration, a potassium-rich diet and potassium supplementation are important to prevent such side-effects.
- High cumulative doses of LAmB should be administered only in centres with the capacity to monitor serum potassium, renal function, and manage electrolyte abnormalities.
- If miltefosine is refused, unavailable or contraindicated, consider alternative treatment with LAmB.
- Improvement of skin lesions before the end of treatment might compromise adherence, especially to the longer (paromomycin plus miltefosine) regimen. Patients should be educated.

Implementation considerations : please refer to [section 5.1](#) for full details

^a Studies on LAmB and miltefosine by dose are summarized in Annexes 5 and 6, respectively; no or very low-certainty evidence for a dose–relation.

4.4.1 LAmB (total dose, 30 mg/kg administered IV in six doses of 5 mg/kg twice a week for 3 weeks) is suggested rather than miltefosine (2.5 mg/kg to children 2–11 years or 100 mg/day orally for 12 weeks in divided doses)

(**Conditional** recommendation, **low-certainty** evidence)

Rationale

A total of 40 studies were selected, comprising 4067 PKDL patients. The previously recommended treatments, ranked by preference, were AmB deoxycholate (1 mg/kg per day by infusion, up to 60–80 doses over 4 months) or miltefosine orally for 12 weeks at the dosages cited above. Both treatment options were recommended by WHO in 2010 (1). Recommendation of AmB deoxycholate was based on descriptive studies, reports of expert committees or the opinions of respected authorities with clinical experience. The recommendation of miltefosine was based on one small clinical trial. The safety of courses of miltefosine longer than 4 weeks has not been evaluated. Recently, ocular adverse events that caused panophthalmic manifestations in a few cases have been reported in PKDL patients given miltefosine for 12 weeks, which led to a review of the evidence on the safety of longer regimens containing miltefosine.

The GDG omitted studies of SSG and AmB deoxycholate because of the known fatal and high toxicity of the drugs and the long duration of miltefosine administration (12 weeks), due to safety concerns. It selected new evidence in which one of the current standard-of-care regimens was compared with a new regimen for further assessment. Older studies with regimens of known high toxicity that would no longer be deemed acceptable were omitted.

- The summary of findings is based on one RCT of 100 PKDL patients in India (78).
- The GDG was concerned about ocular involvement as an adverse event after long-term administration of miltefosine (12 weeks), operational challenges of following up patients and a relative lack of eye specialists or trained optometrists.
- In view of the better ocular safety profile of LAmB, the GDG considered that its safety outweighed its slightly (non-statistically significant) lower cure rate than miltefosine. Miltefosine, which is associated with a higher rate of adverse events, including gastrointestinal and ocular effects, was therefore considered to be less suited for 12-week treatment than LAmB (5 mg/kg twice a week for 3 weeks up to a total dose of 30 mg/kg). Furthermore, problems of adherence can be expected with a 12-week regimen, especially if skin lesions start to improve before treatment is completed. Concern was also raised about the acceptability of contraception during and up to several months post-treatment with miltefosine in all settings and also about potential lack of awareness of the teratogenicity of miltefosine among health-care personnel.

Summary of data on efficacy and safety

LAmB rather than miltefosine might result in:

- little to no difference in clinical cure at the end of treatment (RR 1.00; 95% CI 0.96; 1.04; *low-certainty evidence*);
- a **lower cure rate** 12 months after the intervention (RR 0.86; 95% CI 0.70; 1.05; *low-certainty evidence*);
- an **increased risk of relapse** 12 months after the intervention (RR 1.96; 95% CI 0.80; 4.77; *very low-certainty evidence*);
- no difference in the risk of SAEs (No SAEs were reported in either group.); and
- an **increase in the risk of adverse events** (RR 1.46; 95% CI 1.11; 1.93; *low-certainty evidence*).

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Despite marginal differences in critical outcomes, the desirable effects were considered to moderately favour LAmB, in view of the long duration (12 weeks) of miltefosine, low adherence and its limited use in women of child-bearing potential, with mandatory use of contraception during and several months after treatment. Some GDG members noted that most of the side-effects of miltefosine occur within the first 4 weeks when it is taken at home and that the reported frequency of side-effects may therefore be inaccurate. Particular concern was expressed about the ocular side-effects that may result from a longer regimen (12 weeks) of miltefosine.

The GDG discussed the risk of SAEs due to a longer regimen of miltefosine and to high cumulative doses of LAmB, particularly severe hypokalemia (87,88). The GDG noted that hypokalemia is a predictable adverse effect of LAmB. The symptoms and signs of hypokalemia are readily recognized, confirmed by serum potassium testing, and can generally be prevented and managed through appropriate monitoring, a potassium-rich diet, and potassium supplementation. In contrast, ocular adverse events associated with miltefosine are unpredictable, sometimes irreversible and more difficult to detect particularly when miltefosine is administered at home. Furthermore, some symptoms are irreversible or have sequelae, *e.g.* uveitis. Further advice is provided in section 5.1 on implement considerations.

Contextual factors – stakeholders' views

- LAmB is probably more acceptable than miltefosine because of difficulty in compliance to 12 weeks of miltefosine treatment and the risk of ocular adverse events. Although LAmB can be stored at ambient temperature (<25 °C), temperature excursions may occur in field use in hot climates. Miltefosine is an oral drug that has fewer storage requirements; however, administration requires direct observation.
- There was a negligible difference in resource use.
- The requirements for screening for pregnancy and contraception in the case of miltefosine may reduce gender equity.

Resources required

- No studies on **cost-effectiveness** were available.
- No formal costing studies were available for either treatment regimen. The resources required for **LAmB** were estimated to be moderately higher than those required for miltefosine, mainly due to the high direct cost of the drug and the resources required for hospitalization for 3 weeks. Even if hospital and transport expenses are provided for free as an incentive, the total costs of hospitalization for patients are still often high. The GDG took into account the fact that WHO will donate AmBisome® up to 2025, reducing the procurement cost to virtually nil (79). The GDG also considered potential continuation of the AmBisome® donation in view of the success of VL elimination programmes and the commitment of the pharmaceutical industry to the Kigali Declaration² (80).
- For **miltefosine**, the resources considered included those for ocular monitoring and for pregnancy testing and contraception for several months.

2 At the time of publishing this guideline, the AmBisome donation programme was extended up to 2030

Equity

- Use of miltefosine may disadvantage women of childbearing potential due to its teratogenic risks, low awareness among health-care workers and the requirement for reliable contraception.
- Children may face disproportionate risks of ocular side-effects, as timely monitoring is more difficult for this group.
- Severely malnourished or impoverished patients may experience more gastrointestinal side-effects, which may reduce their compliance with therapy and increase the risk of treatment discontinuation.
- A potential future shortage of LAmB could create inequity.

Acceptability

- LAmB administration may be less acceptable to patients because of the requirements for hospitalization and monitoring, which may also decrease its acceptability by health workers.
- A 12-week miltefosine regimen is poorly acceptable for PKDL, which is non-fatal and because lesions often improve before completion of therapy, often resulting in discontinuation.
- The prolonged contraception requirement (8 months) for miltefosine may reduce its acceptability, particularly for women and their families.

Feasibility

- Hospital administration and monitoring requirements for LAmB limit the feasibility of its administration, especially in decentralized settings.
- Ensuring adherence to a 12-week miltefosine regimen is challenging, as patients may stop treatment once their lesions improve.
- Routine ocular monitoring with miltefosine, especially in children, is difficult, as children may not selfreport early ocular adverse events.

Key research gaps:

- The report of the source study did not include all-cause mortality, treatment adherence, withdrawals from treatment, workload of health-care staff or patient satisfaction.
- Comorbidity: Seropositivity for HIV, hepatitis B and C, tuberculosis, any malignancy and any other infectious diseases were not included in the source study.
- Pregnant and lactating women were excluded from the source study.
- No information on patients' perspectives of either treatment regimen was available at the time of formulation of the recommendation.

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4.4.2 A combination of LAmB (total dose, 20 mg/kg administered IV on days 1, 4, 8, 11 and 15) plus miltefosine (allometric oral dose BID for 21 days) or LAmB monotherapy (total dose, 20 mg/kg administered IV on days 1, 4, 8, 11 and 15) is suggested for treatment of PKDL.

Conditional recommendation, **very low-certainty** evidence

Summary of evidence

- The recommendation is based on one RCT with 126 PKDL patients in India (81).
- Addition of miltefosine to treatment did not appear to increase the clinical cure rate significantly but resulted in more adverse events, including potentially irreversible ocular toxicity in the absence of monitoring. The acceptability of contraception can be a concern with use of miltefosine in some settings, as is the limited awareness of clinicians of the requirement for contraception during and until 5 months post-miltefosine in some settings.
- Overall, the certainty of the evidence was too low for a recommendation to be formulated for either regimen.

Key findings

The combination of LAmB plus miltefosine compared with LAmB alone may result in:

- no difference in all-cause mortality at 12 months (RR 3.00; 95% CI 0.12; 72.27; *low-certainty evidence*) and at 24 months (RR 0.94; 95% CI 0.82; 1.08; *low-certainty evidence*);
- little or no difference in the clinical cure rate at 12 months (RR 1.06; 95% CI 0.61; 1.81; *low-certainty evidence*);
- an **increase in the cure rate** at 24 months (RR 1.15; 95% CI 0.85; 1.55; *low-certainty evidence*);
- a **reduction in the risk of relapse** at 24 months (RR 0.20; 95% CI 0.02; 1.76; *very low-certainty evidence*);
- little or no difference in the occurrence of SAEs at 12 months (RR 3.00; 95% CI 0.12; 72.27) (*low-certainty evidence*) [The authors concluded that any SAEs were not related to the study drug.];
- an **increased risk of adverse events** at 12 months (RR 2.72; 95% CI 1.80; 4.11) (*low-certainty evidence*) [More patients in the group receiving miltefosine reported gastrointestinal disorders, vomiting and nausea. No ocular events were reported in either group.]; and
- **higher withdrawal rates** at 12 months (RR 3.00; 95% CI 0.63; 14.30) and 24 months (RR 1.60; 95% CI 0.55; 4.62) (*low-certainty evidence*).

Contextual factors – stakeholders' views

- Screening for pregnancy and contraception required for miltefosine administration might reduce gender equity.
- Compliance with the difficulties of miltefosine treatment could reduce its acceptability.

Resources required

- No studies on **cost-effectiveness** were available.
- No formal costing studies were available for either treatment regimen. LAmB for 2 weeks would be required in both treatment regimens. Addition of miltefosine for 3 weeks to the treatment regimen would not greatly increase the direct cost of the drugs. Any additional resources required by adding miltefosine would mainly be the costs for contraception, pregnancy testing and ocular monitoring. Overall, the difference in resources required for the two treatment regimens was considered to be negligible.

Equity

- Addition of **miltefosine** to treatment could compromise equity in certain settings, depending on the availability and acceptability by patients and their families of contraception. In addition, the poor awareness by health-care workers about the teratogenic potential of miltefosine could put women of childbearing potential at a disadvantage. Children might also be at proportionally higher risk of ocular side-effects with miltefosine, as monitoring might be more difficult in this subgroup. Severely malnourished or impoverished patients could disproportionately suffer from gastrointestinal side-effects of miltefosine if no food is available to accompany miltefosine intake.

Acceptability

- Concern about the acceptability of **LAmB** includes potentially poor acceptability of hospitalization. In addition, the monitoring required during LAmB administration might not be acceptable for all health-care workers. These concerns would, however, apply to the same extent in the two treatment options.
- **Miltefosine** might have limited acceptability in some settings, mainly because of the requirement for contraception during and up to 5 months after treatment. The acceptability and use of contraception differ notably in Bangladesh, India and Nepal. The rate of contraceptive use among married women of reproductive age in 2022 was about 62% in Bangladesh, 58% in India and 50% in Nepal (82).

Feasibility

- Ocular monitoring and early detection of ocular adverse events might be difficult in some settings, especially in children, who are less likely to report ocular issues.

Implementation considerations

Serum potassium levels should be monitored for all patients on high-dose LAmB regimens. For full details, see section 5.1 on implementation considerations

Key research gaps

- Neither the workload of health-care staff nor patient satisfaction was reported.
- Comorbidity: The study did not report on patients with severe disease, haemoglobin < 5 g/dL, other skin diseases, abnormal liver function tests, history of allergy or hypersensitivity to the study drugs, a positive HIV test or being on immunomodulator therapy.
- No children under the age of 7 years were included in the study.
- No data were provided on the availability and acceptability of contraception in the region.
- No information was provided on the awareness of health-care workers about the teratogenic effects of miltefosine administration.
- Accurate estimates of the risk of ocular events with miltefosine for 21 days were not available.

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4.4.3 A combination of LAmB (total of 15 mg/kg administered IV on days 1, 8 and 15) plus miltefosine (100 mg/day orally after the first dose of LAmB and continued daily until the end of 45 days) is suggested rather than miltefosine monotherapy (100 mg/day orally for 90 days)

Conditional recommendation, **very low-certainty evidence**

Rationale

- The recommendation was based on findings from one prospective cohort study of 32 people with PKDL (83).
- Combination therapy with LAmB plus miltefosine did not appear to result in a higher cure rate or more adverse events, although the certainty of the evidence is very low.
- The toxicity profile of miltefosine monotherapy for 90 days was found to be unacceptable for treatment of a non-fatal disease such as PKDL.

Key findings

The combination of LAmB and miltefosine as compared with miltefosine monotherapy might result in:

- little to no difference in clinical cure at 1 month after treatment (RR 1.00; 95% CI 0.89; 1.12; *very low-certainty evidence*);
- a **higher cure rate** at 18 months (RR 1.32; 95% CI 0.98 to 1.78; *very low-certainty evidence*);
- little to no difference in the risk of relapse at 6 months (RR 0.33; 95% CI 0.01 to 7.62; *very low-certainty evidence*);
- a **reduced risk of relapse** at 18 months (RR 0.11; 95% CI 0.01 to 1.91; *very low-certainty evidence*);
- little or no difference in the risk of SAEs at 90 days (No events were reported in either group.); *very low-certainty evidence*; and
- little or no difference in withdrawal from treatment at 90 days (No patients withdrew from either group.); *very low-certainty evidence*.

None of the patients in either group reported SAEs or withdrew from treatment.

Contextual factors – Stakeholders' views

- In general, patients prefer oral medication to injections. Further, the side-effects of LAmB are of less concern than those of miltefosine.
- More importantly, PKDL patients may have only a cosmetic problem; hence, compliance with hospitalization to receive medication may be poor. Therefore, oral medication only (miltefosine monotherapy) may be more feasible than the combination regimen.
- The cost of the combination regimen is higher, as it requires hospitalization and a greater burden on the patient and the caregiver. As LAmB is administered only on days 1, 8 and 15, in theory, patients could return for each infusion, although this would increase movement of patients.
- Miltefosine monotherapy enhances accessibility, especially for individuals living in rural areas.

Resources required

- No studies on **cost-effectiveness** were available.
- No formal costing studies were available for either treatment regimen. The direct cost of drug purchase is much higher for **LAmB** than for miltefosine; the combination therapy (LAmB plus miltefosine) is therefore substantially more expensive. Resources for hospitalization for 2 weeks should also be taken into account.
- The duration of therapy with **miltefosine** is shorter than that for the combination regimen (45 versus 90 days in the monotherapy regimen). This would probably not, however, result in a large difference in the resources required for contraception or ocular monitoring.
- The overall resources required for combination therapy are therefore assumed to be moderately higher for the combination therapy (LAmB plus miltefosine) than for monotherapy (miltefosine).

Equity

- Use of **miltefosine** could compromise equity, depending on the availability and acceptability of pregnancy testing and contraception. Although the duration of miltefosine monotherapy is twice as long as for combination therapy, both regimens would require three injections of contraception to cover duration of therapy and the full 5-month post-treatment period.
- Severely malnourished patients could disproportionately suffer gastrointestinal side-effects of miltefosine if no food is available to accompany miltefosine intake, particularly in the longer miltefosine monotherapy treatment regimen.

Acceptability

- Concerns about the acceptability of use of **LAmB** include a potentially low acceptability of hospitalization. In addition, the monitoring required during LAmB administration might not be acceptable to all health-care workers.
- The toxicity of **miltefosine** for 90 days would not be acceptable from a clinical or a patient perspective, particularly as PKDL is a non-fatal disease. As PKDL lesions can be expected to improve before the end of treatment, patients might find it unacceptable to continue treatment for several weeks longer, particularly with the longer (miltefosine monotherapy) regimen. No data were available, however, to support this statement.

Feasibility

- Administration of **LAmB** and the required monitoring can be challenging in some settings.
- Adherence to a long oral regimen of **miltefosine** at home might be difficult, as patients might be inclined to stop treatment once their skin lesions start to improve after a few weeks of treatment. This can be expected to be more problematic with monotherapy (90 days miltefosine) than with the combination regimen (45 days miltefosine). The feasibility of ocular monitoring and early detection of ocular adverse events might be challenging in some settings, particularly with the longer regimen and especially in children, who are less likely to report any ocular issues.

Key research gaps:

- Patients seropositive for HIV, hepatitis B or C or tuberculosis or with any other serious ailment and pregnant and lactating women were excluded from the study.
- The study did not report treatment adherence, the workload of health-care staff or patient satisfaction.
- No children <9 years were included in the study.
- Accurate estimates of the risk of ocular events were not available for miltefosine for 45 days versus 90 days.



5

Antileishmanial medicines and implementation considerations

NAVIGATION

- | | |
|-----|--|
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| 5.2 | Access to quality-assured medicines |
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5.1 Implementation considerations

The GDG recognized several factors that might influence successful implementation of its recommendations.

Lipid formulations of AmB

Amphotericin is a polyene antibiotic. Several lipid-based formulations such as LAmB, AmB lipid complex and AmB colloidal dispersion have been used in treatment; however, most clinical trials have been conducted with a reference LAmB formulation. All other lipid formulations should be evaluated first for their toxicity, bioequivalence and efficacy before they are used clinically.

These formulations are given by IV infusion over 2 h. Mild infusion reactions (fever, chills and rigour) are the most frequent side-effects; less frequent effects are chest tightness, chest pain, breathlessness, flushing, tachycardia, low blood pressure and musculoskeletal pain (described as joint, back or bone pain). These side-effects typically resolve when the infusion is stopped and may not occur during future infusions or at a slower rate. Other common side-effects include hypokalaemia, leading to tiredness, confusion, muscle weakness or cramps. Transient nephrotoxicity or thrombocytopenia is also seen occasionally.

Safety of LAmB at higher doses for PKDL

Limited published data are available on the safety and efficacy of LAmB given at high total cumulative doses (50–90 mg/kg) for treatment of PKDL. Those available were for small patient cohorts in East Africa (84,85). A LAmB regimen at a total cumulative dose of 30 mg/kg divided into six doses of 5 mg/kg was given over 3 weeks on an ambulatory basis in Bangladesh. The doses and frequency were chosen to minimize the impact on patients' daily lives. LAmB is known to be safe treatment for VL at similar doses (86). A total of 1292 PKDL patients were treated in Bangladesh at this dose (87), among whom one presumed and six confirmed cases of rhabdomyolysis, a rare adverse event, occurred. Retrospective analysis of data on all 1292 patients revealed another 19 possible cases of rhabdomyolysis. Most (21) of the cases occurred in women under the age of 26 years. A causal link to LAmB was considered probable in 23 and possible in 3 of the 26 patients (88). A dose–relation was considered. PKDL treatment was resumed with a potassium monitoring and supplementation protocol for the remainder of the study. No case of rhabdomyolysis was reported after potassium monitoring and supplementation and administration of potassium-rich food.³

Another 265 PKDL patients were treated by MSF with LAmB at 30 mg/kg (5 mg/kg, twice a week for 3 weeks) in Bangladesh and India, with potassium monitoring and supplementation for all patients. No cases of rhabdomyolysis occurred. Severe hypokalaemia (defined as serum potassium ≤ 2.5 mmol/L) was seen in 6.5% of patients in Bangladesh and 0.6% of patients in India. In another prospective cohort study with LAmB at 15 mg/kg (five doses of 3 mg/kg over 15 days) for PKDL in Bangladesh, no rhabdomyolysis and no severe hypokalaemia (< 2.5 mmol/L) were observed.³

Physicians should be aware of the signs and symptoms of hypokalemia (nausea, vomiting, weakness, muscle pain and anorexia) and should explain the benefits and risks of this therapy to patients before administering this dose.

A high-dose LAmB regimen should be provided in hospitals where blood potassium levels and other haematological and biochemical profiles can be monitored, at baseline, during treatment and up to 2–4 weeks after treatment. Patients should be given potassium-rich food such as bananas, oranges, tomatoes, beans, spinach, baked potatoes, sweet potatoes, peas and cucumbers and potassium supplementation. If hypomagnesaemia is also observed, both supplements are given.

3 MSF, personal communication, December 2024.

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Miltefosine

Miltefosine is an alkyl phospholipid (hexadecylphosphocholine), which was originally developed as an oral anticancer drug but was shown to have antileishmanial activity. Miltefosine commonly causes gastrointestinal side-effects such as nausea, vomiting, diarrhoea, abdominal discomfort and decreased appetite. Patients also report systemic complaints such as headache, dizziness, fatigue and malaise. Most episodes occur early in the course of treatment, are brief and then lessen in intensity and resolve as treatment is continued. Elevated liver enzyme levels and changes in renal function can occur, which are typically mild but require monitoring. Dermatological reactions such as rash and pruritus have been observed, and some males have reported testicular pain. Rare but serious reactions include hypersensitivity and ocular toxicity with visual disturbance, which require immediate evaluation.

Early-onset gastrointestinal symptoms are an important cause of poor adherence, dehydration and weight loss if not managed properly. Practical measures for minimizing gastrointestinal side-effects include taking the medicine with food, if tolerated, and in divided doses if several doses are to be taken. When feasible, directly observed treatment improves adherence. In areas of food insecurity, provision of food for unsupervised doses is advised. In a subset of patients, symptoms can persist or recur intermittently throughout the full course of treatment. In such instances, clinical evaluation, symptomatic management or temporary interruption of therapy, supportive care or alternative regimens are recommended.

Miltefosine is potentially embryotoxic and teratogenic and should not be used during pregnancy. It is slowly eliminated, with detectable plasma levels for weeks after treatment ends. Simulation studies have shown that plasma concentrations may remain above the safety threshold for reproductive toxicity for up to 5 months after 28 days treatment in some patients. Women of child-bearing potential should be tested for pregnancy before initiation of treatment and use adequate contraception during and after treatment. A pharmacokinetics modelling study showed that, for the standard 28-day miltefosine regimen, post-treatment contraceptive coverage of at least 5 months after the last dose of miltefosine should be recommended. For shorter regimens (e.g. 5, 7 or 10 days), at least 2 months of contraceptive coverage is considered adequate (67). Use of long-acting reversible contraceptive methods or depot preparations may provide more reliable coverage than barrier or short-course oral methods because they improve adherence and avoid drug-related vomiting. Vomiting or diarrhoea during miltefosine therapy may reduce the absorption of oral contraceptives, potentially compromising their effectiveness. In such cases also, women should be advised to use an additional, non-oral method of contraception.

The tolerability of miltefosine in malnourished patients was reported as acceptable in HIV-co-infected VL patients in Ethiopia; ⁴ however, no data are available on severely malnourished children. Such patients should be admitted and provided with food before miltefosine administration, under direct supervision.

The frequency of ocular adverse events remains unknown, even with the short miltefosine regimen. Routine pre-treatment eye examinations and post-treatment follow-up should be conducted as part of active surveillance and risk minimization measures (see Annex 1).

The pharmacokinetics of miltefosine differs significantly in adults and in children. Children, especially those weighing <30 kg, achieve lower plasma concentrations than adults at the same mg/kg dose (89). Such underexposure is correlated with higher rates of relapse and treatment failure in paediatric VL

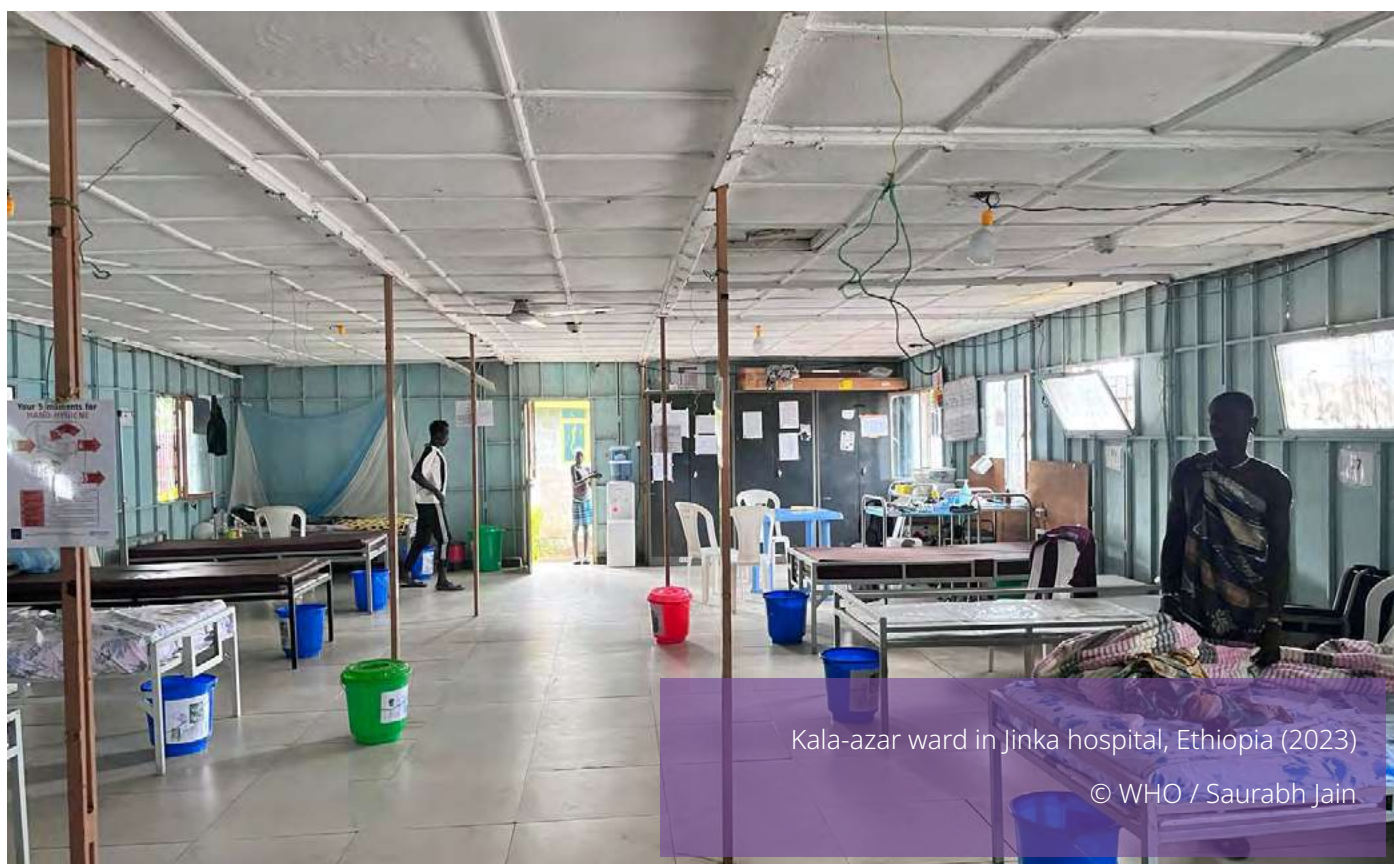
patients (90). Allometric miltefosine dosing achieves similar steady-state concentrations in children and adults, reducing the risk of under-treatment. Simplified allometric weight band-based dosing for patients weighing <30 kg is expected to be effective and safe, as exposure to the drug is weight- rather than age-dependent (see Annex 2).

