Vector control by insecticide-treated nets in the fight against visceral leishmaniasis in the Indian subcontinent, what is the evidence?

Bart Ostyn1, Veerle Vanlerberghe1, Albert Picado2, Diwakar Singh Dinesh3, Shyam Sundar4, François Chappuis5, Suman Rijal6, Jean-Claude Dujardin1, Marc Coosemans1, Marleen Boelaert1 and Clive Davies2

1 Institute of Tropical Medicine, Antwerp, Belgium
2 London School of Hygiene and Tropical Medicine, London, UK
3 Rajendra Memorial Research Institute of Medical Sciences, Agamkuan, Patna, India
4 Banaras Hindu University, Varanasi, India
5 Geneva University Hospitals, Geneva, Switzerland
6 BP Koirala Institute of Health Sciences, Dharan, Nepal

Summary

Visceral leishmaniasis (VL) is a deadly vector-borne disease that causes an estimated 500 000 new cases a year. In India, Nepal and Bangladesh, VL is caused by Leishmania donovani, which is transmitted from man to man by the sandfly Phlebotomus argentipes. In 2005, these three countries signed a memorandum of understanding to eliminate VL from the region. Integrated vector management is one of the pillars of this elimination strategy, alongside early case detection and treatment. We reviewed the evidence of effectiveness of different vector control methods, to examine the potential role of insecticide treated bednets (ITNs). Indoor residual spraying has shown poor impact for various reasons and resistance to DDT is emerging in Bihar. Environmental management performed poorly compared to insecticide based methods. ITNs could give individual protection but this still needs to be proven in randomized trials. Given the constraints of indoor residual spraying, it is worthwhile to further explore the use of ITNs, in particular long lasting ITNs, as an additional tool in the VL elimination initiative.

Keywords indoor residual spraying, insecticide susceptibility, insecticide-treated nets, Leishmania donovani, Phlebotomus argentipes, vector control, visceral leishmaniasis, review, India, Nepal

Introduction

Visceral leishmaniasis (VL), also known as kala azar (KA) is a life-threatening vector-borne disease with a fatal outcome if left untreated. In the Indian subcontinent, VL is mainly caused by L. donovani (Swaminath et al. 1942; Dinesh et al. 2000; Kumar et al. 2001), which is transmitted from man to man by the sandfly Phlebotomus argentipes (Diptera: Psychodidae) (Swaminath et al. 1942; WHO 1984, 1990, Mukhopadhyay & Chakravarty 1992; Dinesh et al. 2000). In contrast to the zoonotic VL in the Mediterranean region and the New World (caused by L. infantum) where an animal reservoir is involved (Ashford 1996), VL caused by L. donovani is exclusively anthropotonic.

The annual incidence of kala-azar cases is estimated at 0.5 million and the prevalence at 2.5 million (WHO 1998). In 2005, the governments of India, Bangladesh and Nepal signed a memorandum of understanding for the elimination of the disease at the World Health Assembly in Geneva. Their aim is to reduce the yearly incidence of VL to less than one per 10 000 population by 2015 (Bhattacharya et al. 2006). Elimination is deemed feasible, since man is the only reservoir and P. argentipes the only vector. Moreover, new tools for diagnosis (recombinant K39 dipstick) and new drugs (miltefosine, paromomycin) have recently become available, which make more decentralized case management possible. Furthermore, VL is rather well confined in the Indian subcontinent. VL is endemic in 96 districts in India, e.g. the adjacent states of Bihar, Jharkhand, West Bengal and Uttar Pradesh, in 12 districts in south-eastern Nepal, and in 19 districts in Bangladesh.

The VL elimination strategy comprises a combination of early case detection and management and vector control. At present, there is no commercial vaccine for any type of leishmaniasis, but trials with a vaccine against cutaneous leishmaniasis (CL) are ongoing (Davies et al. 2003). The strategy of case-finding and treatment is thus one of the
mainstays of the elimination initiative. It is so far mainly ‘passive’ as it targets only those patients who consult health services with symptoms, and treatment is restricted to symptomatic patients only because the drugs are too toxic to be used in asymptomatic carriers of the infection. The challenge for the elimination initiative will be to shift to a more active case detection strategy, through decentralization and outreach activities. The importance of the asymptomatically infected persons as a reservoir of L. donovani parasites is yet unclear, but annual incidence rates and prevalence of asymptomatic infection is much higher than that of kala azar disease (Singh et al. 2002; Sundar et al. 2006a; Sundar et al. 2006b) and parasite DNA has been detected in asymptomatic seropositive individuals by polymerase chain reaction (Salotra et al. 2001).

