Efficacy and community-effectiveness of insecticide treated nets for the control of visceral leishmaniasis: A systematic review

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Abstract

Visceral leishmaniasis (VL) has been targeted for elimination from Southeast Asia (SEA). The disease has been endemic in SEA, and in other parts of the world involving both humans and animals. One of the key strategies for combating VL is controlling for the vector sandfly. There are a few vector control strategies that are currently in practice. We sought to assess the efficacy and community effectiveness of insecticide treated nets (ITNs) in controlling the burden of sandfly and the occurrence of VL among humans. We conducted a systematic review following a study protocol and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria. 6331 initial hits were retrieved from Google Scholar, Lilacs, PubMed, Science Direct, WHOlis, WHOiris and PAHOiris. 25 met the full inclusion criteria. Findings show that the insecticide impregnated bednets and the commercially treated long lasting insecticidal nets (LLINs) are effective in controlling sandflies, with mortalities as high as 75% lasting over a year; although their role in controlling VL in the community was not extensively studied, since effectiveness was usually measured with sandflies densities. Findings also show that insecticide impregnated bednets are low cost and well accepted in the community, however, early erosion of insecticides from nets could occur. Some studies also showed that killing of sandflies may not translate into reduction of VL, therefore sandfly knock down and killing data needs to be interpreted with caution. Conclusions of this review are (1) combining insecticide impregnated bednets, as targeted interventions, with another vector control measure, particularly indoor residual spraying, and in conjunction with case detection, could be the way forward to controlling VL in resource limited settings. (2) Given the current low incidence of VL in SEA, it can be difficult to further research the community effectiveness of those control measures in reducing VL.
Visceral leishmaniasis (VL) is a vector borne disease endemic in Southeast Asia (SEA) and present in other regions of the world. In SEA the disease has been targeted for elimination. VL is transmitted by different species of sandflies and key strategies against VL rely on the control of the vectors. This systematic review assesses the efficacy and community effectiveness of insecticide treated nets (ITNs) in controlling sandflies and VL occurrence among humans. After a revision of 6331 initial hits, 25 studies were included in this systematic review. Main findings indicated that insecticide impregnated bednets and long-lasting insecticidal nets (LLINs) can effectively control sandflies, however, it was not possible to fully assess the role of ITNs in controlling VL transmission. Additional results showed that insecticide impregnated bednets are low cost and well accepted in the community, however early erosion of insecticides from the nets could occur. If insecticide impregnated bednets are combined with other vector control measures, such as indoor residual spraying, and together with case detection, it could be an important strategy to control VL in resource limited settings.

Introduction

Visceral leishmaniasis (VL), also known as kala-azar, as a Neglected Tropical Disease of poverty, has been targeted for elimination from Southeast Asia (SEA) [1]. Efforts have also been made to control for the disease in other parts of the world, where VL can involve both humans and animals [2].

As per a 2012 estimate, there were 200,000 to 400,000 VL cases from 79 countries and 20,000 to 40,000 deaths annually in the previous five years [3]. Eighty percent of global VL cases were then reported from the South Asian eco-epidemiological hotspot comprising countries including Bangladesh, India and Nepal. More recent data show that globally 23,804 cases were reported to WHO in 2015, of which 9,249 (39%) were from the South Asian hotspot [4]. Annual cases of kala-azar in these South Asian countries declined from 77,000 cases in 1992 to fewer than 7000 in 2016 [5]. Sporadic cases are also reported from the other countries in the SEA region including Bhutan, Myanmar, Sri Lanka and Thailand.

VL is transmitted by different species of sandflies, mainly the vectors Phlebotomus argentinaeps and different species of the sandflies Lutzomyia [2,5]. Among the strategies being in place for prevention, control and elimination, effective vector control is one [6]. In different parts of the world, in different settings, varying vector control measures are in place [7]. Investigations have been conducted to understand the effectiveness of those measures using a wide range of study designs in various settings and on different vector species. A recently conducted meta-review by Montenegro et al. on vector control measures for both VL and cutaneous leishmaniasis (CL) have found significant research gaps [7]. Gaps were specifically identified in the availability of robust and comparable study designs, and comparability of settings and interventions. Human outcome parameters of vector control measures were missing and the majority of studies were embedded in programme assessments, meaning that the single interventions are not sufficiently assessed individually and the combination of interventions not assessed systematically.

In this systematic review, we focused on insecticide treated nets (ITNs) and its efficacy and community-effectiveness for the control of VL and its vectors globally. We present our findings with recommendations for policy, identify critical gaps in evidence base and for further research studies.
Methods

Search strategy, databases and search terms

In response to the above-mentioned meta-review of vector control interventions for the control of CL/VL [7] and the subsequent gap-analysis, this systematic review has been undertaken along with other systematic reviews for different vector control interventions. The present study focuses on ITNs, including bednets, to control VL. Key difference to previously published work is the inclusion of studies with randomisation, but also those without randomisation, considering that a lot of studies analysing vector control methods have been undertaken without randomisation processes.

As a first step a study protocol was established. The systematic review follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria [8].

All searches have been carried out until 17 of October 2020, using the following databases: Google Scholar (considering the database is sorted by relevance, we screened the first 200 hits only, after establishing that for most of our searches no relevant hits were found after screening the first 100 hits), Latin American and Caribbean Health Sciences Literature (LILACS), PAHOiris, PubMed, ScienceDirect, WHO Library Database (WHOlis) and WHOiris.

The searches were performed without restriction to language, publication year or region of publication. Searches were performed in English with a focus on primary research articles with no restriction to a specific study design.

1. Disease: “Visceral Leishmaniasis” (MeSH terms and “major topic” function were used where supported by the database)
2. Intervention: “ITN” or “Insecticide treated nets” and its potential variations (MeSH terms were used, where supported by the database)
3. Vectors for transmission of visceral leishmaniasis were used as free-text terms.
4. Inclusion criteria were all studies focusing on 1) Visceral leishmaniasis 2) Insecticide treated nets or synonyms, and 3) all primary research methods were included.

Exclusion criteria were conference or opinion articles, editorials or any articles without clear primary research methodology. Furthermore, the reference lists of all included articles were manually searched for additional articles. As for grey literature, guidelines, not older than 5 years, for VL were screened, including reference lists.

All searches performed have been documented, including the selection process. Two data extractors (CAMQ and CB) independently screened titles and abstracts and applied inclusion and exclusion criteria. In case of disagreement a third researcher (SRR) was involved to reach consensus.

The included studies have been categorised for further analysis into the following categories:

1. Research articles focused on ITN interventions only
2. Research articles focused on comparing ITN with at least one other intervention

Finally, each of the above-described categories are divided 3) into the subcategories a) interventional [cluster randomised controlled trial (cRCT), randomised controlled trial (RCT), non-randomised controlled trial and community intervention trials] or b) observational study designs. We also aimed to analyse according to geographical regions, due to the different vectors involved in the context of VL.
Quality assessment

Quality assessment has been performed using the CONSORT checklist [9] for a) RCTs and cRCTs, for b) other studies, CONSORT has been used, excluding the criteria for randomisation. The CONSORT checklist for RCTs is composed of 25 items, a high-quality study would have most of the items fulfilled in the study, for example, a study fulfilling 25 out of the 25 items of the checklist would have a quality equal to 100%. For other studies, the elimination of the randomisation criteria from the CONSORT checklist resulted in a list of 18 items. In this case, a high-quality study, not being RCT or cRCT, would have most of the 18 items of the checklist fulfilled. Studies have not been excluded following the quality assessment, but analysis and reporting reflected the quality assessment.

Data extraction and analysis

Data have been extracted in a predefined data extraction matrix and analysed by author, year of publication, country/geographical region, study type, methods used, sample size, follow up period, study arms and interventions included, different vectors and entomological outcome indicators, human outcome indicators, reported conclusions, limitations and quality assessment scores. For p-values, 5% level of significance was used for all the studies. Evidence tables were developed for presentation of data and analysis.

Results

Descriptive results

Results of searches. 6331 initial hits were retrieved on the seven included databases. After assessing by title and abstract, 354 articles were further screened. Removing 318 duplicates 37 articles were fully assessed, and 25 were included after full application of inclusion and exclusion criteria. (see Fig 1). Of the 25 finally included studies, 22 were retrieved on PubMed, 2 on Google Scholar, and one additional recommendation by an expert that met the inclusion criteria was added (Table 1).