Pentavalent antimonials

An SSG injection may be given IM or IV, either by infusion (over 5–10 min) or by slow injection through a fine needle (23–25 gauge; 0.6–0.5 mm) to avoid a risk of subsequent thrombosis. The quality of pentavalent antimonials, like other medicines, should be assured, as substandard medicines can cause severe toxicity and death. Patients should be monitored by serum chemistry, complete blood counts and electrocardiography. Electrocardiographic changes depend on the dose and duration of treatment, the commonest being T-wave inversion, a prolonged Q–T interval and arrhythmia. Cardiotoxicity and sudden death are serious but uncommon side-effects. Prolongation of a corrected Q–T interval (>0.5 s) signals the likely onset of serious and fatal cardiac arrhythmia. Pancreatic enzyme concentrations are commonly raised, but clinical pancreatitis is uncommon. If serious side-effects arise (in most cases hepato- or cardiotoxicity), the drug should be changed (1).

Paramomycin

Paramomycin (aminosidine) is an aminoglycoside antibiotic. It is usually administered IM. The 15 mg/kg sulfate is equivalent to 11 mg/kg of base, and the 20 mg/kg sulfate is equivalent to 15 mg/kg of base. Mild pain at the injection site is the commonest adverse event (55%). Reversible ototoxicity occurs in 2% of patients. Renal toxicity is rare. Some patients may develop hepatotoxicity, indicated by raised hepatic enzyme concentrations; tetany has also been reported. A topical formulation is also recommended for cutaneous leishmaniasis (1).



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5.2 Access to quality-assured medicines

Diagnostics and medicines for VL must be continuously available, affordable and accessible to health systems and to all patients. A functioning supply chain is essential, and all the factors that influence it must be managed (91). Manufacturing capacity determines availability, as most leishmanial medicines are produced by only one or a few producers. Problems of quality, low production capacity and lack of an adequate global forecast regularly result in stock ruptures in endemic countries. Cessation of production is a threat if the supplier base is not expanded, given the small market and the decreasing global caseload. Forecasting and quantification of the necessary supplies are based mainly on previous consumption; however, the VL case load can vary considerably from year to year due to inconsistent surveillance, outbreaks or fluctuation due to climatic conditions.

For manufacturers, the long lead time means that they must complete a full batch production line (minimal order requirement), and national programmes and clinicians might have difficulty in obtaining small quantities of the medicines ad hoc. Suboptimal stock planning and management or complex procurement procedures also result in shortages at health facilities. Supply chains are further strained by lack of registration and importation requirements in endemic countries. Functional drug forecasting and adequate monitoring systems for supply chains and logistics are essential at national level to ensure an uninterrupted drug supply and to minimize delays in importing medicines. The same challenges apply to the supply of diagnostic tools, as the market is relatively small and not profitable. Moreover, diagnostic kits of uncertified quality circulate in endemic regions. Even when medicines to treat VL are available, drugs for the management of cutaneous and mucocutaneous forms of the disease, which might also be present in immunocompromised patients and in high-burden countries, are generally not readily available.

Affordability is another crucial issue. The price of these relatively expensive medicines has fallen due to negotiations by WHO and other partners; however, there is no drug donation programme for leishmaniasis, except for LAmB (AmBisome®) from Gilead Sciences for certain low- and middle-income high-VL burden countries in eastern Africa and South-East Asia (80).

After procurement has been negotiated, medicines may still not be registered in the countries in which they are to be used. If medicines are not registered, special permission for their import is required. Registration is often lacking in countries with very few cases, and medical practitioners in those countries experience great difficulty in obtaining the small quantities of medicines they require.

Access to good-quality antileishmanial medicines has improved in the past decade. WHO supports the establishment of an emergency rotating buffer stock to mitigate shortages and promotes pooled procurement through regional approaches. Although all VL medicines are on the WHO Model List of Essential Medicines (92), only a few are either prequalified by WHO or approved by a stringent regulatory authority. Still, manufacturers should engage in procedures to ease procurement in the future (e.g. proper registration, request for pre-qualification), and purchasers could join forces to require that manufacturers exercise stringent quality assurance (i.e. the WHO Prequalification Programme). The cost of registration is an additional disincentive in many countries. In 2021, a generic LAmB was registered by a stringent regulatory authority (93), and a generic miltefosine has been prequalified (94,95). Overall monitoring of access to antileishmanial medicines must be strengthened, with pricing, registration and global needs.

5.3 Pharmacovigilance

Pharmacovigilance systems are usually designed to monitor side-effects, adverse reactions and drug interactions; however, their scope should be broadened to address the growing problem of substandard and counterfeit medicines and to monitor the development of drug resistance. Substandard medicines have led to avoidable deaths and iatrogenic side-effects. Routine monitoring of resistance should be included in the early stages of research and development (96).

A distinction must be made between adverse events and adverse drug reactions when determining the severity of adverse events and their relation to exposure to a product. Once an adverse event has been detected, its maximum severity should be established and graded according to international standards. It should be determined whether the event was caused by the product or by other medicines administered concomitantly or was due to another illness. SAEs should be investigated immediately and reported rapidly. Quality assurance and regulatory mechanisms are critically important.

Pharmacovigilance systems in VL-endemic countries should be improved, with a multi-disease approach. Issues of toxicity, adherence, treatment response and resistance have affected treatment programmes, and programmes for reporting these events should be strengthened. Multidisciplinary national pharmacovigilance centres should be established and their capacity strengthened for regular analysis of data on safety to identify and review signals, generate hypotheses and ensure regular reporting and feedback. Pharmaco-epidemiological methods should include post-licensing clinical trials to assess the effectiveness and safety of medicines, case-control studies and active population-based evaluation of marketed products authorized for use.

The current WHO Drug Monitoring System has an extensive network, with 170 member countries. All countries should establish a national pharmacovigilance centre to record reported adverse drug reactions in order for them to be included in Vigibase, the WHO global database of individual case safety reports. Vigibase has been used to monitor antileishmanial medicines for adverse drug reactions, including those with serious outcomes.

5.4 Follow-up of patients and indicators for monitoring and evaluation

Follow-up of VL patients is an important aspect of patient management, as the treatment outcome (cure, relapse or death) is related to the control and elimination of the disease. Additionally, in South-East Asia, VL cases are to be followed up to 3 years to identify the occurrence of PKDL (17).

PKDL cases in eastern Africa and South-East Asia manifest distinctly. The primary end-point of definitive cure in eastern Africa was considered as 100% resolution of lesions in grade III patients at 12 months' follow-up, while the primary efficacy end-point in South-East Asia was definitive cure at 12 months, defined as complete resolution of papular and nodular lesions and >80% re-pigmentation of macular lesions. The remaining patients, particularly those with macular lesions, can be followed up to 24 months.

The main objectives of monitoring and evaluating a leishmaniasis control programme are to:

- collect, process, analyse and report or disseminate information relevant to leishmaniasis;
- verify that activities have been implemented as planned to ensure accountability and address problems in a timely manner;
- provide feedback to the relevant authorities to improve future planning; and
- document whether the planned strategies have achieved the expected outcomes.

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Monitoring involves routine tracking of programme performance by record-keeping, reporting, surveillance and periodic surveys. The objectives are to verify progress or the status of implementation, ensure accountability, detect problems and constraints, promote evidence-based planning and provide timely feedback so that adjustments can be made as necessary. Monitoring indicators include input, process, output and outcome indicators, which can be derived from annual programme reports (Table 6).

Evaluation consists of periodic assessment of changes in targeted outcomes or results that can be attributed to a programme. The objectives are to assess the impact and effectiveness of a control intervention after a certain time. A monitoring and evaluation framework can provide reliable information at local, national or international level.

Table 6. Indicators for monitoring VL and PKDL

Type of indicator	Recommended indicators
Input	National guidelines adopted
Process	Human resources, training, supplies and commodities
Output	Number or proportion of health facilities in endemic districts providing treatment for VL and PKDL Number of VL and PKDL cases detected disaggregated by age and sex Pregnancy status of the patient and pregnancy outcome (pregnancy register for females of childbearing potential on the miltefosine regimen) Number of VL and PKDL cases treated Numbers of confirmed VL relapse cases within 6 months and beyond
Outcome	Proportion of early diagnosis of all detected cases Proportion of VL and PKDL cases cured: initial and final cure rates Case fatality rate
Impact	Morbidity attributed to VL Mortality attributed to VL

Surveillance should be strengthened to determine and record cause-specific mortality as well as overall mortality due to VL. The Neglected tropical diseases road map 2021–2030 (17) has set an ambitious target of global elimination of VL as a public health problem (defined as < 1% case fatality rate due to primary VL) and PKDL targets for South-East Asia by 2030. Additionally, the strategic framework for VL elimination in eastern Africa (3,18) includes targets to be achieved by 2030, which should stimulate national programmes to strengthen leishmaniasis surveillance.

5.5 Prevention of antimicrobial resistance

Factors that encourage the development of drug resistance include use of less effective regimens, inadequate dose or duration of treatment, irregular treatment, use of substandard medicines, poor surveillance of treatment outcomes, lack of biomarkers for parasite resistance and lack of national plans for surveillance of drug resistance.

In a study in South-East Asia of the factors that contribute to low efficacy of antimonials for treatment of VL in HIV-negative patients, 73% of 312 patients consulted a local healer, and only 27% went to a qualified medical practitioner (97). Furthermore, 58% took regular treatment and 42% irregular treatment, with almost 50% of patients taking incomplete treatment, such that only 26% of patients had received an adequate dose and duration of treatment. This was considered to have played an important role in the development of resistance to antimonials.

Although multidrug therapy has the potential advantage of reducing the probability of selection of drug-resistant parasites, thereby prolonging the life of available medicines, observation of decreasing cure rates could be the first sign of the development of drug resistance. WHO recommends counselling and follow-up of all VL and PKDL cases and routine monitoring of cure rates. WHO will regularly evaluate treatment efficacy and clinical outcomes to monitor potential drug resistance, as appropriate. Laboratory surveillance for drug resistance should be integrated into national plans for antimicrobial resistance rather than in a vertical approach. In addition, monitoring of access to quality-assured leishmanial medicines should be strengthened, with pricing, registration, drug policies and quality assurance at all levels. Uncontrolled access to medicines (e.g. over the counter) could lead to misuse, suboptimal treatment and, in the long term, drug resistance.

5.6 National guidelines

National leishmaniasis control programmes should include recommendations on VL and PKDL in relevant policy and guidance. Consultations with stakeholders, including patients and communities, will increase uptake and dissemination of guidelines. Every measure should be taken to extend access to treatment and services for VL and PKDL patients. Delays in diagnosis and lack of proper management (e.g. timely treatment of VL episodes, detection and management of other opportunistic infections, nutritional support, correction of anaemia) compound the poor outcomes of these patients. Secondary and tertiary health-care facilities should be equipped with the necessary diagnostics and essential medicines and build adequate human resource capacity for managing such patients. VL management requires a comprehensive, multi-level approach among national programmes and joint guidelines with skin NTDs for PKDL management.

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5.7 Coordination among programmes for control of leishmaniasis, for NTDs, leprosy and vector-borne diseases and national antimicrobial resistance policies

Whenever possible, synergy and coordination should be established among programmes for leishmaniasis, NTDs and vector-borne disease control in countries and areas where these conditions overlap. Coordination and synergy are vital to tackle VL. Efficient links and integrated programme management should be established at all levels.

The aim of optimal management of VL and PKDL is not only to cure VL and PKDL but also to reduce transmission. Access to diagnosis and treatment remains a challenge in many under-resourced VL-endemic countries. Few health facilities offer full services for diagnosis and management of VL and nutritional, blood transfusion and other necessary services, and patients are often referred to specialized centres.

Suggested areas for coordination are screening strategies in high-prevalence areas, increasing awareness and clinical suspicion of VL and PKDL by health-care workers, follow-up of patients, social benefits or incentives for VL relapse patients, PKDL cross-reporting with leprosy programmes, identification of bottlenecks in integration of VL and PKDL with other programmes and addressing them as required.

As VL and PKDL patients act as reservoirs of infection, use of insecticide-treated bednets and other personal protection by VL or PKDL cases and close contacts could decrease the likelihood that sandflies will feed on infected individuals. Other vector control methods should be implemented as per national protocols through integrated vector management, whenever applicable.



Pain is
the fifth
vital sign

5

Kala-azar treatment ward in Fik Hospital, Ethiopia (2024)

© WHO / Saurabh Jain



Development of these guidelines was based on systematic review of the available evidence on the treatment of VL and PKDL. For most of the guidelines, however, the available evidence was limited to single clinical trials, trials with small samples or observational studies with heterogeneous interventions and end-points. Thus, the recommendations are based on low-certainty evidence or, in some cases, on expert opinion.

In view of the challenges of conducting good-quality clinical research in the settings in which VL and PKDL typically occur and the time required for elimination programmes, research focused on essential case management would provide more conclusive evidence for stronger recommendations. Studies should therefore (i) reflect comparable dosing and methods to assess the effects of treatment of both VL and PKDL, (ii) reflect as closely as possible the spectrum of cases seen in routine practice and (iii) have similar end-points. These could be achieved by conducting well-conducted, simple, randomized, pragmatic trials of existing therapeutic options. Sharing of data for the conduct of individual case meta-analyses would also be valuable. Useful supporting information can be derived from pharmacovigilance, observational studies, case-control studies and case series reports. Importantly, operational research on programme data to generate evidence for better patient care is encouraged.

Given the limited number of treatments for VL and PKDL, development of new drugs, further optimization of current dosing regimens for special populations, such as pregnant women, people with severe malnutrition and young children, and studies on immunology and vaccines are also encouraged.

Table 7 lists some directions to researchers and funders on research priorities.

Table 7. Research priorities and suggested approaches

Thematic area: VL and VL relapse	
Recommendations and observations	Research priorities and suggested approaches
<u>Eastern Africa</u> Recommended regimens for primary VL: ▫ paromomycin plus miltefosine versus SSG plus paromomycin versus SSG (limited clinical trials) ▫ Multidose LAmB for severely ill patients (observational studies)	▫ Develop a common strategic framework for treatment trials, and harmonize end-points: initial cure, definitive cure, relapse, death. ▫ Conduct pragmatic trials with randomization of patients to two or more interventions; consider adaptive trial designs.
<u>South-East Asia Region</u> Recommended regimen for VL relapse and treatment failure: limited data and studies; recommendations based on expert opinion	▫ Compare treatment outcomes of different regimens with harmonized methods in pragmatic trials, observational studies or programme data. ▫ Document case studies and case series for meta-analysis of treatment outcomes. ▫ A prospective cohort of VL patients should be followed up to identify relapses, and treatment outcomes of relapse should be systematically documented. ▫ Study the pharmacokinetics and pharmacodynamics of antileishmanial drugs to understand adequate dosing.

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Thematic area: PKDL

Recommendations and observations Research priorities and suggested approaches

Eastern Africa

PKDL treatment: paromomycin plus miltefosine versus LAmB plus miltefosine (single study)

- Harmonize PKDL diagnosis and severity grading.
- Harmonize treatment end-points.
- Conduct pragmatic treatment trials or, when not possible, observational studies.
- Conduct further clinical investigation of other, shortened combination regimens to determine optimal dose regimens.
- Explore the role of immune modulation therapy for VL to decrease the risk of PKDL.
- Identify immune changes and triggering factors for PKDL that could be targets for prevention or treatment of PKDL.

South-East Asia Region

PKDL treatment: LAmB versus miltefosine
LAmB plus miltefosine versus LAmB
LAmB plus miltefosine versus miltefosine
with various regimens, doses, schedules and end-points

- Currently, no regimen offers a good choice of treatment due to limitations in efficacy, safety and duration of treatment. Conduct a network meta-analysis of existing trials and individual patient data to derive the optimal dose of LAmB to obtain acceptable cure rates.
- Conduct pragmatic trials with harmonization of dose, schedules and end-points, or use programme data to identify better treatment options for PKDL.
- Conduct further clinical investigation of shortened combination regimens to determine optimal dose regimens.
- Explore the role of immune modulation therapy for VL to decrease the risk of PKDL.
- Identify immune changes and triggering factors for PKDL that could be targets for prevention or treatment of PKDL.
- Identify early markers as surrogate end-points associated with a therapeutic response and long-term cure.
- Determine the minimal duration of treatment required for each drug, both in combination and as monotherapy.

Thematic area: safety

Recommendations and observations Research priorities and suggested approaches

All clinical trials and routine clinical practice, particularly with newly recommended treatment regimens, should collect and report safety data.

- Strengthen the pharmacovigilance system to obtain more information on safety, especially for newly recommended regimens (e.g. use of miltefosine in children with malnutrition).
- Monitor and describe ophthalmic and fertility (in both sexes) complications of miltefosine and its outcomes in clinical studies and in clinical practice.

Thematic area: diagnosis and test-of-cure

Recommendations and observations Research priorities and suggested approaches

Standardize diagnosis of PKDL and VL relapse and test of cure.

- Harmonize the approach for PKDL diagnosis, severity grading and test of cure.
- Harmonize the approach for diagnosis of VL relapse (clinical vs parasitological) and outcome definitions.
- Achieve consensus on the definition of VL and PKDL cure (clinical, parasitological or immunological).
- Identify biomarkers for test of cure of VL, predicting and diagnosing VL relapse and PKDL.
- Investigate the role of (automated) imaging techniques in PKDL evaluation.

Thematic area: drug dosing

Recommendations and observations Research priorities and suggested approaches

Different drug doses and dosing schedules are used, complicating comparisons, meta-analyses and generalizability.

- Collect additional anthropometric data on relevant populations (children, malnourished people) to verify the appropriateness and applicability of miltefosine allometric dosing.
- Use modelling to simplify miltefosine allometric dosing schedules.
- Identify the optimal dose schedule for LAmB, and investigate harmonization of LAmB dose and schedule in VL, PKDL and VL relapse treatment.

Thematic area: special populations

Recommendations and observations Research priorities and suggested approaches

VL and PKDL in pregnant women, young children and the elderly

- Report treatment outcomes, pregnancy outcomes and effects on newborns.
- Establish pregnancy registries modelled on those for other diseases, such as HIV and malaria.
- Pool individual patient data (case studies or case series) for meta-analysis.
- Determine the appropriateness of current dosing regimens for pregnant women to ensure adequate drug exposure.
- Determine the appropriateness of current dosing regimens for young children and people with severe malnutrition to ensure adequate drug exposure.

VL and HIV

- Refer to the VL–HIV guidelines for suggested research priorities.

Asymptomatic VL infection

- Explore the role of primary prophylaxis or preventive therapy, particularly in anthroponotic transmission regions.

Thematic area: cost effectiveness

Recommendations and observations Research priorities and suggested approaches

Cost implications of different regimens in different regions

- Compare the programmatic costs of different VL and PKDL regimens.
- Conduct studies of the acceptability of different treatment regimens of VL and PKDL by patients and health-care providers.



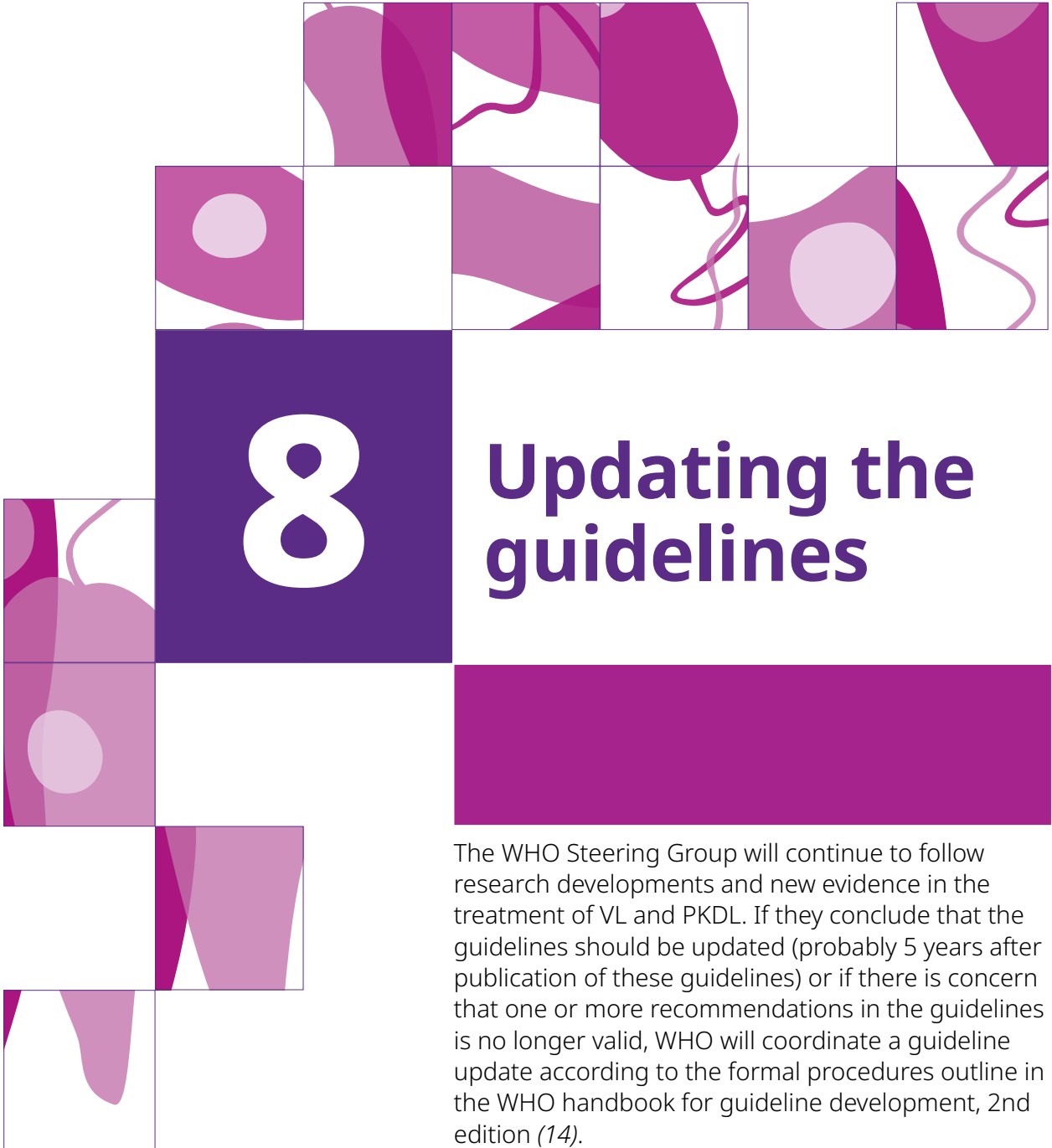
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Publication, dissemination and evaluation

These guidelines will be posted on the WHO website with links to related websites, social media and other platforms. In addition, they will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities and nongovernmental organizations. They will be translated into the official United Nations languages pertinent to VL and PKDL. It is expected that the reviews will be published in peer-reviewed journals.

Local adaptation of the guideline will be supported by WHO country offices and ministries of health. Additional tools will be developed to support country implementation. Inclusion of VL in national treatment protocols and field implementation will be monitored through existing support activities and at the annual WHO coordination meeting on VL.

Use of these guidelines will be evaluated to determine the extent to which the recommendations have been introduced into national policies and programmes. The results will be published annually in WHO reports, in updates on leishmaniasis surveillance published in the Weekly Epidemiological Record and in country profiles regularly published by WHO.

