Research to support the elimination of visceral leishmaniasis

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

Overview and highlights

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.
**BL10 summary**

<table>
<thead>
<tr>
<th>Generic stage</th>
<th>Corresponding stage for research on access</th>
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<tbody>
<tr>
<td>7. Recommended for disease control use</td>
<td>Intervention/strategy implemented at scale</td>
</tr>
<tr>
<td>6. Testing in real-life settings</td>
<td>Research on scale-up</td>
</tr>
<tr>
<td>5. Finalization or intervention</td>
<td>Intervention/strategy recommended for use</td>
</tr>
<tr>
<td>4. Testing under controlled conditions</td>
<td>Multicentric evaluation of intervention/strategy and its cost-effectiveness</td>
</tr>
<tr>
<td>3. Initial design or intervention</td>
<td>Design new/improved interventions/strategy</td>
</tr>
<tr>
<td>2. Targeted studies to fill critical gaps</td>
<td>Exploratory research for possible solutions</td>
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<tr>
<td>1. Knowledge review</td>
<td>Problem/situation analysis</td>
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**Fig. 2.** Framework for monitoring milestones of downstream research (illustrative for BL9–11)
2. Key stakeholders, roles and responsibilities

The major partnerships are illustrated in Table 1.

**TABLE 1. OPERATIONAL PARTNERSHIPS AND ROLES**

<table>
<thead>
<tr>
<th>Operational partner</th>
<th>Role</th>
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| **VL control programmes:**  
  - Health ministries of India, Nepal, Bangladesh  
  - WHO–South-East Asia Regional Office | Help to define and set research strategies and implementation of evidence-based interventions |
| **Academic institutes:**  
  - Indian Council of Medical Research  
  - Rajendra Memorial Research Institute of Medical Sciences (India)  
  - International Centre for Diarrhoeal Disease Research (Bangladesh)  
  - National Institute of Prevention and Social Medicine (Bangladesh)  
  - Koirala Institute of Health Sciences (Nepal)  
  - Tribhuvan University (Nepal) | Collaborate and undertake research activities |
| **Financial institutions:**  
  - World Bank (through India)  
  - GTZ/BMZ (Federal Ministry for Economic Cooperation and Development, Germany) | Donors, financial support |
| **Public-private partnerships:**  
  - Drugs for Neglected Diseases Initiative (DNDi)  
  - Institute for OneWorld Health (iOWh)  
  - Infectious Disease Research Institute (IDRI)  
  - Industry: InBios, Paladin, Gilead | Collaborate in product development for VL control |
3. Implementation plan for 2009–2013 and progress

3.1 Progress and key milestones

Progress highlight 1: evaluation of improved therapies

The year 2009 has been important with respect to TDR-supported progress on treatment of VL and PKDL, building on previous studies reporting that in a small number of patients the combination of AmBisome® plus miltefosine was effective in treating VL. TDR has therefore initiated a larger study in two sites in India to confirm these observations and has confirmed that through combining AmBisome® with miltefosine, it is possible to reduce the treatment time by half, to 14 days from the current treatment of 28 days with oral miltefosine alone. This will increase compliance and reduce the likelihood of resistance developing against miltefosine. This further sets the stage for testing different combinations to identify the optimum combination and this is being conducted by DNDi through open discussions with TDR.

PKDL represents a much more difficult condition to treat than VL but must be a priority since this represents an important reservoir for Leishmania. TDR has supported a study showing that 12 weeks of miltefosine was effective in treating PKDL. This is also a major improvement over the current practice of using a 6-month treatment with pentavalent antimony. TDR will initiate a larger study in Bangladesh to confirm these observations from India.

Increasing evidence, including the Madrid meeting on VL treatment (July 2009), shows that AmBisome® may be important in the VL elimination strategy. TDR is at the forefront of supporting the first AmBisome® trials in Bangladesh and Nepal; these will be important for the licensing of AmBisome® for use in these countries.

