

Review Article

Indian J Med Res 136, July 2012, pp 22-31

Vector control interventions for visceral leishmaniasis elimination initiative in South Asia, 2005-2010

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Received January 21, 2011

The Visceral Leishmaniasis (VL) Elimination Initiative in the Indian subcontinent was launched in 2005 as a joint effort between the governments in the Region (India, Nepal and Bangladesh) and the World Health Organization (WHO). The objective is to reduce the annual VL incidence below 1/10,000 inhabitants by 2015 based on detection and treatment of VL cases and vector control. We present here a review of studies published in the period 2005-2010 on the efficacy of different tools to control *Phlebotomus argentipes*. The review indicates that the current indoor residual spraying (IRS) and novel vector control methods mainly insecticide treated nets (ITN) have low effectiveness for several reasons. Efforts to improve quality of IRS operations and further research on alternative and integrated vector control methods need to be promoted to reach the VL elimination target by 2015.

Key words Elimination - indoor residual spraying - insecticide treated nets - integrated vector control - *Phlebotomus argentipes* - visceral leishmaniasis

Introduction

Kala azar, also known as visceral leishmaniasis (VL), is the second largest parasitic killer in the world after malaria¹. In May 2005, the governments of India, Nepal and Bangladesh committed themselves to mutual co-operation towards elimination of kala-azar from their countries by 2015 by signing a Memorandum of Understanding during the World Health Assembly in Geneva. Most of the estimated 200 to 400 thousand annual VL cases reported worldwide are located in South Asia (SA)^{2,3}. In this Region the highest burden of the disease is concentrated in northern India (32813 and 25113 cases reported in 2005 and 2010, respectively), mainly Bihar State; eastern Bangladesh

(6892 cases in 2005 and 2763 cases in 2010) and the south-eastern districts in Nepal (1463 and 418 cases in 2005 and 2010, respectively)⁴. However, these figures are based on official reports and are considered to be an underestimation of the real number of VL cases⁵.

Though isolated case reports on VL attributed to *Leishmania tropica* exist⁶, in India, Nepal and Bangladesh VL is mainly caused by the parasite species *Leishmania donovani*, which is transmitted from man to man by the sandfly *Phlebotomus argentipes* (Diptera; Psychodidae)⁷. The objective of the Visceral Leishmaniasis Elimination Initiative is to reduce VL incidence below 1 per 10 000 per year at district, subdistrict or *upazilla* level in India, Nepal

and Bangladesh, respectively by 2015. Elimination was deemed feasible as man and *P. argentipes* are the only known host and vector for *L. donovani*, respectively in this Region. The elimination should be also favoured by the availability of a new oral drug (miltefosine) and a reliable rapid diagnostic test (rK39 dipstick). The fact that VL was limited to 96 districts and the positive experiences in controlling the disease using indoor residual spraying (IRS) were considered favourable factors. Furthermore, the initiative was strongly supported by the governments of the three affected countries and the WHO^{2,8}. The strategy for VL elimination in SA is based on case detection and management as well as vector control. Due to the limited number of VL drugs available and the increasing number of unresponsive cases to pentavalent antimonials (the first line treatment for over 70 years) in Bihar (up to 60% in some areas) and emerging resistance in other regions⁹, the control of *P. argentipes* in endemic regions should be prioritized. In this paper, we review the evidence on vector control available in 2005 and the recent advances in the field over the period 2005 to 2010.

Situation in 2005

P. argentipes sandflies are described as peridomestic insects, mainly endophilic and endophagic (mainly feed indoors) and most active when people are asleep¹⁰. During daytime these are not very active, but seek shelter in dark, cool places. The sandflies feed on plant sugars, and only the female fly needs a bloodmeal to acquire the necessary protein for egg production. Vector density peaks in March-May and October-November in India⁸ and is related to temperature and rainfall¹¹.