Description of included studies

Time and geographical clustering of studies. All included articles were published between 1995 and 2019. Articles were published by different groups of authors and focusing mostly (20 articles) on South Asia (Bangladesh, India and Nepal). Ritmeijer, Davies [10] and Elnaiem, Elahi [11] focused on Africa (Sudan), Courtenay, Gillingwater [12] and Alexander, Bruce [13] on Latin America (Brazil and Colombia, respectively) and Karakus, Kasap [14] on Turkey.

Methods/designs applied by the studies. The 25 studies selected for the review included both interventional (23 studies) and observational designs (two studies) (Table 1). Among the 23 interventional studies, 11 are cRCTs (including one multi-country, two paired and one community RT), two are RCTs, one is a non-randomised controlled trial [15], and 10 are community interventions trials including comparison-based intervention studies, pre-post designs and cross-over field trials. Among the two observational studies, one followed a cohort design (10) and the other followed a retrospective cohort design [16]. Surveys and in-depth interviews were also part of few studies [11,17,18].

Types of interventions. The interventions evaluated or assessed in the studies included impregnation of existing bed nets with a slow-release insecticide tablet/KO Tab 1-2-3 (eight studies), long-lasting insecticidal nets, Long-lasting or long lasting insecticidal or insecticide-treated or insecticide impregnated nets or bed-net (18 studies) including PermaNet, PermaNet...
2.0, PermaNet nets with different mesh sizes (156 holes/in$^2$, 196 holes/in$^2$, 625 holes/in$^2$), polyester, resin coating, containing deltamethrin, PermaNet 3.0, Olyset and Olyset Plus (Table 1). Interventions combining multiple vector control methods (Indoor residual spraying (IRS) +long-lasting insecticidal net (LLIN), IRS+KOTAB, LLIN+outdoor spraying) were also assessed in 2 studies.

**Types of outcome measures.** Studies involved outcome measures focusing on sandfly vectors (entomological) and human hosts parameters (Table 1). There were several entomological outcomes in the included articles, in some cases the studies evaluated more than one entomological outcome. The measured outcomes included sandfly density (17 studies), sandfly mortality (eight studies), and Insecticide residue on ITNs, sandfly landing and knock down of sandflies (six studies). Among the human outcomes there were perception, acceptance, access, utilization, maintenance and satisfaction regarding ITNs (10 studies), feeding on human blood and sandfly biting (two studies), and VL incidence, *Leishmania donovani* (*L. donovani*)
Table 1. VL ITN evidence table.

| Author, Year, Country (Districts, study design) | Sample size/Follow up period | ITN Interventions | Vector/parasite species | Results: hematocrit outcome indicators | Results: hematocrit outcome indicators | Limitations described | Quality assessment score for authors (CONSORT 2010 checklist) |
|-----------------------------------------------|-----------------------------|-------------------|------------------------|---------------------------------------|---------------------------------------|------------------------|----------------------------------------------------------|
| Huda 2019, Bangladesh (Chittagong) Cluster Randomized Controlled Trials (cRCT) | The total number of HHs for the FC+ITN intervention was 17,250 (8,625 pp.). The trial activity period was from June 2018 to April 2019, 3 months of pre-intervention, 3 months of intervention and 3 months of follow up. In total 214 sandfly traps were deployed. Sandfly density was assessed 3-5 days before starting the intervention and 1 week after its initiation. | ✓ | Phlebotomus argentipes | At baseline, the average female P. argentipes density per household was about 52.3 (95% CI = 16.5 - 98.1) female P. argentipes in the FC+ITN intervention. The mean reduction of female P. argentipes density in the ITN arm ranged from -1.1 (95% CI = 0.5 - 1.6) to -1.6 (95% CI = 0.2 - 3.0) female P. argentipes. The adjusted intervention effect of ITNs was statistically significant in the district of Mymensingh and Trishal subdistrict. The incidence of VL in Bangladesh; Efficacy based on WHO criteria. The incidence of VL in Bangladesh was 0.38% for the intervention and 1.1% for the control group, which was the aim of the present study. However, the study showed a trend of reduced VL incidence compared to the intervention. The overall prevalence of VL in blood donors was 0.15%. The overall risk of visceral leishmaniasis (VL) during the two-year follow-up was 0.38%, which was the aim of the present study. The sensitivity of the intervention was statistically significant. | ✓ | ✓ | ✓ | ✓ |
| Picado 2010, India and Nepal (Paired cRCT) | A total of 942 households were randomly allocated to intervention (ITN) arm with 471 households (22 villages) and 471 households (22 villages) without ITNs. The trial activity period was from March to December 2009, 12 months of pre-intervention, 3 months of intervention and 3 months of follow up. | ✓ | Phlebotomus argentipes | For the effect on sand fly mortality. The Abbott's bioassay showed a significantly higher mortality of P. argentipes in the intervention arm. Efficacy based on WHO criteria. There was a slightly higher mortality in the intervention group compared to the control group, but this effect was not significant. | ✓ | ✓ | ✓ | ✓ |
| Plas-B R 2010, India and Nepal (Paired cRCT) | A total of 1,200 households were randomly allocated to intervention (ITN) arm with 600 households (30 villages) and 600 households (30 villages) without ITNs. The trial activity period was from March to December 2009, 12 months of pre-intervention, 3 months of intervention and 3 months of follow up. | ✓ | Phlebotomus argentipes | The risk of seroconversion during the two-year follow up was significantly different between countries. The risk of seroconversion in the intervention group was lower in India than in Nepal. Efficacy based on WHO criteria. There was a significantly lower risk of seroconversion in India than in Nepal, but the interaction was not significant. There was a significantly lower risk of seroconversion in the intervention group compared to the control group. Efficacy based on WHO criteria. The overall risk of visceral leishmaniasis (VL) during the two-year follow up was 0.3%, which was the aim of the present study. The overall risk of visceral leishmaniasis (VL) during the two-year follow up was 0.38%, which was the aim of the present study. There was a slightly higher risk of seroconversion in India than in Nepal, but the interaction was not significant. | ✓ | ✓ | ✓ | ✓ |

(Continued)
Table 1. (Continued)

| Author, Year, Country (Study design) | Samples size/Follow up period | ITN interventions | Vector/parasite species | Results: Human outcome indicators | Results: Entomological outcome indicators | Limitations described | Quality Assessment scores by the authors | Quality assessment checklist |
|-------------------------------------|-----------------------------|-------------------|-------------------------|----------------------------------|-----------------------------------------|----------------------|------------------------------------------|-----------------------------|
| Das 2010 [25] Nepal/Arrest and Morang (RCT) [25] | November-December 2006, November-December 2007 | PermaNet and Mamba mosquito net | Phlebotomus argentipes (non-vector) | Prevalence of P. argentipes 19% and 9% | Prevalence of P. argentipes 19% and 9% | The physical condition of the LNs was assessed after 6 and 22 months of household use. | The data on the number of sandfly washes used to evaluate the insecticidal nets with KO Tab 1-2-3 according to ITNs impregnation with insecticide, the physical condition of the LNs tested with HPLC results should be interpreted with a degree of caution, as the value for washing frequency was that reported by the head of household rather than by the person actually using the LNs for killing sandflies. The LANs used were not randomly assigned to intervention and control groups; which showed that interventions and control groups regarding the distribution of Phlebotomus argentipes were not adjusted for any baseline characteristics. The difference in the baseline characteristics between the number of sandflies per house was reported but no differences were observed between groups of intervention. | 