In this paper we focus on the second pillar of the VL elimination strategy, vector control. Insecticide spraying during the malaria eradication campaigns of the 1950s wiped out the VL epidemics for several years. When VL resurged in northern India at the end of the 1970s, Indoor Residual Insecticide spraying (IRS) became the main strategy for sandfly control in the Indian subcontinent, and remains so today. Meanwhile new vector control methods such as insecticide-treated bednets (ITNs) are being widely adopted as an important alternative method for malaria control. For this paper, we reviewed the efficacy of IRS for controlling anthroponotic VL (AVL) in the Indian subcontinent and looked at the evidence or potential for control by ITNs and other insecticide treated materials.

Methods

Search strategy

All searches were conducted in the MEDLINE database through PubMed. No articles on vector control in leishmaniasis were found in the Cochrane library. No language restrictions, publication year or report type-limitations were set for database searches. For each subject, additional articles were obtained through citation tracking of review and original papers, and completed with unpublished results and personal communications.

In order to make an inventory of current evidence and knowledge on vector control methods in leishmaniasis, we first looked for reviews using the general search terms: ‘prevention and control’ [Subheading] and ‘Leishmaniasis’ [Mesh], review. One hundred and fifty-eight review articles were screened and 22 articles were retained for relevance to the subject. Biological methods, environmental management, and chemical control were separately explored using references through the snowball method.

In the second step, for each type of intervention (biological methods, environmental management, and chemical control), searches were done for information on the relevant countries (India, Nepal, Bangladesh) and vector (P. argentipes). When data was scarce or absent, searches were widened to others types of leishmaniasis, other countries, and other vectors.

For insecticide spraying methods and specific insecticide susceptibility studies we used the search-terms ‘Phlebotomus’ [Mesh] and ‘Insecticides’ [Mesh] or ‘Insecticide Resistance’ [Mesh], ‘Insecticide Resistance’ [Mesh], Phlebotomus argentipes, and Insecticide, susceptibility, Phlebotomus argentipes. For insecticide treated bednets in Leishmaniasis, we used the search-terms ‘bednets, leishmaniasis, Phlebotomidae’.

Data management

The findings on IRS and ITN were further organized by (i) entomological evidence, (ii) epidemiological evidence, and (iii) evidence on feasibility, cost-effectiveness and acceptability. Entomological endpoints, such as vector density, are widely used to evaluate vector control methods and are based on the assumption that vector abundance and incidence are closely, if not linearly, related. However, there is little data available to support this hypothesis (Lane 1991). Therefore epidemiological evidence, such as the disease outcomes, are a more appropriate tool to inform control policy. The decisions made by policy makers are not only based on this evidence but need to be complemented with data on feasibility, cost-effectiveness and acceptability.

Results

The main sandfly vector control methods are: biological control, environmental management and chemical control.

Biological methods

In laboratory studies, infecting sandflies with different organisms such as nematodes (Secundino et al. 2002; Kakarsulemankhel 2003), bacilli (De Barjac et al. 1981; Yuval & Warburg 1989; Robert et al. 1997; Wahba et al. 1999; Wahba 2000) viruses and fungi (Warburg 1991; Reithinger et al. 1997) characteristically kill pre-adult and adult sandflies or, in the case of some ectoparasitic yeast and fungi, reduce their mobility (Warburg 1991). These methods have not yet been studied in the field, as the sandfly breeding sites are difficult to target (Kishore et al. 2006). Some plants, such as Solanum jasminoides, Ricinus communis, or Bougainvillea glabra, are toxic for adult...
sandflies (Schlein et al. 2001). There exists no evidence that any of these approaches is giving results in operational conditions.