Indoor residual spraying

There is historic evidence that insecticide spraying during the malaria eradication campaigns of the 1950s-1970s had a drastic impact on transmission of *L. donovani* in the Indian subcontinent¹². This observation was supported by the fact that VL did not reappear in areas where IRS was continued in the 1970s-1980s such as Assam¹³. However, the information on the effect of IRS on *P. argentipes* density was limited to a few studies only¹⁴⁻¹⁶. IRS campaigns in India in the early 1990s (*i.e.* 2 annual blanket rounds in endemic districts) reduced the number of reported cases, but their effect was limited in time as the VL cases started to rise again early in the 21st century^{12,17,18}. Nevertheless, IRS was recommended

as the main vector control strategy in 2005⁸. When the VL elimination programme was launched the spraying strategies (*i.e.* time and number of rounds, insecticide used) varied among countries. Despite some reports on DDT-resistance¹² India decided to use DDT while Nepal used lambda-cyhalothrin¹⁹. In Bangladesh, vector control activities for VL were rather limited or nonexistent²⁰. The Regional Technical Advisory Group (RTAG) to the VL Elimination Initiative recommended that IRS should be standardized between countries (*i.e.* spraying calendar and strategies) and optimised (*i.e.* use of geographical information systems, GIS). It was also suggested that the efficacy of IRS to control VL and the development of insecticide resistance should be monitored in the Region. The effectiveness of these spraying programmes was not the only issue of concern, other problems are their side effects on health and environment and their sustainability. Several factors such as cost of the insecticides, the logistical constraints and the low acceptance by the community compromise the longer-term effectiveness and sustainability of this intervention²¹.

Insecticide treated nets

Insecticide treated nets (ITN) were suggested as a potential complement to IRS⁸. *P. argentipes* peridomestic behaviour suggests that ITN would be an appropriate tool to control *L. donovani* vector in the Indian subcontinent¹². However, in 2005 there was no evidence on the effectiveness of ITN to prevent VL in the Region, apart from a few observational studies in Nepal and Bangladesh suggesting that untreated bednets provide some degree of personal protection against VL¹².

Alternative vector control methods

Alternative vector control technologies have been proposed. For example, plastering of walls and floors using mud and lime plaster was associated with a decrease in *P. argentipes* indoor density compared to controls in a pilot study in India²². However, this and other environmental management (EVM) methods needed further evaluation.

Situation in 2010

Since 2005 a number of studies have been published covering different areas related to *P. argentipes* control in the Indian subcontinent. The results from recent studies on the impact of IRS (Table I), ITNs and EVM (Table II) on *P. argentipes* density and VL are discussed below.

Table I. Studies on the effect of indoor residual spraying (IRS) on *Phlebotomus argentipes* and visceral leishmaniasis conducted recently in the Indian subcontinent

Type study	Location	Population	Outcome	Effect	Comments	Ref. Nos
IRS - Effect on vector						
Cluster randomized controlled trial	India (1 site), Nepal (2 sites) & Bangladesh (1 site)	24 clusters (50 - 100 households) per arm (6/site): IRS and Control arms	<i>P. argentipes</i> indoor density measured by CDC light traps at baseline and 5 months post-intervention. 2 consecutive nights in 5 households per cluster (n=90)	72.4% reduction <i>P. argentipes</i> indoor density	DDT in India, Deltamethrin in Bangladesh and alpha-cypermethrine in Nepal	23-25
Pre-post intervention	India (Bihar)	119 villages in 4 VL endemic districts	<i>P. argentipes</i> collected using aspirator method at baseline, one and 3 months post-DDT spraying	Reduction in the number of houses with <i>P. argentipes</i> in 3/4 districts	Spraying monitored by researchers. Details on statistical methods used not provided. Measure of the effect not provided. No concurrent controls.	26
Observational	India (Bihar)	4 districts: 2 highly endemic (Vaishali & Muzaffarpur) and 2 low endemic (Patna and Nalanda)	Differences on the number of households with <i>P. argentipes</i> , vector density between high and low endemic districts	Low endemic districts had significantly higher <i>P. argentipes</i> density and more households with <i>P. argentipes</i> than high endemic districts	The number of households and villages monitored are not provided. Measure of the effect not provided	27
IRS - Effect on human						
Observational	India (Bihar)	22 districts sprayed with DDT between 15/02/2007 and 15/04/2007 by government	Differences on the number of VL cases reported in December 2006 and December 2007	VL incidence decreased in 15 districts but increased in 4. Three districts did not have data in December 2006		26