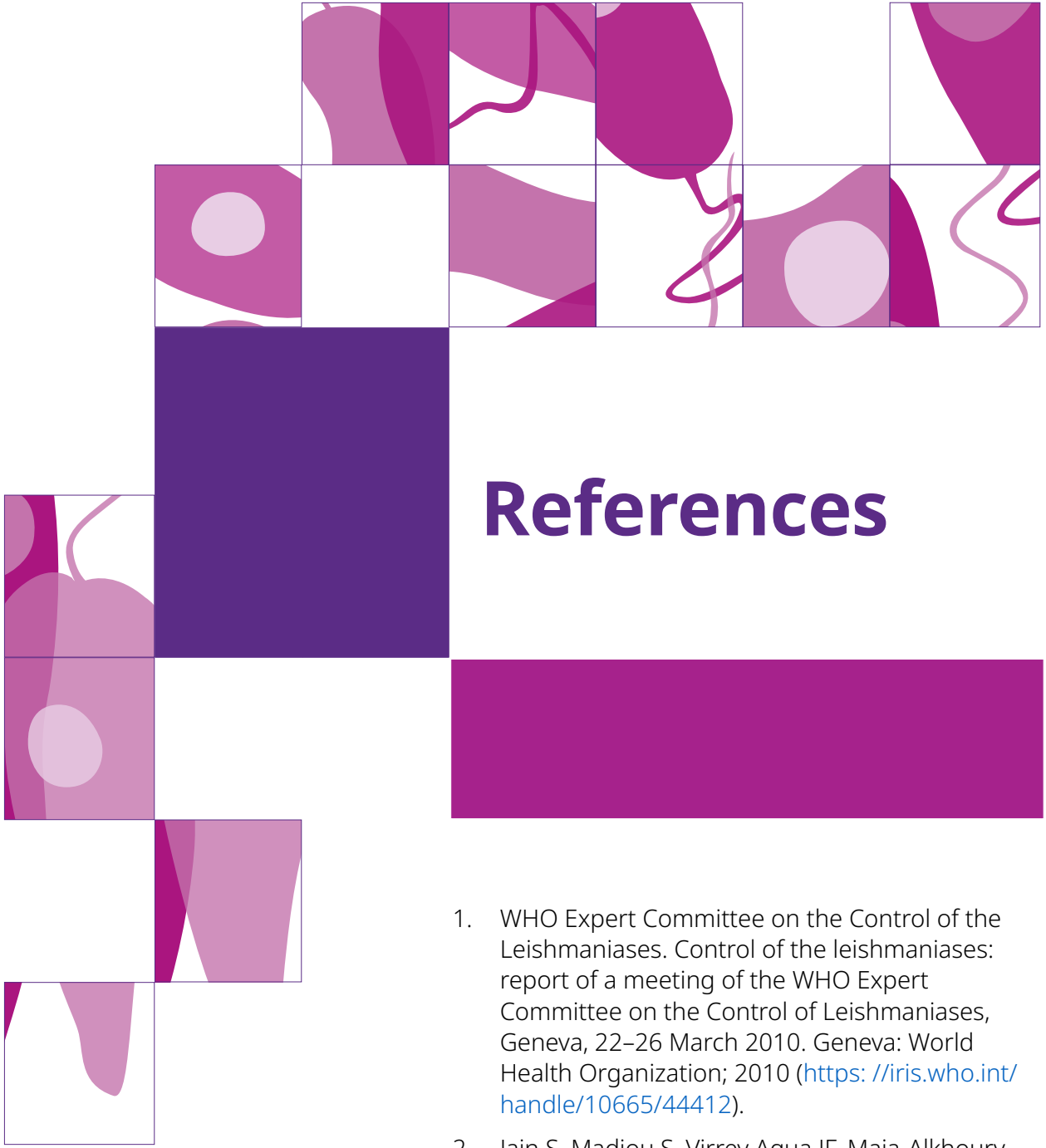


8

Updating the guidelines

The WHO Steering Group will continue to follow research developments and new evidence in the treatment of VL and PKDL. If they conclude that the guidelines should be updated (probably 5 years after publication of these guidelines) or if there is concern that one or more recommendations in the guidelines is no longer valid, WHO will coordinate a guideline update according to the formal procedures outline in the WHO handbook for guideline development, 2nd edition (14).

As the guidelines near a 5-year review period, WHO, with partners, will be responsible for conducting a search for new evidence. WHO will welcome suggestions for additional questions for evaluation in the guideline when it is due for review.



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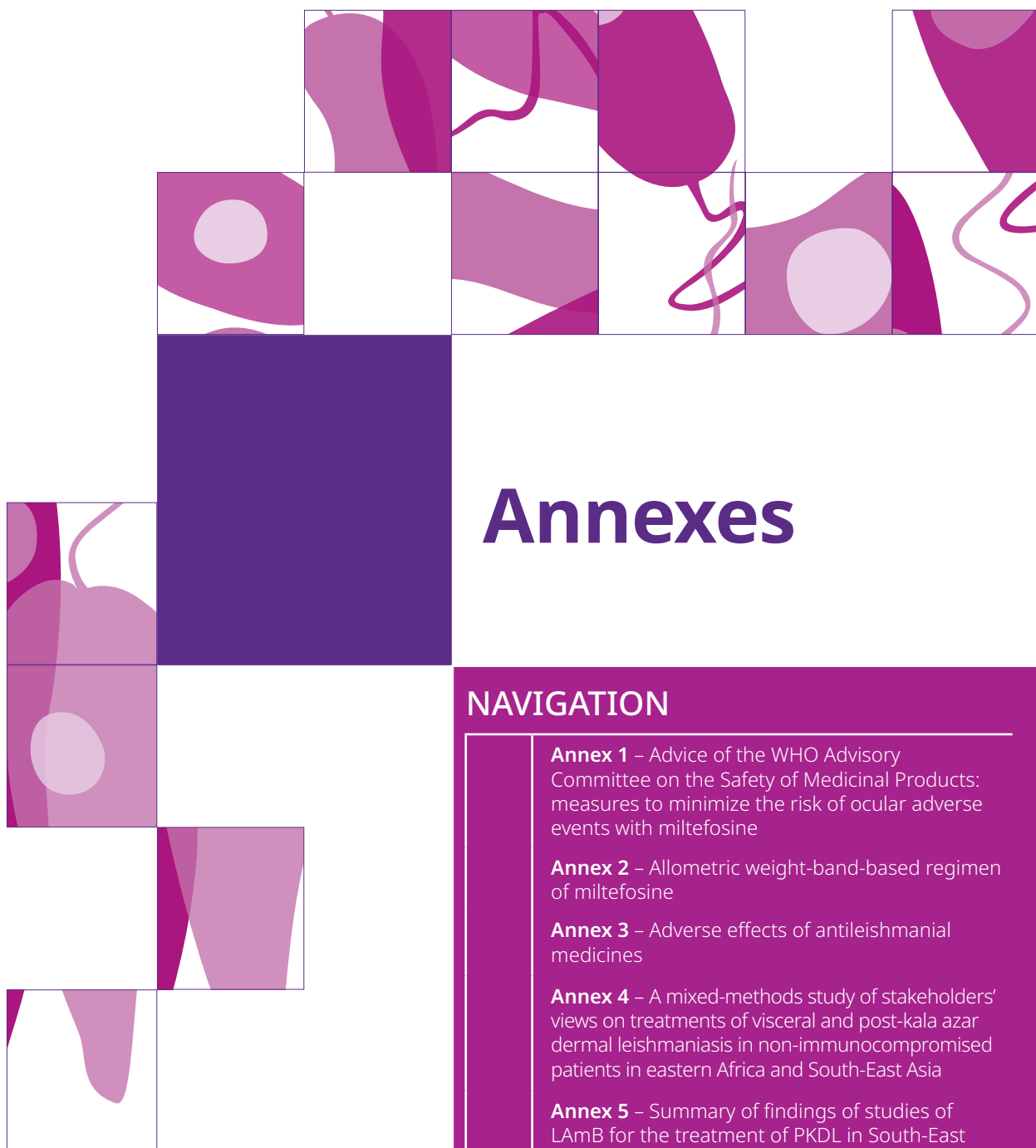
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Annexes

NAVIGATION

Annex 1 – Advice of the WHO Advisory Committee on the Safety of Medicinal Products: measures to minimize the risk of ocular adverse events with miltefosine

Annex 2 – Allometric weight-band-based regimen of miltefosine

Annex 3 – Adverse effects of antileishmanial medicines

Annex 4 – A mixed-methods study of stakeholders' views on treatments of visceral and post-kala azar dermal leishmaniasis in non-immunocompromised patients in eastern Africa and South-East Asia

Annex 5 – Summary of findings of studies of LAmB for the treatment of PKDL in South-East Asia

Annex 6 – Summary of findings of studies of miltefosine for the treatment of PKDL in South-East Asia

Annex 7 – Systematic review on treatments for visceral leishmaniasis (VL) and Post-kala-azar dermal leishmaniasis (PKDL) in East Africa and South-East Asia – Methods

Annex 8 – Systematic review on treatments for visceral leishmaniasis (VL) and Post-kala-azar dermal leishmaniasis (PKDL) in Eastern Africa and South-East Asia – Search strategy, PRISMA flowchart, excluded studies



Annex 1

Advice of the WHO Advisory Committee on the Safety of Medicinal Products: measures to minimize the risk of ocular adverse events with miltefosine

The WHO Advisory Committee on the Safety of Medicinal Products supports the recommendations of the WHO ad-hoc Multidisciplinary Technical Group (MTG) (Appendices 1–3), which was established to investigate signals of ocular adverse events after use of miltefosine. The Group provides the following advice to minimize the risks of ocular adverse events in patients exposed to miltefosine.

Information for patients

- Before starting treatment containing miltefosine, tell your health-care professional whether you currently have any eye problem or history of eye problem, as an ocular examination should first be performed in such situations.
- If you experience any eye discomfort during treatment, discontinue miltefosine immediately, and contact your nearest health-care centre or a health-care professional as soon as possible.
- Please contact your nearest health-care professional if you have any question or concern.

Information for health-care professionals

- Before starting miltefosine treatment, collect the patient's history of eye disorders and conduct an eye examination as appropriate.
- In case of current or a history of ocular disorder, the benefits and the risks of treating a patient with miltefosine should be carefully considered, and advice from an ophthalmologist should be sought where feasible.
- All patients should be informed before starting treatment that if eye problems occur during treatment (e.g. red eyes, increased watering, eye pain, blurred vision), they should discontinue miltefosine and contact their health-care professional immediately.
- If ocular complications occur and an association with miltefosine cannot be excluded, miltefosine should be discontinued immediately and an alternative treatment for leishmaniasis should be initiated if necessary. As miltefosine has a very long half-life (>6 days), ocular changes may not be reversible without treatment, even after discontinuation of miltefosine. An eye specialist should be consulted in such cases to avoid the possibility of permanent damage.
- Please refer to the Guiding principles in Appendix 2 for prevention, early detection and management of eye complications in patients treated with miltefosine for further information.
- Suspected adverse events should be reported to local health authorities and the national pharmacovigilance programme without delay.

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Appendix 1. Executive summary of the WHO ad hoc Multidisciplinary Advisory Group: miltefosine and ocular events

Miltefosine is an oral anti-infective agent and one of the medicines with established efficacy in the treatment of some clinical forms of leishmaniasis, a parasitic infection spread by sandflies. After reports of serious ocular events in patients treated with miltefosine for PKDL, the WHO Advisory Committee on the Safety of Medicinal Products and the WHO Regional Office for South-East Asia Regional Technical Advisory Group on Visceral Leishmaniasis expressed concern and requested the WHO to establish a multidisciplinary technical group of experts.

WHO established the MTG⁵ to review, evaluate and interpret all available data on ocular adverse event associated with use of miltefosine in leishmaniasis and to provide WHO with:

- scientific advice on a possible causal relation between miltefosine and ocular adverse events;
- recommendations on whether risk minimization measures should be updated and, if so, details of recommended measures, including how their effectiveness would be measured;
- recommendations on risk communication to patients and health-care professionals; and
- recommendations on whether further studies should be conducted to address any remaining uncertainties and, if so, advice on their design.

The MTG met on 10 October, 2 November and 30 November 2022 and adopted its final recommendations in December 2022, which were presented to the WHO Advisory Committee on the Safety of Medicinal Products on 14 December 2022.

Results

Ocular involvement has been described in the various clinical forms of leishmaniasis in humans (such as conjunctivitis, eyelid involvement, retinal disorders and, rarely, keratitis) and in certain animal species (dogs, cats, mice, hamsters and guinea-pigs). Analysis of miltefosine-containing products by the German Federal Institute for Drugs and Medicines and the Indian Pharmacopoeia Commission provided no indication that the tested products were of considerably reduced pharmaceutical quality or unsafe for human use. In non-clinical studies, ocular adverse reactions were reported in rats after administration of miltefosine, especially retinal atrophy. A non-clinical ophthalmological study also reported partially reversible, dose- and time-dependent changes at a high dose. No ocular changes were observed in dogs. In humans, 114 case reports were identified from Vigibase, three field studies conducted in India and other literature. In the 83 cases for which causality could be assessed, a causal relation between the observed ocular event and the intake of miltefosine was considered to be possible. The cases included two with a positive re-challenge, one of which with a twice positive at re-challenge and two cases of negative re-challenge. One case of keratitis was identified after a 27-day course of miltefosine therapy, despite a negative skin biopsy for Leishman-Donovan bodies, which may indicate a direct effect of miltefosine without underlying PKDL.

Between 2004 and the end of 2013 (i.e. before the new treatments emerged), about 300 000 patients

5 For the detailed terms of reference and the list of members, see [here](#)..

with VL in India were treated with miltefosine for 28 days (the treatment then recommended). Between 2014 and October 2022, 8633 patients with PKDL in India were treated with miltefosine for 12 weeks. Despite this much higher exposure to miltefosine, only five reactions were reported and suggested a milder reaction. Ocular symptoms, including keratitis, keratopathy and acute scleritis, uveitis, ocular hyperaemia (increased ocular vascularity) and visual impairment up to blindness, developed between a few days and several weeks after initiation of treatment, in both men and women, including in children <18 years (the youngest being 8 years old).

The vast majority of cases related to treatment for PKDL in South Asia may suggest that PKDL is a predisposing factor for the observed adverse ocular effects with miltefosine. (The evidence was not sufficient to confirm or rule out whether a similar risk may be expected in African PKDL, in view of important differences in clinical characteristics, personal risk factors, health-care systems and treatment guidelines.) The majority (68%) of the ocular adverse events considered to be at least possibly related to administration of miltefosine occurred after the recommended 28 days of treatment. When information was available, most of the cases resolved (sometime partly) after miltefosine was withdrawn, sometimes after treatment with steroids (mostly eye drops), sometimes oral and topical antibiotics and/or further medication was started. In some cases, however, the adverse ocular event, including loss of vision, persisted after miltefosine was withdrawn. No further risk factor was identified. The frequency of adverse ocular events during treatment with miltefosine could not be estimated due to limitations such as the size of the studies, possible underreporting and the absence of a comparator group, and the mechanism that might cause keratitis and other ocular adverse reactions remains unclear. In an investigation in VigiBase up to October 2022 of other drugs used in the treatment of PKDL, 168 reports of ocular events were found. Only three reports were not related to miltefosine but to LAmB, including one report of ocular events. Overall, the ocular lesions observed with miltefosine have rarely been described with any other anti-leishmanial drug.

Conclusions and recommendations

The available data indicate that a causal relation between ocular adverse events and exposure to miltefosine is at least a reasonable possibility. Ocular adverse events have been observed mainly during treatment of patients with PKDL in South Asia in both men and women, including in children under 18 years, usually beyond 28 days of treatment. No further risk factor could be identified. When information was available, most cases resolved after miltefosine was withdrawn; however, in some cases, the adverse ocular event led to permanent loss of sight. The frequency of adverse ocular events during treatment with miltefosine could not be estimated, and the mechanism of action remains unclear.

As a precautionary measure, and although the risk appears to be reported mainly in patients with PKDL in South Asia, the following recommendations should also be considered for other patients exposed to miltefosine. In order to minimize the risk of ocular adverse events in patients exposed to miltefosine, the MTG recommended inclusion of a warning and listing of possible ocular adverse events in the summary of product characteristics and the patient information leaflet. In addition, the MTG provided guiding principles for the prevention, early detection and management of eye complications in patients treated with miltefosine. They recommended that a patient information brochure based on MTG recommendations be developed by WHO to facilitate risk communication. They further requested WHO to publish a communication on its website, to encourage communication of the MTG conclusions through its disease programmes and to provide information to investigators on ongoing clinical trials. In countries where it is feasible, a direct communication to health-care professionals might be considered by national regulatory authorities. The MTG also recommended active surveillance, supported by a follow-up questionnaire, to further characterize the risk, its frequency and the effectiveness of risk minimization measures. The MTG considered that a study of miltefosine pharmacokinetics and of the presence of parasites and immune reactions in patients with PKDL would be helpful for assessing the specificity and causality of this adverse event in patients.

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Appendix 2. Guiding principles for prevention, early detection and management of eye complications in patients treated with miltefosine

The guiding principles proposed in this document should be carefully adapted to local contexts. Roles, lines of communication and pathways of referral for health personnel should be clearly defined to effectively detect, prevent and manage eye complications in patients treated with miltefosine. In general, health personnel (e.g. physicians, dermatologists, pharmacists, disease programme officers, ophthalmologists and any other relevant health-care professionals and health workers) who are associated with leishmaniasis and other conditions for which miltefosine is prescribed should be aware of the risk of eye complications during or after treatment with miltefosine.

Ophthalmologists who practise in areas in which leishmaniasis is prevalent should have access to tertiary centres when required. When ophthalmologists are not available, general practitioners should refer patients to an eye specialist. Collaboration with national blindness prevention and control programmes should be considered as required.

When starting treatment with miltefosine: Confirm the condition or diagnosis that requires administration of miltefosine. The experts agreed that, in certain settings, a probable diagnosis is sufficient to prescribe miltefosine, e.g. in the context of elimination of VL in South-East Asia.

- a. Confirm whether the patient was previously treated with miltefosine and, if so, whether any adverse event occurred.
- b. Collect the contact details of patients for follow-up
- c. Explain to patients the diagnosis, treatment choices, duration of treatment and possible side-effects of prescribed drug(s).
- d. Explain to patients that there will be frequent follow-ups and give them a patient information brochure, if available.
- e. Conduct an eye examination for any concomitant eye conditions (see checklist).
 - In patients with a severe ocular disorder (especially keratitis, uveitis, scleritis), initiation of miltefosine should be deferred until complete resolution of lesions. An ophthalmological consultation may be required for diagnosis and management.
 - If the patient has a history of recurrent episodes of ocular redness and/or pain and any known immune disorder affecting the eyes, a review of all records and a proper eye examination are recommended before initiation of miltefosine.
 - If the patient has a history of ocular changes during miltefosine treatment for VL or previous PKDL, an interval of at least 4 weeks should be ensured before initiation of miltefosine (terminal half-life of the drug, ~31 days). Such patients should be followed up more frequently, preferably every 2 weeks.
- f. Patients and their family members should be counselled about the possible risks and adverse events of the prescribed drug(s).
- g. They should be advised to stop treatment with miltefosine immediately and report to the nearest

health centre or health worker if any ocular symptoms are seen. One or several of the following symptoms that occur in a single or both eyes require immediate attention: redness,

- irritation,
- watering,
- pain,
- photophobia (unable to tolerate light),
- loss or dimming of eyesight,
- cloudy appearance or
- white spots in the eye.

All patients on miltefosine should be followed up at frequent intervals during treatment for a minimum of 2 months after treatment. An eye examination at completion of 4 weeks of therapy is critically important.

Pre-prescription eye check-up

Is there any current diagnosed or undiagnosed eye problem?

- 1) If yes, what kind of eye problem? Redness
 - i) Pain
 - ii) Irritation
 - iii) Watering
 - iv) Discharge
 - v) Photophobia (intolerance to light)
 - vi) Low vision. If available: visual acuity
 - colour vision
 - vii) Cloudy appearance of the eye
 - viii) White spots in the eye
 - ix) Corneal infiltration
 - x) Corneal ulceration
 - xi) Abnormality of eye lid or eyelashes
 - xii) Any other symptom (please specify)
- 2) In which eye? Right, left, both
- 3) How long has the eye problem been present?
- 4) Any ophthalmic consultation? If so, diagnosis by ophthalmologist:
- 5) Any treatment for the eye problem?
- 6) Medications prescribed for eye problem
- 7) Name and place of eye treatment facility:
- 8) Have the symptoms:
 - persisted
 - resolved
 - deteriorated?

If an eye adverse event occurs: Patients should be referred immediately to a health-care professional, and treatment with miltefosine should be stopped.

Patients and health personnel: The adverse event should be reported to local health authorities and the pharmacovigilance programme. Any ocular adverse event should be reported to WHO by national authorities for further analysis and guidance.

The following recommendations are made, when feasible.

- a. The patient should be referred and/or taken to the nearest higher health facility with eye care

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or ophthalmology services and/or referred to an ophthalmologist. Tele-consultation with an ophthalmologist may be considered.

b. Eye specialists are invited to consider the following.

- An anterior segment inflammation such as episcleritis, scleritis, limbal nodules, keratitis, especially peripheral corneal infiltrations, should be suspected. A meticulous history should be taken about any trauma and about concomitant medication during leishmaniasis treatment.
- A corneal smear or an appropriate microbiological sample may be taken if facilities are available and if deemed necessary by the treating ophthalmologist. Treatment should not, however, be delayed if a sample is not available.

c. A history of miltefosine intake and of common eye infections should be taken.

- Features of inflammation of eye structures such as the sclera and cornea can be managed with topical steroids and antibiotics, as required, with other symptomatic management such as cycloplegic drops and artificial tears, depending upon the severity and other concomitant or super-added infections.
- If symptoms involve both eyes, associated underlying systemic disease conditions (e.g. diabetes mellitus, immunosuppressive disorders) should be ruled out.
- All patients who do not respond to the above or who worsen after 1 week of therapy should be referred to higher centres for ophthalmic consultation. Compliance with the treatment of the ocular adverse event(s) should be checked.
- Patients of extreme age (paediatric or elderly) should be observed closely or referred to centres with facilities for ophthalmic consultation.
- Refractory errors and other eye conditions such as cataract and glaucoma should be managed in coordination with the national blindness prevention and control programme.

Appendix 3. Follow-up questionnaire

After a report of an ocular event in a patient treated with miltefosine is received on a standard reporting form, this follow-up questionnaire is to be used by disease and/or pharmacovigilance programmes to systematically collect key information. It is not intended for front-line staff.

The objectives of this follow-up questionnaire are to:

- (1) better characterize the risk, especially risk factors and occurrence in clinical forms other than PKDL, and
- (2) assess the effectiveness of the recommended risk minimization measures.

The collected information should be shared with both the disease and the pharmacovigilance programme without delay. Any ocular adverse event should be reported to WHO by national authorities for further analysis and guidance.

The information provided in previous report(s) should not be sought again to the reporter. To derive more information, the questionnaire may be administered by any convenient means (e.g. face to face, telephone, email). Several follow-ups may be conducted if important information is missing. Reasonable attempts should be made to contact the reporter again if no response is received.

Appendix 3A: Information about the patient and the reporter

1. Information about the patient (information at the time of the suspected drug consumption)

Initials/Name: Other patient ID:	Sex: ☐ Male ☐ Female ☐ Other	Date of birth: ____/____/____
	If pregnant. Trimester: I II III	or, Age: ____Years ____Months ____Days
	date of last menstrual period: ____/____/____	or, Patient age group (if exact age not known):
		☐ 0 < 1 year
Breast-feeding? ☐ Yes ☐ No		☐ 1–5 years
Patient weight (kg, other units) _____ (if available)		☐ > 5 years–18 years
Patient height (cm/other units) _____ (if available)		☐ > 18 years–60 years
		☐ > 60 years

2. Information about the reporter

- ☐ Physician ☐ Pharmacist ☐ Other health professional ☐ Lawyer ☐ Consumer
- ☐ Other non-health professional (specify):

Reporter's name (given and family names):

Designation:

Address: Locality, district, province

E-mail address:

Telephone:

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Appendix 3B. Concomitant drug(s) and any other information

B. 1. Miltefosine

Brand name of drug:

Daily dose(s):

Indication for use, type of leishmaniasis:

Date treatment was started: ____/____/____

Date treatment was stopped: ____/____/____

Outcome of the suspected reaction after stopping the treatment:

Symptoms:

☐
☐
☐

Date of control: ____/____/____

Outcome: Persisted / resolved / deteriorated

Outcome: Persisted / resolved / deteriorated

Outcome: Persisted / resolved / deteriorated

Was treatment re-started? ☐Yes ☐No

If treatment was re-started: Date treatment with miltefosine

was started: ____/____/____

Any ocular event after restart? ☐Yes ☐No

If Yes, please provide details: ____/____/____

Date treatment was ended/discontinued: ____/____/____

Outcome of symptoms after discontinuation:

Symptoms:

☐
☐
☐

Date of control of symptoms outcome: ____/____/____

Outcome: Persisted / resolved / deteriorated

Outcome: Persisted / resolved / deteriorated

Outcome: Persisted / resolved / deteriorated

B.2. Any other suspected and concomitant drugs, including traditional medicines:

Product name and form (e.g. tablet)	Dose/unit	Manufacturer	Batch/lot number	Route of administration	Indication	Treatment started	Treatment stopped
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Suspected drugs

____/____/____ ____/____/____

____/____/____ ____/____/____

____/____/____ ____/____/____

____/____/____ ____/____/____

____/____/____ ____/____/____

Product name and
form (e.g. tablet)

Dose/unit

Manufacturer

Batch/lot
numberRoute of
administration

Indication

Treatment started

Treatment
stopped

Concomitant products

____/____/____ ____/____/____

____/____/____ ____/____/____

____/____/____ ____/____/____

____/____/____ ____/____/____

Action taken on medication(s):☐ Drug (s) stopped☐ Dose reduced☐ Dose increased☐ Dose not changed☐ Monitoring increased☐ Unknown☐ Not applicable

Outcome of the suspected reaction after action taken on the medication, including if the drug was later reintroduced:

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Appendix 3C. Information about the ocular adverse event and any other adverse event

C.1. Ocular adverse event

I. Reaction onset (DD/MM/YYYY): ____/____/____

II. Describe reaction (include any relevant tests/laboratory data):

Reaction:	Left eye	Right eye	Reaction: Low vision	Left eye	Right eye
Pain	☐	☐	Loss/Dimness of eyesight	☐	☐
Eye discharge	☐	☐	Eye irritation and/or watering	☐	☐
Redness	☐	☐	Whitening of black part of the eye/ cloudy appearance	☐	☐
Intolerance to light (photophobia)	☐	☐			
Visual acuity test:	_____	_____			

III. Any other ocular reaction? (Please specify)

IV. Were there any eye symptoms with previous treatment with miltefosine or another antileishmanial drug?

If yes, please specify:

C.2. Seriousness

I. Serious?

☐ Death

☐ Life-threatening

☐ Disability

☐ Hospitalization

☐ Congenital abnormality

☐ Other important medical event (please specify):

C.3. Causality assessment as per the WHO-Uppsala Monitoring Centre system for standardized case causality assessment ([link to the use of the WHO-UMC system for standardised case causality assessment](#))

- ☐ Certain
☐ Probable/Likely
☐ Possible
☐ Unlikely
☐ Conditional/Unclassified
☐ Unassessable/Unclassifiable

Provide rationale for the assessment:

C.4. Treatment of the ocular adverse event (if any)

Treatment of ocular event ☐ Yes ☐ No

If yes, please specify:

Professional consulted:

- ☐ Ophthalmologist consulted. Date: ____/____/____
☐ Any other health-care professional (please specify):

Details of medicinal treatment:

Product name and drug form (e.g. tablet)	Dose/unit	Route of administration	Indication	Treatment started	Treatment stopped
				____/____/____	____/____/____
				____/____/____	____/____/____
				____/____/____	____/____/____
				____/____/____	____/____/____
				____/____/____	____/____/____

Other treatments, including surgical treatment:

C.5. Any other adverse event:

Reaction onset (DD/MM/YYYY): ____/____/____

Describe suspected adverse drug reaction(s) in chronological order (e.g. symptoms, aggravation, laboratory reports, etc.):

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Appendix 3D. Outcome of the event

Date of assessment: ____/____/____

I. Outcome of the treatment:

☐ Recovering

☐ Not recovered

☐ Recovered

☐ Unknown

☐ Recovered with sequelae

☐ Died. Date of death (DD/MM/YYYY): ____/____/____

Appendix 3E. Medical history and any other relevant information

HIV (please specify)

Date of diagnosis: ____/____/____

Antiretrovirals (dose and date): Viral load: CD4 count: Concomitant opportunistic infections such as cytomegalous virus, *Herpes* virus, toxoplasmosis, other:

Tuberculosis (please specify)

Diabetes (please specify)

Hypertension (please specify)

Trachoma (please specify)

Any other condition/ relevant information:

Appendix 3F. Pre-prescription eye examination details, if available

F.1. Before treatment was started:

Was there any current diagnosed/undiagnosed eye problem? ☐ Yes ☐ No

If yes, what kind of eye problem?