**Environmental management**

So far, knowledge on the breeding sites of *P. argentipes* is poor (Sivagnaname & Amalraj 1997; Sivagnaname 2006). Sudhakar et al. (2006) describes the presence of larval stages of sandflies in alluvial, alkaline soil. Kumar et al. (1995b) comments that the damp and dark corners of cattle sheds, where humus is present, and the cracks and crevices in the walls are favourable conditions for *P. argentipes* breeding. A study in Bihar found immature stages of *P. argentipes* mainly in human dwellings (Dhiman et al. 1983), while another study found most positive samples inside cattle sheds, some in mixed dwellings and none in houses without cattle (Kesari et al. 2000). An environmental management strategy, making in-house breeding of the sandflies impossible by filling cracks and crevices in walls by mud and lime, was implemented in Bihar. This reduced sandfly density (Kumar et al. 1995b), but cracks and crevices reappeared within 7 months.

In epidemiological studies in Nepal and in Bangladesh, the proximity of cattle has been identified as a protective factor (cattle as preferred blood source) (Mukhopadhyay & Chakravarty 1987; Bern et al. 2000; Bern & Chowdhury 2006). No evidence was found on environmental interventions tackling the proximity of cattle.

**Chemical control**

The main chemical control methods to combat sandflies are indoor spraying of residual insecticides and the use of insecticide impregnated materials such as sheets, veils, curtains and bednets. The principle of insecticide treated bednets (ITNs) is to act as baited traps, alongside a deterrent and repellent effect. Another promising chemical control method is the use of synthetic pheromones to attract adult sandflies into traps, but evidence is not yet available (Kishore et al. 2006).

**Indoor residual spraying**

Indoor residual spraying (IRS) involves coating the walls and other surfaces of a house with a residual insecticide. For several months, the insecticide will kill all susceptible insects that come in contact with these surfaces. IRS prevents VL transmission by decreasing the sandfly survival, but it has no barrier effect. Most intense transmission of *L. donovani* in the Indian subcontinent occurs during two periods: a pre-winter peak in September–November and a post-winter peak in March–May. During the rainy season (monsoon) from June to September, the numbers of sandflies are low, in contrast to other insects (Dhanda et al. 1983; Dhiman & Sen 1991; Dinesh et al. 2001). Timing of spraying is important. The residual activity of the insecticide must last through the periods of intense VL transmission or the spraying has to be repeated. To obtain a mass effect, i.e. protecting also persons in houses which were not sprayed, IRS must be applied to >70% of households in that area (CDC 2006). The Indian Kala azar Control Program has applied the strategy of two rounds of DDT spraying per year since 1991.

**Entomological evidence**

House spraying is reasonably effective against endophilic sandfly species such as *Lu. verrucarum* and *Lu. peruensis* (Davies et al. 2000), *Lu. longipalpis* and *Lu. ovallesi* (Feliciangeli et al. 2003a; Feliciangeli et al. 2003b) and *Lu. intermedia* (Falcao et al. 1991) in the New World, and *P. papatasi* (Benzerroug et al. 1992) and *P. sergenti* (Reyburn et al. 2000) in the Old World. In contrast, blanket house spraying failed to reduce the abundance of exophilic sandflies such as *Lu. nuneztovari* in Bolivia (Le Pont et al. 1989), which have a relatively low probability of contact with the treated surfaces (walls and ceilings).

*Phlebotomus argentipes*, in the Indian subcontinent, is endophilic. When in the early 1990s in the VL-endemic states of Bihar and West Bengal in India a new vector control strategy was introduced, based on two rounds of indoor residual DDT spraying, entomological studies from that time confirmed the reduction in vector abundance after spraying (Joshi & Rai 1994; Kaul et al. 1994; Mukhopadhyay et al. 1996). It is believed that, despite reports of resistance (Table 1) *P. argentipes* is still highly susceptible to DDT in most of the endemic areas (Kumar 2006).

In 2003, Alexander and Maroli published a review of all insecticide susceptibility studies on various phlebotomine sandflies. Environmental Health Project (EHP) presented the status of insecticide resistance to *P. argentipes* in a 2004 report (Mittal et al. 2004). Table 1 includes all relevant data from both publications, as well as an update from our literature search until the end of 2006.