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Table 1. (Continued)

| Author, Year, Country (District)/study design, Sample size/Follow-up period | ITN interventions | Vector or parasite species | Results: Human outcome indicators | Results: Entomological outcome indicators | Limitations described | Quality |
|---|---|---|---|---|---|---|
| Joshi, 2009 (Bangladesh, both and Nepal) cRCT [21] | 24 clusters per site (consisting of 120 HH per site, Bangla, Bangladesh, Nepal, and Nepal) | Long-lasting PermaNet nets ✓ | PermaNet vs. standard mosquito nets, and PermaNet vs. the increase in the proportion of sandfly exposure | Incidence of L. donovani infection: non-susceptible VL incidence | The estimated intervention effect in terms of reduction in sandfly counts is simple model showed a 75.4% reduction for EVM and a 45.7% reduction for LLIN. | 16/25 |
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| Picado, et al., 2010 (Philippines) cRCT [22] | 24 clusters per site (consisting of 120 HH per site, Bangla, Bangladesh, Nepal, and Nepal) | Long-lasting PermaNet nets ✓ | PermaNet vs. standard mosquito nets, and PermaNet vs. the increase in the proportion of sandfly exposure | Incidence of L. donovani infection: non-susceptible VL incidence | The estimated intervention effect in terms of reduction in sandfly counts is simple model showed a 75.4% reduction for EVM and a 45.7% reduction for LLIN. | 16/25 |
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| Chowdhury, et al., 2011 (India and Nepal) cRCT [23] | 12 clusters per site (consisting of 120 HH per site, Bangla, Bangladesh, Nepal, and Nepal) | Long-lasting PermaNet nets ✓ | PermaNet vs. standard mosquito nets, and PermaNet vs. the increase in the proportion of sandfly exposure | Incidence of L. donovani infection: non-susceptible VL incidence | The estimated intervention effect in terms of reduction in sandfly counts is simple model showed a 75.4% reduction for EVM and a 45.7% reduction for LLIN. | 16/25 |
| 12 clusters per site (consisting of 120 HH per site, Bangla, Bangladesh, Nepal, and Nepal) | PermaNet vs. standard mosquito nets, and PermaNet vs. the increase in the proportion of sandfly exposure | Incidence of L. donovani infection: non-susceptible VL incidence | The estimated intervention effect in terms of reduction in sandfly counts is simple model showed a 75.4% reduction for EVM and a 45.7% reduction for LLIN. | The estimated intervention effect in terms of reduction in sandfly counts is simple model showed a 75.4% reduction for EVM and a 45.7% reduction for LLIN. | The estimated intervention effect in terms of reduction in sandfly counts is simple model showed a 75.4% reduction for EVM and a 45.7% reduction for LLIN. | 16/25 |

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Table 1. (Continued)

| Author, Year, Country, Study design | Sample size/Treatment protocol | ITN interventions | Vector parasite species | Results Human outcome indicators | Results Entomological outcome indicators | Limitations & Methodology | Quality assessment scores (CONSORT checklist) |
|------------------------------------|--------------------------------|-------------------|------------------------|---------------------------------|----------------------------------------|---------------------------|------------------------------------------|
| Chowdhury, 2017 Bangladesh (Referral)RCT [30] | 250 houses (100 controls, 150 cases) | − (nets randomly assigned to different treatment groups) | Phlebotomus argentipes | The adjusted odds (LLIN, IRS+KOTAB) showed that the number of L. donovani cases decreased by 97% to 98% for IRS+KOTAB and 95% to 96% for IRS alone. The adjusted odds for IRS+KOTAB were 0.02 (95% CI 0.00-0.47) in comparison with IRS alone. The adjusted odds for IRS+KOTAB were 0.02 (95% CI 0.00-0.47) in comparison with IRS alone. | For the baseline study, the mortality rates were within the expected range, and the proportion of sandfly species was as expected. The baseline study was not designed to investigate the relationship between vector density and human infections. | The study did not include an independent variable for vector density, which may have influenced the results. |
| Alexander, 1995 Colombia, RCT [31] | Three houses, randomized to either an intervention group or a control group | − (nets randomly assigned to different treatment groups) | Phlebotomus argentipes | The mean number of sandfly collections per person-hour in the intervention group was significantly lower than in the control group. The mean number of sandflies per hour in the intervention group was significantly lower than in the control group. | For the baseline study, the mortality rates were within the expected range, and the proportion of sandfly species was as expected. The baseline study was not designed to investigate the relationship between vector density and human infections. | The study did not include an independent variable for vector density, which may have influenced the results. |
| Liao, 2012 China, RCT [32] | − (nets randomly assigned to different treatment groups) | Phlebotomus argentipes | 99% reduction in sandfly density in the intervention group compared to the control group. | The mean number of sandfly collections per person-hour in the intervention group was significantly lower than in the control group. | The study was not designed to investigate the relationship between vector density and human infections. | The study did not include an independent variable for vector density, which may have influenced the results. |
| Lu, 2004 China, RCT [33] | − (nets randomly assigned to different treatment groups) | Phlebotomus argentipes | 99% reduction in sandfly density in the intervention group compared to the control group. | The mean number of sandfly collections per person-hour in the intervention group was significantly lower than in the control group. | The study was not designed to investigate the relationship between vector density and human infections. | The study did not include an independent variable for vector density, which may have influenced the results. |
Table 1. (Continued)

| Author, Year, Country (District: resolution) | Sample size/Follow up period | ITN interventions | Vector parasite species | Results Human outcome indicators | Results Entomological outcome indicators | Limitation or methodological weaknesses | Quality assessment comments (CONSORT checklist) |
|------------------------------------------|-------------------------------|-------------------|-----------------------|---------------------------------|------------------------------------------|------------------------------------------|-----------------------------------------------|
| Mondal 2010 Bangladesh (Mymensingh district) | The study was conducted from March 2009 to August 2009 in the study area. The study area was divided into 9 subdistricts. The sample size was 2,700 households. | ✓ | Phlebotomus argentipes | The results of the household indoor spraying of 1 month after dipping showed that 94.6% of households in Mymensingh and 70% in Rajshahi participated in the study. The study was conducted from March 2009 to August 2009. | Sandfly exposure | Incidence of Leishmania infection / seroconversion / VL subdistrict | sandfly density | sandfly mortality | Insecticide resistance on ITNs | sandfly landing and blood feeding rate of sandflies |
| Mondal 2010 Bangladesh (Rajshahi district) | The study was conducted from March 2010 to August 2010 in the study area. The study area was divided into 6 subdistricts. The sample size was 2,700 households. | ✓ | Phlebotomus argentipes | The results of the household indoor spraying of 1 month after dipping showed that 94.6% of households in Mymensingh and 70% in Rajshahi participated in the study. | sandfly exposure | Incidence of Leishmania infection / seroconversion / VL subdistrict | sandfly density | sandfly mortality | Insecticide resistance on ITNs | sandfly landing and blood feeding rate of sandflies |
| Mondal 2013 Bangladesh (Shabazpur – Golapara Community intervention areas) | The intervention area was a village in Shabazpur Golapara. The control area was a village in Rajshahi. The study area was divided into 3 subdistricts. The sample size was 2,700 households. | ✓ | Leishmania donovani | The results of the household indoor spraying of 1 month after dipping showed that 94.6% of households in Mymensingh and 70% in Rajshahi participated in the study. | sandfly exposure | Incidence of Leishmania infection / seroconversion / VL subdistrict | sandfly density | sandfly mortality | Insecticide resistance on ITNs | sandfly landing and blood feeding rate of sandflies |
| Banjara 2015 Bangladesh, India and Nepal (Community intervention in Bangladesh, India and Nepal) | The study covered 8 villages in each of the 3 countries. The sample size was 2,700 households. | ✓ | Phlebotomus argentipes | During the study it was found that 94.6% of households in Bangladesh, 70% in India, and 99.8% in Nepal participated in the study. | sandfly exposure | Incidence of Leishmania infection / seroconversion / VL subdistrict | sandfly density | sandfly mortality | Insecticide resistance on ITNs | sandfly landing and blood feeding rate of sandflies |

**Author, Year, Country (District: resolution), study design**

**Sample size/Follow up period**

**ITN interventions**

**Vector parasite species**

**Results Human outcome indicators**

**Results Entomological outcome indicators**

**Limitation or methodological weaknesses**

**Quality assessment comments (CONSORT checklist)**

**10.27**

**10.08**

**10.08**
Table 1. (Continued)

| ITN interventions | Vector/parasite species | Baseline entomological outcomes (Continued) |
|-------------------|-------------------------|--------------------------------------------|
| Trial 1: mesh size 15/18, net 200 holes/inch², Trial 2: mesh size 625 | Phlebotomus argentipes | Mosquito density: |
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| | | Sandfly mortality: |
| | | Infection / seroconversion/VL incidence: |
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### Table 1. (Continued)

