

Perspective

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Bridging the gaps in paediatric visceral leishmaniasis treatment: An urgent call to action

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A substantial proportion of those affected by visceral leishmaniasis (VL) in endemic regions are children—a vulnerable group at higher risk of severe outcomes, morbidity, and mortality. It is estimated that children account for around 50% of all VL cases[1], with a similar proportion seen in high-burden areas like Eastern Africa, where half of the cases occur in those under 15 years[2], highlighting the disproportionate impact on children and economically disadvantaged populations. Afflicted children are vulnerable to malnutrition, stunting, impaired cognitive development, school absenteeism and premature death.

Chemotherapy remains the cornerstone of visceral leishmaniasis management, with treatment options limited to a few drugs: antimonials (sodium stibogluconate and meglumine antimoniate), amphotericin B (both deoxycholate and liposomal forms), parenteral paromomycin, and miltefosine. A well-recognised challenge in paediatric diseases is the limited number of randomised clinical trials involving children, leading to a lack of high-quality evidence on drug choices, dosing, and efficacy tailored to this population[3]. Recently, we conducted a systematic review on the efficacy and safety of VL treatment in children[4]. The said gap in children was also evident in visceral leishmaniasis, along with other challenges.

It is crucial to recognise that children are not simply miniature adults. Drug pharmacokinetics are influenced by growth and development, leading to differences in drug responses compared to adults, which can vary further across stages such as the neonatal period, infancy, and adolescence[3,5]. Despite this, VL treatment guidelines are still largely extrapolated from adult data, leaving significant gaps in dosing, safety, and efficacy for paediatric populations.

Our systematic review revealed several disparities in the treatment of paediatric VL[4]. Of 1 186 records screened, only seven trials provided segregated, extractable paediatric data, and just three of those focused exclusively on children. A core message we wish to convey to the scientific community is the striking lack of paediatric-specific randomised trials, despite the high burden of VL in children. While many trials included a substantial number of children, most reported pooled adult and paediatric data, obscuring child-specific outcomes. This gap is also evident in the context of VL-HIV co-infection, as highlighted in the 2021 WHO guideline on treating VL in HIV co-infected individuals[6]. Although the WHO recommended liposomal amphotericin B and miltefosine as first-line therapy, none of the supporting trials included children, leaving the applicability of this combination in paediatric patients unclear. In our review, only two trials provided evidence for this regimen in HIV-negative

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children[7,8], revealing an overall efficacy of over 90%. However, efficacy varied significantly between regions—98.3% in the South-East Asia Region versus 74% in Africa. These disparities, coupled with the lack of child-inclusive data, emphasise the urgent need for paediatric-focused research and separate reporting of paediatric data. The failure of which leads to inequity in health care and compromises child health outcomes in endemic regions.

Miltefosine, the only oral drug for VL, showed the highest rate of paediatric treatment failures in our systematic review. This is likely due to the absence of allometric dosing, which results in lower drug exposure in children compared to adults. One trial reported efficacy as low as 54% when allometric dosing was not practised[7]. Supporting this, another study showed comparable miltefosine exposure between children and adults when allometric dosing was applied[9]. Given that miltefosine is recommended in combination regimens, such as second-line therapy with paromomycin in the Indian subcontinent[10], and with liposomal amphotericin B for HIV-VL co-infection[6], ensuring correct dosing is essential for best efficacy. We would like to highlight that proper allometric dosing of miltefosine is essential for optimal efficacy in children.

The variability and inconsistency of reporting safety data were identified as a barrier to treating children with the available VL drugs. It is noteworthy that only three trials in our review reported adverse events specifically for children. While some studies reported safety data, they often combined adult and paediatric outcomes, limiting their clinical value. Despite children being included in many VL trials, paediatric-specific safety data remain strikingly scarce. We strongly urge investigators to report paediatric outcomes separately, as this would greatly support clinical decision-making and help prevent avoidable harm. Overall, the reviewed regimens showed no major safety concerns. However, antimonial-related toxicities continue to present challenges to treatment completion in children.

We call on the scientific community to unite in addressing the challenges of VL in children. Funders and researchers need to prioritise dedicated paediatric trials and ensure segregated data reporting in mixed-age studies to accelerate evidence generation. The Strategic Plan 2021-2028 launched by Drugs for Neglected Diseases Initiative have recognised this urgency, committing to the inclusion of children in VL trials as part of their broader effort to advance treatment development.

Given that children represent a substantial proportion of those affected, establishing a dedicated paediatric VL pharmacovigilance network is strongly recommended, with contributions encouraged from all relevant research. We urge policymakers and guideline developers to require paediatric data when formulating treatment recommendations. As VL-endemic regions such as South Asia and East Africa often lack the resources to conduct paediatric trials, targeted funding and grant allocation for child-focused VL research should be actively promoted. Journals and reviewers are encouraged to mandate the age-specific reporting of adverse events in VL trial publications.

We advocate for paediatric-specific clinical trials, optimised dosing strategies, and standardised monitoring of adverse events to protect this vulnerable population. The scarcity of evidence for paediatric VL is a solvable crisis. With collective commitment, we can ensure that no child is subjected to substandard care. We call upon the global health community to urgently address this critical evidence gap for the children who represent the future of our world.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Authors' contributions

NLDS was involved in conceptualisation, drafting of the paper and critical revision. MH, TCY and SR were involved in the critical revision. NLDS and CSR performed the literature search. All authors read and approved the final manuscript.

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