Chapter 18
The Efficacy of Long Lasting Insecticidal Nets for Leishmaniasis in Asia

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Abstract Vector control is an important part of controlling arthropod-transmitted diseases such as leishmaniasis, dengue, lymphatic filariasis, and malaria. Selecting the most appropriate vector control measures is essential. The current vector control strategy for visceral leishmaniasis (VL), which is the most severe form of leishmaniasis, is based on indoor residual spraying (IRS) in the Indian subcontinent. However, this technique has received critique, not only on its effectiveness and sustainability, but also for its side effects on health and the environment. Long-lasting insecticidal nets (LLINs) have been proposed as an alternative measure to IRS; however, the effectiveness of LLINs is still under the evaluation for vector control of leishmaniasis. This review aims to examine the potential of LLINs for controlling VL in the Indian subcontinent, areas that are some of the most highly endemic for VL.

Keywords Leishmaniasis · Sand fly · Vector control · Long-lasting insecticidal net · Bangladesh

18.1 Vector Control Against Leishmaniasis

Phlebotomine sand flies are the vectors of leishmaniasis, and comprise more than 40 species of *Phlebotmus* in the Old World and 30 species of *Lutzomyia* in the Americas [1]. *Leishmania* parasites are transmitted through the bites of infected female phlebotomine sand flies. The epidemiology of leishmaniasis depends on the behavior of the sand fly species, the characteristics of the parasite species, the reservoir species, ecological conditions at the transmission sites, and the symptoms and cultural practices of the human host. Therefore, the most appropriate control

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measures will differ by country. Several factors to be considered when choosing control measures against sand flies are listed as follows [2]:

1. Has the vector been identified?
2. Is the transmission cycle partially or totally anthroponotic?
3. If zoonotic, is the reservoir species known?
4. Does transmission occur in or around houses, or in some extradomiciliary situation such as inside a forest?
5. Is transmission by sand flies seasonal or year-round?
6. Is there an infrastructure present that would allow organized, sustainable measures to be used?
7. Are the human communities at risk willing to participate in the control measures proposed?
8. What methods are available and are there practical, legal, environmental, or cultural constrains on their use?

Sand fly breeding sites remain unknown and are difficult to find in nature, thus source reduction targeted at pupae or larvae is not an option for practical control measures against sand flies. Most vector control efforts are primarily focused on the adult sand flies to reduce their contact with humans. Indoor residual spraying (IRS) and insecticide-treated bed nets (ITNs) are key components of vector control programs for leishmaniasis.

There is historic evidence that house spraying with DDT during the malaria eradication campaigns of the 1950s–1960s had a drastic impact on transmission of *Leishmania donovani* in the Indian subcontinent [3], but it returned to previous levels, or higher, when spraying was stopped [4, 5]. There is another experience in the early 1990s, where IRS campaigns in the VL endemic sites of Bihar and West Bengal in India reduced the number of reported cases, but their effect was limited in time as VL cases started to rise again early in the 21st century [6]. Although IRS is a reasonably effective method against endophilic sand fly species such as *Phlebotomus papatasi*, *P. sergenti*, and *P. argentipes* in the Old World [7], IRS has been criticized for being costly, not easily accepted, and not sustainable [8, 9] (Fig. 18.1). The kala-azar control program in the Indian subcontinent has applied the strategy of 2 rounds of insecticide spraying per year because the effectiveness of IRS does not last very long, mainly related to housing materials used in the area [10]. IRS also needs trained personnel for not only the insecticide application, but also for the appropriate application of safety procedures. Nevertheless, IRS was recommended as the main vector control strategy against visceral leishmaniasis (VL) in the Indian subcontinent [11].

Insecticide treated nets (ITNs) serve as a physical barrier that functions to reduce human-vector contact. ITNs is the most sustainable method of reducing intradomiciliary transmission of leishmaniasis, and it does not require the technical training and special implements required for IRS. However, there are few observational studies on ITNs conducted in the Indian subcontinent. Herein we review the current

Fig. 18.1 Insecticide sprays of IRS used in Bangladesh for vector control programs. A large number of sprayers and educated workers are needed

knowledge on the efficacy of ITN against sand fly vectors and inquire into the potential of ITN for controlling VL in the Indian subcontinent, especially in Bangladesh.

18.2 Vector Control by Long-Lasting Insecticidal Nets Against Visceral Leishmaniasis

There are 2 types of insecticide treated nets: conventional treated nets and long-lasting insecticidal nets (LLINs). A conventional treated net is a mosquito net that has been treated by dipping it in one of the insecticides recommended by the World Health Organization (WHO). At the present moment, alpha-cypermethrin, cyfluthrin, deltamethrin, etofenprox, lambda-cyhalothrin, and permethrin are WHO recommended insecticide products for the treatment of mosquito nets for malaria vector control [12]. To maintain the efficacy of the applied insecticide, the net must be treated again after it has been washed 3 times, or at least once a year even if it is not washed [13].