| Author, Year, Country (District/state/province, study design) | Sample size/Follow-up period | ITN interventions | Vector/parasite assessment | Results: Human outcome indicators | Results: Entomological outcome indicators | Limitations described | Quality Assessment scores (CONSORT checklist) |
|-------------------------------------------------------------|------------------------------|-------------------|----------------------------|-----------------------------------|-------------------------------------------|------------------------|-----------------------------------------------|
| Singh 2016 (India) | The study was conducted in four villages in Bihar. Households in Patna district of Bihar were part of the study. The intervention and follow-up periods were from August 2007 to November 2008. | ✓ PermaNet 156 mesh/inch², ✓ PermaNet 196 mesh/inch², ✓ PermaNet 156 mesh/inch² + 75 cm border of fine cloth. | Phlebotomus argentipes. | At the four open LLINs were accepted by communities, all those distributed free of cost. Household surveys indicated that PermaNet 156 mesh/inch² was preferred by 87.92%, while PermaNet 196 mesh/inch² + 75 cm border was the least preferred 54.2%, as the net does not provide air circulation during sleep at night. | The evaluation of P. argentipes population density at the first month of post-intervention of 14.1% were as follows: In Hulashchak, 47% in Gonpura and 92% in Duparchak. The maximum evaluation of P. argentipes populations were 36.66% and 53.9% in Hulashchak and Duparchak respectively. This was reduced to 14% in Hulashchak and 31.4% in Duparchak. In Gonpura sharp decline was observed during the post intervention period minimum 72.41% post intervention. | Not specified | 19/18 |
| Dinesh 2008 (India) | The study was conducted in the state of Bihar. Three border villages of Madhubani, Bhagalpur, and Patna were selected to carry-out the study. With a total of 40 HHs, the households were chosen for the intervention back drop and follow-up was 3 and 6 month and evaluation was done up to April 2010. | ✓ PermaNet 196 mesh/inch² and ✓ PermaNet 156 mesh/inch² and ✓ PermaNet 196 mesh/inch² + 75 cm border of fine cloth. | Phlebotomus argentipes and Sergentomyia Spp. | Compared with LC, there was a significant reduction in male and female P. argentipes with PermaNet 196 mesh/inch² and PermaNet 196 mesh/inch² + 75 cm border of fine cloth. These reductions were not significant for female P. argentipes. The significant reduction in male P. argentipes was higher compared to PermaNet 196 mesh/inch². This reduction could have a role in reduction of mortality. CDC light trap collections performed better than aspirator collection for all the 'groups', except for the controls of P. argentipes. | The significant reduction in male P. argentipes 92%, 87.92 and 91.27% were also noted in treated villages Hulashchak, Gonpura and Duparchak, respectively. As such, decline was not observed, while compare to between the study arms there was significant reduction in females of P. argentipes populations throughout the year 85–100%. The significant reduction in male P. argentipes populations throughout the year is 100–100%, in Hulashchak it was 71.87, while 87.92 and 91.27% were also noted in treated villages Hulashchak, Gonpura and Duparchak, respectively. | Not specified | 19/18 |

(Continued)
| Author, Year, Country, Study design | Sample size/Follow up period | ITN interventions | Vector parasite species | Results: Human outcome indicators | Results: Entomological outcome indicators | Limitations described | Quality assessment | Quick summary of main findings per study (CONSORT checklist) |
|-----------------------------------|-------------------------------|-------------------|-----------------------|-------------------------------|--------------------------------|---------------------|-----------------|-----------------------------------------------------|
| Courtenay 2007 Brazil [Not from the South Asian regional initiative] Intervention Study (Consensus study) [12] | District/ subdistrict) study | Long-lasting Bed nets, Long-lasting Bed nets, Long-lasting Bed nets, Long-lasting Bed nets, Long-lasting Bed nets | Lutzomyia longipalpis, Lutzomyia longipalpis, Lutzomyia longipalpis, Lutzomyia longipalpis, Lutzomyia longipalpis | Perception, acceptability, maintenance and satisfaction regarding ITNs | Sandfly density, Sandfly mortality, Sandfly landing inside and outside ITNs, Sandfly landing inside and outside ITNs | Sample size could have limited the results. A potential predominant limiting factor for ITN efficacy in this study region is a social barrier to accepting and using ITNs. The study revealed that the use of ITNs is associated with a significant reduction in sandfly density and mortality. However, the study did not evaluate the impact of ITNs on disease transmission. | 12/18 | 12/18 |
| China 1998 Sudan [Not from the South Asian regional initiative] Intervention study (Consensus of surveys) [11] | The study was conducted in two villages (Bellow and Ai-Elgamel) within 1 District of Sudan National Park (1995) and 1 village (Ai-Elgamel) within 1 District of Sudan National Park (1995) | ITNs | P. orientalis, P. orientalis, P. orientalis, P. orientalis, P. orientalis | A total of 30 females sandfly were collected inside houses during the 30 trapping nights per study. Adjusting for house and night effects, the mean absolute number of female sandflies collected per night (ITN) houses was 16.4, which was not significantly different from the number of 16.0 collected in houses with untreated nets. The mean number collected per night was significantly lower in treated nets, compared with untreated nets (n = 4310 females) within 1 h (39.5%) or 1–2 h (49.9%) of potential sandfly exposure. The duration of exposure to sandfly bites was shorter in treated net users than in untreated net users, and this may have contributed to the lower mean sandfly biting rate outside the net. | The mortality rate of sandflies landing on ITNs was reduced during the four months of the study. The mortality rate of sandflies landing on ITNs was reduced during the four months of the study. The mortality rate of sandflies landing on ITNs was reduced during the four months of the study. The mortality rate of sandflies landing on ITNs was reduced during the four months of the study. The mortality rate of sandflies landing on ITNs was reduced during the four months of the study. | Sample size and design limited the results. | 8/18 | 8/18 |
Table 1. (Continued)

| Author, Year, Country (Study design), sample size/Follow up period | ITN interventions | Vector/parasite species assessment | Results/Outcome measures | Limitations/Methodology | Quality assessment score/Consort checklist |
|---------------------------------------------------------------|-------------------|----------------------------------|--------------------------|------------------------|------------------------------------------|
| Kumar 2017, India (Cluster randomized trial) | ✓ Perma Net 3.0 IRS+ITN | Phlebotomus argentipes/Leishmania donovani | Bed nets Long-lasting Combinations Perception, acceptability, maintenance and satisfaction scores regarding ITNs | The study was conducted in the Samastipur district, 4 villages of the district were selected for the intervention. In Dighaipur, Talabdehi, Sibra and Kishangam (total 600 HHs) were targeted for the study. The study period was from October 30th to October 2015. | The expected outcome at the village of Sahnitola (control) was compared with the intervention (Mirzapur, Bisanpur). In total 400 HHs were targeted for the study. The study period was from October 2014 to October 2015. | 15/18 |
| Chowdhury 2019, Bangladesh (Retrospective cohort study) | ✓ ✓ | Phlebotomus argentipes/Leishmania donovani | Office interaction with more than 92% had at least one bed net in their house at time of household survey. Interventions: IRS- 40%, IRS+ITN- 59%, ITN alone- 2% | The study was conducted in the three years period from October 2001 to 2007 in three intervention areas: Sibra, Dighaipur and Kishangam. The intervention areas were IRS- 40%, IRS+ITN- 59%, ITN alone- 2%. | The comparison was continued in the three intervention areas: Sibra, Dighaipur and Kishangam. The intervention areas were IRS- 40%, IRS+ITN- 59%, ITN alone- 2%. | 10/18 |

Observational Studies

Cluster randomized trials (Trial ID) Bangladesh (Retrospective cohort study) [22] Three intervention areas with a total of 16321 (n=10758) in intervention (Sibra, Dighaipur and Kishangam) vs. control (Kishangam) population. Follow-up period for the three interventions was: 30/09/2001 (period of observation-10/10/2001) (100/period of observation-10/10/2002) (100) period of observation-10/10/2003) (100). | ✓ ✓ | Phlebotomus argentipes/Leishmania donovani | Office interaction with more than 92% had at least one bed net in their house at time of household survey. Interventions: IRS- 40%, IRS+ITN- 59%, ITN alone- 2% All respondents facilitated by the provision of provided bed nets (IRS- 40%, IRS+ITN- 59%, ITN alone- 2%). The intervention was conducted for 12 months in the intervention areas. | A total of 400 VL case were recorded in the three years period from October 2001 to 2007 in three intervention areas: Sibra, Dighaipur and Kishangam. The intervention areas were IRS- 40%, IRS+ITN- 59%, ITN alone- 2%. | The expected outcome at the village of Sahnitola (control) was compared with the intervention (Mirzapur, Bisanpur). In total 400 HHs were targeted for the study. The study period was from October 2014 to October 2015. | 15/18 |
Table 1. (Continued)

| Author, Year | Country (District/subdistrict), study design | Sample size/Follow up period | ITN interventions | Vector/parasite species | Results: Human outcome indicators | Results: Entomological outcome indicators | Limitations described | Quality scores by the authors | Quick assessment according to the CONSORT checklist |
|--------------|-------------------------------------------|-------------------------------|-------------------|-----------------------|----------------------------------|------------------------------------------|----------------------|--------------------------|------------------------------------------|
| Ritmeijer 2007 | Sudan [19] (4 districts) cluster-randomized, intervention and control groups | 154734 (20 villages) insecticide-tr eated net | ✓ | Phlebotomus orientalis | 36% decline in VL incidence | Sandfly exposure 12.3% | Sandfly density 55% | Sample size issue | 15.0/12 |