	Left eye	Right eye		Left eye	Right eye
Pain	☐	☐	Low vision	☐	☐
Eye discharge	☐	☐	Loss/dimness of eyesight	☐	☐
Redness	☐	☐	Eye irritation and/or watering	☐	☐
Intolerance to light (photophobia)	☐	☐	Whitening of black part of the eye/ coudy appearance	☐	☐
Visual acuity test	_____	_____			

Please provide any other relevant information from the pre-prescription ophthalmic examination:

Appendix 3G: Risk minimization measures

I. Was there regular follow up of the patient? ☐ Yes ☐ No

If yes, how frequent?

Was an eye examination performed at 4 weeks? ☐ Yes ☐ No

When was the last follow up? Date: ____/____/____

II. Was the patient and/or family members informed about the risks of ocular adverse event with miltefosine before starting treatment? ☐ Yes ☐ No

Was the patient and/or family members advised to immediately stop the treatment with miltefosine and report to the nearest health centre or health worker if any ocular symptoms was noted? ☐ Yes ☐ No

Were the patient and/or family members provided with a patient information brochure? ☐ Yes ☐ No

III. Was the patient referred to an eye care facility or ophthalmology services? ☐ Yes ☐ No

Was the patient referred to an eye care facility or ophthalmology services? ☐ Yes ☐ No

Date: ____/____/____

IV. Please provide any other relevant information on risk minimization measures:

Annex 2

Allometric weight-band-based regimen of miltefosine

Miltefosine dose levels per weight band for an allometric weight band-based regimen:

Weight band range (kg)	Selected daily dose (mg)
<6	20
6.00–9.99	30
10.00–14.99	50
15.00–19.99	60
20.00–24.99	70
25.00–29.99	80
30–44.99	100
≥45	150

Herrera AM, Karlsson MO, Svensson EM, Dorlo TPC. Weight-band based simplification of oral allometric miltefosine dosing in pediatric patients with visceral leishmaniasis in Eastern Africa (<https://www.page-meeting.org/Abstracts/weight-band-based-simplification-of-oral-allometric-miltefosine-dosing-in-pediatric-patients-with-visceral-leishmaniasis-in-eastern-africa/>).

Annex 3

Adverse effects of antileishmanial medicines

Drug: Miltefosine			
Organ system	Very common side-effects (≥ 1/10 patients)	Common side-effects (≥ 1/100 to < 1/10 patients)	Uncommon (≥ 1/1 000–< 1/100); rare (≥ 1/10 000–< 1/1 000); very rare (< 1/10 000)
Gastrointestinal disorders	Vomiting, diarrhoea	Anorexia, nausea	Abdominal pain, thrombocytopenia
Hepatobiliary disorders	Increased activity of liver enzymes		
Renal and urinary disorders		Increased blood urea nitrogen, creatinine	
Immune disorders			Steven–Johnson syndrome
Drug: Paromomycin			
Organ system	Very common side-effects (≥ 1/10 patients)	Common side-effects (≥ 1/100 to < 1/10 patients)	Uncommon (≥ 1/1 000–< 1/100); rare (≥ 1/10 000–< 1/1 000); very rare (< 1/10 000)
Skin		Pruritus	
Eye ^a			Inflammation of various eye structures, e.g. keratitis, uveitis
Gastrointestinal disorders		Nausea, metallic taste	Vomiting
General	Headache, lethargy, mild injection-site pain	Pyrexia, reversible abnormal audiogram	Injection site swelling, abscess, ototoxicity, conductive deafness, proteinuria
Hepatobiliary disorders		Transient increases in alanine and aspartate transaminases	Increased alkaline phosphatase, blood bilirubin
Liposomal amphotericin B			
Organ system	Very common side-effects (≥ 1/10 patients)	Common side-effects (≥ 1/100 to < 1/10 patients)	Uncommon (≥ 1/1 000–< 1/100); rare (≥ 1/10 000–< 1/1 000); very rare (< 1/10 000)
Skin		Pruritus	

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General and infusion related	Chills/rigour, fever, nausea, vomiting, hypertension, tachycardia, breathlessness, hypoxia, rash, anaemia, insomnia, malaise, fatigue, confusion, muscle weakness or cramps	Chest tightness, chest pain, breathlessness, difficulty in breathing (possibly with wheeze), flushing, vasodilation lowering blood pressure, musculoskeletal pain (described as joint pain, back pain or bone pain), stomach pain, headache, bleeding into skin, unusual bruising and prolonged bleeding after injury, fits or seizures, pain and swelling around the infusion site	Heart attack, severe swelling around lip, eyes or tongue, muscle breakdown, bone and joint pain
Hepatobiliary disorders	Increased alkaline phosphatase		
Gastrointestinal disorders	Diarrhoea, nausea, vomiting		
Blood disorders	High blood sugar, low potassium, low magnesium, low calcium, low sodium		Anaemia with symptoms of excessive fatigue and breathlessness after light activity, pale complexion, interference in blood phosphorus test results
Renal and urinary disorders	Increased blood urea nitrogen, increased creatinine		Kidney failure
Drug: Amphotericin B deoxycholate			
Organ system	Very common side-effects ($\geq 1/10$ patients)	Common side-effects ($\geq 1/100$ to $< 1/10$ patients)	Uncommon ($\geq 1/1\,000$ – $< 1/100$); rare ($\geq 1/10\,000$ – $< 1/1\,000$); very rare ($< 1/10\,000$)
General and infusion related	Fever (sometimes accompanied by shaking chills, usually within 15–20 min of initiation of treatment), malaise, weight loss, hypotension, tachypnoea, pain at the injection site with or without phlebitis or thrombophlebitis, generalized pain, including muscle and joint pains	Flushing, anaphylactoid and other allergic reactions, bronchospasm, wheezing, rash, in particular maculopapular, pruritus	

Cardiopulmonary		Cardiac arrest, shock, cardiac failure, pulmonary oedema, hypersensitivity pneumonitis, arrhythmia, including ventricular fibrillation, dyspnoea, hypertension	
Hepatobiliary disorders			
Gastrointestinal disorders	Anorexia, nausea, vomiting, diarrhoea, dyspepsia, cramping, epigastric pain	Acute liver failure, hepatitis, jaundice, haemorrhagic gastroenteritis, melena	
Blood disorders	Normochromic, normocytic anaemia	Agranulocytosis, coagulation defects, thrombocytopenia, leukopenia, eosinophilia, leukocytosis	
Renal and urinary disorders	Decreased renal function and renal function abnormalities, including azotaemia, hypokalaemia, hyposthenuria, renal tubular acidosis and nephrocalcinosis. Usually improves with interruption of therapy but some permanent impairment, especially in patients receiving large amounts (> 5 g) of amphotericin B or other nephrotoxic agents	Acute renal failure, anuria, oliguria	
Neurological symptoms		Convulsions, hearing loss, tinnitus, transient vertigo, visual impairment, diplopia, peripheral neuropathy, encephalopathy, other neurological symptoms	
Drug: SSG			
Organ system	Very common side-effects (≥ 1/10 patients)	Common side-effects (≥ 1/100 to < 1/10 patients)	Uncommon (≥ 1/1 000–< 1/100); rare (≥ 1/10 000–< 1/1 000); very rare (< 1/10 000)
General and infusion related	Flushing, sweating, fever, rash, yellow skin and eyes, pain and thrombosis on IV administration, pain at injection site if given IM, abdominal pain, anorexia, malaise, myalgia, arthralgia, headache and lethargy	Anaphylaxis, rigour, exacerbation of lesions on the cheek, substernal pain	

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Cardiopulmonary	Fatal cardiac arrhythmia, changes in electrocardiogram, including reduction in T-wave amplitude, T-wave inversion and QT prolongation, transient coughing	Pneumonia	
Hepatobiliary disorders	Transient rise in serum lipase and amylase, symptomatic pancreatitis		
Gastrointestinal disorders	Bleeding from nose or gums		
Blood disorders			Transient reductions in platelets, leukocytes and haemoglobin
Neurological symptoms	Vertigo		
Drug: Meglumine antimoniate			
Organ system	Very common side-effects ($\geq 1/10$ patients)	Common side-effects ($\geq 1/100$ to $< 1/10$ patients)	Uncommon ($\geq 1/1\,000$ – $< 1/100$); rare ($\geq 1/10\,000$ – $< 1/1\,000$); very rare ($< 1/10\,000$)
General and infusion related	Headache, general malaise, difficulty in breathing, skin rash, facial oedema. Precautions to be taken before systemic administration: a protein-rich diet throughout treatment, correction of iron-deficiency anaemia or specific deficiencies to be corrected before treatment. Cardiac, hepatic and renal functions must be monitored throughout the treatment (Instructions from product package insert)		
Cardiopulmonary	Cardiac changes (dose-dependent and generally reversible): T-wave insertion and QT interval prolongation		Cardiac arrhythmia
Gastrointestinal disorders	Abdominal pain, increased liver enzyme activity		Pancreatitis

Renal and urinary disorders			Acute renal insufficiency
Drug: Pentamidine			
Organ system	Very common side-effects (≥ 1/10 patients)	Common side-effects (≥ 1/100 to < 1/10 patients)	Uncommon (≥ 1/1 000– < 1/100); rare (≥ 1/10 000– < 1/1 000); very rare (< 1/10 000)
General	Local pain at injection site, induration, sterile abscess, nausea, vomiting, abdominal pain, hypotension, syncope, hypoglycaemia, diabetes mellitus		
Blood and lymphatic system	Leukopenia, thrombocytopenia, anaemia		
Metabolism and nutrition	Azotaemia	Hypoglycaemia, hyperglycaemia, hyperkalaemia, hypocalcaemia, hypomagnesaemia	
Nervous system	Syncope, dizziness		
Vascular	Hypotension, flushing		
Cardiopulmonary	QT interval prolongation, cardiac arrhythmia		
Gastrointestinal	Nausea, vomiting, taste disturbance		Pancreatitis (rare)
Hepatobiliary	Abnormal liver function		
Skin and subcutaneous tissue	Rash		Stevens-Johnson syndrome (frequency unknown)
Renal and urinary	Acute renal failure, macroscopic haematuria		

^a WHO Advisory Committee on the Safety of Medicinal Products: Measures to minimize the risk of ocular adverse events with miltefosine. Geneva: World Health Organization; 2023 (<https://cdn.who.int/media/docs/default-source/medicines/pharmacovigilance/miltefosine-2023.pdf>).

Annex 4

A mixed-methods study of stakeholders' views on treatments of visceral and post-kala azar dermal leishmaniasis in non-immunocompromised patients in eastern Africa and South-East Asia

A technical team of methodologists from the American University of Beirut and members of the WHO secretariat conducted a mixed-methods study based on an online survey and virtual in-depth interviews. The objectives were to assess evaluation of different outcomes after treatment, feasibility, acceptability, resource use and equity of the recommendations (Fig. A4.1).

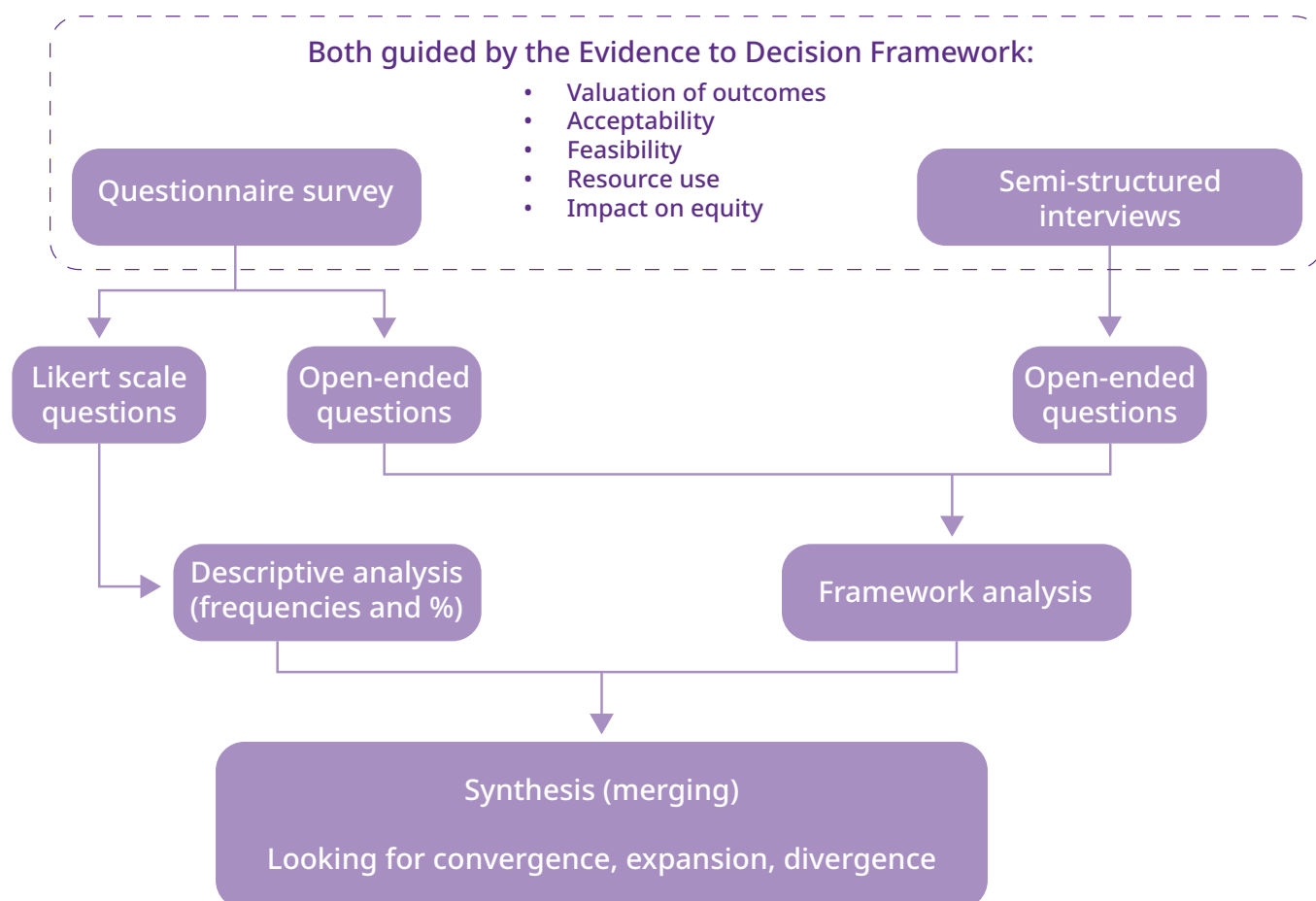


Fig. A4.1. Study design

The participants were stakeholders in eastern Africa and South-East Asia. Another arm of the study, with the same objectives, is under way to explore the perspectives of patients.

The stakeholders included national NTD programme officers, national ministry of health staff, sub-national programme managers, physicians and nurses; representatives of nongovernmental

organizations; academic researchers; and members of the WHO Regional Technical Advisory Group on VL. Participants in the online survey were recruited through WHO regional and country offices and partners' listserves. The respondents were invited to indicate whether they were interested in participating in an in-depth interview, and those who agreed were interviewed. Data were collected between 24 October and 15 November 2023. The in-depth interviews were conducted between 3 and 26 November 2023.

The online survey contained structured questions. Participants were asked to rank their responses on a scale from 1 to 9 (1–3, less important; 4–6, important; and 7–9, critical). Each question was followed by a probing open-ended question, to which participants could add more information to their ranking.

The same questions were used for the in-depth interview, although the interviewer probed for responses of greater depth and breadth.

We received from 163 responses from South-East Asia and 154 from eastern Africa; however, only 66 and 63 partially or fully completed responses, respectively, were included. We conducted 12 interviews, six in each region.

Table A4.1. Survey participants' characteristics

South-East Asia Region		Eastern Africa	
Country of residence	No. (%)	Country of residence	No. (%)
India	46 (70)	Ethiopia	18 (20)
Bangladesh	10 (15)	Kenya	11 (17)
Nepal	9 (14)	South Sudan and Sudan	10 (16)
Other	1 (1)	Other (Chad, Congo, Egypt, Uganda and others)	24 (38)
Profession	No. (%)	Profession	No. (%)
Physician	21 (32)	Physician	25 (40)
Manager	14 (21)	Manager	16 (25)
Other (e.g. medical director, epidemiologist)	31 (47)	Other (e.g. medical director, epidemiologist)	22 (35)
Level of responsibility	No. (%)	Level of responsibility	No. (%)
Institution	11 (17)	Institution	7 (11)
Block	9 (13)	District	4 (6)
District	11 (17)	National	23 (37)
National	13 (20)	Regional	5 (7)
Regional	11 (17)	International	15 (24)
International	7 (10)	Other	6 (10)
Other	4 (6)	Not applicable	3 (5)
Type of organization	No. (%)	Type of organization	No. (%)
WHO	17 (26)	WHO	16 (25)
Government	17 (26)	Government	28 (45)

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South-East Asia Region		Eastern Africa	
Nongovernmental	27 (41)	Nongovernmental	14 (22)
Other	7 (11)	Other	4 (6)
		Missing	1 (2)
Experience in providing direct care to patients	No. (%)	Experience in providing direct care to patients	No. (%)
Direct care	43 (65)	Direct care	35 (56)
No direct care	16 (24)	No direct care	19 (30)
Not applicable	7 (11)	Not applicable	9 (14)

Evaluation of outcomes

The following outcomes of treatment were evaluated by non-patient stakeholders: mortality, clinical cure at the end of treatment and 6 months after treatment, failure to cure, relapse, adverse events and drug resistance. Participants ranked the outcomes as “not important”, “important” or “critical”.

VL in eastern Africa and South-East Asia

1. Mortality within the post-treatment follow-up period of 6 months

This was a critical outcome for most participants (84% in eastern Africa and 69% in South-East Asia). Mortality outcomes were attributed to: *clinical factors, including patient co-morbidities, < 5 years of age (P12) and early diagnosis (P01); health-care delivery factors such as testing for hypersensitivity before administering AmBisome (P05); and public health factors, consisting of lack of training of health-care professionals for treating cases; however, once trained, “they made sure that we actually understood what we were doing and then the responsibility to take care of VL patients” (P08).* According to one participant, mortality is not well understood as an outcome.

Case fatality rate within 6 months is 3%, much higher than any other diseases and there must be significant numbers of patients being missed. It is incumbent on the system to ethically investigate thoroughly and understand why. There are lots of weaknesses where the system is not capable of handling complex medical problems (P10).

2. Initial cure

Initial cure is defined as “at the end of the treatment, or 15 days after the treatment starts for short-course regimen (< 5 days), patients show no fever, regression of splenomegaly (even partial) and return of appetite and/or gain in body weight” was critical for 81% and 69% of participants in eastern Africa and South-East Asia, respectively. *According to participants, initial cure was a critical outcome because it defined the “prognosis...as good or bad” (ID 175) and for “risk stratification” as indicated by one participant: Because most of the deaths are happening early in the treatment phase, it is important that protocols be devised to identify patients who are going to be at risk of death. I would rather like to see in the protocols a system of what questions to ask? How frequently to follow? What investigations to be conducted. What*

demographics to be captured so that you can risk profile each case. So I would rather incorporate that into the definition of initial cure” (P10).

Initial cure is critical, because “from a programmatic public health perspective, it means success” (P04).

Initial cure should, however, not be based only on symptom relief: it is important to “have a confirmatory/ parasitological evidence of cure” (ID 157).

3. Final cure

Final cure, defined as a “patient who after initial cure remains symptom-free at six months after the end of treatment”, was ranked as critical by 84% and 67% of non-patient stakeholders in eastern Africa and South-East Asia, respectively. *It is critical for patients, as “every patient really likes to be symptom free, [besides] it has economic implication for patients” (P01). From a programmatic perspective, it is critical, as the target is “zero kala-azar transmission, then you need more effective treatment” (P04).* Like initial cure, final cure must be a confirmatory parasitological test for final cure.

Assessment of ‘final cure’ should not be made merely on clinical grounds in VL patients. I’m of opinion that a patient with or without initial good prognosis/cure if found to be symptom free and devoid of all clinical/laboratory derangements that were present at baseline can be considered to have achieved a final clinical cure. Besides, there must be one or more laboratory evidences of parasitic clearance as well (ID 175).

4. Relapse

Relapse, defined as “recurrence of VL symptoms with parasitological confirmation at any time point after initial cure”, was considered critical by 82% and 58% in eastern Africa and South-East Asia, respectively. *It is critical because it “maybe because the medications were not enough” (ID 161) and also, from a health-care system perspective, it reduces “admission to hospital, number of days” (P02). In any case, a confirmatory parasitological such as the “Q PCR should be an option for declaration of relapse” (ID 137).*

For some participants, relapse was important rather than critical, as it is treatable. *“Less devastating than failure because there are better treatments. We provide the same drug. We provide AmBisome and it is acceptable” (P03).*

5. Adverse events

The definition of adverse events in this study was: any injury related to medical management, in contrast to complications of disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care. Adverse drug event are medication-related adverse event.

In eastern Africa and South-East Asia, 66% and 58% of non-patient stakeholders indicated that adverse events were critical.

Adverse events were considered critical because some medications are known to cause “ototoxicity and cardiotoxicity” (P09), and some adverse events are “irreversible such as miltefosine’s induced corneal ulcer” (D 118). It is critical that health-care professionals be vigilant about “patients (especially those getting prolonged treatment and or high dose of treatment); [they] need to be counselled properly before treatment” (D 118). Hence,

it is rather more important to educate and train health-care personnel about the means by which adverse events can be prevented and facilitate them to implement all such means in routine practice (ID 175).

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As important as well is to have a

pharmacovigilance specific for VL online form to report side effects sponsored by WHO ... only serious side effects are reported ... even a small ADR is an ADR ... All ADR should be reported (P02)

6. Failure to cure

Failure to cure occurs when the “signs and symptoms persist or recur during treatment or up to the initial treatment outcome assessment”. This was ranked as critical by 78% and 65% of non-patient stakeholders in eastern Africa and South-East, respectively.

It is a critical outcomes because it

enables the manager/organization to check on the the delivery of care, the compliance/adherence issues by the patient and the possible effectiveness of the treatment modalities. Identifying these contributing factors, among others, can help the organization or the provider address the concerns and contribute to the betterment of the patient. (ID 94).

The impact on patients is “devastating, after taking several injections, painful and not responding to treatment, patients are unhappy... frustrated” (P03), and, from a public health perspective, “complete treatment is important for interruption of transmission of kala-azar” (ID 161).

7. Drug resistance

Drug resistance, defined as

the decrease or absence of activity of a specific drug against a previously susceptible population of Leishmania parasites through the acquisition of molecular resistance mechanisms leading to reduced or a lack of clinical efficacy even at the highest tolerated doses

was perceived as critical by 70% and 60% among non-patient stakeholders in eastern Africa and South-East Asia, respectively. If drug resistance occurs, it is critical to know whether the resistance is due to the host, i.e. “the patient may not respond to treatment” (P12) due to pre-existing medical conditions or to the drug. The latter is critical because, first and foremost, there are “very few VL drugs, and those need to be effective” (ID 119), otherwise it will result in the death of many patients. Secondly, it may mean that “the parasite is changing to make itself more resistant to the medication” (P12). Hence, “monitoring of drug resistance [should] be performed under operational research” (ID 161).