In future the choice of insecticide will thus be important as susceptibility of sandflies is likely to vary from one village to another depending on its history of spraying and frequency of sprays (Singh et al. 2001; Dhiman et al. 2003).
### Table 1 Overview of susceptibility studies of *P. argentipes* sandflies (updated from Alexander and Mansli (2003) and EHP (2004))

<table>
<thead>
<tr>
<th>References</th>
<th>Year</th>
<th>Country (state or zone)</th>
<th>District</th>
<th>Insecticides tested</th>
<th>Susceptibility status</th>
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</thead>
<tbody>
<tr>
<td>Kaul et al. (1978)</td>
<td>1978</td>
<td>India – Bihar</td>
<td></td>
<td>DDT, dieldrin</td>
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<td>Joshi et al. (1979)</td>
<td>1979</td>
<td>India – Bihar</td>
<td></td>
<td>DDT, dieldrin</td>
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<tr>
<td>Hari (1983)</td>
<td>1983</td>
<td>India – Bihar</td>
<td></td>
<td>DDT</td>
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<tr>
<td>Mukhopadhyay et al. (1992)</td>
<td>1990</td>
<td>India – Bihar</td>
<td>Patna, Bhojpur</td>
<td>DDT, Samaestipur</td>
<td>S</td>
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<tr>
<td>NMEP (1991)</td>
<td>1991</td>
<td>India – Bihar</td>
<td>Sahabganj</td>
<td>DDT</td>
<td>R</td>
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<tr>
<td>Mukhopadhyay et al. (1992)</td>
<td>1992</td>
<td>India – Bihar</td>
<td>NA</td>
<td>DDT</td>
<td>R</td>
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<tr>
<td>Kaul et al. (1994)</td>
<td>1991</td>
<td>India – Uttar Pradesh</td>
<td>Varanasi</td>
<td>DDT</td>
<td>S</td>
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<tr>
<td>Kaul et al. (1993)</td>
<td>1993</td>
<td>India – Bihar</td>
<td>Patna, Vaishali</td>
<td>DDT</td>
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<td>Palit et al. (1994)</td>
<td>Not rep.</td>
<td>India – Bihar</td>
<td>Patna</td>
<td>DDT, dieldrin</td>
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<td>Kumar et al. (1995a)</td>
<td>1994</td>
<td>India – Bihar</td>
<td></td>
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<tr>
<td>Mukhopadhyay et al. (1996)</td>
<td>1994</td>
<td>India – West Bengal</td>
<td>North and South 24-Paraganas</td>
<td>DDT</td>
<td>T</td>
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<tr>
<td>Anon. (1997)</td>
<td>1997</td>
<td>Nepal – Janakpur</td>
<td>Dhanusa</td>
<td>Lambda-cyhalothrin 1% Deltamethrin 0.25% Benidocarb</td>
<td>S T S T</td>
</tr>
<tr>
<td>Amalraj et al. (1999)</td>
<td>Not reported</td>
<td>India – Pondicherry</td>
<td></td>
<td>DDT, BHC, lambda-cyhalothrin, malathion Deltamethrin, permethrin</td>
<td>T</td>
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<tr>
<td>Singh et al. (2001)</td>
<td>1998, 1999</td>
<td>India – Bihar</td>
<td>Patna, Samastipur</td>
<td>DDT</td>
<td>S</td>
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<td>Dhiman et al. (2003)</td>
<td>2001</td>
<td>India – Bihar</td>
<td>Vaishali</td>
<td>Deltamethrin</td>
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<tr>
<td>Kishore et al. (2004)</td>
<td>2002</td>
<td>India – Bihar</td>
<td>Patna, Muzaffarpur and Vaishali</td>
<td>DDT</td>
<td>S R</td>
</tr>
</tbody>
</table>

S, susceptible; T, transient; R, resistant.
Epidemiological data

Direct evidence of the impact of house spraying on leishmania transmission was only found in a few published trials and these relate mainly to cutaneous leishmaniasis and to sandfly species other than *P. argentipes*.

In the Peruvian Andes, the incidence of susceptible householders acquiring zoonotic CL was significantly reduced by 54% as a result of spraying interior walls and ceilings with lambda-cyhalothrin (25 mg/m²) (Davies et al. 2000). In a trial with residual pyrethroid spraying (lambda-cyhalothrin (30 mg/m²) in Afghanistan, the incidence of anthroponotic CL (ACL) amongst residents of sprayed houses was 4.4% compared to 7.2% in controls (OR 0.60, 95% CI 0.3–0.95) (Reyburn et al. 2000).