IRS, indoor residual spraying; VL, visceral leishmaniasis

Indoor residual spraying

The only cluster randomized controlled trial evaluating the impact of IRS on vector density was conducted in India, Nepal and Bangladesh in 2006-2007²³. The same study also assessed the effect of longlasting insecticidal nets (LN) and EVM on *P. argentipes* density. A total of 96 clusters each counting between 50 to 100 households were studied at 4 sites: one in India, one in Bangladesh and two in Nepal. These clusters were selected based on past VL incidence and matched with control by pre-intervention vector density. The trial had four arms (IRS, EVM, LN and Control)

with 24 clusters in each (6 clusters per arm and site). The impact of the different vector control methods was assessed by comparing the *P. argentipes* captures in five households per cluster between intervention and control groups. The sandfly density was measured by CDC light traps, a tool that was found appropriate to measure *P. argentipes* density²⁴, on two consecutive nights at baseline (November 2006) and 5 to 6 months post-intervention (April 2007). The results were analysed as a pool (4 sites together) and per site using a mixed Poisson regression model. IRS of houses and cattle sheds, supervised by the researchers, reduced the indoor *P. argentipes* density by 72.4 per cent in

Table II. Studies on the effect of insecticide treated nets (ITN) and environmental management (EVM) on *Phlebotomus argentipes* and visceral leishmaniasis conducted recently in the Indian subcontinent.

Type study	Location	Population	Outcome	Effect	Comments	Ref. No.
ITN - Effect on vector						
Cluster randomized controlled trial	India (1 site), Nepal (2 sites) & Bangladesh (1 site)	24 clusters (50-100 households) per arm (6/site): LN (PermaNet) and Control arms	<i>P. argentipes</i> indoor density measured by CDC light traps at baseline and 5 months post-intervention. 2 consecutive nights in 5 households per cluster (n=90)	43.7% reduction <i>P. argentipes</i> indoor density	LN reduced vector density in India and Bangladesh but not in Nepal	23-25
Cluster randomized controlled trial	India and Nepal	6 clusters (350-1500 people) per arm. 3 intervention (LN) and 3 control clusters per country. LN distributed PermaNet	<i>P. argentipes</i> indoor density measured by monthly CDC light traps captures: 3 months pre-distribution LN and 12 post-intervention. One night per month in 10 households per cluster	<i>P. argentipes</i> indoor density reduced by 24.9% after 12 months of LN use	Density decreased to 31.9% when governmental IRS was included in the analyses. LN also significantly reduced Anopheline density (22.9%)	34
Non-randomized controlled trial	Bangladesh	2 intervention sites (8287 and 35442 inhabitants) and 4 control sites in VL endemic districts Intervention: dipping pre-owned untreated nets in KO-Tab 123 (slow release deltamethrin)	Sandfly indoor density measured by CDC light traps captures: baseline, 4 wk, 12 and 18 months post-intervention. 50 and 26 households were monitored in intervention and control sites respectively	The use of ITN reduced sandfly density by 60% at 18 months post-intervention	Impact of ITN on sandfly density but not on <i>P. argentipes</i> , in particular. Over 95% of households in the intervention sites participated and over 90% of the pre-owned nets were treated	49
Household randomized controlled trial	India (Bihar)	3 VL endemic hamlets In each hamlet 16 houses were selected and allocated to (2 houses/arm): PermaNet, Olyset, PermaNet control and untreated net	<i>P. argentipes</i> indoor density monitored by CDC light traps (one night) at baseline, 3, 6 and 9 wk	Olyset and PermaNet significantly reduced male <i>P. argentipes</i> but not female <i>P. argentipes</i>	Baseline captures were unbalanced among groups. Routine IRS did not modify the results	33
ITN - Effect on human						
Cluster randomized controlled trial	India and Nepal	26 clusters (350-1500 people), 16 in India & 10 in Nepal selected based on past-VL incidence. 13 LN (PermaNet) and 13 control clusters. 12691 people were followed for the main outcome	No. of DAT seroconverters over 24 months. No. VL cases as secondary outcome	Risk of seroconversion over 24 months LN clusters reduced by 10% compared with control clusters. Risk of clinical visceral leishmaniasis reduced by 1%. Non statistically significant and wide confidence intervals. Adjustment for covariates did not alter these conclusions.	LN reduced the risk of malaria by 54% in the adjusted model. Adjusting for effect of routine IRS did not modify the results.	35