Fig. A4.2 illustrates the evaluation of each VL outcome.

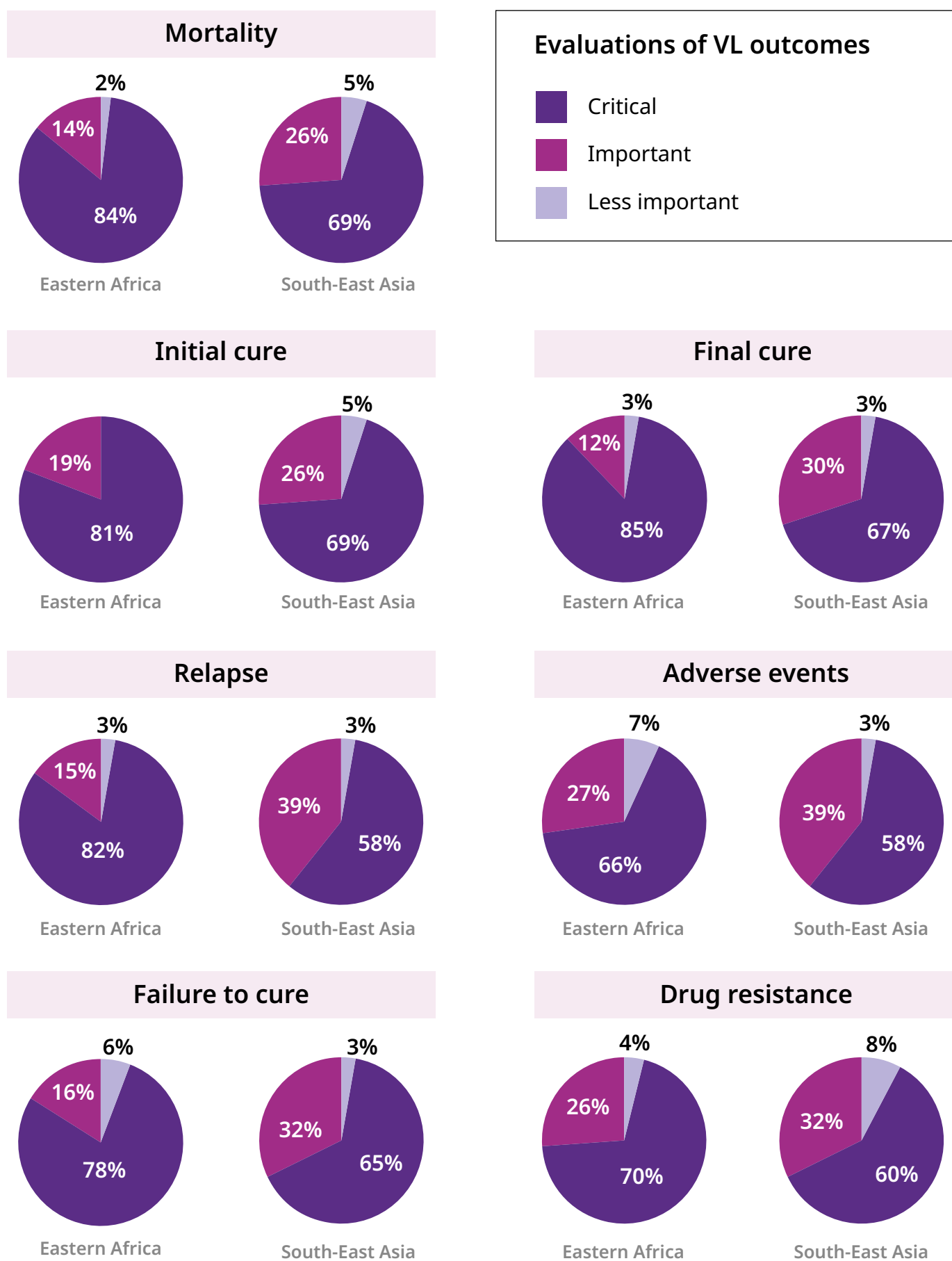


Fig. A4.2 Evaluations of VL outcomes

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PKDL in eastern Africa and South-East Asia

1. Mortality within the post-treatment follow-up of 12 months

Mortality within the post-treatment follow-up of 12 months was an important outcome for 49% of non-patient stakeholders in eastern Africa and important or less important for 38% of non-patient stakeholders in South-East Asia. Mortality is an extremely rare outcome.

As PKDL is a skin condition as a result of an immunological response to a VL infection, and is generally self-healing in East Africa, death of a PKDL patient will be extremely rare, and may be caused by concurrent VL disease (ParaKDL) (ID 116).

2. Initial cure

Initial cure, defined as “at the end of the treatment”, was critical for 59% of respondents in eastern Africa, while 44% of those in South-East Asia indicated that it was either critical or important. *Initial cure is critical or important because, from a programmatic perspective, it is “a crucial indicator to monitor, as they serve as reservoirs for the parasite, enabling the persistence of transmission within the population” (ID113).*

Initial cure should not, however, be based only on symptom relief, because “those signs that you can depend [are] enough.... We do not have any test of cure.” (P12)

3. Final cure

Final cure, defined as 12 months after completion of the treatment, although “some scars can be permanent”, was ranked as critical for 57% and 53% of non-patient stakeholders in eastern Africa and South-East Asia, respectively. It was also indicated, however, that final cure should not be

based [only] on the number of months that had elapsed after completion of treatment. A carefully defined state of ‘final cure’ is an important tool in program planning and evaluation. (ID 139)

4. Relapse

Relapse, defined as “recurrence of VL symptoms with parasitological confirmation at any time point after initial cure”, was considered critical by 56% and 60% of participants in eastern Africa and South-East Asia, respectively. *It is an important outcome, as “relapse of PKDL lesions do suggest decreased susceptibility of the parasite or incomplete treatment for various reasons.” (ID 157)*

5. Adverse events

The definition of adverse events in this study was the following: ... any injury related to medical management, in contrast to complications of disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat and the systems and equipment used to deliver care. Adverse drug events are medication-related adverse events.

Adverse events were considered critical by 61% and 71% of non-patient stakeholders in eastern Africa and South-East Asia, respectively,

considering that PKDL is typically a skin manifestation which does not cause ill-health, debilitation, or physical discomfort, and is typically self-healing, adverse drug events are a critical issue, which may shift the benefit-harm balance, especially when resulting in permanent damage (e.g. blindness) (ID116).

6. Failure to cure

Failure to cure, defined as “signs and symptoms [that] persist or recur during treatment or up to the initial treatment outcome assessment”, was ranked as critical by 53% of non-patient stakeholders in both eastern Africa and South-East Asia.

It is a critical outcome because

failure to cure may indicate an undiagnosed underlying immune-suppressive disease, resulting in an inability to generate an effective immune response which triggers the healing process (ID116)

and can “lead to further disease transmission” (ID167).

7. Drug resistance

Drug resistance, defined as

*the decrease or absence of activity of a specific drug against a previously susceptible population of *Leishmania* parasites through the acquisition of molecular resistance mechanisms leading to reduced or a lack of clinical efficacy even at the highest tolerated doses*

was perceived as critical by 58% and 57% of non-patient stakeholders in eastern Africa and South-East Asia, respectively. It is critical, “since there are limited drugs for leishmaniasis treatment, there should be test of efficacy for these drugs.” (ID 55)

Fig. A4.3 provides the evaluation of each outcome.

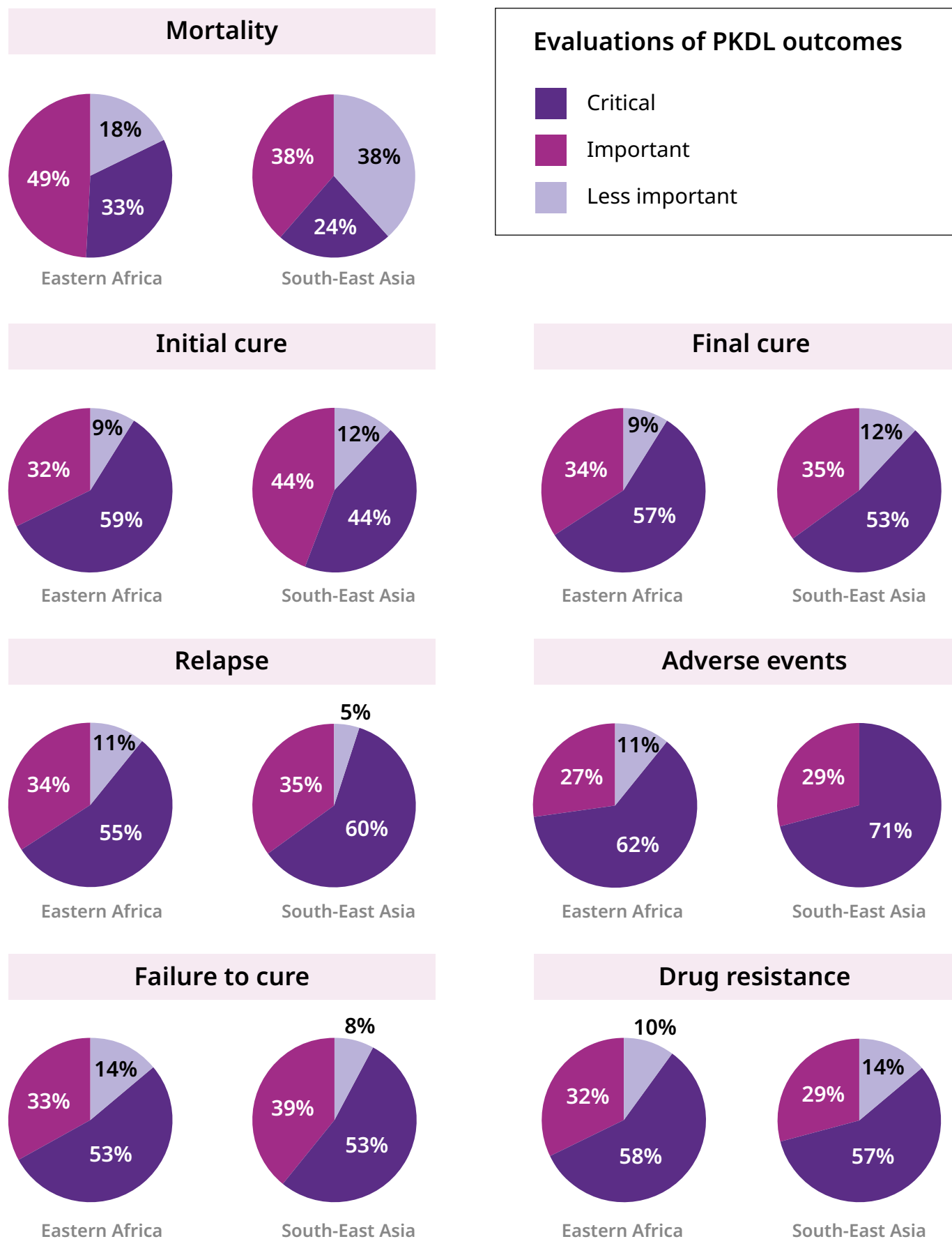


Fig. A4.3. Evaluation of each PKDL outcome

Acceptability, feasibility, resource use and equity

We examined contextual factors related to implementation of the guidelines by addressing each of the following issues: acceptability, feasibility, resource use and impact on equity in both eastern Africa and South-East Asia among stakeholders. Participants ranked their evaluation of outcomes as “not important”, “important” and “critical”.

VL in eastern Africa

Should VL patients in East Africa receive paromomycin 20 mg/kg per day IM once a day for 14 days in combination with miltefosine orally, miltefosine for 14 days or SSG at 20 mg/kg per day IM/IV in combination with paromomycin 15 mg/kg per day IM for 17 days? Should VL patients in eastern Africa receive SSG in combination with paromomycin? Overall, stakeholders indicated that it would be more acceptable to administer a combination of drugs when one is administered orally and the overall treatment duration is shorter. In view of the deadly nature of VL, however, the most important criteria would be the effectiveness of drugs and the reduced side-effects, which, according to their experience, are properties of SSGs.

Paromomycin plus miltefosine is also feasible; however, three challenges associated with administration of miltefosine were cited. *First, its use requires screening for pregnancy and contraception for women of reproductive age, which may require partners' approval, and in most cases, is not culturally feasible. Miltefosine “requires additional screening for pregnancy, contraception” (ID 22), which, in some cultures might be a serious problem, “because they don't accept contraception in general” (P08) and “women in the countryside cannot decide on their own because she has to talk to the husband and so on and the husband might not agree.” (P12)*

Secondly, administration of miltefosine requires that patients have a meal before taking the dose, which some patients might not be able to afford. More importantly, health-care providers have to monitor patients for about 30 min after they take the drug to make sure they do not vomit. Thirdly, patients who take miltefosine at home may unintentionally forget to take their medications.

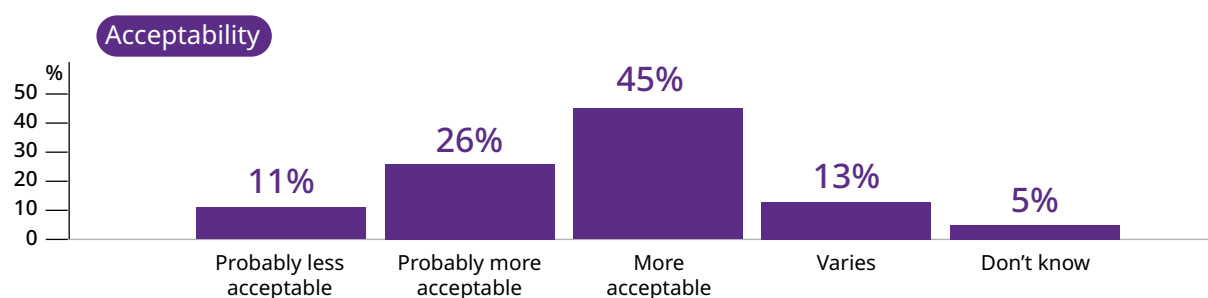
Adherence to the new paromomycin plus miltefosine regimen may also be a challenge. Patients who come daily for their paromomycin injection will receive their observed first daily dose of miltefosine. As many patients cannot have a meal just before taking the first dose of miltefosine, however, they are at increased risk of vomiting. Patients must therefore be monitored for 30 min after taking miltefosine and receive a replacement dose in case of vomiting. Adherence to miltefosine cannot be monitored and may unintentionally be forgotten or intentionally skipped by patients suffering gastrointestinal side-effects (ID 116).

The paromomycin plus miltefosine regimen resulted in larger savings in the health-care system as it can be administered to outpatients. It is also favourable for patients as its duration is shorter, saving the cost of transport and reducing wage losses.

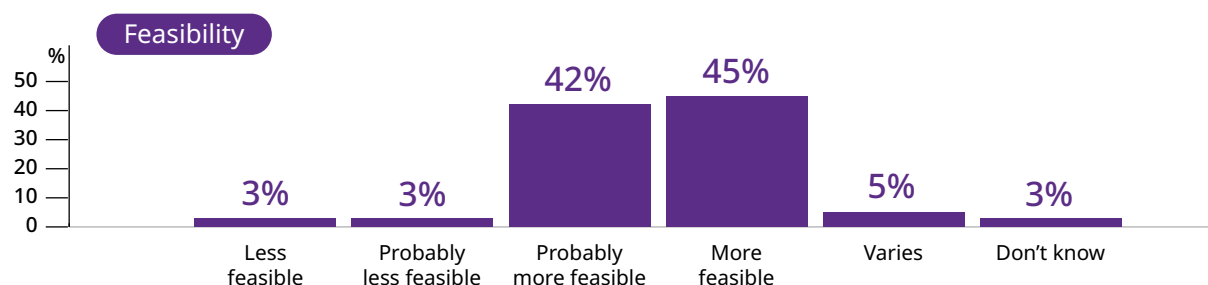
In terms of equity, gender is a concern because of the effects on women of reproductive age. Overall, the recommended treatment would free more hospital beds, increasing the capacity of the health-care system to admit more vulnerable patients and reducing the burden of caregivers, who often accompany patients to hospital, losing wages and requiring accommodation and food.

Fig. A4.4 illustrates the responses of non-patient stakeholders.

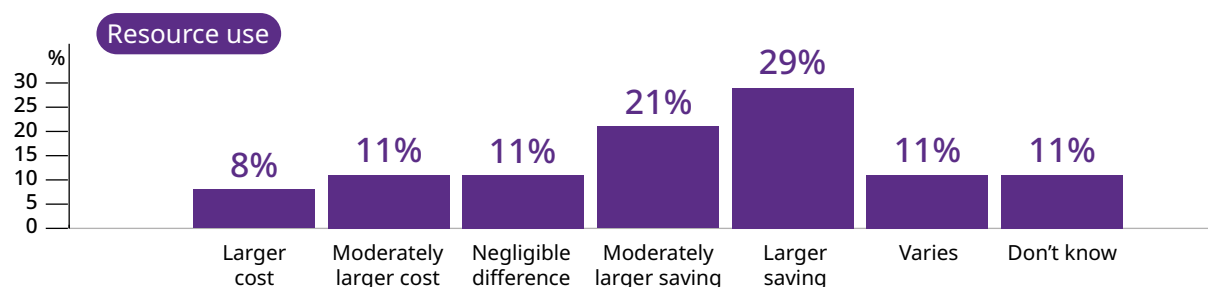
A. Impact on acceptability of proposed therapy as compared with current practice



B. Impact on feasibility of proposed therapy as compared with current practice



C. Impact on resource use of proposed therapy as compared with current practice



D. Impact on equity of proposed therapy as compared with current practice

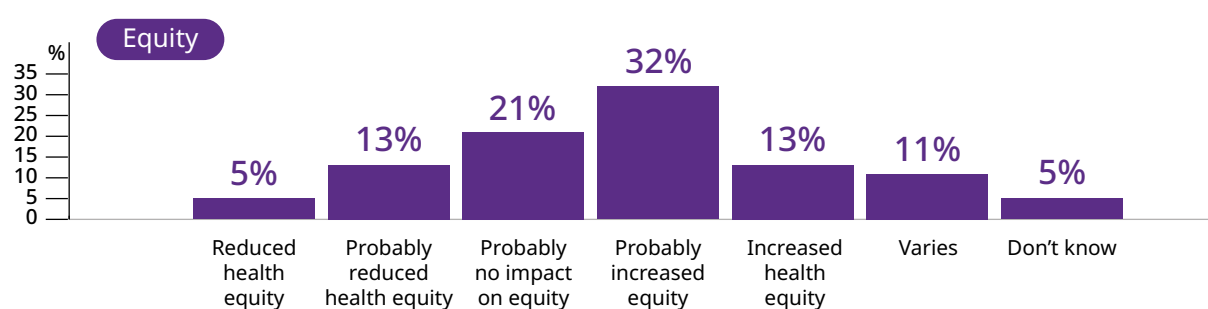


Fig. A4.4. Impact of proposed therapy as compared with current practice on acceptability (A), feasibility (B), resource use (C) and equity (D)

Relapse of VL in South-East Asia

- According to the non-patient stakeholders, use of LAmB or LAmB combined with paromomycin or miltefosine would be more acceptable, as use of LAmB for relapsed VL patients has been studied extensively and found to be even more effective when combined with other drugs. Use of alternatives to LAmB would be risky, as studies of use of alternatives in new VL cases have not found them to be effective. They also cautioned against use of a single high dose of LAmB, as its potential side-effects may be detrimental for patients.
- In terms of feasibility, non-patient stakeholders considered the advantages and disadvantages of LAmB or LAmB combined with other drugs (paromomycin plus miltefosine). LAmB is administered for a short duration, which is an advantage, and less drug resistance has been found when it is combined with other drugs. One challenge, however, is that LAmB requires proper cold chain storage in central hospitals, while the alternative drugs can be administered in community centres.
- Administration of a single dose of LAmB dose requires less resources.
- The impact on equity of the recommended treatment is equivalent to that of current practice, except for the gender inequity associated with miltefosine.

PKDL in eastern Africa

Should PKDL patients in eastern Africa receive paramomycin at 20 mg/kg once a day IM for 14 days in combination with miltefosine at an allometric dose orally BID for 42 days or LAmB at 5 mg/kg per day IV BID for 7 days (total dose, 20 mg/kg) in combination with miltefosine orally BID for 28 days? Acceptability is equivocal. The side-effects of miltefosine, e.g. ocular side-effects, are a concern, as it would be given for 42 days. They are less of a concern for paramomycin, which is administered for only a short duration. There are likely to be fewer side-effects of LAmB combined with miltefosine, as miltefosine is given for a shorter duration.

Paromomycin plus miltefosine may be more feasible than LAmB plus miltefosine. LAmB requires cold chain monitoring in hospitals, and administration of LAmB requires training of health-care providers. In both situations, proper administration of miltefosine must be monitored. The availability of LAmB may be a further challenge.

In terms of resource use, it is expected that paramomycin plus miltefosine will result in larger savings, as administration does not require hospitalization.

Gender equity was raised as a concern for women of reproductive age.

PKDL in South-East Asia

Should PKDL patients in South-East Asia receive LAmB at a total dose of 30 mg/kg, administered in six doses of 5 mg/kg twice a week for 3 weeks or miltefosine at 2.5 mg/kg to children between 2-11 years or 100 mg/day orally for 12 weeks? LAmB is probably more acceptable than miltefosine, as compliance with treatment with the latter is difficult and it is associated with ocular toxicity. The high dose of LAmB is another concern.

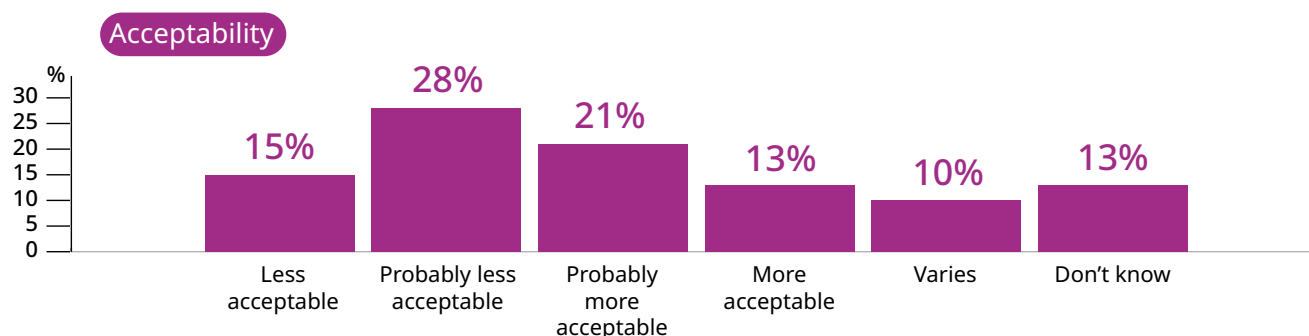
Storage and administration of LAmB were also cited barriers to implementation, while miltefosine is an oral drug, with fewer logistical storage requirements, although its administration does require monitoring.

There was a negligible difference in terms of resource use.

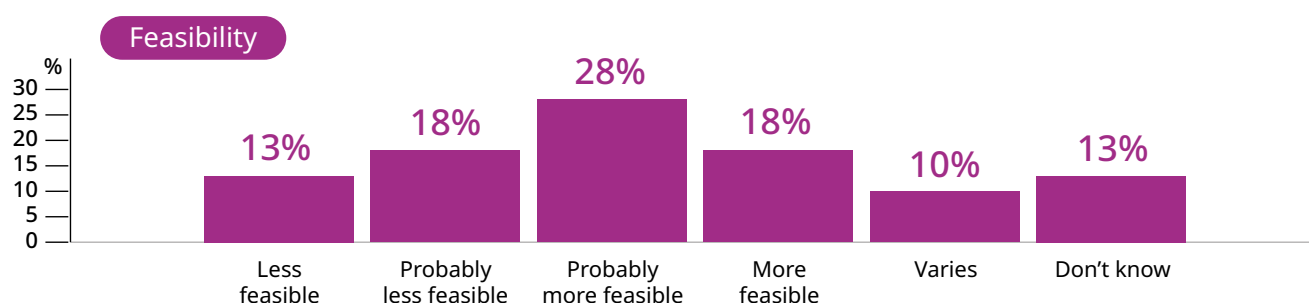
Screening for pregnancy and contraception can potentially reduce gender equity.

Fig. A4.5 illustrate the responses of non-patient stakeholders.