The study found that the number of cases reported by villages increased from 20 villages in the study, numbers in 10% range. In the three villages of Arikub, Taluka, Alieh Dupert and Dinka, all 158 cases were recorded to be by households in the range of 20–25% were compatible to the sleeping habits. Of 129 cases, 72 (57.6%) were reported to be by family members alone, 57 (44.0%) were reported to be by family members alone, and the rest of 55.3% were reported to be by family members alone. During April and May, which are the hottest months of the year, people shift to sleeping outdoors, and bednet use increased to 43%. After the first rains in June, people shift to sleeping indoors, and bednet use increased to 55%. Sleeping behaviour was found to be due to the protective effect of ITNs on children and the different seasons also play a role in the use of ITNs by the HHs.

VL, Visceral Leishmaniasis; cRCT, cluster-randomized controlled trial; ITN, insecticide-treated net; Pop., population; RCT, randomized controlled trial; HH, household; FC, fever camp; CI, confidence interval; NKTA, no kala-azar transmission activity; DWL = insecticide impregnated durable wall lining; LN/LLIN, Long-lasting insecticidal net; KD, Knock down effect; HPLC, high performance liquid chromatography; IRS, indoor residual spraying; EVM, environmental modification; KOTAB, insecticide K-O TAB 1-2-3; OUT, insecticide spraying in potential breeding sites outside of house using chlorpyrifos 20EC; PBO, piperonyl butoxide; PT, Permanent; OT, Olyset; LC, local polyester untreated nets; PC, PermaNe t Control; DEET, N,N-Diethyl-meta-toluamide; DNP, Dinder National Park; RI, reduction due to intervention; IR, incidence rate; MSE, Médecins Sans Frontières.
infection, and seroconversion (four studies). Like the entomological outcomes, some studies also measured more than one human outcome.

Quality analysis
There was a high variability of appropriateness of study designs, study sizes and consistent limitations in finding sufficient number of VL cases in low incidence settings. Variations were also observed for the comparability between the intervention and control arms, the way vector density was measured, and cases were identified, and also how potential confounders were taken care of. As a result, the quality assessment scores performed using the CONSORT checklist varied from 10/18 to 21/25 (Table 1). No study was excluded because of a low score.

Analysis of results
Entomological outcomes

Sandfly density. A study from Bangladesh testing both KO Tab 1-2-3 (KOTAB) impregnated bed nets and LLIN showed that LLIN was effective from second follow-up (at 4 months) onwards through to the end of the 22 months follow up period [28]. The adjusted model for LLIN showed that the vector density (males plus females) reduction was 9% to 78% and the rate ratio was between 0.91 and 0.32 for two years. In the KOTAB arm, a significant sand fly density (males plus females) reduction was observed only at the third (at 5 months), sixth (14 months), seventh (15 months) and eighth (18 months) follow-up measurements. For the other combined intervention arms: The combination of IRS with LLIN (IRS+LLIN) or with KOTAB (IRS+KOTAB) and with outdoor spray (IRS+OUT) showed statistically significant *Phlebotomus argentipes* (males plus females) reductions almost all through the study period. The adjusted model showed that the effects of IRS+LLIN and IRS+KOTAB on sandfly density reduction (males plus females) were 23.0% to 85.0% and 16.0% to 86.0%, respectively. The combination of LLIN with outdoor spray (LLIN+OUT) was found to be effective throughout the study period at a highly significant level. The reduction of *P. argentipes* sand fly density (males plus females) in this case was 26.0% to 86.0%.

In another study from Bangladesh, the mean reduction of female *P. argentipes* counts in the ITN arm ranged from $-6.10$ (95% CI: $-3.04, -9.19$) to 0.81 (95% CI: 0.01, 1.60). The adjusted intervention effect of ITN was statistically significant on reduction of the incidence rate of female *P. argentipes* sandfly count up to 3 months post-intervention [19]. In another study, a dipping programme significantly reduced the sandfly density (males plus females) in the intervention areas compared to the control areas. The observed reduction by the intervention was about 60% for 18 months period [15]. The reduction in sandfly density (males plus females) after 2 weeks of bednet impregnation (KOTAB 123) was 86.5% and 32.6% in India and Nepal, respectively as compared to baseline and the reduction after 4 weeks was 94.6% and 12.5% in India and Nepal, respectively [30].

In a multi-country cRCT in Bangladesh, Nepal and India, bed nets impregnation with KO Tab 1-2-3 reduced female sand fly density through to 9 months [20]. In India and Nepal, in a paired cRCT, indoor density of *P. argentipes* (males plus females) was reduced by 25% in the study clusters that used treated nets compared with control clusters [21]. The effect was not significantly different in the two countries. The analyses carried out on *P. argentipes* females also found a significant reduction in density of 11.6% [26]. For LLIN in Nepal, vector density (males plus females) dropped from 7.9 to 0.9 per house per night by LT collections and from 1.8 to 0.5 per house per morning aspirator collections in three follow-up surveys after intervention [24].
When the net effect of individual intervention in reducing sandfly count (males plus females) was estimated, the following was found: a 72.4% reduction for IRS, a 42.0% reduction for EVM and a 43.7% reduction for LLIN (PermaNet) [25]. Both IRS and ITNs were associated with a 70–80% decrease in the density of *P. argentipes* 4 to 5 months after the intervention (males plus females). Households (HHs) in the ITN arm continued to show significantly lower vector density compared with the control arm, 11 months after intervention (60% lower densities) [27]. In a study from India, the highest monthly percent reduction (% RI) of sandfly density (males plus females) was observed at the sites with IRS and ITN (93.59–100%) as compared to either at the control site (with 0% reduction) or with single intervention of IRS (with 4.29–86.77%) or with ITN (PermaNet 3.0) (60.18–97.01%). At the site with the combined treatment of IRS and ITN, no re-emergence of sand flies was recorded till 13 months following the intervention [34].

While compared between two mesh sizes in a cross-over design [31], fewer *P. argentipes* (males plus females) were captured inside the 625 (holes/inch$^2$) mesh nets (n = 514 *P. argentipes* in net B) compared to 156 (holes/inch$^2$) mesh nets (n = 561 in net A). In this trial it was observed that the use of 625 mesh size nets reduced by 77% and 78% the number of female *P. argentipes* and total *P. argentipes* captured inside the nets, respectively, compared to 156 mesh size nets (A). When compared with untreated nets (n = 577), fewer *P. argentipes* were collected inside the treated nets (n = 527). Using a-cypermethrin treated nets reduced by 77% and 61% the number of female and total *P. argentipes* captured inside the nets, respectively, compared to untreated nets.

In another study in Bihar, India, three different mesh sizes of PermaNet LLINs were evaluated—156 mesh/inch$^2$, 196 mesh/inch$^2$ and 196 mesh/inch$^2$ + 75 cm border of fine cloth [18]. LLINs were distributed to cover all the members of the family. The reduction of *P. argentipes* population (males plus females) observed in the first month of post-intervention of LLINs were as follows: 100% in Hulashchak, 87.3% in Gonpura and 85.55% in village Duparchak. The minimum reduction of *P. argentipes* population were 36.66 and 35.55% in 9th and 13th month, while a sharp increase was noticed in 12th month in Hulashchak. In Gonpura sharp decline recorded throughout the year between 73.41 to 100%, minimum in 12th month 72.41% post intervention. Dhuparchak where mesh size was 196 + 75 cm of border found maximum decline in *P. argentipes* population throughout the year 85–100%, in 8th month of treatment only 71.1% decline was recorded. In the entire intervention period, maximum reduction 93.67% was observed in Duparchak PermaNet 196 mesh/inch$^2$ + 75 cm border followed by Gonpura PermaNet 196 mesh/inch$^2$ 91.90% and 74.29% in Hulashchak PermaNet 156 mesh/inch$^2$; when compared to control all the LLINs were significant; while compared to between the study arms there was no significant p values. The significant reduction in gravid *P. argentipes* by 71.87%, 87.92% and 91.27% were also noted in treated villages Hulashchak, Gonpura and Duparchak, respectively.