Contd.....

Type study	Location	Population	Outcome	Effect	Comments	Ref. No.
EVM - Effect on vector						
Cluster randomized controlled trial	India (1 site), Nepal (2 sites) & Bangladesh (1 site)	24 clusters (50-100 households) per arm (6/site): Plastering of walls and Control arms	<i>P. argentipes</i> indoor density measured by CDC light traps at baseline and 5 months post-intervention. 2 consecutive nights in 5 households per cluster (n=90)	42.0% reduction <i>P. argentipes</i> indoor density	Mud plastering in Bangladesh did not reduce vector density. Lime plastering was effective in India and one site in Nepal only	23-25
ITN, insecticide treated nets; EVM, environmental management; LN, longlasting insecticidal nets; IRS, indoor residual spraying; VL, visceral leishmaniasis; DAT, direct agglutination test						

intervention clusters compared to control. This effect was consistent in all sites²³ and confirmed in Nepal where additional entomological surveys were conducted²⁵. However, the site specific results should be interpreted with caution as the number of replicas was limited (6 clusters per arm and site), the insecticides used were different (DDT in India, deltamethrin in Bangladesh and alpha-cypermethrine in Nepal) and exterior as well as interior walls were sprayed in Bangladesh but not in the other sites. In India, a similar effect of IRS on *P. argentipes* density was also observed in a “before-after comparison” study in 119 villages in 4 endemic districts in Bihar²⁶. The IRS activities conducted from February 15 to April 15, 2007 as part of the national programme were supervised by the researchers. *P. argentipes* indoor density was evaluated by aspirator method at baseline and at one and three months post-spraying. The percentage of houses with *P. argentipes* significantly decreased after IRS in 3 of the 4 districts. Unfortunately the effect was only assessed for a maximum of 3 months and no details on the statistical methods or the magnitude of the effect were provided. In the same study, the number of reported VL cases in December 2006 and 2007 in 19 districts in Bihar were compared. The incidence decreased in 15 districts but increased in four. The latter increase was associated with a rise in the number of cases reporting to public health facilities where miltefosine was provided. No formal statistical analyses were conducted to study the association between IRS and reported VL²⁶, and no controls were included in the study. The same authors reported an observational study (1998-2008) on the association between VL cases and vector density in four districts in Bihar: two highly endemic (Vaishali and Muzaffarpur) and two low endemic (Patna and Nalanda)²⁷. Low endemic districts had higher *P. argentipes* density but lower VL incidence than high endemic districts. The authors

hypothesised that higher level of *P. argentipes* exposure in Patna and Nalanda, where IRS was occasional and on focal basis, would confer some degree of protection against *L. donovani* infection. This protection would be provided by the regular exposure to sandfly saliva²⁷. However, this may be an oversimplification as the risk factors associated to *L. donovani* infection and VL are quite complex²⁸. Further, this hypothesis was not supported by the observations in Nepal where focal and occasional spraying had little impact on VL incidence²⁹. Moreover, in Bangladesh where vector control activities were almost inexistent since the early 1980s the VL incidence has been rising since then²⁰.