Combination AmBisome® + miltefosine in India

The progress report of the combination AmBisome® + miltefosine therapy study in India was reviewed during the last Strategic and Scientific Advisory Committee (SAC) meeting (6–8 July, 2009). SAC recommended, and DSMB endorsed, that the trial was ceased given that there was little additional clinical meaning to be gained from increasing the sample from 121 patients (the number of subjects enrolled by the time the report was submitted to SAC) to 150 patients as originally planned. Increasing the number to 150, including the follow-up, would delay the publication of this study by almost 1 year and it was felt that these results should be communicated through peer review as soon as possible. With the current enrolment of 121 patients resulting in 118 cures, two failures and one death, the proportion of successes is 98%.

Miltefosine treatment of PKDL in India

The study to assess the safety and efficacy of miltefosine is almost complete in patients with PKDL in India; this could extend the use of miltefosine to PKDL treatment. The study evaluated the efficacy of treating PKDL patients with 8 or 12 weeks of miltefosine. Preliminary results show that the 12-week regimen is much better than 8 weeks: 93% versus 64% cure rate at 12 months of follow-up.

AmBisome® use in Bangladesh and Nepal

Phase 3 studies in Bangladesh and Nepal to evaluate the efficacy and safety of a short course of AmBisome® in a dose of 3 mg/kg daily for 5 days have been approved by SAC and the Ethics Review Committee (ERC) and are expected to start by the middle of 2010. These studies are essential for the licensing of AmBisome® to be used alone or in combination in these countries.
**Miltefosine use in Bangladesh**

A phase 4 study in Bangladesh for the treatment of VL with miltefosine was completed by October 2008; however, data cleaning and analysis has taken longer than anticipated. The study involved 979 subjects, both children and adults. Although data analysis has not been completed, preliminary results show a cure rate of 85 and 97%, respectively. Both compliance and efficacy were found to be satisfactory.

**Pharmacovigilance for use of miltefosine**

TDR supported the production and completion in 2009 of a pharmacovigilance handbook and CD to be used by doctors, health care workers and patients to raise awareness about kala azar and avoid side-effects and document adverse events 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. The handbook and CD will be made available to district hospitals and primary health centres in VL-endemic areas.

TDR is also considering the feasibility and cost of using case management software for VL surveillance that can also be used to support pharmacovigilance.

**Progress highlight 2: define optimal and most cost-effective elimination strategy to combine case management and vector control**

The case detection, case management and vector control programmes initiated in 2007 have successfully progressed to the stage in 2009 where they are now being scaled up to multiple centres. It is satisfying that we are now scaling up our research findings into the national control programmes involving millions of inhabitants in the Indian subcontinent.
Fig 3 and Fig. 4 summarize the studies on case detection and case management that have been conducted through different stages, from phase 1 conducted in 2007, phase 2 in 2008, phase 3 in 2009 and phase 4, initiated in 2009.

Key observations on case-finding and case management follow.

• Compared to phase 2 findings in 2008, in 2009 a lower annual incidence rate was estimated in the study districts: roughly 19 cases per 10,000 inhabitants (elimination target in 2015 is one per 10,000), but with a considerable variation between study districts and countries – the highest was in Bangladesh and the lowest was in Nepal.

• In districts with a relatively poor PCD system, house-to-house screening can almost double the number of VL cases encountered in 1 year.

• PCD is expensive for patients because they first use costly non-governmental providers before they come to the diagnostic centres (India and Nepal).

• An important benefit of ACD is the detection of the epidemiologically important PKDL cases. Here, however, case holding proves to be a challenge.

• Piloting the decentralized miltefosine treatment in India and Nepal at PHC/community level showed good compliance monitoring by providers and patient acceptance compared to control districts with routine treatment at hospital level.

• Private sector use by patients with VL in India (a pattern which is not fully understood and requires further research) and delays in treatment-seeking in all study areas were found to be high.