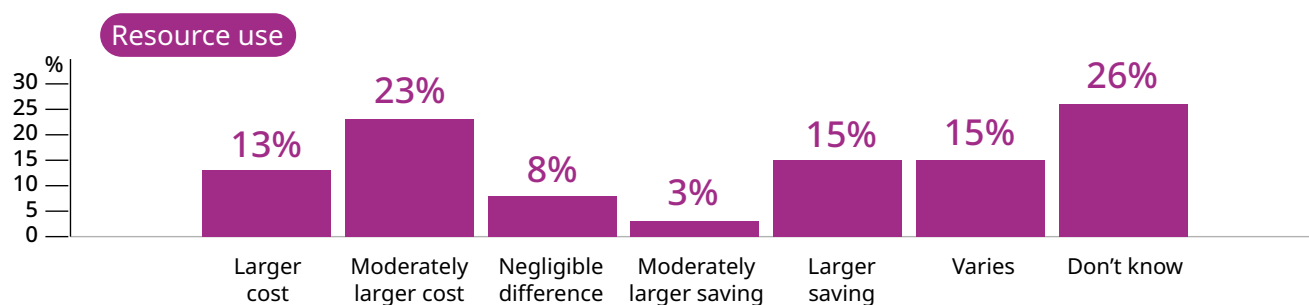
A. Impact on acceptability of proposed therapy as compared with current practice



B. Impact on feasibility of proposed therapy as compared with current practice



C. Impact on resource use of proposed therapy as compared with current practice



D. Impact on equity of proposed therapy as compared with current practice

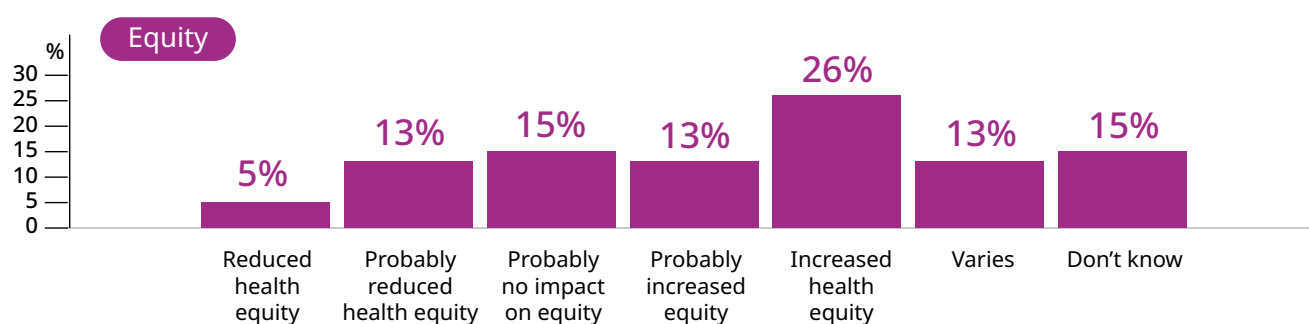


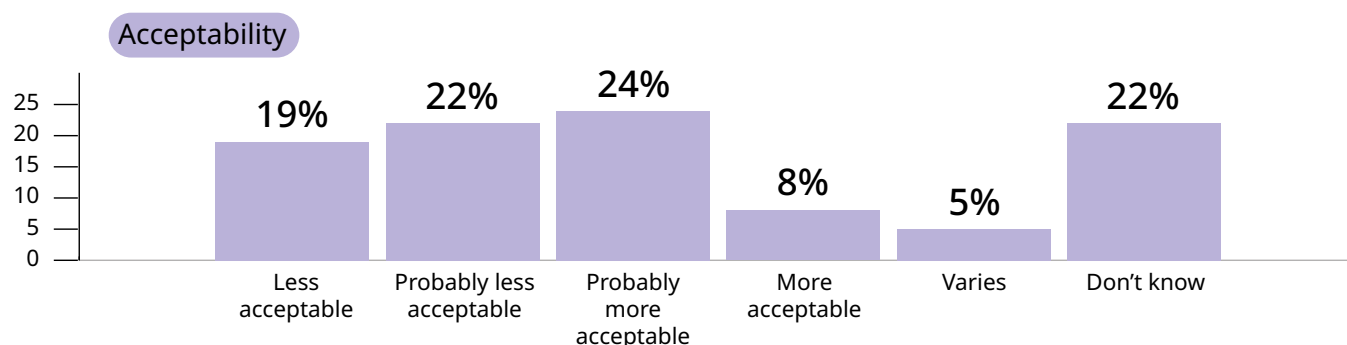
Fig. A4.5 Impact of proposed therapy as compared with current practice on acceptability (A), feasibility (B), resource use (C) and equity (D)

Should PKDL patients in South-East Asia receive LAmB in three IV injections of 5 mg/kg given on days 1, 8 and 15 in combination with miltefosine 100 mg/day orally after the first dose of LAmB and continued daily until the end of 45 days, or miltefosine 100 mg/day orally for 90 days (except for children aged 9–12 years and weighing <25 kg, who are given 50 mg/day for 90 days)? In general, patients prefer administration orally rather than by injection. Furthermore, the side-effects of LAmB confer less risk than those of miltefosine. As PKDL patients have only a cosmetic problem, hospitalization to receive medication may reduce compliance with treatment, and oral medication may be more acceptable. Furthermore, treatment is provided on alternative days, requiring frequent transport to receive treatment.

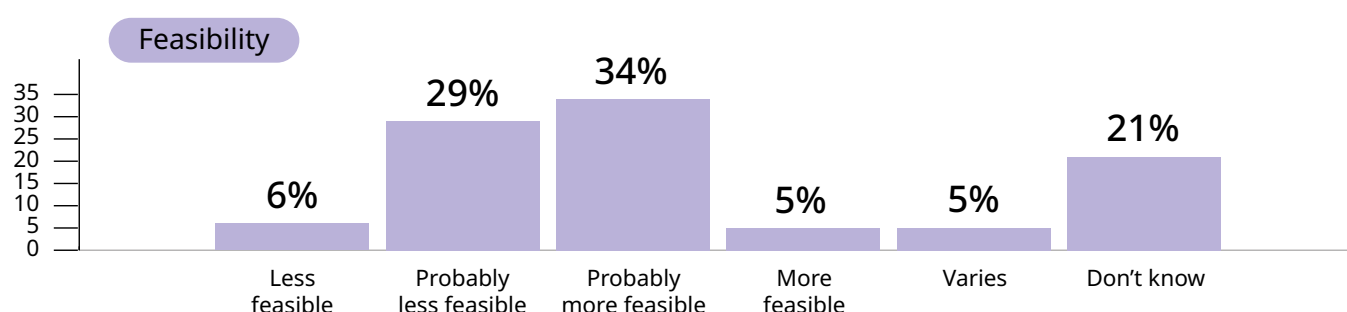
The proposed treatment would result in greater cost, as it requires hospitalization and a burden on the patient and caregivers. Miltefosine is more accessible, particularly for individuals living in rural areas.

Fig. A4.6 provides the responses of non-patient stakeholders.

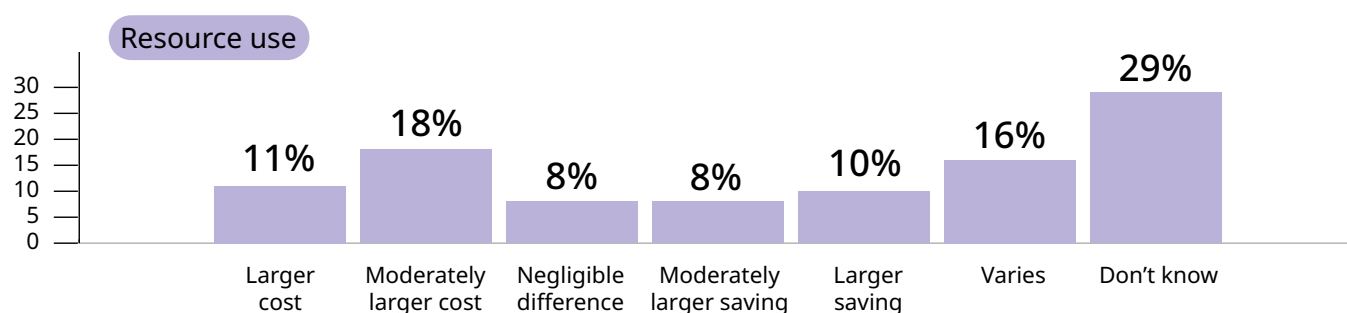
A. Impact on acceptability of proposed therapy as compared with current practice



B. Impact on feasibility of proposed therapy as compared with current practice



C. Impact on resource use of proposed therapy as compared with current practice



D. Impact on equity of proposed therapy as compared with current practice

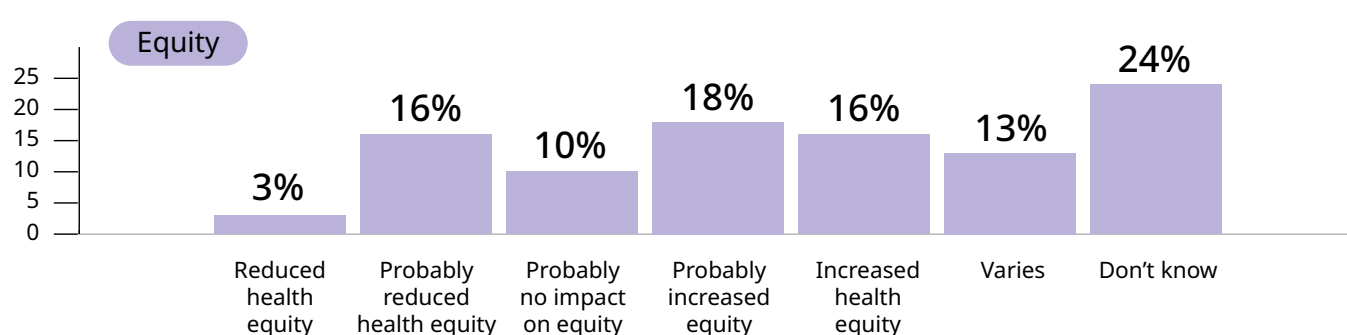


Fig. A4.6 Impact of proposed therapy as compared with current practice on acceptability (A), feasibility (B), resource use (C) and equity (D)

Annex 5

Summary of findings of studies of LAmB for the treatment of PKDL in South-East Asia

LAmB by dose for the treatment of PKDL	
Patient or population:	Children and adults with PKDL
Setting:	South-East Asia
Intervention:	LAmB monotherapy
Outcomes:	Cure
No. of participants (studies):	(10 non-single arm studies or single arms in comparative studies or RCTs) ^a
Certainty of evidence (GRADE):	very low ^b ⊗○○○
LAmB dose	Impact
LAmB 15mg/kg total dose	<u>3 single arm studies</u> report on LAmB 15mg/kg total dose: 213/272 most lesions resolved at 12 months follow up (32/272 showed improvement) (1, N=272, age not reported), 27/272 no improvement/new lesions, LAmB, 15 mg/kg IV in 5 doses of 3 mg/kg over 3 weeks) ▫ 213/280 cured at 12 months (32 major improvement, 7 lost to follow up (2, N=280, mean age 29.5 (15.8)), 15/280 no/limited improvement, 13/280 new lesions, LAmB, 15 mg/kg IV given over 15 days in 5 biweekly doses of 3 mg/kg ▫ 147/167 cured at 13 months (3, N=272, age not reported), relapse not reported, Liposomal amphotericin B 15 mg/kg IV total, given in 5 doses of 3 mg/kg over 3 weeks
LAmB 20mg/kg total dose	<u>1 arm of an RCT</u> reports on LAmB 20mg/kg total dose: 34 of 59 cured at 24 months, 18/63 cured at 12 months (4, N=63, age 7-59 years), 45/63 non-responders at 12 months, 25/59 non-responders at 24 months, 5/63 relapses at 24 months, Liposomal Amphotericin B 5 x 4 mg/kg on days 1, 4, 8, 11, and 15: total dose 20 mg/kg.
LAmB 30mg/kg total dose	<u>4 studies</u> (1 arm of an RCT, 1 arm of a comparative trial and 2 single arm studies reports) on LAmB 30mg/kg total dose: 75/89 cured (India), 70/88 cured (Bangladesh) cured (substantial or complete cure in those who completed follow up (1,2,3, N=442 (110 Bangladesh, 161 India, age not reported), no relapses, LAmB, 30 mg/kg IV in 6 doses of 5 mg/kg over 3 weeks

Jump to chapters			
Table of contents	1 Introduction	3 Background	6 Research
	2 Development of the guidelines	4 WHO Recommendations	7 Publication, dissemination and evaluation
	5 Medicines and implementation	8 Updating the guidelines	References Annexes

LAmB 30mg/kg total dose (continued)	▫ 35/47 final cure at 12 months follow up (5, N=50, age 23.4 (12.8)), relapse at 12 months follow-up 12/47, Liposomal amphotericin B total dose of 30 mg/kg, administered in six doses of 5 mg/kg, biweekly for 3 weeks ▫ 129/160 cured at 13 months (3, N=271, age not reported), relapse not reported, Liposomal amphotericin B 30 mg/kg IV total, given in 6 divided doses of 5 mg/kg over 3 weeks ▫ 91.6% initially cured at 3-5 months (6, N=12, age not reported), 1/12 relapse at 12 months, Liposomal Amphotericin B 0.5 mg/kg IV daily, 20 infusions for 3 courses at an interval of 15 days between each course
LAmB 40mg/kg total dose	<u>1 single arm study</u> reports on 40mg/kg total dose: 4/4 cured (1 after first cycle/3/4 after second cycle (7, N=4, 34-60 years), no relapses, LAmB, 20 mg/kg on alternate days in 4 divided doses (5 mg/kg/day), duration and route of administration not reported, 2 x cycles 28 days apart
LAmB 60mg/kg total dose	<u>1 arm of a non-randomized trial</u> reports on 60 mg/kg total dose: 83% of 12 initially cured at 3-5 months (6, N=12, age not reported), 1/12 relapses at 12 months, Liposomal Amphotericin B 1 mg/kg IV on alternate days, 20 infusions for 3 courses at an interval of 15 days between each course
LAmB – no dose reported	<u>2 studies</u> report on LAmB with no dose reported: 4/4 cured at 6 months (8, n=4, 14-60 years), relapse not reported, multi-dose LAmB (dose/schedule not reported) ▫ Cure not reported (9, N=155, all ages), relapse not reported, LAmB monotherapy (dose /schedule not reported)

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

^a Non randomised studies rated as low certainty evidence

^b Downgraded by one or more level for study design: single arm, non-comparative study

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Annex 6

Summary of findings of studies of miltefosine for the treatment of PKDL in South-East Asia

Miltefosine by dose for the treatment of PKDL

Patient or population:	Children and adults with PKDL
Setting:	South-East Asia
Intervention:	Miltefosine
Outcomes:	Cure
No. of participants (studies):	(24 non-randomized studies or single arms in comparative studies or RCTs) ^a
Certainty of evidence (GRADE):	very low ^b ⊗○○○

Miltefosine dose	Impact
Miltefosine 2.5 mg/kg per day in children	<u>Two single-arm studies</u> report use of miltefosine at 2 or 5 mg/kg in children: 6/6 cured at 12 months (1; n=6, <18 years), no relapses, miltefosine, 2.5 mg/kg per day orally for 12 weeks ▫ Cure not reported (2; 2019, n=80, 4–17years), relapse not reported, miltefosine (directly observed treatment), median dose 2.8 mg/kg per day oral (range, 1.8–3.9 mg/kg per day) for 12 weeks
Miltefosine 2.5 mg/kg per day in children and adults	<u>One single-arm study and three arms</u> of two RCTs report on 2.5 mg/kg per day in children and adults: 40/46 cured at 12 months (3, n=50, mean age, 28.9 (18.7), 6/46 relapses at 12 months, miltefosine 2.5 mg/kg or 100 mg/day orally for 12 weeks ▫ 14/18 cured at 12 months (4, n=18, mean age (SD) 29 (12), 1/18 relapses at 12 months, miltefosine 2.5 mg/kg per day orally for 12 weeks ▫ 13/18 cured at 12 months (4, n=18, mean age (SD) 24(9), 3/18 relapses at 12 months, miltefosine 2.5 mg/kg per day orally for 8 weeks ▫ Cure not reported (5, n=29, age median 26 (22–24), relapses not reported, miltefosine, 2.5 mg/kg per day orally for 12 weeks

Miltefosine 50 mg/day	<u>Four single-arm studies</u> report on 50 mg/day in children and adults: 6/6 cured at 12 months (6, n=6, age 5–65 years, miltefosine, 50 mg orally BID for 8 weeks) ▫ 2/2 cured (follow-up time not reported) (7, n=2, 36–60 years, miltefosine (50-mg oral doses given BID)
Miltefosine 50 mg/day (continued)	▫ 9/9 cured (follow-up time not reported) (8), n=9, age 14–50, miltefosine 50 mg BID for 12 weeks ▫ Cure not reported (9, n=194, 15–60 years, relapse not reported, miltefosine, 50 mg orally BID for 84 days)
Miltefosine 50 mg/day or 2.5 mg/kg per day in children	<u>One retrospective cohort study</u> reported on miltefosine 50 mg/day or 2.5 mg/kg per day in children ▫ 91/107 cured at 18 months (10, n=282, age 5–64 years, 12/107 relapses during 18 months, miltefosine 50 mg orally thrice daily for 2 months or BID for 3 months for adults and 2.5 mg/kg per day for 3 months in children. ▫ 5/5 cured at 18 months (10, n=5, age 5–64 years, no relapses during 18 months, miltefosine 50 mg orally thrice daily for 2 months or BID for 3 months for adults and 2.5 mg/kg per day for 3 months in children (plus Amphotericin B)
Miltefosine dose by weight in adults 50–150 mg/day and 2.5 mg/kg per day in children	<u>Four single-arm studies</u> report dosing by weight in adults and 2.5 mg/kg per day in children: 11/27 cured at 16 weeks (11, n=27, 10–60 years), 3/27 relapses at 12 weeks, miltefosine, 2.5 mg/kg per day (children aged 2–11 years) or 50–150 mg/day by body weight (aged ≥ 12 years) orally for 12–16 weeks ▫ 28/29 cured at 12 months (12, n=33, > 10 years), no relapse, miltefosine, 2.5 mg/kg per day (children) or 50–150 mg/day by body weight orally for 12 weeks ▫ 228/235 cured at 12 months (13, n=300, mean, 28 years, 7/235 relapses at 12 months, miltefosine, 2.5 mg/kg per day (children 2–11 years), 50 mg/day (≥ 12 years and < 25 kg body weight) or 100 mg/day (≥ 12 years and > 25 kg body weight) orally for 12 weeks ▫ 15/15 cured at 12 months (14, n=16, age not reported, 2/15 relapses at 18 months, miltefosine orally for 12 weeks at dosea: children aged 2–11 years, 2.5 mg/kg per day; 12 years and < 25 kg body weight, 50 mg/day; 25–50 kg, 100 mg/day; > 50 kg, 150 mg/day

Miltefosine doses 50–100 mg/day in adults and children	Five single-arm studies report various miltefosine doses: 3/14 cured at 12 months ([9 treatment or follow-up ongoing] 15, n = 14, age mean (SD) 24.4 (8.6), no relapses, miltefosine, 50 or 100 mg/day for 12–16 weeks ▫ 12/16 cured at 18 months (16, n = 16, age 15–60, 4 /18 relapsed after 12 months, miltefosine 100 mg/day orally for 90 days; except for 3 children aged 9–12 years weighing <25 kg who were given 50 mg/day for 90 days ▫ 2/3 cured at 84 days (17, n = 3, age 13–34 years, miltefosine 50 or 100 mg/day for 84 days ▫ 2/3 cured at 4–7 months (18, n = 3, 25–45 years, one relapse after 3 months, miltefosine , 50–100 mg BID orally for 8 weeks ▫ 4/4 discontinued miltefosine after eye complications (19, n = 4, 12–52 years, miltefosine, 60–150 mg/day orally for 84 days
Miltefosine 100 mg/day	<u>Two single-arm studies</u> report on miltefosine 1 000 mg/day in adults: 2/2 cured at 5 weeks (20, n = 2, age 23–27, relapse not reported, miltefosine 100 mg/day for 3 months) ▫ 5/5 discontinued miltefosine due to severe side-effects (21, n = 5, age 16–45, miltefosine , 100 mg/day orally for 35–65 days)
Miltefosine 150 mg/day	<u>One single-arm study</u> reported on miltefosine 150 mg/day in adults ▫ 23/26 cured at 12 months (22, n = 26, 17–60 years, no relapses at 12 months, miltefosine, 150 mg/day orally for up to 90 days)
Miltefosine no dose reported	<u>One single-arm study</u> reported on miltefosine with no dose reported: Cure not reported (23, n = 181, all ages, relapse not reported, miltefosine monotherapy (dose and schedule not reported)

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

^a Non randomised studies rated as low certainty evidence

^b Downgraded by one or more level for study design: single arm, non-comparative study

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Annex 7

Systematic review on treatments for visceral leishmaniasis (VL) and Post-kala-azar dermal leishmaniasis (PKDL) in East Africa and South-East Asia – Methods

Methods

We conducted a systematic review including search, screening and selection of studies, data extraction and management, data analysis, GRADE and interpretation of findings, and final report in accordance with general Cochrane recommendations (1). We used DistillerSR (2), an online collaborative software, for screening and data extraction and to facilitate project management in real-time.

In parallel with screening and data extraction for the systematic review, we collected contextual factors for the Evidence to Decision (EtD) framework.

Review questions

1. What is the efficacy and safety of different pharmacological treatments for the management of people diagnosed with PKDL in Eastern Africa?
2. What is the efficacy and safety of different pharmacological treatments for the management of people diagnosed with PKDL in South-East Asia?
3. What is the efficacy and safety of different pharmacological treatments for the management of immunocompetent people diagnosed with visceral leishmaniasis in Eastern Africa?
4. What are the efficacy and safety of the different pharmacological treatments for the management of immunocompetent people diagnosed with a relapse of visceral leishmaniasis in South-East Asia?

Objectives

- To evaluate the efficacy and safety of different pharmacological treatments for the management of individuals diagnosed with PKDL who live in Eastern Africa and South-East Asia.
- To evaluate the efficacy and safety of different pharmacological treatments for the management of immunocompetent individuals diagnosed with visceral leishmaniasis who live in Eastern Africa.
- To evaluate the efficacy and safety of different pharmacological treatments for the management of immunocompetent individuals diagnosed with a relapse of visceral leishmaniasis who live in South-East Asia.

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Population, Intervention, Comparisons, Outcomes, Study design (PICOS)

PICO 1	What is the efficacy and safety of different pharmacological treatments for the management of people diagnosed with post-kala-azar-dermal leishmaniasis (PKDL) in Eastern Africa?
Population	People with a diagnosis of PKDL who live in Eastern Africa PKDL diagnosis: as reported in the individual studies East Africa: Djibouti, Eritrea, Ethiopia, Kenya, Somalia, South Sudan, Sudan, Tanzania, Uganda Subgroups of interest include: ▫ Children ▫ Pregnant women ▫ Comorbid conditions (VL and PKDL at the same time, HIV coinfection) ▫ Severity of the disease^a ▫ Primary episode and relapse
Intervention	Antileishmanial medicines include: ▫ Pentavalent antimonials (meglumine antimoniate and sodium stibogluconate) ▫ Amphotericin B deoxycholate ▫ Lipid formulations of amphotericin B^b ▫ Miltefosine ▫ Paromomycin^c ▫ Azoles: ketoconazole, itraconazole ▫ Allopurinol ▫ Combinations of the above
Comparison	▫ Monotherapy vs. combination therapy (i.e., more than one medication is prescribed in the same regimen) ▫ Antimonials vs. non-antimonials ▫ Multiple doses vs. single dose
Outcome	Critical outcomes ▫ All-cause mortality ▫ Death due to leishmaniasis ▫ Clinical cure- healing of the lesion (rash disappearance): • at the time of completion of the treatment • 6-12 months after completion of treatment • 12 months after completion of treatment • may be reported as time to clinical cure

Outcome (continued)	▫ Treatment failure ▫ Relapse* – defined as diagnosis of the disease at any time after successful treatment (clinical cure), i.e., ≥ 6 months ▫ Treatment adherence ▫ Adverse events and serious adverse events related to treatment (e.g., ocular disorders such as ulcerative keratitis, leukocoria, ocular hyperaemia, photophobia, and blindness) Important outcomes ▫ Other complications related to the intervention ▫ Withdrawal from studies for any reasons ▫ Workload of healthcare staff ▫ Patient satisfaction
	*All patients having a relapse of the disease should be confirmed by medical personnel.
Review type	Intervention review
Study design	▫ Systematic reviews of randomised controlled trials (RCTs) ▫ RCTs ▫ Observational comparative studies for effectiveness ▫ All study designs for safety We included relevant full-text studies, conference abstracts, unpublished data provided by the WHO, and ongoing studies. Pre-clinical, qualitative research, modelling studies, and studies performed under laboratory conditions were excluded. Single case reports were also excluded.

^a PKDL in Eastern Africa is graded according to severity, grade 1-3. 80% of PKDL cases resolve spontaneously.

^b Liposomal amphotericin B 5 mg per kg intravenous infusion at D1, D3, D5, and D7 (20 mg per kg total) plus miltefosine in allometric doses orally for 28 days.

^c Paromomycin 20 mg per kg per day intramuscular for 14 days plus miltefosine in allometric doses orally for 42 days.

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PICO 2	What is the efficacy and safety of different pharmacological treatments for the management of people diagnosed with PKDL in South-East Asia?
Population	People with a diagnosis of PKDL who live in South-East Asia PKDL diagnosis: as reported in the individual studies South-East Asia: Bangladesh, Bhutan, India, Nepal, Sri Lanka Subgroups of interest include: □ Children □ Pregnant women □ Comorbid conditions (VL and PKDL at the same time, HIV coinfection) □ Severity of the disease □ Primary episode and relapse
Intervention	Antileishmanial medicines include: □ Pentavalent antimonials (meglumine antimoniate and sodium stibogluconate) □ Amphotericin B deoxycholate □ Lipid formulations of amphotericin B □ Miltefosine □ Paromomycin □ Azoles: ketoconazole, itraconazole □ Allopurinol □ Combinations of the above
Comparison	□ Monotherapy vs. combination therapy (i.e., more than one medication is prescribed in the same regimen) □ Multiple doses vs. single dose □ 4 weeks vs. more than 4 weeks
Outcome	Critical outcomes □ All-cause mortality □ Clinical cure- healing of the lesion (rash disappearance): • at the time of completion of the treatment • 6 -12 months after completion of treatment • 12 months after completion of treatment □ Relapse* – defined as diagnosis of the disease at any time after successful treatment (clinical cure), i.e., ≥ 6 months □ Treatment adherence □ Adverse events and serious adverse events related to treatment

Outcome (continued)	Important outcomes ▫ Other complications related to the intervention ▫ Withdrawal from studies for any reasons ▫ Workload of healthcare staff ▫ Patient satisfaction *All patients having a relapse of the disease should be confirmed by medical personnel.
Review type	Intervention review
Study design	▫ Systematic reviews of randomised controlled trials (RCTs) ▫ RCTs ▫ Observational comparative studies for effectiveness ▫ All study designs for safety We included relevant full-text studies, conference abstracts, unpublished data provided by the WHO, and ongoing studies. Pre-clinical, qualitative research, modelling studies, and studies performed under laboratory conditions were excluded. Single case reports were also excluded.

