# Research to support the elimination of visceral leishmaniasis

TDR BUSINESS LINE **10**

World Health Organization

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

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# List of abbreviations

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| **ACD** | Active case detection |
| **BL10** | Business Line 10 |
| **BMZ** | Federal Ministry for Economic Cooperation and Development (Germany) |
| **CFR** | Case-finding rate |
| **DNDi** | Drugs for Neglected Diseases initiative |
| **ERC** | Ethics Review Committee |
| **EVM** | Environmental management |
| **GCP** | Good clinical practice |
| **GTZ** | Deutsche Gesellschaft für Technische Zusammenarbeit |
| **GTZ-IS** | Deutsche Gesellschaft für Technische Zusammenarbeit international services |
| **HI** | Health information |
| **ICDDR,B** | International Centre for Diarrhoeal Disease Research, Bangladesh |
| **ICMR** | Indian Council of Medical Research |
| **IDRI** | Infectious Disease Research Institute |
| **IEDCR** | Institute of Epidemiology, Disease Control & Research |
| **iOWH** | Institute for OneWorld Health |
| **IRB** | Institutional review board |
| **IRS** | Indoor residual spraying |
| **LLIN** | Long-lasting insecticide-treated net |
| **M&E** | Monitoring and evaluation |
| **NIPSOM** | National Institute of Preventive and Social Medicine |
| **NTD** | Neglected Tropical Diseases (WHO department) |
| **PCD** | Passive case detection |
| **PCDT** | Point-of-care diagnosis and treatment |
| **PHC** | Primary health centre |
| **PI** | Principal investigator |
| **PKDL** | Post-kala azar dermal leishmaniasis |
| **R&D** | Research and development |
| **RTAG** | Regional technical advisory group |
| **SAC** | Strategic and Scientific Advisory Committee |
| **SEARO** | WHO Regional Office for South-East Asia |
| **STAC** | Scientific and Technical Advisory Committee |
| **TDR** | UNICEF, UNDP, World Bank, WHO Special Programme for Research and Training in Tropical Diseases |
| **VL** | Visceral leishmaniasis |
| **WHO** | World Health Organization |

# Overview and highlights

Visceral leishmaniasis (VL) is a fatal disease with an estimated incidence of 500 000 cases per year. Of these, 60% occur in the Indian subcontinent (India, Bangladesh and Nepal), mainly among the poorest population groups living in rural areas. New drugs and diagnostics have created an important new opportunity for improved disease management and even elimination of VL as a public health problem from the Indian subcontinent. In 2005, the health ministers of Bangladesh, India and Nepal signed a Memorandum of Understanding for joint efforts to eliminate VL by the year 2015. To achieve the elimination objectives, substantial progress is needed to increase availability of existing rapid diagnosis and effective therapies and to implement effective vector control.

The overall objective of TDR is to support research to develop and validate cost-effective interventions and strategies for the elimination of VL from the Indian subcontinent. An effective elimination strategy must target both the vector and the human reservoir, and this is reflected in the research supported by TDR as detailed herein. Implementation research supported by TDR in the three countries is also expanding, and the knowledge gained is being integrated into national elimination programmes. The envisioned end-product is the establishment of evidence-based and cost-effective strategies that combine vector control, active case detection and effective diagnostics and treatments. The impact will be the elimination of VL as a public health problem in the Indian subcontinent.

## Key highlights

Major progress has been made during the year on several important fronts, including case detection, vector control, identification of improved treatments for VL and post-kala azar dermal leishmaniasis (PKDL), and advocacy. These are briefly described below.

### Therapy for VL and PKDL (Treatment strategies)

A study to determine the efficacy and safety of a 14-day therapy combining miltefosine + liposomal amphotericin B (AmBisome®) was completed in India. Preliminary results showed an efficacy of the combination regimen of above 97% cure. This finding is important for the VL national elimination programme since it reduces therapy from the standard 28 days to 14 days. Reducing the number of days of treatment will prevent the development of resistance to miltefosine and will lead to increased treatment compliance, making the regimen more acceptable for individual patients and also more suitable for the region-wide elimination programme.

In another TDR-supported clinical trial completed in 2009, the efficacy of treating PKDL patients with 8 or 12 weeks of miltefosine was determined in India. Preliminary results show that the 12-week regimen is much better than 8 weeks, yielding a 93% versus 64% cure rate, respectively, at 12 months of follow-up. This study is central to the success of the VL elimination programme since PKDL subjects remain an important human reservoir for *Leishmania donovani,* particularly in Bangladesh where there are almost as many PKDL patients as VL patients. Notably, the current PKDL treatment standard is a 6-month course of treatment with pentavalent antimony, a totally intolerable treatment. Prior to this study, the evidence on the efficacy of PKDL treatment with drugs other than antimony was scarce.

### Case detection and case management (Preventive strategies)

Results from these studies conducted between April and November 2009 in 5 highly endemic districts showed that the annual incidence of VL in the endemic districts in 2009 was slightly lower than

in 2008, but 19 times higher than the elimination target for 2015 (less than one case annually per 10 000 inhabitants). The same studies underlined that in districts with a relatively poor passive case detection (PCD) system, active case-finding can double the number of VL cases diagnosed annually. The studies also compared different active case detection (ACD) methods and underlined the fact that ACD is the only means of effectively identifying "silent" PKDL cases, which constitute major reservoirs of continued disease transmission. Efforts required to identify one new VL case, in terms of numbers of household visits and associated cost per visit, varied according to the case detection strategy and level of endemicity. Interim results suggest adoption of a stratified case detection approach: the "camp approach" (mobile teams visiting endemic villages) in highly endemic areas; the "index case approach" (mobile teams doing house-to-house screening around index cases reported through the passive surveillance system) in lower endemicity areas; the "blanket approach" (house-to-house screening) in outbreak situations; and "passive surveillance" in middle-to-low endemicity areas with a traditionally well-established surveillance system. These findings, together with the findings on the feasibility of decentralized VL case management, are now being made available through documents and training activities to the national health services which will be the implementers of the next phase of studies on a large scale.