The application of different case detection methods according to endemicity level and performance level of the passive surveillance system would maximize

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**Question:**
What is people’s knowledge about VL and health-seeking behaviour when affected by VL?

**Phase I results:**
- Adequate knowledge about VL in India & Nepal, deficient in Bangladesh
- Long delay in diagnosis and treatment, often due to lack of resources
- Private sector important in India, public sector in Bangladesh and public sector and private pharmacies in Nepal

**Question:**
Can adequate drug management at PHC/community level improve public health sector use (India) & patient satisfaction, reduce treatment delay and strengthen adherence?

**Phase II results:**
Case management study hampered by reduced availability of 1st-line drugs in Nepal and India, no oral VL drug in Bangladesh; however, positive pilot experience with drugs management at PHC/community level & patients’ increased satisfaction

**Question:**
Given improved drug availability at PHC, what are favoring and limiting factors for adequate case-management and compliance in the research settings (sub-districts)?

**Phase III interim results:**
Performance (quality) of health staff at PHC level in patient management is still hampered; patient satisfaction in public sector is reasonable; indicators to be used in a monitoring tool kit for case management need further evaluation

**Question:**
What are constraints of patient management at PHC level in large geographical areas & what are possible answers?

**Phase IV to be measured:**
Prospects & constraints of health services-based, village-based case management through national programmes including modified DOT (directly observed therapy)

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Fig. 4. Summary of case management studies: health-seeking behaviour
the efficiency of case detection in terms of number and cost of houses visited to find one new case. The stratified approach looks like this: “camp approach” (mobile teams visiting endemic villages) in highly endemic areas; “index case approach” (mobile teams doing house-to-house screening around index cases reported through the passive surveillance system) in lower endemicity areas; “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.

VL vector control

Fig. 5 summarizes the sequence of VL vector studies, phases 1–3.

Phase 1 studies showed that IRS, and to a lesser extent EVM and LLINs, significantly reduced sandfly densities for at least 5–6 months in study households. Mud plastering did not reduce sandfly densities (Bangladesh study). Lime plastering in India and in one site in Nepal resulted in a significant reduction of sandfly densities, but not in the second Nepali site (where it is believed the lime was inactivated by acid soil). Lime plastering was also a more costly intervention — although as an effective, environmentally sustainable and traditional communal practice with high user acceptance it has inherent long-term advantages for sustaining vector control that could warrant further exploration.

Phase 2 studies showed that there were important performance issues in the national IRS programmes (India and Nepal) resulting in substandard bioassay results and vector trapping in sentinel houses. In Bangladesh, the impregnation programme for existing bednets (carried out under the supervision of the research teams) was successful in terms of high acceptance and user satisfaction; programme costs, as well as the long-lasting effect of the chemical under real-life conditions, are still being monitored.

Phase I results: RS and less LIN & EVM are efficacious when applied by researchers. Very limited vector control in Bangladesh but high coverage with non-impregnated bed nets.

Phase II results: Effectiveness of IRS with DDT in India and with pyrethroids in Nepal is limited. In Bangladesh massive net treatment is highly acceptable and feasible; high efficacy up to at least 6 months.

Phase III interim results: Validation of a monitoring tool kit & assessment of costs. Analysis in pilot district of feasibility, cost and acceptance of LLIN / IRS.

Phase IV to be measured: Prospects and constraints of a monitoring toolkit when applied by programme officers; level of programme improvement by using the toolkit.

Fig. 5. Sequence and summary of VL vector studies that will be adapted.
Phase 3 studies reconfirmed and quantified the deficiencies of national IRS programmes and developed and evaluated a monitoring toolkit for national vector control programmes. This will now be applied on a large scale in the forthcoming phase 4 studies. Standard operational procedures (SOPs) for the application of the toolkit have been developed and national programme managers have been trained to use it.