PICO 3	What is the efficacy and safety of different pharmacological treatments for the management of immunocompetent people diagnosed with visceral leishmaniasis (VL) in Eastern Africa?
Population	Immunocompetent people diagnosed with VL in Eastern Africa VL diagnosis: as reported in the individual studies East Africa: Djibouti, Eritrea, Ethiopia, Kenya, Somalia, South Sudan, Sudan, Tanzania, Uganda Subgroups of interest include: ▫ Children ▫ Pregnant women ▫ Severely acute malnutrition in women and children ▫ Comorbid conditions (e.g., VL and PKDL at the same time) ▫ Severity of the disease ▫ Primary episode and relapse
Intervention	Antileishmanial medicines include: ▫ Pentavalent antimonials (meglumine antimoniate and sodium stibogluconate) ▫ Amphotericin B deoxycholate ▫ Lipid formulations of amphotericin B ▫ Paromomycin (aminosidine)^a ▫ Pentamidine isethionate ▫ Miltefosine ▫ Azoles: ketoconazole, itraconazole ▫ Combinations of the above

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Comparison

- Monotherapy vs. combination therapy (i.e., more than one medication is prescribed in the same regimen)
- Antimonials vs. non-antimonials
- Multiple doses vs. single dose

Outcome

Critical outcomes

- All-cause mortality
- Clinical cure- disappearance of symptoms and negative diagnostic test:
 - at the time of completion of the treatment
 - 6 -12 months after completion of treatment
 - 12 months after treatment
- Relapse* – defined as diagnosis of the disease at any time after successful treatment (clinical cure)
- Treatment adherence
- Adverse events and serious adverse events related to treatment (e.g., gastric intolerance due to miltefosine in severely malnourished children)

Important outcomes

- Other complications related to the intervention
- Withdrawal from studies for any reasons
- Workload of healthcare staff
- Patient satisfaction
- PKDL

*All patients having a relapse of the disease should be confirmed by medical personnel.

Review type

Intervention review

Study design

- Systematic reviews of randomised controlled trials (RCTs)
- RCTs
- Observational comparative studies for effectiveness
- All study designs for safety

We included relevant full-text studies, conference abstracts, unpublished data provided by the WHO, and ongoing studies.

Pre-clinical, qualitative research, modelling studies, and studies performed under laboratory conditions were excluded. Single case reports were also excluded.

^a In various doses

PICO 4	What is the efficacy and safety of different pharmacological treatments for the management of immunocompetent people diagnosed with a relapse of VL in South-East Asia?
Population	Immunocompetent people diagnosed with a relapse of VL in South-East Asia VL relapse diagnosis: VL diagnosis some time after treatment success/cure has been established, or as reported in the individual studies South-East Asia: Bangladesh, Bhutan, India, Nepal, Sri Lanka Subgroups of interest include: ▫ Children ▫ Pregnant women ▫ Severely acute malnutrition in women and children ▫ Comorbid conditions (e.g., VL and PKDL at the same time) ▫ Severity of the disease ▫ People who had first-line treatment and present with symptoms any time after the initial care vs. People who could not have first-line treatment and present with symptoms any time after the initial care
Intervention	Antileishmanial medicines include: ▫ Pentavalent antimonials (meglumine antimoniate and sodium stibogluconate) ▫ Amphotericin B deoxycholate ▫ Lipid formulations of amphotericin B ▫ Paromomycin (aminosidine) ▫ Pentamidine isethionate ▫ Miltefosine ▫ Azoles: ketoconazole, itraconazole ▫ Combinations of the above Rescue treatment in case of non-response: conventional amphotericin B deoxycholate infusions or liposomal amphotericin B at higher doses.
Comparison	▫ Monotherapy vs. combination therapy (i.e., more than one medication is prescribed in the same regimen) ▫ Multiple doses vs. single dose ▫ 4 weeks vs. more than 4 weeks
Outcome	Critical outcomes ▫ All-cause mortality ▫ Clinical cure- disappearance of symptoms and negative diagnostic test: • at the time of completion of the treatment • 6 -12 months after completion of treatment • 12 months after completion of treatment ▫ Relapse* – defined as diagnosis of the disease at any time after successful treatment (clinical cure)

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Outcome (continued)

- Treatment adherence
- Adverse events and serious adverse events related to treatment

Important outcomes

- Other complications related to the intervention
- Withdrawal from studies for any reasons
- Workload of healthcare staff
- Patient satisfaction
- PKDL

*All patients having a relapse of the disease should be confirmed by medical personnel.

Review type

Intervention review

Study design

- Systematic reviews of randomised controlled trials (RCTs)
- RCTs
- Observational comparative studies for effectiveness
- All study designs for safety

We included relevant full-text studies, conference abstracts, unpublished data provided by the WHO, and ongoing studies.

Pre-clinical, qualitative research, modelling studies, and studies performed under laboratory conditions were excluded. Single case reports were excluded.

Search strategy

Electronic Search

An electronic search was conducted in the following databases: The Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials, Medline, and Embase. No date, publication status (published, unpublished, in press, and in progress) or language restrictions were used. In addition, we also searched ClinicalTrials.gov, ISRCTN, and the WHO Trials Registry for ongoing studies.

The four PICOs were combined into one search. The search strategy is available in Appendix 1 and Annex 8. We used a study design filter for comparative studies for efficacy/effectiveness and an adverse events filter to include all studies on safety. We also designed a geographic filter to limit the retrieval of studies to those conducted in the regions of interest.

Searching other resources

The reference lists of included studies and relevant systematic reviews was also scanned for additional relevant references. Researchers and organisations working in the field were also be contacted by the WHO for additional data.

Selection of studies

Two review authors independently screened all citations and abstracts identified by the search. We obtained full reports for potentially eligible studies, and these were also independently screened by two review authors. We resolved any disagreements by consensus or by involving a third reviewer.

Data extraction

One reviewer extracted data using pre-tested data extraction forms. A second reviewer crosschecked the extracted data. We resolved any disagreements about data extraction by referring to the study report and through discussion. For each included study, data on study setting/area, inclusion and exclusion criteria, methodology, patient diagnosis and characteristics, interventions, and outcome data was extracted.

Assessment of risk of bias in included studies

For RCTs or quasi-RCTs, we used the Cochrane Risk of Bias tool for RCTs version 2.0 (3).

For observational studies with a control group, we used the Cochrane Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) (4). We considered the most important confounders to be diagnostic or treatment delay, severity of disease, co-morbidity, age, sex, malnutrition.

The results of the risk of bias assessments were tabulated and we also provided an evaluation of the overall quality of the included studies. These assessment assisted with applying GRADE to the evidence at the outcome level.

Data analysis

We conducted random effects model meta-analysis in RevMan Web or STATA.

Where meta-analysis was not deemed appropriate (for example, when there was limited evidence, incomplete reporting of outcomes, studies of different designs or different interventions), we synthesized data narratively (5).

Measures of treatment effect

For dichotomous outcomes, we used risk ratios (RR) with their respective 95% confidence intervals (CIs).

For continuous outcomes, we used the mean difference (MD) if outcomes were measured in the same way between trials.

For time-to-event outcomes, we used hazard ratios (HR) with their respective 95% CIs.

Unit of analysis

We included cluster-randomized trials in the analyses along with individually randomized trials.

For multiple arm studies, we included pair-wise comparisons of the intervention groups that were relevant to the review and meet our inclusion criteria.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the studies in each analysis, but we also inspected heterogeneity visually. We planned to explore heterogeneity through pre-specified subgroup analyses, but there were too few studies to conduct these analysis.

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Dealing with missing data

We noted levels of attrition for each study arm, and we considered substantial levels of missing data in the risk of bias assessments.

Sensitivity analysis

We had planned performing the following sensitivity analyses, but not enough studies were included:

- restricting the analysis to published studies; and
- studies with low risk of bias.

Summarizing and interpreting results

We used the GRADE approach to interpret findings and create a 'Summary of findings' table for each PICO following the GRADE handbook (6,7). The tables provided the effect estimate and the associated certainty of evidence for each outcome of interest. It also allowed the guideline panel to judge the overall certainty of evidence for the PICO question.

References

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- Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355: i4919; doi: <https://doi.org/10.1136/bmj.i4919>.
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- Schünemann H, Brożek J, Guyatt G, Oxman A, editors. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. Available from <https://gdt.gradeapro.org/app/handbook/handbook.html>
- Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ 2016;353:i2016.

Appendix 1. Search strategy

Leishmaniasis Pharmacological Treatments (4 PICOs Combined) –

Ovid Multidatabase: **Embase** (1947 to 2023 May 31), **MEDLINE** (1946 to May 31, 2023),
EBM Reviews - Cochrane Central Register of Controlled Trials (inception to April 2023)

1. exp Leishmaniasis/
2. leishmania*.mp.
3. (kala azar or kalaazar or postkalaazar or espundia).mp.
4. 1 or 2 or 3
5. (miltefosin* or Impavido).mp.
6. Amphotericin B/
7. (amphotericin or pentamidine or ketoconazole or fluconazole).mp.
8. Pentamidine/
9. Ketoconazole/
10. Fluconazole/
11. Antimony Sodium Gluconate/
12. Meglumine Antimoniate/
13. Antimony/
14. ((anti leishmania* or antileishmania*) adj (pharmaco* or drug or drugs or medication* or medicine*)).ti,ab,kf.
15. (pentavalent adj3 antimon*).mp.
16. Urea stibamine.mp.
17. (AmBisome or aminosidine sulphate or Mefloquine).mp.
18. pentavalent Sb.mp.
19. sodium stibogluconate.mp.
20. Paromomycin/
21. (SbV or Sb5*).mp.
22. Pentoxifylline/ or Mefloquine/
23. (paromomycin or pentoxifylline).mp.
24. (meglumine antimoniate or Antimony Sodium Gluconate).mp.
25. or/5-24
26. 4 and 25
27. limit 4 to "therapy (best balance of sensitivity and specificity)"
28. 26 or 27
29. exp animals/ not humans/

30. 28 not 29
31. exp Drug Therapy/
32. ((pharmaco* or drug or drugs or medication* or medicine*) adj (treat* or therap* or manag*)).ti,ab,kf.
33. pharmacotherap*.ti,ab,kf.
34. 31 or 32 or 33
35. 4 and 34
36. 35 not 29
37. 30 or 36
38. africa/ or exp africa, eastern/ or burundi/ or djibouti/ or eritrea/ or ethiopia/ or kenya/ or rwanda/ or somalia/ or south sudan/ or sudan/ or tanzania/ or uganda/
39. indian ocean islands/ or comoros/ or madagascar/ or mauritius/ or reunion/ or seychelles/
40. malawi/ or mozambique/
41. (east africa* or eastern africa* or burundi* or urundi* or comoro* or comore* or comorian* or mayotte* or djibouti* or french somaliland* or eritrea* or ethiopia* or kenya* or madagasca* or malagasy* or malawi* or nyasaland* or mauritius* or mozambique* or mozambican* or rwanda* or rwandese or ruanda* or ruandese or seychell* or somali* or sudan* or tanzania* or tanganyika* or uganda*).mp,jw,cp,in,go,gc,ia.
42. 38 or 39 or 40 or 41
43. bangladesh/ or bhutan/ or exp india/ or nepal/ or pakistan/ or sri lanka/
44. Indian Ocean Islands/
45. afghanistan/ or iran/
46. Myanmar/
47. Tibet/
48. (afghan* or bangladesh* or bengal* or bangal* or bhutan* or india* or iran* or maldives* or maldivian* or indian ocean or myanmar* or burma* or burmese or nepal* or pakistan* or sri lanka* or ceylon* or south asia* or southern asia* or tibet* or kashmir*).mp,jw,cp,in,go,gc,ia.
49. (Delhi or Kathmandu or Lhasa or Bombay or Mumbai or Calcutta or Islamabad or Karachi or Peshawar or Colombo or Dhaka or Kabul or Kabol or Kandahar or Naypyidaw or Tehran or Thimphu or Kolkata or Lahore or Bengaluru or Bangalore or Chennai or Hyderabad or Ahm?dabad or Pune or Surat or Yangon or Chattogram or Kanpur or Jaipur or Faisalabad or Lucknow or Mashhad or Nagpur or Coimbatore).mp,jw,cp,in,go,gc,ia.
50. or/43-49

51. ((east* adj2 africa*) or Zambia* or Zimbabw* or Crozet Islands or Iles Crozet or "Scattered Islands" or "Iles Eparses" or "Addis Ababa" or Asmara or Anananarivo or Arusha or Axum or "Bahir Dar" or Berbera or Bulawayo or Dese or Eldoret or Garissa or Geita or Gondar or Great Rift Valley or Hargeisa or Hargeysa or Hola or Jinja or Iringa or Kigoma or Jimma or Korogwe or Nairobi or "Dar es Salaam" or Mombasa or Mogadishu or Dodomoa or Bujumbura or Mbeya or Lusaka or Harare or Kakamega or Kampala or Kigali or Kire Dawa or Kikuyu or Kisumu or Kitale or Kitui or Lilongwe or "Lake Victoria" or "Lake Tanganyika" or Lamu or Lodwar or Lokichogio or Malindi or Machakos or Marka or Machakos or Maputo or Maralal or Mek?ele or Mek ele or Mekele or Meru or Musoma or Mtwara or Mumias or Moshi or Moroni or Morogoro or Mwanza or Naivasha or Nanyuki or Nakuru or Namanga or Nyeri or "Port Louis" or Puntland* or Nyahururu or Kismayo or Ruiru or Rwenzori Mountains or Sinyanga or Songea or Tanga or Tabora or Taita Hills or Webuye or Zanzibar or ((Adiharush or Ali-Addeh or Alinjugur or Buramino or Dadaab or Dagahaley or "Dollo Ado" or Fugnido or Hagadera or Hilaweyn or Ifo or Kakuma or Kambioos or "Kayaka II" or Kobe or "Kyangwali Nakivale" or Nyarugusu or "Wad Sherife" or Bokolmanyu or Melkadida or Rwamanja) adj5 (camp or refug*))). mp,jw,cp,in,go,gc,ia.
52. ("Addis Abeba" or Antananarivo or Asmera or Dodoma or Salisbury or Juba or Khartoum or Khartum or Khurtum or Muqdish* or Victoria or Omdurman or Matola or Nyala or Blantyre).mp,jw,cp,in,go,gc,ia.
53. 51 or 52
54. 42 or 50 or 53
55. 37 and 54
56. exp Leishmaniasis/
57. leishmania*.mp.
58. (kala azar or kalaazar or postkalaazar or espundia).mp.
59. 56 or 57 or 58
60. (miltefosin* or Impavido or Miltex or Abelcet* or Amphotec* or Fungizon* or Mysteclin*).mp.
61. Amphotericin B/ or amphotericin B lipid complex/
62. (amphotericin or pentamidine or ketoconazole or fluconazole or Nebupent or Pentam or Pentostam or Glucantime).mp.
63. Pentamidine/
64. Ketoconazole/
65. Fluconazole/
66. antimony gluconate/
67. meglumine antimonate/
68. Antimony/
69. ((anti leishmania* or antileishmania*) adj (pharmaco* or drug or drugs or medication* or medicine*)).ti,ab,kw.
70. (pentavalent adj3 antimon*).mp.

71.	Urea stibamine.mp.
72.	(AmBisome or aminosidine sulphate or Mefloquine).mp.
73.	pentavalent Sb.mp.
74.	sodium stibogluconate.mp.
75.	Paromomycin/
76.	(SbV or Sb5*).mp.
77.	Pentoxifylline/ or Mefloquine/
78.	(paromomycin or pentoxifylline).mp.
79.	(meglumine antimon?ate or (Antimony adj2 Gluconate)).mp.
80.	or/60-79
81.	59 and 80
82.	limit 59 to "therapy (maximizes specificity)"
83.	81 or 82
84.	(animal experiment/ or exp animal/) not (human experiment/ or exp human/)
85.	83 not 84
86.	drug therapy/
87.	((pharmaco* or drug or drugs or medication* or medicine*) adj (treat* or therap* or manag*)).ti,ab,kw.
88.	pharmacotherap*.ti,ab,kw.
89.	86 or 87 or 88
90.	59 and 89
91.	90 not 84
92.	85 or 91
93.	africa/ or exp africa, eastern/ or burundi/ or djibouti/ or eritrea/ or ethiopia/ or kenya/ or rwanda/ or exp somalia/ or south sudan/ or sudan/ or tanzania/ or uganda/
94.	indian ocean islands/ or comoros/ or madagascar/ or mauritius/ or reunion/ or seychelles/
95.	malawi/ or mozambique/
96.	(east africa* or eastern africa* or burundi* or urundi* or comoro* or comore* or comorian* or mayotte* or djibouti* or french somaliland* or eritrea* or ethiopia* or kenya* or madagasca* or malagasy* or malawi* or nyasaland* or mauritius* or mozambique* or mozambican* or rwanda* or rwandese or ruanda* or ruandese or seychell* or somali* or sudan* or tanzania* or tanganyika* or uganda*).mp,cp,in,go,gc,ad,jx.
97.	("Addis Abeba" or Antananarivo or Asmera or Dodoma or Salisbury or Juba or Khartoum or Khartum or Khurtum or Muqdish* or Victoria or Omdurman or Matola or Nyala or Blan-tyre).mp,cp,in,go,gc,ad,jx.

98. or/93-97
99. bangladesh/ or bhutan/ or exp india/ or nepal/ or exp pakistan/ or sri lanka/
100. Indian Ocean Islands/
101. afghanistan/ or iran/
102. Myanmar/
103. Tibet/
104. (afghan* or bangladesh* or bengal* or bangal* or bhutan* or india* or iran* or maldives* or maldivian* or indian ocean or myanmar* or burma* or burmese or nepal* or pakistan* or sri lanka* or ceylon* or south asia* or southern asia* or tibet* or kashmir*).mp,cp,in,go,gc,ad,jx.
105. or/99-104
106. ((east* adj2 africa*) or Zambia* or Zimbabw* or Crozet Islands or Iles Crozet or "Scattered Islands" or "Iles Eparses" or "Addis Ababa" or Asmara or Anananarivo or Arusha or Axum or "Bahir Dar" or Berbera or Bulawayo or Dese or Eldoret or Garissa or Geita or Gondar or Great Rift Valley or Hargeisa or Hargeysa or Hola or Jinja or Iringa or Kigoma or Jimma or Korogwe or Nairobi or "Dar es Salaam" or Mombasa or Mogadishu or Dodomoa or Bujumbura or Mbeya or Lusaka or Harare or Kakamega or Kampala or Kigali or Kire Dawa or Kikuyu or Kisumu or Kitale or Kitui or Lilongwe or "Lake Victoria" or "Lake Tanganyika" or Lamu or Lodwar or Lokichogio or Malindi or Machakos or Marka or Machakos or Maputo or Maralal or Mek?ele or Mek ele or Mekele or Meru or Musoma or Mtwara or Mumias or Moshi or Moroni or Morogoro or Mwanza or Naivasha or Nanyuki or Nakuru or Namanga or Nyeri or "Port Louis" or Puntland* or Nyahururu or Kismayo or Ruiru or Rwenzori Mountains or Sinyanga or Songea or Tanga or Tabora or Taita Hills or Webuye or Zanzibar or ((Adiharush or Ali-Addeh or Alinjukur or Buramino or Dadaab or Dagahaley or "Dollo Ado" or Fugnido or Hagadera or Hilaweyn or Ifo or Kakuma or Kambioos or "Kayaka II" or Kobe or "Kyangwali Nakivale" or Nyarugusu or "Wad Sherife" or Bokolmany or Melkadida or Rwamanja) adj5 (camp or refug*))).mp,cp,in,go,gc,ad,jx.
107. (Delhi or Kathmandu or Lhasa or Bombay or Mumbai or Calcutta or Islamabad or Karachi or Peshawar or Colombo or Dhaka or Kabul or Kabul or Kandahar or Naypyidaw or Tehran or Thimphu or Kolkata or Lahore or Bengaluru or Bangalore or Chennai or Hyderabad or Ahm?dabad or Pune or Surat or Yangon or Chattogram or Kanpur or Jaipur or Faisalabad or Lucknow or Mashhad or Nagpur or Coimbatore).mp,cp,in,go,gc,ad,jx.
108. or/98,105-107
109. 92 and 108
110. 55 use medall
111. 109 use emczd
112. 26 or 35
113. 54 and 112
114. 113 use cctr
115. 110 or 111 or 114
116. remove duplicates from 115

Annex 8

Systematic review on treatments for visceral leishmaniasis (VL) and Post-kala-azar dermal leishmaniasis (PKDL) in Eastern Africa and South-East Asia – Search strategy, PRISMA flowchart, excluded studies

Search strategy

Leishmaniasis Search Strategies for Pharmacological Treatments (4 PICOs Combined)

Ovid Multidatabase: Embase (1947 to 2023 May 31), MEDLINE (1946 to May 31, 2023), EBM Reviews - Cochrane Central Register of Controlled Trials (inception to April 2023)

1. exp Leishmaniasis/
2. leishmania*.mp.
3. (kala azar or kalaazar or postkalaazar or espundia).mp.
4. 1 or 2 or 3
5. (miltefosin* or Impavido).mp.
6. Amphotericin B/
7. (amphotericin or pentamidine or ketoconazole or fluconazole).mp.
8. Pentamidine/
9. Ketoconazole/
10. Fluconazole/
11. Antimony Sodium Gluconate/
12. Meglumine Antimoniate/
13. Antimony/
14. ((anti leishmania* or antileishmania*) adj (pharmaco* or drug or drugs or medication* or medicine*)).ti,ab,kf.
15. (pentavalent adj3 antimon*).mp.
16. Urea stibamine.mp.
17. (AmBisome or aminosidine sulphate or Mefloquine).mp.