With regard to VL and its vectors in the Indian subcontinent, data and studies are scarce. There is historical evidence that insecticide spraying during the Indian National Malaria Eradication Programme of 1958–1970 has had a drastic impact on transmission of *L. donovani*. No cases of VL were reported from the state of Bihar during that period, presumably because populations of *P. argentipes* had been effectively suppressed by DDT house-spraying against the malaria vector *Anopheles culicifacies*. However, within months after the programme being halted, the first cases of kala-azar reappeared, and a very important VL epidemic struck Bihar at the end of the 1970s (Joshi et al. 2003; Kishore et al. 2006).

In the Indian VL-endemic states of Bihar and West Bengal, a new vector control strategy was introduced by the National Malaria Eradication Programme in 1992, based on indoor residual DDT spraying in two rounds per year. During implementation of these programmes, kala-azar cases showed a sharp decline from 1993 continuing until 1999 (Figure 1) (Kishore et al. 2006). Since 2000 however, the number of cases significantly increased again, which raises doubts on the continued effectiveness of the vector control strategy. Other explanations may be increased incidence of treatment failure (parasite resistance to antimonials) and the emergence of HIV-co-infections (Mathur et al. 2006).

In Nepal, malaria and VL used to be a serious public health problem before the 1950s. Intensive DDT spraying undertaken in the 1960s and 1970s to eradicate malaria apparently was effective on KA. During the mid 1970s the insecticide spraying program was stopped. As of 1980 cases of VL reappeared, probably facilitated by migration of people between Nepal and the neighbouring Indian state of Bihar. In 1992 the IRS program policy consisted of spraying (lambda-cyhalothrin) in only those villages where VL cases were recorded. In the following years it was extended to all endemic districts with DDT, malathion and lambda-cyhalothrin (Joshi et al. 2003). Nevertheless, Siraha district in the Southeast, which has received annual residual insecticide spraying for over 10 years (1991–2001) has been continuously and severely affected by VL. The trends of disease incidence even show an increase in cases and in geographical spread (Joshi et al. 2003, 2006).

Feasibility, cost and acceptability

In the last decade, VL epidemiological data indicate that the impact of IRS in the Indian-Nepalese VL endemic region decreased (Figure 1) (Joshi et al. 2003). Several factors might contribute to this: (1) the timing and the number of rounds of insecticide spraying may not have been optimal to control *P. argentipes*, especially at times when the main objective was malaria control; (2) long gaps between two rounds and the short residual effect of the insecticides (Joshi et al. 2003) may have allowed the vector...
to rebuild its numbers (Bora 1999) and in this way resistance may have developed; (3) ‘patchy’ geographical coverage of spraying (Mukhopadhyay et al. 1992); (4) community-related factors, such as poor user acceptance and low community participation during the spraying campaigns (Joshi et al. 2003); (5) program-related issues, such as cuts in public spending, lack of trained manpower, managerial problems, corruption and mismanagement of the stocks of insecticide product including its diversion to the black market for agricultural purposes (Curtis 1994).

The effectiveness of these spraying programmes is not the only issue for concern; also important are their side effects on health and environment, and their potential for sustainability, which depends on the cost of the insecticides and their application, in addition to the above mentioned factors.

Insecticide-treated nets

The effectiveness of untreated bed nets as a tool for prevention of parasite transmission depends on mesh size, behaviour of the vector in terms of biting habits (indoors vs. outdoors), and on sleeping habits. Phlebotomus argentipes sandflies live in and around houses and biting occurs at night, mainly between 9 PM and 1 AM, peaking at 11–12 PM (Dinesh et al. 2001). Bednets could thus be a useful tool in VL control, however, in order to be physically sandfly-proof, bednets need to have a fine mesh (>200 holes/inch² mesh), finer than those used against malaria mosquitoes.

Evidence of the effect of untreated bednets on VL incidence comes from observational studies and is not always convincing: Bern et al. (2000) showed a protective effect in Nepal (OR 0.20, P < 0.001) and Bangladesh (Bern et al. 2005) (OR 0.69, P = 0.01), but Schenkel et al. (2006), in Nepal, did not. In the latter study the bednets were in poor condition and in none of the studies the mesh size of the nets was specified.