## Vector control (Preventive strategy)

Our previous first phase studies on vector control management had shown that indoor residual spraying (IRS) and, to a lesser extent, environmental management (EVM), as well as long-lasting insecticide-treated nets (LLINs), significantly reduced sandfly densities when applied by research teams but were much less effective in phase two studies when delivered through national programmes in India and Nepal. Major reasons for low efficacy of IRS were, among others, substandard spraying owing to insufficient training and supervision of spraying squads. In Bangladesh, in the absence of a national vector control programme, the mass treatment of existing non-impregnated bednets with slow-release insecticides was fairly easy to organize, was well accepted by the population, and had a significant vector reduction effect for 12 months and longer. Based on these studies, a monitoring and evaluation (M&E) toolkit for IRS and LLIN programmes was developed, validated and made available to vector control services in India and Nepal. The appropriate application of this toolkit on a large scale is now being tested.

## Pharmacovigilance

TDR supported the production and completion in 2009 of a pharmacovigilance handbook and CD to enhance the understanding and appreciation of kala azar by both health care providers and patients, and to raise awareness of potential side-effects associated with miltefosine treatment. The CD documents the story of a typical patient with kala azar and includes a description of the symptoms, diagnosis, treatment, side-effects and follow-up - including the completion of the patient card to ensure compliance and help monitor adverse events. Notably, the CD and handbook emphasized the importance of contraception in women of childbearing age because of the potential teratogenicity of miltefosine. This material was prepared by Dr Nilima Kshirsager from the Department of Infectious Diseases of Maharashtra University, Nashik, India. This handbook and CD are being made available to district hospitals and public health centres in VL-endemic areas.

## Advocacy and TDR's role in policy

TDR staff members met on several occasions in 2009 with ministers and secretaries of health from India, Bangladesh and the Bihar state to apprise them of the kala azar situation in their jurisdictions and to provide advice on intensifying the elimination efforts in the region. This resulted in parliamentary level discussions, raising the profile of the kala azar issue more broadly among policy-makers.

It was however learned that although there is strong commitment at the government level, this is not resulting in better management of kala azar at the village level. TDR will continue its major effort on the ground level to provide evidence to inform policy that will intensify the elimination efforts at the village level.

# 1. Context, strategic objectives and framework

## 1.1 Poverty/equity context

VL is a serious disease with major public health implications in the Indian subcontinent (Bangladesh, India and Nepal), East Africa (Ethiopia, Kenya and Sudan) and Latin America (Brazil). The incidence is an estimated 500 000 cases per annum, mostly affecting the poorest and most marginalized communities living in primarily rural areas. Of the annual cases, 60% occur in about 109 districts of India, Bangladesh and Nepal, where about 150 million people are at risk of developing VL.

Vector transmission is closely related to poor housing conditions, due to cattle and people often sleeping under one roof. Early symptoms of VL are often not reported to health workers, delaying treatment in areas of poor access, with the result that a large number of people continue to harbour the parasite and remain a source for new infection and continued transmission. Another source of infection is PKDL cases which remain "silent" and undetected in the community. PKDL is a condition that can occur in patients after the initial cure where the parasite relocates from the internal visceral organs to the skin, where it can be taken up by the sandfly vector.

One of the key challenges of the VL elimination strategy, therefore, is how to address the realities of people's health-seeking behaviour, and respond with a more active approach to case detection and treatment strategies in the context of poverty, poor accessibility and inadequate health services. Other challenges are the different applications of VL drugs (such as when and how to use oral, intramuscular or intravenous treatments) and their safety in malnourished and often overworked populations, as well as the individual's acceptance of the treatment, its possible side-effects, and the feasibility of case management at the primary health care level. TDR-supported implementation research must consider all of these issues in its current and future research activities.

Research on VL elimination encompasses a dynamic process of needs-based research to generate evidence to advise on policies and strategies in support of the elimination programmes. It is enhancing health research and leadership in disease endemic countries, building bridges between academic institutions and health services, and improving access to superior proven interventions. Elimination of VL will promote equity and poverty reduction, and will improve socioeconomic development of the targeted populations. Social science considerations are also an important complement in these restricted environments in addition to biological, epidemiological and ecological research.

## 1.2 Strategic objectives

### Overall objective

The overall strategic objective of this research is to develop and validate innovative and efficient interventions and strategies for the elimination of VL from the Indian subcontinent.

### Specific objectives

- Define research needs and priorities with major stakeholders, and provide technical guidance for research on the elimination of VL, in which investigators and programme managers from India, Nepal and Bangladesh play a major role.
- Generate evidence on cost-effective elimination strategies using optimal interventions across case detection, diagnosis, treatment and vector control.
- Evaluate how best to use existing diagnostics and therapies at the field level.

## 1.3 Strategic framework

The expected end-products will be evidence-based, cost-effective case-finding and case management systems using safe and effective drugs combined with cost-effective integrated vector management. Essential deliverables will be available by 2013 so that further scaling-up to all VL-endemic districts can be initiated; currently work is being scaled-up from the sub-district level (India and Bangladesh) and national level (Nepal) with coverage of several million population in the study areas. The outcome will be the adoption of evidence-based policies by the VL elimination programmes and the impact will be the elimination of VL as a public health problem in the Indian subcontinent.

Activities, end-products, expected outcomes and impact are presented in **Fig. 1**, and the monitoring of the milestones is shown in **Fig. 2**.