A cross-over study from Brazil testing deltamethrin impregnated bed nets against *Lutzomyia longipalpis*, has shown that the mean number of sandflies (males plus females) collected per night under treated nets was 1.3, which was significantly fewer than the mean of 2.6 collected under untreated nets. These data indicate that the insecticide increased the barrier effect of untreated nets by an average of 39.2%. The insecticide also reduced the percentage of (collected) sandflies landing under nets from 71.4% in untreated to 14.5% in treated households, representing a reduction of 79.7% [12]. Another study from the Latin America (Colombia) has shown that deltamethrin impregnated curtain did not significantly reduce the mean numbers of sandflies collected per man-hour in rooms [13].
**Sandfly mortality.** A wide range of mortality rates for sandfly have been found in studies at varying intervals with different interventions. A dose-response relationship has been observed with higher mortality rates in earlier follow-ups.

The Abbott’s corrected sand fly (males plus females) mortality rate (inside of test containers) [mean and 95%CI] at 1, 3, 9 and 12 months after bed nets impregnation with KO Tab 1-2-3 was respectively 75% (71%-79%), 67% (64%-74%), 63% (57%-68%) and 49% (43%-55%) [20]. In another study, for the same intervention, mortality (inside of test containers) of *P. argentipes* sandfly (males plus females) was 51.7% at the 12 months follow up [19]. In an earlier investigation in Bangladesh, sandfly (males plus females) mortality (inside of test containers) at 24 h after they had been exposed to the treated nets was high at 1 month and at 12 months after the dipping. However, thereafter, the mortality rate dropped but remained at about 80% threshold level even at 18 months after dipping across the two districts–Mymensingh and Rajshahi [15]. In a longer follow-up up to 20 months, Chowdhury, Faria [28] have shown sandflies (males plus females) mortality (inside of test containers on K-O TAB 1-2-3 impregnated nets dropped from 88.37% at 3 months to 69.12% at 20 months after use. In the same study, mortality for LLIN was also tested and found to remain as high as 83% at 20 months of use. In a cross-over design in Nepal involving two mesh sizes, the mean *P. argentipes* (males plus females) mortality (inside test containers per LLIN was 98% and 94% for the two treated nets with 200 mg/m² and 160 mg/m², respectively [31]. The laboratory sample of a 625 mesh net with 200 mg/m² of alpha-cypermethrin had an average mortality (inside test containers) of 97%.

In a study in Brazil, the 24-hour mortality rate (outside of test containers) of all sandflies (males plus females) collected under ITNs was 97.7%, compared with 0% under untreated nets. Mortality rates (outside of test containers) for the sandflies (males plus females) on the surface of the net and landing on collectors under ITNs were 32/32 and 4/5 compared with 0/23 and 0/56 under untreated nets, respectively [12]. In Colombia, *Lu.youngi* showed significant knockdown within 1 h (13.2%) and mortality after 24 h (43.4%) of exposure to impregnated curtains [13]. *Lu. Youngi* collected resting on impregnated bednets showed a mean knockdown rate of 7.1% after 1h and mortality of 39.7% after 24h, significantly higher (p < .05) than the rates for those caught resting on untreated walls of houses without impregnated bednets or curtains. In a study in Turkey, testing different insecticide-treated bed net set ups including indoor and outdoor, and taking down and not taking down the nets, sandflies (males plus females) mortality rate (inside test containers) was found to be 100% for all the groups, whereas the group representing participants who preferred to sleep outdoors over the 6-month transmission period and did not take down their bed nets had a lower mortality rate (inside test containers) (44.4%) by the end of 24 h. The control group, which used untreated bed nets, 3 out of 120 specimens died after 24h [14]. In Sudan, the mortality rate (inside test containers) of *P. orientalis* (females) was 100% (n = 4310 females) within 1 h post-exposure for 30s to cage netting treated with lambda-cyhalothrin. For the untreated controls (n = 4310 females) the survival rate (inside test containers) was 100% for 24 h [11].

**Insecticide residue on ITNs, sandfly landing and knock down (KD) of sandflies.** After 22 months of use, 36.6% of nets (PermaNet 2.0) in India and 22.2% in Nepal were still intact [22]. The chemical analysis showed that the average concentration of deltamethrin in the treated nets dropped over 18 months from 24 to 9.5 mg/m² [15]. When compared, the reduction of insecticidal content of IRS was faster and more pronounced (exhibiting corrected sandflies (males plus females) mortality rate as 52.38%, 58.33%, 45.45% & 50.00%) as compared to ITN (PermaNet 3.0) (with corrected sandflies (males plus females) mortality rate as 84.44%, 82.50%, 77.78% & 83.33%) over the period of 13 months since intervention. [34].
Use of deltamethrin impregnated net in a Brazilian community showed reduction in the percentage of (collected) sandflies (males plus females) landing under nets from 71.4% in untreated to 14.5% in treated households, representing a reduction of 79.7% [12]. The absolute number of sandflies (males plus females) landing exterior to ITNs was reduced despite a similar abundance of sandflies in rooms with the two respective treatments. The rate of 24-h mortality (outside of test containers) amongst sandflies (males plus females) collected exterior to ITNs was 67.7%, compared with 0.4% of those collected exterior to untreated nets (outside of test containers). Within ITN houses, the 24-h lethality effect of the insecticide was greater inside than outside the net, and greater amongst flies (males plus females) alighting on the walls than landing outside the nets.

The mean sandflies (males plus females) KD per swatch ranged from 88.5–99.0% after 12 months and 87.6–99.0% after 24 months, as observed in a multicountry study involving India and Nepal [22]. The mean mortality per swatch ranged from 91.0–100.0% after 12 months and 87.6–100.0% after 24 months. Bioassays were performed to test residual efficacy of DDT in the intervened households; regarding these results, there was 60% sandflies (males plus females) mortality (inside test containers) in test against LN PermaNet 2.0 within the 3 min of exposure time. The test against DDT on wall illustrated 50% mortality of sandflies (males plus females) with 30 min time of exposure in the study area. LN PermaNet 2.0 showed higher efficacy by having higher sandflies (males plus females) mortality with low does and exposure time compared with DDT [32].

Human outcomes

**Perception, acceptance, access, utilization, maintenance and satisfaction regarding ITNs.** A study from Nepal showed that 72% of the respondents perceived a reduction of sandflies after bed net impregnation with insecticide [29]. Transient itching was reported by 4.8% of HHs with ITN [20]. Unpleasant smell was reported in 3.2% of ITN houses. After 22 months of use, 36.6% of nets in India and 22.2% in Nepal were still found to be intact [22]. The results of the household interview surveys at 1 month after dipping with KO Tab 1-2-3 in Bangladesh showed that 94.4% of respondents in Putijana and 70.0% in Deopara perceived them to be protective against sand flies and other insects [15]. The levels of acceptance dropped 6 months later to 84.4% in Putijana and 50.0% in Deopara as a decrease in efficacy against insect nuisance was perceived by the communities. In another study in Bangladesh, the use of impregnated bed-nets was found to be very high (99.8%) [17].

In a multi-country community intervention trial involving Bangladesh, India and Nepal, the bednet impregnation rate was 82.1% in Bangladesh, 81.5% in India, and 99.8% in Nepal [30]. When PermaNets were distributed as a part of intervention in Bihar, India, all the three types LLINs were accepted by communities, as these were distributed free of cost. Household survey revealed that PermaNet 156 mesh/inch\(^2\) mesh was preferred by 100%, PermaNet 196 mesh/inch\(^2\) by 91.7%, while PermaNet 196 mesh/inch\(^2\) and 75 cm border was the least preferred 54.2% as this net did not provide air circulation during sleep at night [18]. In another study from India, were IRS and ITN were evaluated in combination, all respondents facilitated with ITNs, confirmed the proper usage of provided bed nets as well as the continuous good physical conditions of the nets. Almost the only reported side effect was unpleasant smell, particularly in the 2 arms that included IRS and IRS with ITN. The perception of added benefits (mainly reduction in nuisance of insects) was highest in villages where ITNs were involved [18]. In Bangladesh, of the intervention HHs more than 92.2% had at least one bed net in their house at the time of the household survey. Among those, 80.1% were ITNs, either self-impregnated with K-O TAB 1-2-3 or LLIN, the others were non-impregnated commercial nets [16].
In Sudan, bednets were most frequently used during the rainy season. During April and May, which are the hottest months of the dry season and the early part of the VL transmission season, bednet use was <10%. After the first rains in June, people shifted to sleeping indoors, and bednet use increased to 55%. Sleeping behaviours tend to reduce the protective effect of ITNs on children and the different season also play a role in the use of ITNs by the HH members [10]. Overall satisfaction was achieved in Indian villages involving ITNs as compared to the village with IRS as single intervention with 87% acceptability [34].