In eastern Sudan, where another sandfly, P. orientalis, transmits VL, the mean total number of bites/man/night was investigated with human volunteers, staying either under an impregnated bednet (156 mesh, lambda-cyhalothrin 10 mg/m²), an untreated bednet or without a bednet. Sandfly biting was 0 for persons using impregnated bednets, but was also significantly reduced for persons staying under untreated nets (6.92 ± 2.71 bites/man/night vs. 32.0 ± 8.3 for persons without bednets) (Elnaiem et al. 1999b).

Insecticide-treated bednets (ITN) were shown over the past two decades as one of the most effective methods of reducing man-vector contact in intra- and peri-domestic transmission of vector-borne diseases (Curtis 1991; Curtis et al. 2003) and in particular of malaria. In most studies, the insecticides used were synthetic pyrethroids (permethrin, deltamethrin, lambda-cyhalothrin), which combine the properties of low to moderate mammalian toxicity (Wells et al. 1986; Curtis 1991; Zaim et al. 2000), low volatility and high insecticidal activity.

Insecticide treated nets combine the individual protection of a bednet (barrier-effect) with the effect of insecticide. Due to the deterrent and repellent effect of the insecticide, mesh size does not matter as long as the insecticide remains active. As with residual spraying, vector abundance inside houses is expected to be reduced, giving relative protection to people inside the room but outside the net. Furthermore, ITNs have the added benefit to act as ‘baited traps’, with the odour of the sleeper as bait. In terms of acceptability, ITNs theoretically have the advantage that less insecticide is used and that the household exerts control over its application, thus depending less on the performance of a top-down planned disease control programme. In contrast, ITNs require a change in sleeping habits so implementation of the tool does not stop with delivery of the nets. Where IRS, if applied to all houses, provides passive protection to the whole community, this community effect with ITNs will only be obtained if the majority of households use the nets.

Another weakness of ITN strategies until recently was the need to re-impregnate the nets yearly (Chavasse et al. 1999). This constraint has been overcome as nets can now be re-impregnated with a long-lasting formulation which renders the nets and its insecticide wash-resistant (Yates et al. 2005). Long lasting insecticide-treated nets (LLIN) have the insecticide coated on, or incorporated within the fibres of the netting fabric (polyethylene or polyester) during the manufacturing process. In all three cases the insecticide remains present in sufficient amount during the lifespan of the net (estimated at 3–5 years, or at least 20 washes) (Kayedi et al. 2007). The WHO Pesticide Evaluation Scheme (WHOPES), considering safety, efficacy and wash-resistance, recommends three brands of LLIN for the prevention and control of malaria: Olyset (WHO 2001) PermaNet 2.0 (WHO 2004) and Interceptor (WHO 2007).

Entomological evidence

Materials treated with synthetic pyrethroids (permethrin, deltamethrin, lambda-cyhalothrin) have been tested in laboratory and field conditions against different types of sandflies. Results from several countries including Italy (Maroli & Lane 1989; Bongiorno et al. 2005), Burkina Faso (Majori et al. 1989), Sudan (Elnaiem et al. 1999a), Kenya (Mutunga et al. 1993; Basimike & Mutenga 1995), Afghanistan (Reyburn et al. 2000), Iran (Nadim et al. 2005), and in most studies.
Vector control by insecticide-treated nets in the fight against visceral leishmaniasis

