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Editorial

Implementation research to support the initiative on the elimination of kala azar from Bangladesh, India and Nepal – the challenges for diagnosis and treatment

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Background

Visceral leishmaniasis (VL), known as kala azar, is a parasitic disease caused by *Leishmania* transmitted by sand flies which causes about 59 000 deaths per year and 2.4 million disability-adjusted life years (DALYs) lost (World Health Report 2002). India is the most affected country in the world and, together with Bangladesh and Nepal, accounts for about 300 000 cases annually and thus 60% of the global burden of the disease. In the three Indian subcontinent countries, kala azar is endemic in 109 districts and an estimated 190 million people are at risk of infection. The actual incidence rate of the disease is estimated to be about 8–10 times higher than the reported one in all three countries (Singh *et al.* 2006). More than 50% of the cases are reported from the border districts and an extension to new geographical areas has been observed. The disease occurs predominantly among the poorest of poor (Alvar *et al.* 2006). Because of breeding habits and focal distribution of the sand fly vector, cases tend to cluster in households.

On the Indian subcontinent, the mode of transmission is anthroponotic. Humans with kala azar provide the major reservoir for ongoing transmission; post kala azar dermal leishmaniasis (PKDL), though comparatively rare, is a chronic reservoir for initiation of an outbreak. A major challenge is the detection and management of symptomatic and asymptomatic infections which are the source and reservoir for leishmanial infections. Asymptomatic persons considerably outnumber symptomatic patients but the risk factors that influence the progression from asymptomatic infection to full blown disease are not yet clearly understood. Malnutrition is one risk factor for severe forms of the disease (Cerf *et al.* 1987).

Elimination initiative and expert meeting

The governments of Bangladesh, India and Nepal joined forces in 2005 to eliminate the disease from the region. The target is to reduce the incidence rate to below 1/10 000 at district level in India by the year 2010 and at sub-district level in Bangladesh and Nepal by the year 2015. The elimination strategy includes early diagnosis and complete treatment, effective disease and vector surveillance, vector control through integrated vector management including residual spraying, insecticide treated bed nets, if evidences are supportive, and environmental management, social mobilisation and implementation research.

However, in the affected areas the primary health centres are ill-equipped, skilled personnel is often not available and laboratory diagnosis not feasible. Vector control measures such as residual insecticide spraying and the use of insecticide-treated bed nets or curtains, which offer effective protection, are frequently poorly implemented and often beyond the means of families. The cost of VL diagnostic and treatment is largely borne by the patient's

family, enforcing the vicious cycle of poverty and disease (Alvar *et al.* 2006; Meheus *et al.* 2006). In the context of the elimination initiative, TDR/WHO supported implementation research is being undertaken by investigators of the three countries to identify cost-effective strategies for active case finding and Primary Health Care based case management (Mondal *et al.*, unpublished data) as well as efficient high quality vector control interventions (Anand *et al.*, unpublished data). The review of VL diagnosis and treatment options presented here will feed into research about the feasibility of house-to-house detection of new cases and of decentralized patient management and requirements for drug safety monitoring.

In April 2007, an Expert Meeting organised and supported by the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and the German Agency for Technical Cooperation (GTZ) on behalf of the German Federal Ministry of Economic Cooperation and Development was held with experts in clinical medicine, research and programme management. The major goal of the meeting was to review the challenges related to VL case detection and management in the implementation of the regional and national elimination plans, to look at efforts made with regard to diagnostics and treatment and to provide inputs into the design of ongoing implementation research activities.

Diagnosis

Adequate diagnosis is critical for VL and the demonstration of parasites in the spleen is considered the gold standard (Sundar *et al.* 2007). However, routine microscopy misses about 17% of kala azar cases (Sundar *et al.* 2007) and availability of PCR, the most reliable diagnostic means, is limited to well equipped laboratories. During the last years, several tests have become available for field diagnosis of leishmanial infection, all displaying advantages and disadvantages. TDR had commissioned two studies, one in Africa in Ethiopia, Kenya and Sudan and one in India and Nepal, for comparative evaluation of the serological tests with parasitological diagnosis in field settings (Sundar *et al.* 2006, 2007). Of the two tests the DAT-FD (Direct Agglutination Test, freeze-dried) and the rK39 strip test which performed equally well with regard to sensitivity, DAT has the advantage of being a semi-quantitative test, but has several drawbacks that make it less suitable as a field test. It requires multiple pipetting and takes long because of the necessity of overnight incubation. Once the freeze dried antigen is dissolved, it needs to be kept refrigerated until the entire vial is consumed. This is problematic in peripheral health centres where patients do not present in groups. The rK39 test (rK39 immunochromatographic strip test) is simple enough to be performed by a trained paramedic without any equipment and the results are unambiguous. The test can be stored at room temperature and has a shelf life of 18 months. Although the manufacturers recommend use of serum because of FDA approval, there is extensive experience using blood including that from finger prick (Sundar *et al.* 1998, 2007b). The test detects *Leishmania* antibodies. It does not differentiate between active or past or sub-clinical infections. It is currently the most convenient test for peripheral areas of endemic regions. The price of the rK39 test is about 1 US$ compared with US$1.5–2.5 for the DAT-FD (Sundar *et al.* 2007). The KAtex (Latex Agglutination Test) detecting *Leishmania* antigen has limitations in sensitivity. It uses urine which needs to be boiled for 10 min, again a procedure which is problematic for field application. The price is about US$1.5.