LLINs have been developed to overcome these problems. LLINs have the insecticide coated on, or incorporated within the fibers of the netting fabric (polyester, polyethylene, or polypropylene) during the manufacturing process. The WHO Pesticide Evaluation Scheme (WHOPES) evaluated the efficacy, wash resistance, and safety of LLINs and 15 products are recommended for the prevention and control of malaria (Table 18.1). The net must retain its effective biological activity after 20 washes under laboratory conditions and 3 years of recommended use under field conditions [14]. Seven products of 15 are deltamethrin-treated LLINs, 6 products are alpha-cypermethrin-treated LLINs, and 2 products of LLINs are treated with permethrin. The efficacy of these LLINs is

Table 18.1 WHO recommended long-lasting insecticidal nets

Product name	Product type	Status of WHO recommendation	Status of publication of WHO specification
DawaPlus 2.0	Deltamethrin coated on polyester	Interim	Published
Duranet	Alpha-cypermethrin incorporated into polyethylene	Full	Published
Interceptor	Alpha-cypermethrin coated on polyester	Full	Published
LifeNet	Deltamethrin incorporated into polypropylene	Interim	Published
MAGNet	Alpha-cypermethrin incorporated into polyethylene	Full	Published
MiraNet	Alpha-cypermethrin incorporated into polyethylene	Interim	Published
Olyset Net	Permethrin incorporated into polyethylene	Full	Published
Olyset Plus	Permethrin and PBO incorporated into polyethylene	Interim	Published
Panda Net 2.0	Deltamethrin incorporated into polyethylene	Interim	Published
PermaNet 2.0	Deltamethrin coated on polyester	Full	Published
PermaNet 3.0	Combination of deltamethrin coated on polyester with strengthened border (side panels), and deltamethrin and PBO incorporated into polyethylene (roof)	Interim	Published
Royal Sentry	Alpha-cypermethrin incorporated into polyethylene	Full	Published
SafeNet	Alpha-cypermethrin coated on polyester	Full	Published
Yahe	Deltamethrin coated on polyester	Interim	Published
Yorkool	Deltamethrin coated on polyester	Full	Published

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well studied in both laboratory and field testing for mosquito control, but not for sand fly control. The number of LLINs distributed reached more than 143 million annually by 2013 [15] with the majority of nets being distributed in sub-Saharan Africa where malaria is prevalent [16]. The most massive community intervention trial to test the effectiveness of LLINs is the KALANET project that was conducted between 2006 to 2008 in India and Nepal [17]. LLINs treated with deltamethrin were distributed in the 13 intervention clusters, and 12,691 people were tested for infection by direct agglutination testing, including the people in the 13 control clusters. There was no significant difference in the risk of seroconversion over 24 months in the intervention group (5.4 %; 347/6372) compared with the control group (5.5 %; 345/6319) [17]. The most biologically plausible explanation for this result is that a substantial fraction of *L. donovani* transmission occurs outside the house, where any nets would have less impact on preventing sand fly-human contact [17]. Human behavior is also argued to be a factor in that adults are not going to sleep before 9 p.m. [18]. *Phlebotomus argentipes,* which is the vector species in India and Nepal, live in and around houses and biting occurs at night, mainly between 9 p.m. and 1 a.m., peaking at 11–12 p.m. [19]. It should be also noted that a very high percentage of families in the control clusters used untreated nets [18], which may lead to a complex interpretation of the results. The antibody level of approximately 150 people from each cluster (intervention/control) against *P. argentipes* saliva was tested to determine the effect of LLINs on vector sand fly exposure. Although the distribution of LLINs reduced exposure to *P. argentipes* by 12 % at 12 months and 9 % at 24 months in the intervention cluster compared to that seen in the control after adjusting for baseline values, LLINs had a limited effect on sand fly exposure in VL endemic communities [20]. In an entomological survey of the KALANET project, the density/house of *P. argentipes* is significantly reduced by 24.9 % after distribution of LLINs [21]. This suggests a 25 % reduction in sand fly density is not enough to have an impact on disease outcome in India and Nepal [18].