Without doubt, when applied properly IRS significantly reduces the *P. argentipes* indoor density²³. Intensive and correct IRS combined with active detection and treatment of VL cases seems to effectively control *L. donovani* transmission in endemic communities^{18,30}. However, the impact of IRS on VL has not been properly evaluated yet and it seems that the current IRS strategies are failing to control VL in India^{12,17,18}, Nepal¹³ and Bangladesh²⁰. Mondal *et al*³¹ reported that, despite the recommendations from the VL elimination programme⁸, vector control activities are almost nonexistent in VL endemic districts in Bangladesh. In India and Nepal the routine IRS activities conducted as part of the national VL elimination programme were suboptimal in terms of training, equipment, insecticide concentration and application³². It should be noted that even under these suboptimal conditions, IRS reduced the vector density for at least four weeks³². However, other groups reported that governmental IRS campaigns did not have a significant effect on *P. argentipes* indoor density^{33,34} or *L. donovani* infection and VL³⁵. Recently, Dinesh *et al*³⁶ reported decreased susceptibility of *P. argentipes* to DDT in India. Efforts should be made to ensure that

adequate training is provided to local and managerial staff and that IRS activities are properly monitored. WHO/TDR has recently released specific guidelines to monitor IRS in the context of the VL elimination programme³⁷.

Insecticide treated nets

Two cluster randomised trials have been conducted since 2005 in the Indian subcontinent to assess the impact of village-wide distribution of ITNs on *P. argentipes* density^{23,34} though only one included clinical endpoints³⁵. Both trials used the same long-lasting insecticidal nets (PermaNet 2.0 - 55 mg/m², Deltamethrin coated net) in the intervention clusters.

Joshi *et al*²³ conducted a study in VL endemic villages in India, Nepal and Bangladesh. Households in clusters where LNs were distributed had 43.7 per cent less *P. argentipes* compared to control 5 months post-intervention. However, when the impact was analysed per site, the reduction was significant in the Indian and Bangladeshi sites but not in Nepal²³. As part of the KALANET project (*ClinicalTrials.gov* NCT00318721) the effectiveness of LN to prevent VL was assessed in 26 clusters (16 in India and 10 in Nepal) matched by country, population and past VL incidence. All household in intervention clusters (8 in India and 5 in Nepal) received LN in November-December 2006. The control clusters did not receive any treated nets but were allowed to use their own untreated nets. The research team did not interfere with the governmental IRS activities but collected detailed information on the houses sprayed during the trial and considered this in the analysis. The impact of LN on indoor *P. argentipes* density was assessed in a subset of clusters (n=12), six clusters (3 intervention and 3 control) per country. The sandfly indoor density was evaluated in 10 sentinel households and cattle sheds per cluster selected based on their *P. argentipes* density in September 2006. Monthly CDC light trap captures and mouth aspiration collections were conducted before intervention (September-November 2006) and 12 months post-distribution of LN in intervention clusters. The intervention and control clusters had similar pre-intervention *P. argentipes* indoor density. After 12 months of LN use, households in intervention clusters had 24.9 per cent less *P. argentipes* compared to controls measured using CDC light traps. A similar effect was observed in India and Nepal. The effect of the governmental IRS campaign on the sandfly density was limited. When house spraying was accounted for

in the analysis, the reduction of *P. argentipes* density due to LN was 31.9 per cent. The distribution of LN did not have an effect on the number of *P. argentipes* captured in cattle sheds located close to the sentinel households³⁴. The slightly stronger reduction of vector density observed in the trial reported by Joshi *et al*²³, may be related to the study design (*i.e.* inclusion of clusters from Bangladesh), the shorter follow up time (*i.e.* 5 vs 12 months), timing of the post-intervention surveys or the statistical models used to analyse the data, but both trials consistently showed that LN reduced the *P. argentipes* indoor density.