Available drugs

Pentavalent antimonial compounds are the recommended treatment in all parts of the world except for Bihar, India, where 60% of previously untreated patients did not respond to the WHO-recommended treatment of 20 mg for 30–40 days (Sundar 2001). Antimony is toxic and has a treatment related fatality rate of 3–5%. Conventional amphotericin B is therefore currently the drug of choice in Bihar. It achieves a high cure rate of more than 95% but the drug has to be applied in 15–20 daily infusions or on alternate days, for about 1 month. Infusion reactions are frequent and fatal toxicity occurs in 1%. The patient may die of a test dose because of anaphylactic shock. Treatment therefore requires close clinical and laboratory monitoring restricting amphotericin B administration to hospital care. India, at least Bihar, does not have the capacity to admit that many patients for such long periods. Furthermore, the supply of the drug is irregular in the public sector; it is more expensive than antimony and not affordable in the private sector (Sundar *et al.* 2004).

Over the last years, significant progress has been made in developing alternative treatments. In cooperation with WHO/TDR, *Miltefosine*, the first and only oral drug for the treatment of VL, has become more widely available. The development of oral therapy with miltefosine and simple rapid diagnosis with rK39 has led to the Indian subcontinent initiative to eliminate kala azar by year 2015 (TDR 2005). Miltefosine was chosen as the first line drug for the elimination programme. It is given at a dosage of 100 mg/day for 28 days and yields a cure rate of 94% in adults and children (Sundar *et al.* 2002). Miltefosine was also shown to cure antimony refractory cases. Although a very valuable

drug, it does have several drawbacks especially with regard to application at community level: as observed in phase III and IV studies, 2–3% of patients develop severe adverse reactions in the gastrointestinal tract or skin allergy; 1.3% of these have severe vomiting or diarrhoea, 0.6% renal toxicity and up to 1.2% have raised hepatic enzymes (Bhattacharya *et al.* 2007). The drug is contraindicated in pregnancy and contraception is necessary at childbearing age and during breastfeeding. Home treatment is possible but because of its long half life it has a high potential to develop resistance. Compliance needs to be ensured through strictly supervised public distribution system (Sundar & Murray 2005).

Paromomycin, developed by iOWH and TDR, supported by a grant of the Bill and Melinda Gates Foundation, was recently licensed and is produced in India. It yields a cure rate of 94.6% (Sundar *et al.* 2007a). In phase III trials, side effects such as ototoxicity were reversible while nephrotoxicity was not observed. So far, the only major drawback is that it needs to be injected over 21 days and causes pain at the injection site in half of the patients. With a cost of 10 US$ per treatment course, it is affordable and may qualify as a replacement of antimony and conventional amphotericin B in the future.

Liposomal amphotericin B (i. e. AmBisome, Gilead Sciences) has the highest therapeutic index of current antileishmanial drugs. A single dose was shown to cure more than 91% of patients (Sundar *et al.* 2001a). The liposomal formulation has substantially lower toxicity than conventional amphotericin B, no serious adverse reactions were observed. Because of its excellent safety profile, lipocomal amphotericin B is considered by most VL experts as the drug of choice for VL treatment (Aparicio 2007), and is used as first-line treatment in Europe. Phase III and IV trials should be planned to confirm the safety and single dose effectiveness. Very recently and after extensive advocacy by WHO, Gilead Sciences made AmBisome available at a WHO negotiated price of US$20 per 50 mg vial for VL to be distributed through the public health system. The high costs which so far excluded its use in most endemic areas are therefore no longer the stumbling block, and newer vistas open up in the treatment of VL.

Despite initial high efficacy demonstrated by every antileishmanial drug, there is a lurking danger of development of increasing unresponsiveness with passage of time contributed by poor compliance, inherent nature of the drugs, and inefficient public health systems. Thus, there is a need to develop short course multidrug regimens to ensure compliance, and prolong the effective lives of the drugs. The reduced AmBisome price provides several options for these combination therapies. There is a rationale for agencies like TDR, DNDi, Gates Foundation to invest in developing effective short course combinations.