Progress highlight 3: strengthening the link with the regional technical advisory group and national programme managers of the elimination programme

TDR has longstanding experience in the region working through direct interactions, collaborative research and capacity strengthening. The elimination programme created through the WHO regional Office for South-East Asia (SEARO) includes a Regional Technical Advisory Group (RTAG) to oversee and provide technical inputs. TDR is fully recognized by, and participates in, this group’s annual meetings. Furthermore, TDR data analysis and protocol development workshops have been organized in such a way that RTAG members can follow principal investigator (PI) progress and provide direct input into their work. TDR was also invited to the programme managers’ meeting and a high-level meeting of ministries of health from 17 to 20 February 2009 to provide information on research findings in the region, and to the third meeting of the RTAG held in Dhaka, Bangladesh, in December 2009.

3.2 Significance of implementation research to TDR goals

This implementation research programme is a good example of how research can inform control and vice versa. It is also a unique example of how research may be scaled up from typically limited project areas to large-scale interventions managed by national programmes; this is a major objective of TDR. Policy-makers, RTAG, SEARO and WHO Neglected Tropical Diseases (NTD) acknowledge the stewardship and empowerment role of TDR in research to support the elimination initiative.

PIs of the implementation research were invited by policy-makers to advise on their strategies. Likewise, national programme managers have started to use the tools and strategies developed by TDR-supported research. This is documented in the SEARO report of the programme managers’ meeting in February 2009 in Delhi, and is directly evidenced by the TDR–GTZ training workshop of national programme managers in November 2009 in Kathmandu and in the report of the third RTAG meeting in Bangladesh, December 2009.

A special effort was made in 2009 to estimate the financial, infrastructural, supply and human resource requirements for scaling up the modified strategy to all VL-endemic districts in the three countries through regional experts in collaboration with other partners. This initiative was continued through the training of research teams in how to conduct workload assessment and cost analysis for scaling up case detection and decentralized treatment; the training was undertaken in India in November 2009 by the WHO Human Resources for Health department. All of these capacity-building efforts are within aspects of TDR’s mandate.

3.3 Implications of progress and global context changes

One of the challenging yet positive features is that VL case detection and treatment strategies are not fixed, but change over time; health services and treatment guidelines must adapt to these changes. Thus implementation research involving direct collaboration between academic institutions and health services will be needed to avoid encountering major pitfalls. An example of this changing situation is the new evidence that the combination therapy using a single dose of AmBisome® followed by miltefosine for 2 weeks showed a cure rate of 98%. The use of combination therapies, instead of the traditional monotherapy regimens using sodium stibogluconate or miltefosine, will increase patient treatment compliance, potentially reduce drug adverse reactions, and will protect against the development of *Leishmania* parasite resistance to miltefosine. The findings about the usefulness of treating PKDL patients with miltefosine have now stimulated further evaluation of the efficacy of this
regimen in Bangladesh, where the number of PKDL cases is almost as high as VL cases. There is also emerging evidence from India that a single dose (10 mg/kg) of AmBisome® on its own is effective at treating VL, and TDR will need to consider this in its future strategies.

Importantly, TDR is already at the forefront through the planned AmBisome®-alone trials in Nepal and Bangladesh, which are the first such trials in these countries.

The approved phase 4 implementation research projects on case detection and vector control will not only respond to issues discovered during phase 2 and 3 studies, but will also initiate scaling up activities to much larger geographical areas. Continued close cooperation with other partners and high-level policy-makers will be essential.

Cost-effective case detection strategies will be validated in the context of national programmes (including the camp, index case, house-to-house screening and incentive-based approaches as described above) and the performance of PHC services in the management of patients with VL will be analysed. In the vector management package, a complete monitoring and evaluation toolkit for district vector control services will be evaluated for its usefulness, acceptance and cost.

In 2010, a better interlinkage of all components of this business line will be achieved by adapting the findings of new treatment regimens to the public health and clinical services in the target countries, and by supporting the development of a software package which helps to monitor on a continuous basis all aspects of the VL elimination programme.