The KALANET project was the only trial that evaluated the impact of LN on *L. donovani* infection. The direct agglutination test (DAT) was used to compare the risk of *L. donovani* infection over 24 months in 13 clusters where LN were distributed to 13 control clusters. The impact of LN on the number of VL cases was assessed as a secondary outcome. The 26 clusters were selected based on their past VL incidence^{38,39}. Almost 20,000 people were included in the trial and 12,261 of them were enrolled for the main outcome (*L. donovani* infection). Over 24 months the incidence of *L. donovani* infection (5.4 vs 5.5%) and clinical visceral leishmaniasis (0.38 vs 0.40%) were similar in intervention and control groups. The cluster analysis indicated that LN reduced the risk of *L. donovani* infection and VL by 10 and 1 per cent, respectively. These conclusions were not altered when the statistical models were adjusted for IRS, socio-economic status, age and sex. The results of the trial, which were not statistically significant and had large confidence intervals, indicate that large-scale distribution of long-lasting insecticidal nets would not provide much additional protection against VL at village level compared to current control measures in India and Nepal³⁵. LN and untreated nets seem to provide some degree of personal protection because the risk for infection was lower in people using untreated nets or LN compared to people not using any net³⁵. The number of bloodfed *P. argentipes* collected in houses was also lower after untreated nets were used⁴⁰. The investigators of the KALANET trial concluded that LNs have beneficial effects as these they provided some degree of personal protection against *L. donovani* infection and reduced the risk of malaria, and therefore, the use of LN should be promoted in the region. However, the authors warned as well that large-scale distribution of LNs in VL endemic communities in India and Nepal in the current context (*i.e.* suboptimal

IRS and widespread use of untreated nets) would not be sufficient to reduce significantly the *L. donovani* transmission in the community. So vector control activities to prevent VL in endemic communities in India and Nepal cannot rely on LN distribution only.

The main limitation of the KALANET trial was that it used *L. donovani* infection and not clinical VL as the main outcome to assess the impact of LN. Unfortunately the latter would require following a larger number of people for a long period of time because of the long and variable incubation period of VL and the relatively low VL incidence in the region. Bern *et al*²⁸ suggest that using seroconversion (*L. donovani* infection) as the major outcome in intervention trials may lead to erroneous conclusions about the risk of disease. The results of the KALANET trial challenge this theory as (i) the impact of LN on DAT seroconversion and clinical VL were consistent³⁵, and (ii) DAT seroconverters were at higher risk to develop VL than non-seroconverters (Relative Risk=11.5) in the study clusters⁴¹. Similar results were obtained when the impact of LN was assessed using a different serological marker (*i.e.* rK39 ELISA) (J Menten, personal communication), and when a proxy marker of exposure (sandfly saliva antibody) was used⁴².

Several other factors may explain the lack of effect (non-compliance, insecticide resistance, quality of nets, *etc.*), and many of these were studied in the trial. As the use of LN in the intervention clusters was high³⁵ and correct (Vanlerberghe, personal communication) throughout the trial, LN deltamethrin concentration and effectiveness after 24 months of household use were acceptable⁴³ and *P. argentipes* were susceptible to deltamethrin³⁶; the authors suggested that the lack of effect observed may be related to a substantial fraction of *L. donovani* transmission occurring outdoors where LNs would have less impact on preventing sandfly-human contact³⁵. This theory is supported by entomological findings that *P. argentipes* breed preferably in cattle sheds compared to households⁴⁴. Similarly, the fact that LN distributed to some households in VL endemic villages in Bihar failed to reduce indoor female *P. argentipes* suggests that most of the sandflies are breeding outdoors³³. Further, recent studies have captured significant numbers of adult *P. argentipes* outdoors using CDC light traps^{45,46} and a large proportion of these (*i.e.* 90% of female *P. argentipes* collected from palm tree) had fed on humans, suggesting that *P. argentipes* are exophagic^{46,47}. These findings are also supported by epidemiological

findings. Using a recently developed sandfly saliva ELISA to assess the exposure to *P. argentipes*⁴⁸, LN reduced *P. argentipes* exposure only by 9 to 12 per cent and a significant number of individuals had high levels of anti-*P. argentipes* saliva antibodies (*i.e.* 43.5% were ELISA positive) after 24 months of LN use⁴².