Putting case detection and management on the map

As reported at the meeting, the TDR-initiated implementation research revealed an average annual incidence rate of kala azar in the three countries of 21/10.000 (TDR multi centre study, in preparation). To detect one case with fever and a positive rK39 test, 300 households would have to be visited. The recent finding that living within the same household as or within a range of 50 meters of an active case increases the risk of infection by a factor 25, indicates strong clustering and points to a role of active kala azar patients as a predominant infection reservoir (Bern *et al.* 2005). The delay between onset of symptoms and diagnosis, as well as the delay between diagnosis and start of treatment was longer than three weeks in India in 50% of patients (TDR multi centre study, in preparation). This delay provides opportunity for endophagic sand flies to become infected and transmit infection.

Conclusion

There is clear ground for optimism based on the strong political will which lead to increased funding and the establishment of a Regional Technical Advisory Group (RTAG), improved diagnostics and drugs as well as joint research activities generating evidence for cost-effective public health interventions in the VL elimination initiative.

Implementation research will show how the existing health systems in Bangladesh, India and Nepal and already overburdened health workers will be able to cope with yet another task - active case detection of kala azar and treatment of a growing number of patients. In addition, a coordinated effort among the three countries to manage the trans-border flux of cases is needed. From the public health view and guided by research evidence, investment of resources into transmission control and a strong integration of early diagnosis and treatment into the existing health services and improvement of access to diagnosis and treatment for the marginalized poor will be favourable options to reach the goal of elimination of kala azar by the year 2015.

References

Alvar J, Yactao S & Bern C (2006) Leishmaniasis and poverty. *Trends in Parasitology* **22**, 552–557.

Aparicio P Comments (2007) *World Health Organization, First Meeting of the Subcommittee of the Expert Committee on the*

Selection and Use of Essential Medicines. Geneva, 9–13 July 2007 (Section 6.5.2).

Bern C, Hightower AW, Chowdhury R *et al.* (2005) Risk factors for kala azar in Bangladesh. *Emerging Infectious Diseases* **11**, 655–662.

Bhattacharya SK, Sinha PK, Sundar S *et al.* (2007) Phase 4 trial of miltefosine for the treatment of Indian visceral leishmaniasis. *Journal of Infectious Diseases* **196**, 591–598.

Cerf BJ, Jones TC, Sampaio R & Teixeira R (1987) Malnutrition as a risk factor for severe visceral leishmaniasis. *Journal of Infectious Diseases* **168**, 986–993. Quoted in: Jha TK (2006) Drug unresponsiveness & combination therapy for kala-azar. *The Indian Journal of Medical Research* **123**, 389–398.

Meheus F, Boelaert M, Baltussen R & Sundar S (2006) Costs of patient management of visceral leishmaniasis in Muzaffarpur. *Tropical Medicine and International Health* **2**, 1715–1724.

Singh SP, Reddy DC, Rai M & Sundar S (2006) Serious underreporting of visceral leishmaniasis through passive case reporting in Bihar, India. *Tropical Medicine and International Health* **11**, 899–905.

Sundar S (2001) Drug resistance in Indian visceral leishmaniasis. *Tropical Medicine and International Health* **6**, 849–854.

Sundar S & Murray HW (2005) Availability of miltefosine for the treatment of kala-azar in India (perspective). *Bulletin of the World Health Organization* **83**, 394–395.

Sundar S, Reed SG, Singh VP, Kumar PC & Murray HW (1998) Rapid accurate field diagnosis of Indian visceral leishmaniasis. *Lancet* **351**, 563–565.

Sundar S, Agrawal G, Madhukar R, Makharia MK & Murray HW (2001a) Treatment of Indian visceral leishmaniasis with single or daily infusions of low dose liposomal amphotericin B: randomised trial. *British Medical Journal* **323**, 419–422.

Sundar S, Jha TK, Thakur CP *et al.* (2002) Oral miltefosine for Indian visceral leishmaniasis. *New England Journal of Medicine* **347**, 1739–1746.

Sundar S, Mehta H, Suresh AV, Singh SP, Rai M & Murray HW (2004) Amphotericin B treatment for Indian visceral leishmaniasis: conventional versus lipid formulations. *Clinical Infectious Diseases* **38**, 377–383.

Sundar S, Maurya R, Singh RK *et al.* (2006) Rapid, non-invasive diagnosis of visceral leishmaniasis in India: comparison of two immunochromatographic strip tests for detection of anti-K39 antibody. *Journal of Clinical Microbiology* **44**, 251–253.

Sundar S, Singh RK, Bimai SK *et al.* (2007) Comparative evaluation of parasitology and serological tests in the diagnosis of visceral leishmaniasis in India: a phase III diagnostic accuracy study. *Tropical Medicine and International Health* **12**, 284–289.

Sundar S, Jha TK, Thakur CP, Sinha PK & Bhattacharya SK (2007a) Injectable paromomycin for visceral leishmaniasis in India. *New England Journal of Medicine* **356**, 2571–2581.

TDR (2005) *Press release: elimination of kala azar from endemic countries in the South-east Asia region*. http://www.who.int/tdr/diseases/leish/press_release.htm

World Health Report (2002) Reducing Risks, Promoting Healthy Life. World Health Organization, Geneva, Switzerland. pp. 186–192.

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