Epidemiological evidence

We found seven studies (trials and retrospective analyses) that looked specifically at the impact of ITNs on the incidence of CL, and two on VL. In Afghanistan (anthroponotic CL transmitted by P. sergenti), a household study in Kabul compared permethrin treated bed nets with two other treatments (house spraying and impregnated chad-dars (Islamic wrapping cloth used as cover-sheet for sleeping). There was a marked reduction on CL incidence, from 7.2% in the control group to 2.4% in the houses with ITNs and impregnated chad-dars \( P < 0.001, 65\% \) protective efficacy), while in the arm of sprayed houses, the incidence was 4.4% \( \text{WHO 2002) \). In Iran, bednets impregnated with deltamethrin reduced incidence of ACL with 60% in Bam. The cumulative incidence rate in the treated village was 0.01% \( n = 728 \), lower than that found in the control village, 0.03% \( n = 848 \), but the results were inconclusive because no baseline data had been collected, there were no replicas and the incidence in the control group was very low \( \text{Nadim et al. 2000) \). In Shiraz and Sedeh, also in Iran, there was a 97% reduction in ACL incidence by permethrin treated long-lasting bed nets \( \text{Olyset} \) while incidence increased in the control area \( \text{WHO 2002) \}; in Isfahan the incidence of zoonotic CL \( P. \) papatasi dropped to 0 with deltamethrin treated bed nets and curtains \( \text{Yaghoobi-Ershadi et al. 2006) \) and in Mashad, the incidence of ACL \( \text{vector: P. sergenti} \) dropped from 30.3 to 6.9 per thousand \( P = 0.015 \) with deltamethrin treated bednets plus curtains \( \text{Moosa-Kazemi et al. 2007) \). In Turkey, deltamethrin treated bednets reduced ACL incidence in intervention areas from 1.87% to 0.035% in Yenice and from 2.3% to 1.32% in Sırac, while incidence increased in control areas and areas provided with non-impregnated bednets \( \text{Alten et al. 2003) \). Finally, in Syria the CL incidence in the year after distribution of deltamethrin impregnated nets in two intervention villages dropped from 5.1% \( (103/2035) \) to 3.1% \( (59/1910) \) \( P < 0.05 \), compared to two control villages which showed an increase instead \( \text{Tayeh et al. 1997) \). This was confirmed a few years later by a matched cluster randomized trial in 10 other villages, showing a protective efficacy of about 85% \( \text{Jalouk et al. 2007) \). The two studies on VL incidence through the use of ITNs both come from eastern Sudan, with \( P. orientalis \) as vector. In 1995, inhabitants of two villages in Galabat province \( \text{Gaderf state) using bednets impregnated with lindal-}

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L. donovani changed from 7:1 in the non-intervention village to 1:3 in the intervention villages. According to the authors, this was due to reduction in transmission intensity of L. donovani and/or malaria co-infections. The impact of the ITNs was maintained throughout the 3 years of the study. However, the trial was limited to two villages only, as other villages had been enrolled in a vaccination trial (Elneaiem 1996).

A second report from Sudan is an observational study analysing the incidence data of VL from 114 villages that had received ITNs during an epidemic of VL in 1999–2001 (blanket distribution of small mesh deltamethrin 25 mg/m² bednets in the 155 most affected villages). The evaluation demonstrated a significant reduction of VL by village and by month following ITN provision, although usage rates varied greatly between seasons from <10% to 55%. The mean protective effect over the study period was 27%, with the greatest effect 17–20 months post-intervention, with VL cases reduced by 59% (Ritmeijer et al. 2007).

In the same area in Sudan, infection rates of L. donovani in P. orientalis sandflies were studied in 12 VL endemic villages, of which one village was using deltamethrin-impregnated bednets offered to them in 1998 by an international NGO. The research team re-impregnated these bednets at the time of the survey in April 1999. Subsequently, the infection rate of L. donovani in P. orientalis was lowest in the village using the bednets (0.5%) compared to the other villages (1.8–3.7%), but this difference was not statistically significant (Hassan et al. 2004).

We did not find any studies on the impact of ITNs on VL incidence in South East Asia. While ITNs are increasingly being promoted and supplied in the fight against malaria worldwide, in India, Bangladesh and Nepal this has been largely limited to those areas that are high-priority in terms of malaria transmission. These areas do not overlap with those with high kala-azar attack rates. Therefore, so far little evidence is available about potential implications of ITNs in regions where both diseases are co-endemic.

Feasibility, cost and acceptability

Until now, no studies measured the cost and cost-effectiveness of impregnated bednets in the prevention of Leishmaniasis. The cost of intervention of LLIN has been calculated for malaria programs. Assuming 3 years duration and a standard cost of 5 USD per LLIN, the average annual economic cost per ITN distributed in five different African countries varied from 3.47 to 7.64 USD (Yukich et al. 2007).

Acceptability studies, conducted in Africa and Latin-America, have shown that people generally accept nets (Richards et al. 1993; Kroeger et al. 1995; Binka & Adongo 1997). This acceptance is mainly based on their perceived effectiveness in the reduction of the nuisance of the mosquitoes rather than as a device to prevent disease (Gyapong et al. 1996; Koirala et al. 1998). However, health educational campaigns can have a clear impact on acceptance and preventive behaviour (Pardo et al. 2006). In hot weather, bednets with fine mesh have been described as unpleasant to use as they are poorly ventilated (Elneaiem et al. 1999b; Ritmeijer et al. 2007). By the repellent effect of insecticide coated on or in the fabric, a wider mesh can be used overcoming this problem.