Feeding on human blood and sandfly biting. In a study in Nepal and India, for *P. argentipes* the geometric mean of ELISA OD was used to evaluate exposure of sandflies species to human individuals in the study, the results showed that the exposure to the vector was, on average, 12% reduced at 12 months and 9% at 24 months in the intervention group compared to control group [23]. Similar results were obtained for *P. papatasi*: 11% and 9% reduction in LN group at 12 and 24 months respectively, the study evaluated *P. papatasi* but it has not been incriminated as a vector of VL. In addition, the percentages of positive samples for *P. argentipes* ELISA were reduced from 63.2% to 43.5% and from 47.1% to 43.6% in the intervention and control groups respectively over 24 months. For *P. papatasi*, the percentage of positive ELISA samples was not altered after 24 months in the control clusters (17%) but was reduced from 32.6% to 21.8% in the clusters using LN. The study from Sudan showed that sandfly biting was zero for persons using the impregnated bednets (bed nets impregnated with the pyrethroid insecticide lambda-cyhalothrin) and significantly reduced for persons staying under untreated bednets (6.92+/−2.71 bites/man/night), whereas persons without bednets experienced 32.0+/−8.3 bites/man/night [11]. For different sex and age groups of the people living in Bellow and Ai-Elgamel villages, the daily potential duration of exposure the users of impregnated bednet have to the risk of *P. orientalis* biting, was taken as the time after sunset until bed-time, the likely start of bednet use. The majority of people were found to have <1 h (39.5%) or 1–2 h (49.9%) of potential exposure to sandfly bites. Nearly 11% of people were found to be exposed to the risk of sandfly bites for more than 2 h before bed-time. In another study in Latin America, in Colombia, the proportion of Lu. youngi females biting was significantly lower in rooms protected by curtains (0.48 v 0.65, *p* <0.05) but not for Lu.lichyi or Lu. colombiana, although they appeared to less predisposed to bite after passing through impregnated curtains [13].

The duration of exposure to the risk of sandfly bites was associated with gender as well as the age group. Females had significantly less exposure time than males. Children <5 years experienced the least exposure, with most individuals (92.9%) having <1 h exposure. For the age group 6–15 years, potential exposure time was mostly 0–1 h (52.7%) with nearly as many having 1-2h (45.5%), and a negligible proportion having >2 h exposure. Two-thirds (66.8%) of people >16 years old were found to be exposed to risks of sandfly bites for 1–2 h, with lower proportions having <1h (14.8%) or >2 h (3.3%) duration of exposure risk before going to bed. [11]

**VL incidence, *L. donovani* infection, and seroconversion.** From the selected studies, only two considered the effects of ITNs/LLINs on VL incidence [16,17]. After intervention with impregnation of bed nets with KO Tab 1-2-3 in Rajshahi, Bangladesh, VL incidence in intervention and control areas was 2.6 and 8.6 cases per 10,000 persons, respectively [17]. During follow up, annual VL incidence declined in both areas, with a greater reduction in the intervention area (decrease of 35 cases/10,000 persons) than in the control area (decrease of 9.99/10,000). The effect of the intervention in reducing VL-affected HHs in the intervention area compared with the control area was 70.5% by difference-in-difference analysis. By odds ratios, the estimation of the crude protection of HHs in the intervention area was 87% compared with those in the control areas. In a retrospective cohort study in Fulbaria, Bangladesh
where the communities had been benefited previously from a LLIN or K-O TAB 1-2-3 distribution in 1 of three distinct studies, after the three-year intervention period a total of 555 VL cases were identified (178 cases in the intervention area; 48.04/10,000/year) (377 cases in control areas; 107.95/10,000/year). The effect of the intervention was strongly significant. The estimated reduction of VL incidence rate by the intervention was 46.80% (p < 0.0001). Another cohort study in Sudan found that the number of cases reported by village and month was significantly reduced following ITN (insecticide-treated 156-mesh) provision at all 4-month time points up to 20 months post-intervention. The greatest effect was detected 17–20 months post-intervention, with the number of cases on average reduced by 59%. The predicted number of cases in each village and each month in the absence of bednets from June 1999 to January 2001 was 3863, which compares of an observed number during that time of 2803. The investigators estimated that bednet intervention could have reduced the number of cases up to January 2001 by 1060, with a calculated protective effect of 27.4%. [10]

For the primary outcome, being the number of incident L. donovani infections as measured by seroconversion with the direct agglutination test at 12 and 24 months after the intervention, the risk of seroconversion during the two-year follow-up was significantly different between countries: 7.2% in India (529/7368) and 3.1% (163/5323) in Nepal [21]. The overall risk of seroconversion in the intervention (5.4%) and control (5.5%) groups was similar. At cluster level, the risk of infection was reduced by 10% in the intervention clusters compared with control clusters, but this effect was not significant. Longlasting insecticidal nets seemed to have an opposite effect on seroconversion in India and Nepal, but the interaction was not significant.

Discussion

Discussion of key results

Our systematic review has demonstrated that vector control interventions involving insecticide treated nets work effectively in community settings to reduce sandfly density, their exposure to and occurrence of VL among humans in South Asian (India, Bangladesh and Nepal) settings, as well as in other regional settings including in sub-Saharan Africa (Sudan), Latin America (Brazil) and the Mediterranean region (Turkey). Both insecticide impregnated bednets and commercially treated long lasting insecticide treated nets showed some levels of efficacy in the different interventions, with clear dose-response relationship that waned over time. While the community members well accepted the process of impregnating bed nets with slow releasing KO Tab 1-2-3, there could be problems with early erosion of insecticides resulting in effects lesser than expected. These problems did not happen with LLINs, but they could cost more requiring additional resources to ensure the sustainability of their widespread use. The review also found that combining ITNs and another vector control technique would work better than going with either of them separately.

For insecticide impregnated bednets, they had profound effects on sandfly density with its immediate reduction by as high as around 90% during the 2–4 weeks time period after impregnation. This high effectiveness observed in India did not replicate in Nepal. It was hypothesized that other vector control activities that were operating in the communities had reduced the vector density and burden, allowing little room for ITNs to show their effects [30]. In Bangladesh, the community had to wait as long as 5 months after the intervention to see its beneficial effect, which lasted through 18 months with 60% reduction in vector density. It is not clear what resulted in such a delay in receiving the benefits of insecticide impregnated bednets and weather the seasonal variations of the density of sandfly population and thus VL influenced by changes in the ambient weather condition played any role into that [35]. In another multi-country cRCT involving Bangladesh, India and Nepal, the effect of KO Tab 1-2-3 impregnated
bednets did not last beyond 9 months. The investigators suggested that this could be due to operational errors during bed net impregnation and the breakdown of insecticide in nets over time [20]. This apparent weakness of impregnation of bed nets required further attention and support, especially in resource limited settings where this could be the most sustainable and cost-effective way of going with ITNs [15]. In other regional settings like Brazil, effects of deltamethrin impregnated bednets on Lutzomyia longipalpis showed reduction of both sandfly collection and landing under nets significantly. Mortality of P. argentipes was also found to be as high as 75% at 1 month after impregnation in Bangladesh. This effect lasted for a year with 50% sandfly mortality rate. It is important to consider that the effectiveness of ITNs and LLINs interventions were measured with sandflies densities, which has certain level of limitations since most of the included studies did not assess VL incidence as an outcome for the intervention’s effectiveness.

Insecticide impregnated bednets were also perceived to be well protective by the majority of the community members in Bangladesh soon after their introduction. But this perception changed over time along with the reduction of their effects and increase in sandfly nuisance. A small proportion of the community members also reported transient itching and unpleasant smell associated with bednet impregnation. Studies from South Asia as well as from other regional areas have shown significant reduction in human exposure to sandfly bites with this intervention. In Sudan, sandfly biting came down to zero with the use of bednets impregnated with insecticide lambda-cyhalothrin. The duration of exposure to sandfly bites varied by gender, with males being more at risk, and by age group, with under-five children being least exposed. Sleeping behaviour influenced by seasonal and temperature variation also played a significant role in the proper utilization of ITNs in the community. Further investigations are thus warranted to understand the socio-demographic, environmental and behavioural factors that influence the use of ITNs. Although this is the exposure of the insecticides that reduces the burden of sandflies and thus the occurrence of VL, interventions involving ITNs will not achieve its optimal utilization without taking the local contexts into account.