These results do not dismiss the use of LN, or insecticide treated nets in general, as a tool for *P. argentipes* control, especially in Bangladesh where no IRS programme was operating until recently²⁰. A non-randomized controlled trial in two VL endemic districts in Bangladesh found that villages where the bed nets owned by the households were treated with KO-Tab 123 (slow release deltamethrin dipping tablets) had a 60 per cent reduction in indoor sandfly density compared to control after 18 months⁴⁹. Over 95 per cent of households in the intervention sites participated and over 90 per cent of the households' nets were treated. The impact of ITN was measured comparing the sandfly indoor density at 4 wk, 12 and 18 months between 50 and 26 households in intervention and control sites, respectively. The trial results were similar at the different time points and they were not altered when the model was adjusted for presence of cattle sheds and the number of trees around the house⁴⁹. The study was part of an operational research programme so study sites could not be randomized and there were only two intervention areas which had different population sizes (8287 vs 35,442 inhabitants). Baseline characteristics and control sites were not described in detail. The authors analysed the impact of ITN on sandflies in general but not on *P. argentipes* specifically⁴⁹. The authors suggest that higher susceptibility of the vector to insecticide in Bangladesh may explain the differences with the results obtained in previous trials in India and Nepal⁴⁹. Recent studies showed that wild caught *P. argentipes* are fully susceptible to deltamethrin in VL endemic areas in India and Nepal³⁶.

Alternative and integrated vector control methods

The fact the current IRS and LN (or ITN) had an inconclusive impact on *P. argentipes* population and *L. donovani* transmission urges the need to develop alternative vector control methods and assess the impact of integrated vector management (IVM). The impact of plastering household walls on *P. argentipes* density was assessed in 24 intervention sites compared to 24 control clusters in India, Nepal and Bangladesh²³. The overall effect was a 42 per cent reduction in sandfly counts in households in the intervention

clusters. However, there were important differences among sites. In Bangladesh (one site) walls plastered with mud did not reduce *P. argentipes* density. In India (one site) and Nepal (two sites) walls were plastered with lime. Vector densities were significantly reduced in two sites only (one in India and one in Nepal). The authors associated the failure in the second Nepalese site to random error, the quality of the lime applied or the acidity of the soil²³. Currently Genesis laboratories (<http://www.genesislabs.com>) are testing the impact of oral delivery of insecticides to cattle on *P. argentipes* density in Bihar. The preliminary results of this study showed an important reduction in vector density (over 90%) when oral insecticides and IRS were used in VL endemic villages in Bihar⁵⁰. The efficacy of this strategy will need to be tested in a larger trial.

To date there are no studies assessing the effect of combining different vector control methods on *P. argentipes* density or VL. Based on the results described above, an integrated approach using different control methods targeting adult sandflies at different location (*i.e.* IRS in cattle sheds and LN in households) and environmental changes reducing the *P. argentipes* breeding sites may have a greater impact on *L. donovani* transmission than any of these methods alone. Similarly, future trials on *P. argentipes* control methods in the Indian subcontinent should assess the impact of these on other relevant vector borne diseases in the Region, specially malaria⁵¹. As an example, IRS was effectively used to control malaria in the Region until 1970s¹² and cluster-wide provision of LNs in the KALANET trial significantly reduced the indoor density of anophelines by 22.9 per cent³⁴ and the risk of malaria by 54 per cent in VL endemic villages in India and Nepal³⁵. The WHO is promoting integrated vector management to increase cost-effectiveness and sustainability of vector control programmes by optimising the available resources and targeting more than one disease⁵².

Conclusions

The following conclusions can be drawn based on studies described in this review: (i) indoor residual spraying has an important impact on *P. argentipes* density when it is conducted properly, (ii) governmental IRS campaigns were non-existent in Bangladesh up to 2010 and suboptimal in India and Nepal over the period 2005-2010, (iii) to date, there are no prospective studies assessing the impact of IRS on *L. donovani* infection or VL in the Region, (iv) LNs may provide

some degree of personal protection against VL but these had a limited impact on *L. donovani* transmission in VL endemic communities in India and Nepal, (v) entomological studies should be designed to quantify the *L. donovani* transmission outdoors in VL endemic villages in India and Nepal, (vi) ITN seem to have greater effect on *P. argentipes* density in Bangladesh than in India and Nepal, and (vii) impact of integrated vector management on VL and other vector borne diseases in the Region should be tested in prospective studies.

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