3.4 Activities for 2010 and beyond

Specific activities for 2009–2013 are listed in Table 2. In 2009, meetings with RTAG and follow-up meetings for the analysis of phase 3 case-finding, treatment strategies and VL vector control studies with PIs and national control programmes have taken place and these will continue in 2010. Efforts in the next year will be on further defining the best treatments for VL and PKDL in the context of data also being generated from WHO/NTD, DNDi, iOWH and others. Treatment for PKDL still remains a challenge and therefore we are continuing clinical trials for PKDL in Bangladesh.

Key issues include the phase 4 studies on vector control and case management that will be conducted in large geographic areas of the three countries (see Figs 3–5). Phase 3 clinical trials will evaluate using AmBisome® alone in Nepal and Bangladesh to help license the use of AmBisome® for the treatment of kala azar in these countries.

**Single-dose AmBisome® treatment at the community level**

In 2010, we plan to initiate a study to determine the feasibility and logistics of combining active case detection (ACD) and treatment at the community level. A major reason for taking this initiative at this time is that the emerging results from India show that a single dose of AmBisome® is safe and effective in the treatment of VL. It is therefore now feasible to diagnose an individual on one day and treat them on the same or the next day with a single dose of AmBisome®. It is proposed to determine the feasibility of extending this to the community level in clusters of high endemicity using ACD followed by diagnosis and treatment in primary health centres (PHCs) which are generally within a few kilometres of the endemic villages. The rationale is that combining ACD and single-dose AmBisome® treatment at the PHC level will be more effective at identifying and treating cases more rapidly and this will reduce the human reservoir in highly endemic areas, and reduce the burden both on patients and on the larger district hospitals. Efficacy will be determined through follow-up visits at 6, 12 and 24 months to determine long-term cure rates and subsequent PKDL levels in the treated individuals. It will be essential to closely monitor treated patients and establish whether potential side effects can be effectively managed at the PHC level.

It will also be possible to combine the ACD and single-dose AmBisome® treatment with ongoing TDR-supported vector control programmes. Targeting both the reservoir and the vector in the same endemic area would be the most effective approach to reduce new cases in highly endemic areas.
### Table 2. 2009-2013 Activities and Milestones

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Activities</th>
<th>Milestones</th>
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</table>
| 1. Provide stewardship and empowerment role to define needs, research priorities and technical guidance to research for elimination of VL | Annual meeting to reach consensus on policy for elimination (RTAG):  
- Follow-up meetings for the analysis of phase 3–4 case-finding in treatment strategies and VL vector control with PIs and national control programmes  
- Harmonization with other initiatives in the region, particularly with the World Bank in India, KALANET and the German development agency GTZ | Functional link with RTAG and stakeholders to assess and advise on policies for control and elimination strengthened (2013)  
Links with RTAG, control programmes and stakeholders strengthened (2009)  
Consensus on VL elimination policies, methods and guidelines for policy of use of evidence-based interventions developed (2013) |
| 2. Generate evidence on cost-effective elimination strategies using optimal interventions across case detection, treatments and vector control | Case detection/management:  
Compare cost, yield and feasibility of ACD through camp approach, index case approach, award approach and house-to-house approach (blanket approach)  
Assess performance (quality) of health staff at PHC level in patient management and patient satisfaction in public sector; develop and validate indicators to be used in a monitoring toolkit for case management; validate the monitoring toolkit at district level under programme conditions; estimate improved staff performance through standardized training programme. Create evidence regarding reasons for private-sector preference in India; develop/validate interventions and monitor improved public-sector use  
Vector management:  
Validation of a monitoring toolkit (including novel approaches to insecticide detection on surfaces) and assessment of feasibility, costs and acceptability at district and national programme levels  
Analysis in pilot district, and later at scale, of feasibility, cost, acceptance of combined approaches with IRS plus LLINs in Bangladesh (and eventually India and Nepal)  
Analyse new roles assigned to private/public sectors and validate performance and results after training and supportive monitoring | Most cost-effective case detection strategy determined (2010) and tested at scale under programme conditions (2012)  
Monitoring toolkit for staff performance, patient satisfaction, treatment adherence and related issues:  
a) developed and validated (2010)  
b) tested at scale under programme conditions (2012)  
Training programme for VL care providers developed and validated regarding improved knowledge, skills and performance by 2011 and tested under programme conditions (2012)  
Monitoring toolkit of vector management:  
a) developed, validated and cost of application assessed (2010)  
b) tested at scale under programme conditions (2012)  
Feasibility and operational costs of combined IRS/LLIN approach established:  
a) at project level (2010)  
b) at scale in Bangladesh (and later India and Nepal)  
New roles in vector management (including a range of stakeholders) defined and tested in real life of national programmes, and training outcomes validated (2012) |
3. Develop and evaluate improved therapies