Regarding human VL cases, interventions with impregnation of bednets with KO Tab 1-2-3 in Bangladesh has shown around 70% reduction in VL-affected households. In another study from Bangladesh using retrospective cohort design, the estimated reduction of VL incidence rate by the intervention was 47% ($p<0.0001$). The occurrence of VL also came down by almost 60% with a 20 months long lasting effect when commercially treated LLINs were used. This outcome was measured in a cohort study in a different setting in Sudan. Unlike the other recent studies, a paired cRCT from India and Nepal with the intervention using LLINs did not find any significant difference in the risk of seroconversion over 24 months nor in the risk of clinical visceral leishmaniasis, even after adjusting for covariates. Although there were methodological differences between the studies testing similar interventions but in different population, that did not entirely explain the large variations in study findings.

The longer lasting effect of LLINs without needing to treat them in the community make them the ITNs of choice, given sufficient resources are there to roll out at the population level. In the intervention studies, LLINs were distributed free of cost, which would not be the case in a real-life setting involving the entire population. Otherwise, more than one-third of distributed PermaNet 2.0 was found in intact condition even after 22 months of use in India. Although, the average concentration of deltamethrin in the treated nets dropped substantially (from 24 to 9.5 mg/m$^2$) over 18 months, as found in a study in Bangladesh, when comparing to IRS as a vector control measure, this reduction happened even faster with IRS when tested in India [15]. Regarding sandfly mortality, in a longer follow up study in Bangladesh, mortality on K-O TAB 1-2-3 impregnated nets dropped from 88.37% at 3 months to 69.12% at 20
months after use. In the same study, morality for LLIN was also tested and found to remain as high as 83% at 20 months of use.

The choice of an appropriate LLIN also depends on the mesh size and its border. Although showed significant and highest (91%) reduction in gravid *P. argentipes*, the Permanet 196 mesh/inch² +75 cm border was least preferred (as compared to 156 mesh/inch² and 196 mesh/inch²) by only around half of the participants as it did not provide sufficient air circulation at night. The same should also apply to insecticide impregnated bednets, although if the community members treat bednets that they are currently using, they might be used to it and the mesh size might not become an issue for them then.

When compared with IRS, LLINs (PermaNet 3.0) was found to demonstrate stronger individual effect with monthly observation of percent reduction of sandfly density by 60.18–97.01%. The effect combining LLINs and IRS was the strongest (93.59–100%), as found in this Indian study [34]. In another study in Bangladesh, evaluating combined interventions, both LLIN and KOTAB showed similar effectiveness when combined with IRS (maximum around 85%) [28]. When LLIN was combined with outdoor spraying of vector breeding sites with relatively cheaper Chlorpyrifos 20EC [28], it was found to be the most effective in reducing *P. argentipes* sand fly density throughout the study period at a highly significant level (26.0% to 86.0%).

Given the current low incidence of VL in the endemic countries in SEA, as an outcome of the elimination campaign, it is now important to identify the suitable resource-efficient vector control methods to control for the disease. For ITNs, its widespread roll out at the community level could be replaced by targeted interventions in conjunction with IRS, along with case detection.

**Discussion of level of evidence and knowledge gap**

Among the 25 studies included in this review, 23 were interventional studies. Of them, 10 were cRCTs showing robust evidence on the community effectiveness of ITNs including insecticide impregnated bed nets and LLINs on sandfly and VL control. Among the South Asian studies, seven were multi-country evaluations, which allowed for comparison of the effectiveness showing some real-life variations. There were also few follow-up studies generating longer term data from the same population. This allowed demonstration of the waning of insecticide impregnation in the bednets and their effects. From the studies that assessed the impact on ITNs on VL among humans, the majority were observational in nature and were conducted nested within other community interventions. These were efficient use of data and resources producing valuable population estimations. Surveys and qualitative interviews conducted alongside the interventions helped understand the community perception regarding the ITNs. Those studies provided contextual data needed for the successful implementation of the interventions.

There were some important limitations and knowledge gaps in the reviewed studies.

- In one hand, some studies were conducted under fairly controlled conditions which are not easily applicable in a national vector control programme. However, they provided indications of the way in which to undertake treatment programme. On the other hand, designing randomised control trials were also difficult given the unpredictability of the occurrence of VL in small areas, the lack of replicates limited the robustness of the findings. In the given context of very low case incidence as the positive outcome of the elimination campaign in South Asia, the organization of randomised trials was also deemed not feasible, which led to possible biased results. The effects of reduced vector densities on parasite transmission and new infections and cases could not be measured in recent studies as well. For one of the
observational studies, incidence figures used in the epidemiological analysis were derived from clinics led by Doctors without Borders, and therefore only represented reported VL cases, and not true incidence. Moreover, the order with which villages were provided with ITN during the control campaign was significantly biased towards those with more reported cases.

- In several studies, bednet impregnation was carried out only in some target houses, and thus, the community effect was lost. There could also be reporting bias regarding washing/dipping of bednets with insecticide, as the information came from the household heads. The ITNs tested with bioassay were not randomly selected, resulting in possible underestimation of insecticidal effectiveness at the end of the trial.

The site-specific data regarding LLINs and environmental management had to be interpreted with caution because the limited number of clusters per arm provided uncertain estimates with wide confidence Intervals.

- For some studies, the intervention clusters had higher burden of sandflies. This could have underestimated the effect of ITN interventions. Other ongoing vector control activities, especially in the control arms, could also have diluted the effect of the ITN intervention provided through the study. The environmental factors (e.g., temperature, humidity) were not taken into account in most of the studies, although they could have played significant role on sandfly density over time, confounding the effectiveness of ITN interventions. Small sample size in some studies could result in findings with insufficient power. Disproportionate lost to follow-ups in the intervention and comparison clusters could have affected the study findings. The non-significance of the protective effect after 20 months post-distribution is probably a sample size issue, as there are fewer comparisons to make after 20 months. Moreover, clustering effect, especially when analysing number of female *P. argentipes* captured by aspiration in households post-intervention should have been taken into account.

- For the results regarding the protective efficacy of LLINs, it is important to consider that CDC light trap captures/monitor sand flies outside the bed nets, so that the actual protection for people sleeping under a LLIN from infective bites could be different. In addition, results based on aspiration captures in cattle sheds should be interpreted with caution as the number of *P. argentipes* collected was highly variable between and within clusters. The use of cattle sheds in the study may also have precluded an estimate of the absolute barrier effect of the different types of net since cattle sheds also constitute one of the probable breeding and resting sites for *P. argentipes* and some of the sand flies captured inside the nets may have newly emerged from the substrate beneath the net.

- It is important to consider that most of the included studies measured only vector density and mortality as entomological parameters. Therefore, several other entomological parameters are missing, such as entomological inoculation rate. In addition, several studies did not differ from male and female sandflies, which is important because only females are vectors.

**Conclusions**

Our systematic review has found that both the insecticide impregnated bednets and the commercially treated long lasting insecticidal nets are effective in reducing the density of sandflies, although their effects on reducing burden of VL at the population level have not been
researched extensively. Efficacy of both have strong dose response relationships and wane over time. While insecticide impregnated bednets are well accepted in the community, there could be problems that can lead to early erosion of insecticides from the nets. Long lasting insecticidal nets treated commercially do not have that issue but can demand additional resources to sustain their roll out in the community. Insecticide treated nets can even perform better along with indoor residual spraying. Combining comparatively low-cost insecticide impregnated bed nets with indoor residual spraying could be the way forward to controlling visceral leishmaniasis in resource limited settings. Given the current low incidence of VL in Southeast Asia, the effects of vector control measures are difficult to assess on the incidence of the disease. To ensure efficient resource allocation in the post-elimination era, efforts should be made to deliver the vector control interventions in conjunction with case detection in the community.

Supporting information
S1 Text. PRISMA Checklist. (DOCX)
S2 Text. PRISMA Flow Diagram. (DOCX)

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Efficacy and community-effectiveness of ITNs for VL control: A systematic review

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