18.	pentavalent Sb.mp.
19.	sodium stibogluconate.mp.
20.	Paromomycin/
21.	(SbV or Sb5*).mp.
22.	Pentoxifylline/ or Mefloquine/
23.	(paromomycin or pentoxifylline).mp.
24.	(meglumine antimoniate or Antimony Sodium Gluconate).mp.
25.	or/5-24
26.	4 and 25
27.	limit 4 to "therapy (best balance of sensitivity and specificity)"
28.	26 or 27
29.	exp animals/ not humans/
30.	28 not 29
31.	exp Drug Therapy/
32.	((pharmaco* or drug or drugs or medication* or medicine*) adj (treat* or therap* or manag*)).ti,ab,kf.
33.	pharmacotherap*.ti,ab,kf.
34.	31 or 32 or 33
35.	4 and 34
36.	35 not 29
37.	30 or 36
38.	africa/ or exp africa, eastern/ or burundi/ or djibouti/ or eritrea/ or ethiopia/ or kenya/ or rwanda/ or somalia/ or south sudan/ or sudan/ or tanzania/ or uganda/
39.	indian ocean islands/ or comoros/ or madagascar/ or mauritius/ or reunion/ or seychelles/
40.	malawi/ or mozambique/
41.	(east africa* or eastern africa* or burundi* or urundi* or comoro* or comore* or comorian* or mayotte* or djibouti* or french somaliland* or eritrea* or ethiopia* or kenya* or madagasca* or malagasy* or malawi* or nyasaland* or mauritius* or mozambique* or mozambican* or rwanda* or rwandese or ruanda* or ruandese or seychell* or somali* or sudan* or tanzania* or tanganyika* or uganda*).mp,jw,cp,in,go,gc,ia.
42.	38 or 39 or 40 or 41
43.	bangladesh/ or bhutan/ or exp india/ or nepal/ or pakistan/ or sri lanka/
44.	Indian Ocean Islands/
45.	afghanistan/ or iran/
46.	Myanmar/
47.	Tibet/

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			6	Research
			7	Publication, dissemination and evaluation
			8	Updating the guidelines
				References Annexes

48. (afghan* or bangladesh* or bengal* or bangal* or bhutan* or india* or iran* or maldives* or maldivian* or indian ocean or myanmar* or burma* or burmese or nepal* or pakistan* or sri lanka* or ceylon* or south asia* or southern asia* or tibet* or kashmir*).mp,jw,cp,in,go,gc,ia.
49. (Delhi or Kathmandu or Lhasa or Bombay or Mumbai or Calcutta or Islamabad or Karachi or Peshawar or Colombo or Dhaka or Kabul or Kabol or Kandahar or Naypyidaw or Tehran or Thimphu or Kolkata or Lahore or Bengaluru or Bangalore or Chennai or Hyderabad or Ahm?dabad or Pune or Surat or Yangon or Chattogram or Kanpur or Jaipur or Faisalabad or Lucknow or Mashhad or Nagpur or Coimbatore).mp,jw,cp,in,go,gc,ia.
50. or/43-49
51. ((east* adj2 africa*) or Zambia* or Zimbabw* or Crozet Islands or Iles Crozet or "Scattered Islands" or "Iles Eparses" or "Addis Ababa" or Asmara or Anananarivo or Arusha or Axum or "Bahir Dar" or Berbera or Bulawayo or Dese or Eldoret or Garissa or Geita or Gondar or Great Rift Valley or Hargeisa or Hargeysa or Hola or Jinja or Iringa or Kigoma or Jimma or Korogwe or Nairobi or "Dar es Salaam" or Mombasa or Mogadishu or Dodomoa or Bujumbura or Mbeya or Lusaka or Harare or Kakamega or Kampala or Kigali or Kire Dawa or Kikuyu or Kisumu or Kitale or Kitui or Lilongwe or "Lake Victoria" or "Lake Tanganyika" or Lamu or Lodwar or Lokichogio or Malindi or Machakos or Marka or Machakos or Maputo or Maralal or Mek?ele or Mek ele or Mekele or Meru or Musoma or Mtwara or Mumias or Moshi or Moroni or Morogoro or Mwanza or Naivasha or Nanyuki or Nakuru or Namanga or Nyeri or "Port Louis" or Puntland* or Nyahururu or Kismayo or Ruiru or Rwenzori Mountains or Sinyanga or Songea or Tanga or Tabora or Taita Hills or Webuye or Zanzibar or ((Adiharush or Ali-Addeh or Alinjugur or Buramino or Dadaab or Dagahaley or "Dollo Ado" or Fugnido or Hagadera or Hilaweyn or Ifo or Kakuma or Kambioos or "Kayaka II" or Kobe or "Kyangwali Nakivale" or Nyarugusu or "Wad Sherife" or Bokolmanyu or Melkadida or Rwamanja) adj5 (camp or refug*))).mp,jw,cp,in,go,gc,ia.
52. ("Addis Abeba" or Antananarivo or Asmera or Dodoma or Salisbury or Juba or Khartoum or Khartum or Khurtum or Muqdish* or Victoria or Omdurman or Matola or Nyala or Blantyre).mp,jw,cp,in,go,gc,ia.
53. 51 or 52
54. 42 or 50 or 53
55. 37 and 54
56. exp Leishmaniasis/
57. leishmania*.mp.
58. (kala azar or kalaazar or postkalaazar or espundia).mp.
59. 56 or 57 or 58
60. (miltefosin* or Impavido or Miltex or Abelcet* or Amphotec* or Fungizon* or Mysteclin*).mp.
61. Amphotericin B/ or amphotericin B lipid complex/

62.	(amphotericin or pentamidine or ketoconazole or fluconazole or Nebupent or Pentam or Pentostam or Glucantime).mp.
63.	Pentamidine/
64.	Ketoconazole/
65.	Fluconazole/
66.	antimony gluconate/
67.	meglumine antimonate/
68.	Antimony/
69.	((anti leishmania* or antileishmania*) adj (pharmaco* or drug or drugs or medication* or medicine*)).ti,ab,kw.
70.	(pentavalent adj3 antimon*).mp.
71.	Urea stibamine.mp.
72.	(AmBisome or aminosidine sulphate or Mefloquine).mp.
73.	pentavalent Sb.mp.
74.	sodium stibogluconate.mp.
75.	Paromomycin/
76.	(SbV or Sb5*).mp.
77.	Pentoxifylline/ or Mefloquine/
78.	(paromomycin or pentoxifylline).mp.
79.	(meglumine antimon?ate or (Antimony adj2 Gluconate)).mp.
80.	or/60-79
81.	59 and 80
82.	limit 59 to "therapy (maximizes specificity)"
83.	81 or 82
84.	(animal experiment/ or exp animal/) not (human experiment/ or exp human/)
85.	83 not 84
86.	drug therapy/
87.	((pharmaco* or drug or drugs or medication* or medicine*) adj (treat* or therap* or manag*)).ti,ab,kw.
88.	pharmacotherap*.ti,ab,kw.
89.	86 or 87 or 88
90.	59 and 89
91.	90 not 84
92.	85 or 91
93.	africa/ or exp africa, eastern/ or burundi/ or djibouti/ or eritrea/ or ethiopia/ or kenya/ or rwanda/ or exp somalia/ or south sudan/ or sudan/ or tanzania/ or uganda/
94.	indian ocean islands/ or comoros/ or madagascar/ or mauritius/ or reunion/ or seychelles/

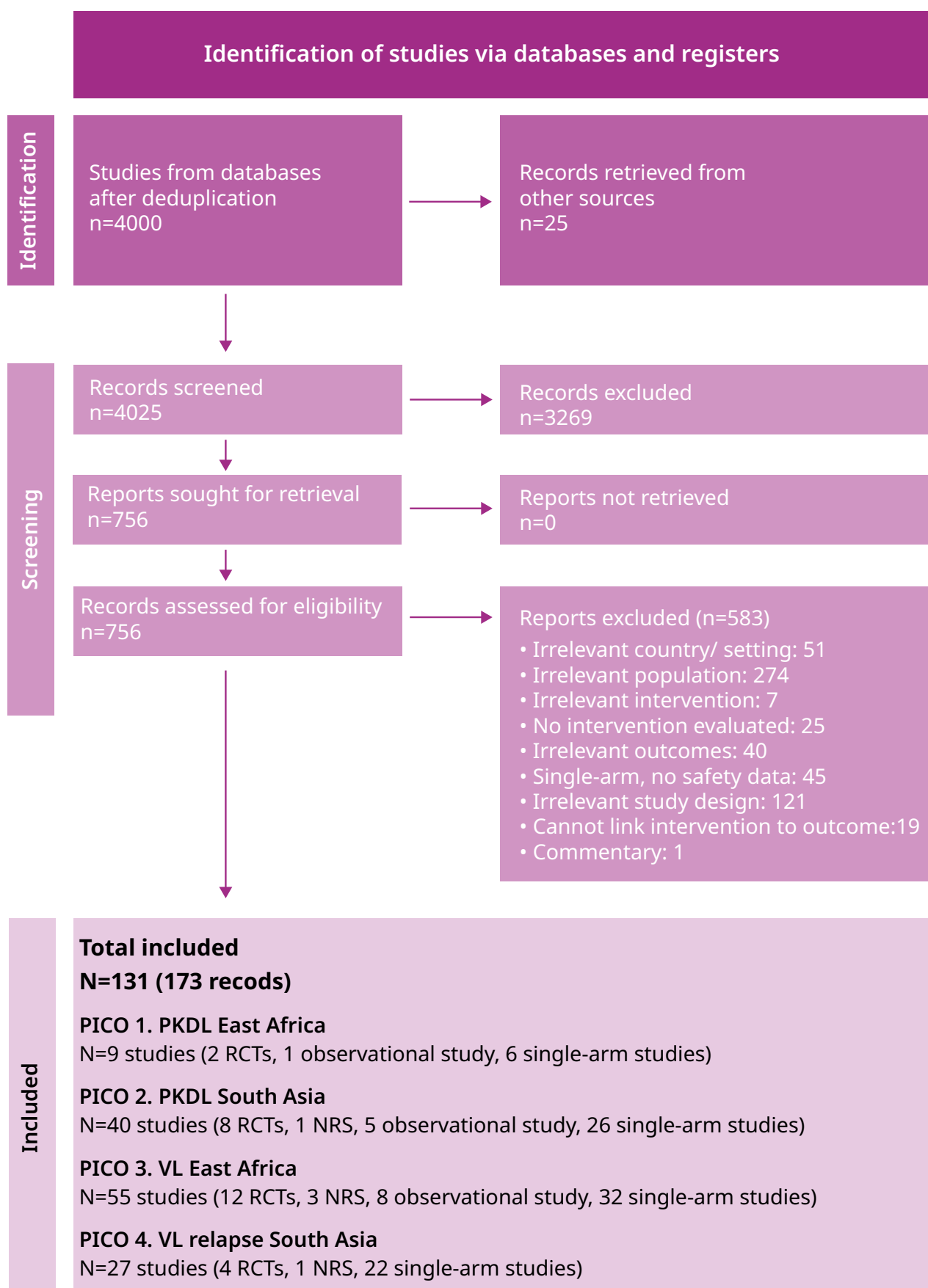
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95. malawi/ or mozambique/
96. (east africa* or eastern africa* or burundi* or urundi* or comoro* or comore* or comorian* or mayotte* or djibouti* or french somaliland* or eritrea* or ethiopia* or kenya* or madagasca* or malagasy* or malawi* or nyasaland* or mauritius* or mozambique* or mozambican* or rwanada* or rwandese or ruanda* or ruandese or seychell* or somali* or sudan* or tanzania* or tanganyika* or uganda*).
mp,cp,in,go,gc,ad,jx.
97. ("Addis Abeba" or Antananarivo or Asmera or Dodoma or Salisbury or Juba or Khartoum or Khartum or Khurtum or Muqdish* or Victoria or Omdurman or Matola or Nyala or Blantyre).mp,cp,in,go,gc,ad,jx.
98. or/93-97
99. bangladesh/ or bhutan/ or exp india/ or nepal/ or exp pakistan/ or sri lanka/
100. Indian Ocean Islands/
101. afghanistan/ or iran/
102. Myanmar/
103. Tibet/
104. (afghan* or bangladesh* or bengal* or bangal* or bhutan* or india* or iran* or maldives* or maldivian* or indian ocean or myanmar* or burma* or burmese or nepal* or pakistan* or sri lanka* or ceylon* or south asia* or southern asia* or tibet* or kashmir*).
mp,cp,in,go,gc,ad,jx.
105. or/99-104
106. ((east* adj2 africa*) or Zambia* or Zimbabw* or Crozet Islands or Iles Crozet or "Scattered Islands" or "Iles Eparses" or "Addis Ababa" or Asmara or Anananarivo or Arusha or Axum or "Bahir Dar" or Berbera or Bulawayo or Dese or Eldoret or Garissa or Geita or Gondar or Great Rift Valley or Hargeisa or Hargeysa or Hola or Jinja or Iringa or Kigoma or Jimma or Korogwe or Nairobi or "Dar es Salaam" or Mombasa or Mogadishu or Dodomoa or Bujumbura or Mbeya or Lusaka or Harare or Kakamega or Kampala or Kigali or Kire Dawa or Kikuyu or Kisumu or Kitale or Kitui or Lilongwe or "Lake Victoria" or "Lake Tanganyika" or Lamu or Lodwar or Lokichogio or Malindi or Machakos or Marka or Machakos or Maputo or Maralal or Mek?ele or Mek ele or Mekele or Meru or Musoma or Mtwara or Mumias or Moshi or Moroni or Morogoro or Mwanza or Naivasha or Nanyuki or Nakuru or Namanga or Nyeri or "Port Louis" or Puntland* or Nyahururu or Kismayo or Ruiru or Rwenzori Mountains or Sinyanga or Songea or Tanga or Tabora or Taita Hills or Webuye or Zanzibar or ((Adiharush or Ali-Addeh or Alinjogur or Buramino or Dadaab or Dagahaley or "Dollo Ado" or Fugnido or Hagadera or Hilaweyn or Ifo or Kakuma or Kambioos or "Kayaka II" or Kobe or "Kyangwali Nakivale" or Nyarugusu or "Wad Sherife" or Bokolmany or Melkadida or Rwamanja) adj5 (camp or refug*))).mp,cp,in,go,gc,ad,jx.

107. (Delhi or Kathmandu or Lhasa or Bombay or Mumbai or Calcutta or Islamabad or Karachi or Peshawar or Colombo or Dhaka or Kabul or Kabul or Kandahar or Naypyidaw or Tehran or Thimphu or Kolkata or Lahore or Bengaluru or Bangalore or Chennai or Hyderabad or Ahm?dabad or Pune or Surat or Yangon or Chattogram or Kanpur or Jaipur or Faisalabad or Lucknow or Mashhad or Nagpur or Coimbatore).mp,cp,in,go,gc,ad,jx.
108. or/98,105-107
109. 92 and 108
110. 55 use medall
111. 109 use emczd
112. 26 or 35
113. 54 and 112
114. 113 use cctr
115. 110 or 111 or 114
116. remove duplicates from 115

PRISMA flowchart

Note: a single search was conducted for all PICOs



Excluded studies (with reason for exclusion)

Ref ID	Bibliography	Reason for exclusion
1	2005. Safety and Efficacy Study of Paromomycin to Treat Visceral Leishmaniasis A Phase 3 Multicenter, Randomized, Controlled, Clinical Trial to Assess the Safety and Efficacy of Injectable Paromomycin in Patients With Visceral Leishmaniasis. (Clinical trial registration record)	Irrelevant population: VL (not relapse) in South-East Asia
4	2006. Combination Chemotherapy for the Treatment of Indian Kala-Azar Combination Chemotherapy for the Treatment of Indian Visceral Leishmaniasis: miltefosine Plus Liposomal Amphotericin B - Dose and Duration Ranging Study. (Clinical trial registration record)	Irrelevant population: VL (not relapse) in South-East Asia
6	2007. Combination Therapy in Indian Visceral Leishmaniasis A Randomised, Open-label, Parallel-group, Safety and Efficacy Study to Evaluate Different Combination Treatment Regimens (Co-administration), of AmBisome, Paromomycin and Miltefosine in Visceral Leishmaniasis (VL). (Clinical trial registration record)	Irrelevant population: VL (not relapse) in South-East Asia
7	2008. Single Infusion of Liposomal Amphotericin B in Indian Visceral Leishmaniasis A Phase III Randomized, Controlled, Clinical Trial to Assess the Safety and Efficacy of Single Infusion of Liposomal Amphotericin B in Patients With Visceral Leishmaniasis. (Clinical trial registration record)	Irrelevant population: VL (not relapse) in South-East Asia
8	2008. An Open Label Randomised Study to Assess the Safety and Efficacy of Short Course Paromomycin in Visceral Leishmaniasis An Open Label Randomised Two -Arm Study to Assess the Safety and Efficacy of Paromomycin Administered Intramuscularly at Two Different Dosing Regimens (14 Days Versus 21 Days) for the Treatment of Indian Visceral Leishmaniasis (VL). (Clinical trial registration record)	Irrelevant population: VL (not relapse) in South-East Asia
9	2008. Safety and Efficacy Study to Evaluate Different Combination Treatment Regimens for Visceral Leishmaniasis Randomized, Open-label, Parallel-group, Safety & Efficacy Study to Evaluate Different Combination Treatment Regimens, of Either AmBisome and Paromomycin, AmBisome and Miltefosine, or Paromomycin and Miltefosine Compared With Amphotericin B Deoxycholate (the Standard) Therapy for the Treatment of Acute, Symptomatic Visceral Leishmaniasis (VL), (Clinical trial registration record)	Irrelevant population: VL (not relapse) in South-East Asia
11	2010. Phase III, Study of Three Short Course Combo (AmBisome®, Miltefosine, Paromomycin) Compared With AmBisome for the Treatment of VL in Bangladesh A Phase III, Open Label, Randomised, Study of Three Short Course Combination Regimens (AmBisome®, Miltefosine, Paromomycin) Compared With AmBisome® Alone for the Treatment of Visceral Leishmaniasis (VL) in Bangladesh, (Clinical trial registration record)	Irrelevant population: VL (not relapse) in South-East Asia
12	2010. Single dose study of Liposomal Amphotericin (AmBisome) Rationalization of single dose 10 mg/kg/bw and 15 mg /kg/bw as compared to 5 mg/kg/bw for four days of Liposomal Amphotericin B with special reference to efficacy and safety profile for treatment of visceral leishmaniasis in Bihar, India, (Clinical trial registration record)	Irrelevant population: VL (not relapse) in South-East Asia
15	2011. An Effectiveness Study of Paromomycin IM Injection (PMIM) for the Treatment of Visceral Leishmaniasis (VL) in Bangladesh (Clinical trial registration record)	Irrelevant study design

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18	2013. Efficacy Trial of AmBisome Given Alone and AmBisome Given in Combination With Miltefosine for the Treatment of VL HIV Positive Ethiopian Patients A Randomized Trial of AmBisome Monotherapy and Combination of AmBisome and Miltefosine for the Treatment of VL in HIV Positive Patients in Ethiopia Followed by Secondary VL Prophylactic Treatment With Pentamidine, (Clinical trial registration record)	Irrelevant population: VL or VL relapse in HIV patients
19	2015. A randomized trial of AmBisomeÂ® single therapy and combination of AmBisomeÂ® and miltefosine for the treatment of Kala Azar in HIV positive patients in India A randomized trial of AmBisomeÂ® monotherapy and combination of AmBisomeÂ® and miltefosine for the treatment of Visceral Leishmaniasis in HIV positive patients in India, (Clinical trial registration record)	Irrelevant population: VL or VL relapse in HIV patients
21	2016. Combination of oral and intravenous drugs for treatment of kala-azar in India Combination chemotherapy against visceral leishmaniasis: comparative evaluation between miltefosine for 4 weeks and 2 weeks miltefosine combined with single dose liposomal amphotericin B in a tertiary care centre in Kolkata, (Clinical trial registration record)	Irrelevant population: VL (not relapse) in South-East Asia
27	2018. Steady State Global Bioequivalence Study of Amphotericin B Liposome for Injection 50 mg/ Vial in Fed Condition Multi-Center, Open-Label, Randomized, Two Treatment, Parallel, Single Period, Multiple-Dose, Steady State, Global Bioequivalence Study of Amphotericin B Liposome for Injection 50mg /Vial in Patients With Visceral Leishmaniasis, (Clinical trial registration record)	Irrelevant population: VL (not relapse) in South-East Asia
33	A, Abubakr O., M, Mohamed M., A, Hatim A., Elamin, Mohamed Y., Younis, Brima M., E, Mona E., Musa, Ahmed M., Elhassan, Ahmed M., G, Eltahir A. 2014. Visceral leishmaniasis-hepatitis B/C coinfections: a rising necessity to triage patients for treatment Annals of Saudi medicine, 34(2): 143-6.	No intervention (e.g., diagnostics, epidemiology)
35	Aalto, M. K., Sunyoto, T., Yusuf, M. A. A., Mohamed, A. A., Van Der Auwera, G., Dujardin, J. C. 2020. Visceral leishmaniasis, Northern Somalia, 2013-2019 Emerging Infectious Diseases, 26(1): 153-154.	Cannot link intervention to outcome ^a
48	Abdel-Hameed, A. A., Harith, A. E., Abdel-Rahim, I. M. 1989. Potential of a direct agglutination test (DAT) for detection of visceral leishmaniasis in a known endemic area in Sudan Tropical Medicine and Parasitology, 40(4): 470-471.	Single arm, no safety outcomes
55	Abdinia, Babak, Oliaei-Motlagh, Mohammad, Teimouri-Dereshki, Amir 2016. Pediatric visceral leishmaniasis in northwest of Iran Medicine, 95(44): e5261.	Irrelevant population: VL (not relapse) in South-East Asia
56	Abdo, M. G., Elamin, W. M., Khalil, E. A. G., Mukhtar, M. M. 2003. Antimony-resistant Leishmania donovani in eastern Sudan: Incidence and in vitro correlation Eastern Mediterranean Health Journal, 9(4): 837-843.	Single arm, no safety outcomes
58	Abdolsalehi, M., Pourakbari, B., Mahmoudi, S., Moradzadeh, M., Keshavarz, H., Mamishi, S. 2020. Clinical and epidemiologic features of visceral leishmaniasis in children: A 6-year study from an Iranian referral hospital Infectious Disorders - Drug Targets, 20(4): 461-466.	Irrelevant country / setting

67	Abongomera, Charles, Diro, Ermias, de Lima Pereira, Alan, Buyze, Jozefien, Stille, Kolja, Ahmed, Fareed, van Griensven, Johan, Ritmeijer, Koert 2018. The initial effectiveness of liposomal amphotericin B (AmBisome) and miltefosine combination for treatment of visceral leishmaniasis in HIV co-infected patients in Ethiopia: A retrospective cohort study PLoS neglected tropical diseases, 12(5): e0006527.	Irrelevant population: VL or VL relapse in HIV patients
68	Abongomera, C., Diro, E., Vogt, F., Tsoumanis, A., Mekonnen, Z., Admassu, H., Colebunders, R., Mohammed, R., Ritmeijer, K., Van Griensven, J. 2017. The Risk and Predictors of Visceral Leishmaniasis Relapse in Human Immunodeficiency Virus-Coinfected Patients in Ethiopia: A Retrospective Cohort Study Clinical Infectious Diseases, 65(10): 1703-1710.	Irrelevant population: VL or VL relapse in HIV patients
76	Abubakar, A., Ruiz-Postigo, J. A., Pita, J., Lado, M., Ben-Ismael, R., Argaw, D., Alvar, J. 2014. Visceral Leishmaniasis Outbreak in South Sudan 2009-2012: Epidemiological Assessment and Impact of a Multisectoral Response PLoS Neglected Tropical Diseases, 8(3): e2720.	Cannot link intervention to outcome ^a
80	Adam, G. K., Ali, K. M., Abdella, Y. H., Omar, S. M., Ahmed, M. A. A., Abdalla, T. M., Ali, A. A. 2016. Trend in cumulative cases and mortality rate among visceral leishmaniasis patients in Eastern Sudan: a 14-year registry, 2002-2015 International Journal of Infectious Diseases, 51: 81-84.	Cannot link intervention to outcome ^a
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87	Aderie, Endashaw M., Diro, Ermias, Zachariah, Rony, da Fonseca, Marcio Silveira, Abongomera, Charles, Dolamo, Bethabile L., Ritmeijer, Koert 2017. Does timing of antiretroviral treatment influence treatment outcomes of visceral leishmaniasis in Northwest Ethiopia? Transactions of the Royal Society of Tropical Medicine and Hygiene, 111(3): 107-116.	Irrelevant population: VL or VL relapse in HIV patients
93	Adriaensen, Wim, Cuypers, Bart, Cordero, Carlota F., Mengasha, Bewketu, Blesson, Severine, Cnops, Lieselotte, Kaye, Paul M., Alves, Fabiana, Diro, Ermias, van Griensven, Johan 2020. Host transcriptomic signature as alternative test-of-cure in visceral leishmaniasis patients co-infected with HIV EBioMedicine, 55: 102748.	Irrelevant population: VL or VL relapse in HIV patients
94	Adriaensen, W., Cuypers, B., Freiria Cordero, C., Mengasha, B., Blesson, S., Cnops, L., Kaye, P., Alves, F., Diro, E., Van Griensven, J. 2019. Host transcriptomic signatures as alternative test-of-cure in visceral leishmaniasis patients coinfecting with HIV European Journal of Immunology, 49(Supplement 3): 1193.	Irrelevant population: VL or VL relapse in HIV patients
106	Agarwal, Pradeep K. 2003. Miltefosine for Indian visceral leishmaniasis The New England journal of medicine, 348(9): 857-8.	Irrelevant study design
109	Aggarwal, P., Wali, J. P. 1988. Kala-azar in north India--nine years' experience Transactions of the Royal Society of Tropical Medicine and Hygiene, 82(3): 415.	Cannot link intervention to outcome ^a
110	Aggarwal, P., Wali, J. P. 1991. Profile of kala-azar in north India Asia-Pacific journal of public health, 5(1): 90-3.	Cannot link intervention to outcome ^a
118	Agrawal, V. K., Singh, Zile 2006. Miltefosine: First Oral Drug for Treatment of Visceral Leishmaniasis Medical journal, Armed Forces India, 62(1): 66-7.	Irrelevant study design

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120	Ahasan, H. A., Chowdhury, M. A., Azhar, M. A., Rafiqueuddin, A. K., Azad, K. A. 1996. Deaths in visceral leishmaniasis (Kala-azar) during treatment The Medical journal of Malaysia, 51(1): 29-32.	Irrelevant population: VL (not relapse) in South-East Asia
121	Ahasan, H. A. M. N., Rafiqueuddin, A. K. M., Azhar, M. A., Chowdhury, M. A. J. 1996. Ketoconazole in the treatment of visceral leishmaniasis (kala-azar) Tropical Doctor, 26(4): 197-198.	Irrelevant population: VL (not relapse) in South-East Asia
128	Ahmad, S., Chandra, H., Bhat, N. K., Dhar, M., Shirazi, N., Verma, S. K. 2016. North Indian state of Uttarakhand: a new hothouse of visceral leishmaniasis Tropical Doctor, 46(2): 111-113.	Irrelevant population: VL (not relapse) in South-East Asia
132	Ahmed, B. N., Nabi, S. G., Rahman, M., Selim, S., Bashar, A., Rashid, M. M., Lira, F. Y., Choudhury, T. A., Mondal, D. 2014. Kala-azar (Visceral Leishmaniasis) Elimination in Bangladesh: Successes and Challenges Current Tropical Medicine Reports, 1(3): 163-169.	Irrelevant study design
133	Ahmed, M. A. M., Suleman, S. M., Kordofani, A. A. Y., Mustafa, M. D. 1988. Outbreak of visceral leishmaniasis in the western bank of the White Nile - Sudan. Report and clinical study East African Medical Journal, 65(12): 824-828.	Single arm, no safety outcomes
139	Ahmed, T. S., Ibrahim Abdallah, E., Wdidi, S. A., Hamouda, D. G., Muddathir, A. R. M., Omer, A. E., Eltayeb, L. B. 2022. Hematological and Biochemical Changes among Visceral Leishmaniasis (Kala-Azar) Patients under Sodium Stibogluconate (SSG) and AmBisome Therapy International Journal of Pharmaceutical Research and Allied Sciences, 11(3): 26-33.	Irrelevant outcomes
140	Aikat, B. K., Sahaya, S., Pathania, A. G. S. 1979. Clinical profile of cases of kala-azar in Bihar Indian Journal of Medical Research, 70(4): 563-570.	Single arm, no safety outcomes
155	Akinsolu, F. T., Nemieboka, P. O., Njuguna, D. W., Ahadji, M. N., Dezso, D., Varga, O. 2019. Emerging resistance of neglected tropical diseases: A scoping review of the literature International Journal of Environmental Research and Public Health, 16(11): 1925.	Irrelevant outcomes
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^a These are observational studies that do not report outcome data stratified by which treatment the patients received.

Direct access to the web annexes



Web annex A.

Systematic review on the treatment of visceral leishmaniasis in eastern Africa



Web annex B.

Systematic review on the treatment of visceral leishmaniasis relapse in South-East Asia



Web annex C.

Systematic review on the treatment of post-kala-azar dermal leishmaniasis in eastern Africa



Web annex D.

Systematic review on the treatment of post-kala-azar dermal leishmaniasis in South-East Asia



Web annex E.

Evidence-to-decision tables



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