Field trials of ITNs have been evaluated Phlebotomine sand flies besides *P. argentipes* and leishmaniasis in some countries. Two field trials in Adana and Sanliurfa, Turkey, where cutaneous leishmaniasis (CL) is endemic, showed a significant reduction in CL incidence in the intervention areas after the introduction of permethrin and PBO impregnated bed nets and K-OTAB impregnated bed nets, respectively [22, 23]. Three trials in Syria where *P. sergenti* is the main vector of anthroponotic CL, showed a significant impact of ITNs use versus that seen with either untreated nets or no intervention, including on confirmed CL incidence [24, 25]. A cluster-randomized trial was conducted over 5 years to compare the relative efficacy and cost effectiveness of IRS and LLINs relative to standard of care environmental management (SoC-EM) in Morocco for CL control. The main findings of this study indicate that both IRS with alpha-cypermethrin and the use of deltamethrin treated LLINs reduced the incidence of CL; however, the reduction due to LLINs did not reach statistical significance and the protective effect size associated with IRS was much larger [26]. These contrasting results suggest that field trials are necessary with different species of sand fly and parasite before adopting ITNs as a means of vector control.

18.3 The Efficacy of Long-Lasting Insecticidal Nets in Bangladesh

In 2005, the governments of India, Nepal, and Bangladesh, in collaboration with the WHO, developed a strategic framework to eliminate VL as a public health problem by 2015. This was defined as reducing the annual VL incidence below 1/10,000 people at the block level via a combination of case management and vector control.

The efficacy of 3 different interventions for vector control for VL: IRS, deltamethrin-treated LLIN (PermaNet®), and environment modification through plastering of walls with lime or mud was evaluated in India, Nepal, and Bangladesh [27]. Insecticides for IRS used in India, Nepal, and Bangladesh are DDT 5 % (target concentration 1 g/m^2), alpha-cypermethrin (target concentration 0.025 gm/m^2), and deltamethrin (K-Otrine 5 %, target concentration 20 mg active ingredient per square meter) respectively. A reduction of intra-domestic sand fly densities measured in the study households by overnight CDC light trap captures was the main outcome measure in this study. IRS was effective in all study areas but LLINs were only effective in Bangladesh and India [27]. In Bangladesh, IRS and LLINs were associated with a 70–80 % decrease in male and female *P. argentipes* density up to

Fig. 18.2 **a**, **b** Permethrin-treated LLINs were distributed as a pilot study in the Pabna district, Bangladesh, in August 2015 under the VL control project of SATREPS. **c**, **d** Housing style in VL endemic area of Bangladesh

5 months after intervention [28]. Sand fly density rebounded by 11 months post-IRS, whereas LLIN-treated households continued to show significantly lower density compared to that seen in households without intervention [28]. Mud plastering of wall and floor cracks did not reduce sand fly density in Bangladesh [27, 28]. The efficacy of LLIN (KO Tab 123, Bayer (Ply) Ltd.) was also evaluated in the VL endemic area of Bangladesh [29]. A significant reduction in sand fly densities was observed for at least 18 months in houses with LLINs compared to that seen in the houses in untreated control communities [29]. The distribution of KO Tab 123 also reduced VL incidence by 66.5 % in the intervention areas [30]. The use of conventional untreated bed nets has become widespread among people in Bangladesh [31]. Permethrin-treated LLINs were distributed as a pilot study in the Pabna district, Bangladesh, in August 2015 under the VL control project of SATREPS, and a utilization rate of distributed LLINs was 100 % up to the present (unpublished data) (Fig. 18.2). The distribution of pyrethroid-treated LLINs with/without IRS will probably be the most effective measure in reducing the vector populations and human-vector contact in Bangladesh.

18.4 Conclusion

The best vector control measure is not an easy decision to make for each leishmaniasis endemic country. There are 4 different types of interactions between humans and *Leishmania* foci that we have to consider before we apply a vector control; (a) an accidental host, (b) the principal or only host, (c) one of several hosts in a stable amphixenosis or (d) a potential host exposed to increased risk of transmission due to rapid multiplication of vectors and reservoir hosts [2]. These interactions are not clear in some endemic countries; for example, the existence of an animal host is a still matter of debate in Bangladesh.

Risk of the appearance of insecticide resistant sand flies due to IRS is also a concern. Various researchers have reported resistance to insecticides such as DDT, deltamethrin, or permethrin among *P. argentipes* in endemic areas of the Indian subcontinent [2, 7]. In a recent susceptibility test of sand flies in 6 districts of the state of Bihar, India, the *P. argentipes* population developed a resistance to DDT in 16 (38.1 %) of 42 villages surveyed and a resistance to malathion in 1 (4.5 %) of 22 villages surveyed [32]. A further fear is that populations of *P. argentipes* may have changed their behavior from being predominantly endophilic (resting indoors) to exophilic (resting outdoors) as a consequence of DDT-based IRS [33]. Although continued research on the biology and behavior of *P. argentipes* in relation to *L. donovani* transmission would be necessary to refine the intervention strategies for VL, LLINs will be a useful tool to reduce or interrupt transmission of VL as alternative or complement to IRS in the Indian subcontinent, especially in Bangladesh. The use of LLINs may also be the most sustainable method of reducing intradomiciliary transmission of *Leishmania* in communities where the diurnal resting sites of vectors or vector species are unknown.

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