Data on net use in Bihar (India) are not available, but data from Nepal (Bern et al. 2000) and Bangladesh (Bern & Chowdhury 2006) show that bed net acceptability is unlikely to be a major concern. Notably, in 3 VL endemic districts of Nepal (Dhanusha, Mahottari and Siraha) an age and gender matched VL case-control study found that more than 70% of the 105 controls reported the regular use of (untreated) bed nets (Bern et al. 2000); and a random survey of 1 800 households in 6 endemic districts (Sarlahi, Jhapa and Chitwan in the east and Kapilvastu, Kanchanpur and Surkhet in the west) found that 76% of households owned at least one (untreated) bed net, while 47% of households reported that all householders used a bed net (Houston & Cchetry 2003). In a community study in a highly affected district in Bangladesh, 86% of the population reported sleeping under a bed net and 91% lived in a house that owned at least one net (Bern et al. 2005). Nevertheless, the main weakness (or strength?) of an ITN strategy is that, contrary to IRS, its use depends on the individual decision beyond the control of the program delivering the tool. Koirala et al. (1998) stressed the need to propose culturally sensitive and appropriate recommendations for VL prevention. Any ITN strategy should take into account the factors that motivate a family to acquire and appropriately use bednets. Trials in malaria control have shown that, in order to achieve a mass or community effect in addition to the personal protection, a high percent of coverage of the community is needed. This suggests that free or heavily subsidized provision of treated nets, comparable to a house spraying campaign, is likely to be more cost-effective than trying to market nets to poor, rural populations (Curtis et al. 2003).

As is the case for all vector control methods, the challenge is to maintain the effort after its initial success. In Syria, after showing the high efficacy of ITNs in preventing ACL, a second study evaluating the impact of interruption on ITN intervention showed a return to pre-intervention prevalences within 1–2 years (Jalouk et al. 2007). LLINs are a major step forwards, as yearly reimpregnation is not necessary, but they also have a limited lifespan and will eventually need to be replaced.
Conclusion

Our review shows that Indoor Residual Spraying with insecticides has been virtually the only strategy for leishmaniasis vector control used in the Indian subcontinent so far. While there is clear evidence on the effect of IRS on vector abundance, past experience in the region and elsewhere has demonstrated the difficulties in its implementation, leading to poor results and emerging resistance to DDT. Nevertheless, DDT remains the insecticide of choice, but in order to achieve optimal outcomes, meticulous planning, good training, supervision, coordination and management will be needed to avoid the pitfalls of the past, and this means heavy logistics and high costs. In some places, alternatives to DDT will be required. When implemented correctly however, IRS has the potential to effectively protect the whole community.

The principle of an ITN combines the effect of individual protection and insect-killing activity while a strong repellent effect could possibly enlarge its efficacy by reducing indoor and peri-domestic vector density. ITNs therefore have the potential to achieve individual protection for VL and users are not dependent on a top-down, government-led intervention. The new long-lasting impregnated bednets make yearly re-impregnation no longer necessary. The use of other insecticide treated materials such as curtains or wall cloths is highly dependent on the repellent effect on the vector involved. However, our review showed the scarcity of data on the effect of ITNs and other insecticide treated materials on *P. argentipes* in the Indian subcontinent, and their impact on disease incidence, is not guaranteed.

Given the existing difficulties in diagnosis and treatment (human reservoir including asymptomatic infections) and the absence of any vaccine, vector control of *P. argentipes* is one of the key strategies in the fight to eliminate VL from the Indian subcontinent. LLINs may be a valuable alternative to the IRS strategy currently in use, in order to maximize the benefits that can be obtained by vector control. One community trial to test the effectiveness of LLIN on leishmaniasis infection is currently underway in this region and its results are eagerly awaited. Better data on insecticide susceptibility and more research on alternative vector control methods are needed to achieve long-lasting results in the fight against kala-azar.

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Corresponding Author Bart Ostyn, Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerpen, Belgium.
Tel.: +32 3 247 66 53; Fax: +32 3 247 62 58; E-mail: bostyn@itg.be