<table>
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<tr>
<th>Objectives</th>
<th>Activities</th>
<th>Milestones</th>
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<tbody>
<tr>
<td></td>
<td>Start phase 3 AmBisome®-alone trials in Bangladesh and Nepal Focus on PKDL</td>
<td>Improved treatment interventions developed and introduced into policy (2012)</td>
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<td></td>
<td>Extension of miltefosine studies for the treatment of PKDL: a) complete miltefosine trial for patients with PKDL in India b) start miltefosine trial for patients with PKDL in Bangladesh</td>
<td>Miltefosine included in VL treatment in Bangladesh (2010)</td>
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<td></td>
<td>Build capacity in Bangladesh and Nepal to conduct studies following GCP requirements</td>
<td>Between 10 and 15 investigators trained in Bangladesh and Nepal in GCP and IRB (2010)</td>
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<td></td>
<td>Determine feasibility of linking ACD with point-of-care diagnosis and treatment (PCDT) in clusters of high infection levels. Patients with VL identified through ACD will be treated at the community level with a single dose of AmBisome®, monitored for adverse events and sent home the following day</td>
<td>AmBisome® included in VL treatment in Bangladesh and Nepal (2011)</td>
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<td></td>
<td>Help evaluate rk39 diagnostics from different manufacturers (with BL7)</td>
<td>Safe and affordable therapy in VL treatment developed (2012)</td>
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<td></td>
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<td>Combination therapy strategy implemented at scale (2012)</td>
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<td></td>
<td></td>
<td>Therapy for PKDL developed and introduced into policy (2012)</td>
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<td></td>
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<td>Dependable, reproducible rk39 diagnosis ensured by 2011</td>
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<td></td>
<td></td>
<td>Initiate implementation research for PCDT (2010)</td>
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<td></td>
<td></td>
<td>Perform 6- and 12-month follow-up visits in subdistricts where PCDT has taken place (2011)</td>
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</table>
4. Conclusions

The major challenges to eliminating VL can be overcome with evidence-based research activities in which researchers and health care providers from India, Nepal and Bangladesh play a pivotal role. Good progress is continuing on key fronts, including case detection, vector control and carrying out essential and timely clinical trials. The outcome of these TDR-supported studies will continue to inform policy that will integrate with national control programmes to establish sustainable strategies for VL elimination. Challenges have been identified through a participatory process, and results from several research projects have already been incorporated into country policies.
5. Annexes

5.1 Publications

Mondal D et al. The potential of insecticide treated bed nets in the visceral leishmaniasis elimination initiative of Bangladesh: an intervention study (submitted).


Hirve SS et al. Yield, costs and feasibility of active and passive case detection in the visceral leishmaniasis elimination initiative in India, Bangladesh and Nepal (submitted).


5.2 BL10 Strategic and Scientific Advisory Committee (SAC) membership

1. Professor Marleen BOELAERT, Chair, Institut de Médecine Tropicale, Epidemiology & Disease Control Unit, Department of Public Health, Antwerpen, BELGIUM

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7. Dr Suman RIJAL, B.P. Koirala Institute of Health Sciences, Department of Medicine, Ghopa, Dharan, NEPAL

8. Professor Shyam SUNDAR, Kala-azar Medical Research Center, Muzaffarpur, INDIA

9. Prof. Gundel Harms-ZWINGENBERGER, Director, Institut für Tropenmedizin Charité - Universitätsmedizin, Berlin, GERMANY
### 5.3 New projects approved by SAC in 2009

<table>
<thead>
<tr>
<th>Project title</th>
<th>Principal investigator</th>
<th>Institution</th>
<th>Country</th>
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<tbody>
<tr>
<td><strong>Implementation research on vector control</strong></td>
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<tr>
<td>Community-based VL vector control through insecticide-treated bednets: feasibility, cost and coverage</td>
<td>Shireen Akhter</td>
<td>NIPSOM</td>
<td>Dhaka, Bangladesh</td>
</tr>
<tr>
<td>Community-based VL vector control through insecticide-treated bednets: feasibility, cost and coverage</td>
<td>Dinesh Mondal</td>
<td>ICDDR</td>
<td>Dhaka, Bangladesh</td>
</tr>
<tr>
<td>Cost-effective integrated vector management as a contribution to the VL elimination initiative</td>
<td>Muari Das</td>
<td>BP Koirala</td>
<td>Sunsari, Nepal</td>
</tr>
<tr>
<td>Usefulness, feasibility and cost of vector control monitoring in kala azar-endemic districts (phase 3)</td>
<td>Chitra Gurung</td>
<td>Tribhuvan University</td>
<td>Kathmandu, Nepal</td>
</tr>
<tr>
<td>Usefulness, feasibility and cost of vector control monitoring in kala azar-endemic districts of Bihar, India</td>
<td>Pradeep Das</td>
<td>ICMR</td>
<td>Patna, India</td>
</tr>
<tr>
<td><strong>Implementation research on case management and treatment</strong></td>
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<tr>
<td>Towards more cost-effective VL case detection and management in endemic districts (phase 3)</td>
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<td>ICMR</td>
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<td>Shyam Sundar</td>
<td>Banaras Hindu University</td>
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<td>Towards more cost-effective VL case detection and management in endemic districts (phase 3)</td>
<td>Arum Sayami</td>
<td>Tribhuvan University</td>
<td>Kathmandu, Nepal</td>
</tr>
<tr>
<td>Cost analysis of various strategies for kala azar case detection and treatment in India, Nepal and Bangladesh</td>
<td>C. P. Takhur</td>
<td>Kala Azar Research Centre</td>
<td>Patna, India</td>
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<tr>
<td><strong>Therapy for VL</strong></td>
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<tr>
<td>Final report, phase 4 study on miltefosine for VL treatment in Bangladesh</td>
<td>M. Rahman</td>
<td>IEDCR</td>
<td>Dhaka, Bangladesh</td>
</tr>
<tr>
<td>AmBisome®/miltefosine combination for VL treatment in India</td>
<td>S. Sundar and P. K. Sinha</td>
<td>ICMR and Banaras University</td>
<td>Patna and Muzaffarpur, India</td>
</tr>
<tr>
<td>Safety and efficacy of oral miltefosine in patients with PKDL</td>
<td>S. Sundar and P. K. Sinha</td>
<td>ICMR and Banaras University</td>
<td>Patna and Muzaffarpur, India</td>
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<td>AmBisome® for the treatment of VL in Bangladesh</td>
<td>M. Rahman</td>
<td>IEDCR</td>
<td>Dhaka, Bangladesh</td>
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<tr>
<td>AmBisome® for the treatment of VL in Nepal</td>
<td>S. Rijal</td>
<td>Koirala Institute of Health Science</td>
<td>Kathmandu</td>
</tr>
</tbody>
</table>
The Special Programme for Research and Training in Tropical Diseases (TDR) is a global programme of scientific collaboration established in 1975. Its focus is research into neglected diseases of the poor, with the goal of improving existing approaches and developing new ways to prevent, diagnose, treat and control these diseases. TDR is sponsored by the following organizations: