Benefit of Insecticide-Treated Nets, Curtains and Screening on Vector Borne Diseases, Excluding Malaria: A Systematic Review and Meta-analysis

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Abstract

Introduction: Insecticide-treated nets (ITNs) are one of the main interventions used for malaria control. However, these nets may also be effective against other vector borne diseases (VBDs). We conducted a systematic review and meta-analysis to estimate the efficacy of ITNs, insecticide-treated curtains (ITCs) and insecticide-treated house screening (ITS) against Chagas disease, cutaneous and visceral leishmaniasis, dengue, human African trypanosomiasis, lymphatic filariasis and onchocerciasis.

Methods: MEDLINE, EMBASE, LILACS and Tropical Disease Bulletin databases were searched using intervention, vector- and disease-specific search terms. Cluster or individually randomised controlled trials, non-randomised trials with pre- and post-intervention data and rotational design studies were included. Analysis assessed the efficacy of ITNs, ITCs or ITS versus no intervention. Meta-analysis of clinical data was performed and percentage reduction in vector density calculated.

Results: Twenty-one studies were identified which met the inclusion criteria. Meta-analysis of clinical data could only be performed for four cutaneous leishmaniasis studies which together showed a protective efficacy of ITNs of 77% (95%CI: 39%-91%). Studies of ITC and ITS against cutaneous leishmaniasis also reported significant reductions in disease incidence. Single studies reported a high protective efficacy of ITS against dengue and ITNs against Japanese encephalitis. No studies of Chagas disease, human African trypanosomiasis or onchocerciasis were identified.

Conclusion: There are likely to be considerable collateral benefits of ITN roll out on cutaneous leishmaniasis where this disease is co-endemic with malaria. Due to the low number of studies identified, issues with reporting of entomological outcome, and few studies reporting clinical outcomes, it is difficult to make strong conclusions on the effect of ITNs, ITCs or ITS on other VBDs and therefore further studies be conducted. Nonetheless, it is clear that insecticide-treated materials such as ITNs have the potential to reduce pathogen transmission and morbidity from VBDs where vectors enter houses.


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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data can be found either within the paper or in referenced manuscripts (for studies included in systematic review).

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Introduction

The World Health Organisation (WHO) promotes the use of Integrated Vector Management (IVM) to control vector borne diseases (VBDs) [1]. Briefly, IVM involves the use of a range of proven vector control tools used either alone or in combination selected based on knowledge of the local vector ecology and epidemiological situation. IVM can involve use of multiple vector control tools against a single disease or alternatively a single tool against multiple diseases. This is particularly the case where vector control interventions are active against more than one disease and VBDs overlap in their distribution.

IVM is a WHO policy for effective, cost effective and sustainable vector control. In order to exploit synergies between VBDs and make vector control more cost effective, IVM advocates for the use of shared interventions across diseases. However, in order to be able to do this it is important to first know whether interventions are effective against multiple diseases. This was the
**Author Summary**

Malaria is a deadly disease caused by a parasite which is transmitted by anopheles mosquitoes. Bednets treated with insecticide are one of the key tools used to prevent malaria and they have been distributed on a large scale in many countries, particularly in Africa. It may be possible to control other diseases transmitted by insects using insecticide-treated bednets because many of these insects also enter houses. We did a review of studies looking at the effectiveness of insecticide-treated bednets, curtains, and house screening against nine major diseases transmitted by insects. We assessed the effect these tools had on reducing numbers of the insects and disease in humans. Insecticide-treated bednets were found to be effective in preventing cutaneous leishmaniasis—a disease transmitted by sandflies—and insecticide-treated curtains and screening showed potential in preventing other insect borne diseases. Although further studies are required, it is clear that insecticide-treated bednets, curtains and screening have the potential to prevent transmission of insect-transmitted diseases.

**Methods**

**Literature search**

The review was carried out according to a protocol and analytical plan that was prepared in advance. A systematic search of published literature was performed in April 2013 and repeated in June 2014 using intervention-specific search terms (for example ITN/LLIN/bednet/curtain/pyrethrum), as well as vector and disease specific search terms. MeSH and DeCS terms were used where appropriate. More detail on the search terms used is given in Supporting Information S1. MEDLINE (1950 -), EMBASE (1980 -) and LILACS (1982 -) databases were searched and no language restrictions were applied. In April 2013 we also searched the Tropical Disease Bulletin (1912 -) database. In addition, we reviewed the reference lists of key review articles and consulted with experts to identify further studies.

The search was conducted as part of a larger systematic review on all types of vector control interventions against eight different VBDs [6]: Chagas disease, cutaneous and visceral leishmaniasis, dengue, human African trypanosomiasis, Japanese encephalitis, lymphatic filariasis and onchocerciasis.

**Study inclusion and exclusion criteria**

Studies were assessed against inclusion and exclusion criteria by AW and SL independently. Studies were included if they compared the efficacy of ITNs, ITCs or ITS versus no intervention (control group) in disease endemic areas. Excluded studies and reasons for their exclusion are detailed in Supporting Information S2. We sought to compare the efficacy of ITNs, ITCs and ITS versus no intervention, rather than assess the efficacy of untreated bednets, curtains or screening or compare these untreated materials to ITNs, ITCs or ITS. We took this decision because bednets being rolled out for malaria control are insecticide-treated. Studies using hand-impregnated nets or factory manufactured LLINs were included. Studies assessed the effect of the intervention on either i) clinical outcomes (incidence or prevalence of disease or infection – whether this was confirmed by the patient, clinical diagnosis or diagnostically differed by study) and/or ii) entomological outcomes (including human biting rate, adult vector density and *Stegomyia* indices, pupal/demographic indices, oviposition rates or ovitrap positivity for dengue vectors).

Adult vector density was measured using a number of techniques including Centers for Disease Control (CDC) light traps, sticky traps, pyrethrum spray catches and resting catches using aspirators. Larval indices extracted for dengue were house index (percentage of houses infested with larvae and/or pupae), container index (percentage of water containers infested with active immatures) and Breteau index (number of positive
containers per 100 houses). We also extracted data on pupae per person (number of pupae collected over the total number of inhabitants of the households inspected), oviposition rates (mean number of Aedes aegypti eggs per trap) and ovitraps positivity (percentage of traps positive for Aedes eggs).

In terms of study designs, we included i) randomised controlled trials (cluster level or individual randomisation), ii) non-randomised trials with pre- and post-intervention data (for both control and intervention areas) and iii) rotational studies (provided there was baseline data or allocation was random or interventions/collectors were rotated appropriately e.g. each house received each intervention). A rotational design is when an intervention(s) is moved between sampling sites for set time periods or, in the case of human landing catches, collectors are rotated between interventions.

Studies performed under laboratory or semi-field conditions (for example, experimental huts) were excluded. We also excluded non-randomised trials without baseline data (for both control and intervention areas), non-controlled programme evaluations and observational studies in which clusters or individuals were not purposely allocated to intervention and control groups.

Data extraction and analysis

AW (or a third party contractor) extracted data from the publications into a pre-designed data extraction form in Microsoft Word (Supporting Information S3), along with data tables and graphs. Graphs were digitised using Engauge Digitizer software (version 5.1, http://digitizer.sourceforge.net/). Preliminary analysis of data tables was conducted in Microsoft Excel. Analysis assessed the efficacy of ITNs, ITCs or ITS compared to no intervention. We used un-adjusted measures (clinical and entomological) throughout. This was for consistency because different studies adjust for different covariates. However, adjusted values, where available are reported for comparison.

Clinical outcomes were reported as either risks or rates of disease or infection in the published papers. Meta-analysis of clinical data (unadjusted risk of disease or infection) was performed in Stata 13 using the metan command (StataCorp, Texas, U.S.A.). Pre-intervention risk ratios were plotted on forest plots alongside post-intervention risk ratios to show comparability of groups at baseline. Statistical heterogeneity was assessed using a $\chi^2$ test. Due to the small number of studies in each comparison, we deemed there to be heterogeneity if the $\chi^2$ test p value was less than 0.1 [7]. If heterogeneity was found, a summary effect measure was calculated using random effect meta-analysis rather than fixed effect meta-analysis. Protective efficacy (PE) was calculated as PE = 1 - (risk ratio of clinical disease or infection during the intervention period) $\times$ 100%. PE (or relative risk reduction) can be interpreted as the percentage reduction in risk of clinical disease or infection associated with the intervention. Standard formulas were used to calculate 95% confidence intervals for risk or rate ratios [8].

Entomological outcomes are reported as means with 95% confidence intervals, where these are reported in the published paper or could be calculated. If there were zero events then we estimated the upper 95% confidence interval as $100 \times (3.7/N)$ where N is the sample size [9]. For entomological outcomes, where data were available for multiple intervention and control sites, we took the average values of the outcome measure, applying equal weight to all sites. A similar approach was taken if data were available for multiple timepoints within a year or transmission season, either pre- or post-intervention. We could not use meta-analysis to analyse the entomological data due to inadequate reporting in the published manuscripts. In almost all the studies the standard error for mean vector density was not reported and could not be calculated from the data presented in the papers. For studies with baseline/post intervention data for control and intervention sites we calculated the percentage reduction in vector density using a difference in differences approach. We estimated the effect of the intervention J using the formula $J = (q_1/q_0)/(p_1/p_0)$, where q1 and q0 are, respectively, the entomological indicators (mean density, or biting rate) observed in the intervention and control areas post-intervention respectively and p1 and p0 are the corresponding baseline estimates of these entomological indicators [10]. We calculated the percentage reduction in entomological indicators as 100 x (1-J). For studies in which only post intervention data were available we calculated the percent reduction in the outcome in the treatment group compared to the control group using the formula $100 \times (1-q1/q0)$ [10]. We were not able to calculate confidence intervals around percentage reductions due to heterogeneity in study designs; e.g. different follow up periods pre- and post-intervention and the way in which the data was reported e.g. the total vector count was reported rather than individual observations.

We followed recommendations made by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group where possible [11,12] (Supporting Information S4: PRISMA checklist).

Risk of bias and study quality assessment

AW and SL assessed independently the risk of bias in the included studies using a risk of bias assessment form. This form was developed for the purposes of this review to assess entomological studies and was adapted from the Effective Practice and Organisation of Care (EPOC) risk of bias assessment form [13] (Supporting Information S5). A judgement of high, low or unclear risk of bias was given for a number of parameters. An overall bias assessment (high/medium/low) was made based on the modal bias risk.

We developed a tool for assessing study quality which primarily concerns the study design and downgrades the score given to the study depending on whether sample size calculations were performed (overall and for entomological sampling), the length of the follow up period and risk of bias (Supporting Information S6). This was loosely based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system of rating quality of evidence [14], but adapted for entomological studies. For the purposes of the quality assessment, we deemed a trial to be a randomised controlled trial if the published paper stated that groups were randomised to intervention or control, even if the process of sequence generation was not described in the paper.

Results

Summary of studies identified and risk of bias and quality assessment

The initial systematic literature search identified 19,115 unique records (Figure 1). 18,617 records were excluded based on review of the title and abstract. 496 full text records were reviewed and of these 310 studies met the inclusion/exclusion criteria across all types of vector control intervention. The update of the search in June 2014 identified 1,991 unique records, of which 125 full-text records were reviewed and 2 studies met the inclusion/exclusion criteria. In total, 21 studies assessed the efficacy of ITNs, ITCs or ITS versus no intervention and the split of these by disease was nine cutaneous leishmaniasis, five dengue, one Japanese encephalitis, three lymphatic filariasis and three visceral leishmaniasis.
Summary tables of the studies identified are given in Supporting Information S7. Only nine of the 21 studies included reported the level of insecticide resistance in the study area or conducted an insecticide bioassay. Of the 21 studies identified, fifteen were deemed to be at low risk of bias, three at medium risk and three at high risk of bias [15] (Supporting Information S8). Twelve studies were deemed to be of high quality, three medium quality and six low quality (Supporting Information S9). No studies that met the inclusion and exclusion criteria were found assessing the efficacy of ITNs, ITCs or ITS against Chagas disease, human African trypanosomiasis or onchocerciasis.

Efficacy of ITNs and ITCs against cutaneous leishmaniasis

A total of six studies assessing the efficacy of ITNs against cutaneous leishmaniasis were identified [15–20]. Of these three reported clinical data only, one reported entomological data only, and two reported both clinical and entomological data. Of the studies reporting clinical data, this was generally either a symptom questionnaire administered to participants or examination of lesions. Two studies utilized either a leishmanin skin test [20] or microscopic examination of skin scrapings from an active lesion [21].

Random effects meta-analysis of the efficacy of ITNs was conducted on data from four studies conducted in Iran (2 studies), Afghanistan and Colombia [17–20] (Figure 2, Table 1). Pre-intervention incidence of cutaneous leishmaniasis was comparable in intervention and control groups in the three studies that reported this data, with 95% confidence intervals for the risk ratio crossing the null value. Random effect meta-analysis indicated a PE of ITNs against cutaneous leishmaniasis of 77% (95% CI: 39%–91%, P = 0.003). Clinical data from one study in Turkey [15] was not suitable for meta-analysis because this study did not report numbers of cases or population at risk. Alten et al. reported a significant reduction in incidence of cutaneous leishmaniasis in
ITN clusters, while incidence in control areas either stayed the same or increased. However, this study was deemed to be at high risk of bias and low quality.

Studies assessing the efficacy of ITNs reported mixed results in terms of effect on sandfly density ranging from a relative increase of 49% to a relative reduction of 96% (Table 2). Although Emami et al. reported a highly significant PE against cutaneous leishmaniasis in Iran, no effect on the mean number of *Phlebotomus sergenti* captured per month was detected in this study [17]. Similarly, Alten et al. reported a beneficial effect of ITNs on clinical disease in Turkey and a percentage increase in vector density relative to the control group was documented [15].

Three studies conducted in Colombia, Venezuela and Burkina Faso assessed the efficacy of ITCs against cutaneous leishmaniasis [16,22,23]. Two studies reported entomological data while one reported both clinical and entomological data. Kroeger et al. demonstrated a high PE against cutaneous leishmaniasis of 93% (95% CI: −16%–100%, p = 0.06) in Venezuela (Table 1) [22]. Studies that measured the entomological effect of ITCs demonstrated a high percentage reduction in vector density of 54%, 87% and 98% (Table 2). However, the 98% reduction was observed in a study that was deemed to be of low quality due to the study design employed (non-randomised pre-post design), few sampling sites for entomological data and short period of follow up.

A study which assessed the efficacy of ITCs and ITS against cutaneous leishmaniasis in Iran reported a PE of 16% (95% CI: 2%–28%, p = 0.03) [21]. This study was deemed to be of low quality due to the study design (non-randomised pre-post design) and high risk of bias.

**Efficacy of ITNs against visceral leishmaniasis**

Three studies assessing the efficacy of ITNs on visceral leishmaniasis were identified [24–27]. Two studies reported only entomological data and one reported both clinical and entomological data. The Picado et al. study [27] did not show a significant effect on incident *Leishmania donovani* infections (PE: 0.3%, 95% CI: −15%–14%, p = 0.97) or incident cases of visceral leishmaniasis (PE: 4%, 95% CI: −81%–48%, p = 0.9) in India and Nepal (Table 1). The same study, however, did appear to show an effect on vector density with a relative reduction in the mean number of *P. argentipes* females per light trap night of 57% [26] (Table 3). Two studies conducted in Sudan [24] and Bangladesh, India and Nepal [25] demonstrated a 100% and 35% (95% CI: −56% to 75%) reduction in vector density, respectively (Table 3).

No studies were identified which assessed the efficacy of ITCs or ITS against visceral leishmaniasis.

**Efficacy of ITNs and ITCs against lymphatic filariasis**

Two studies assessing the efficacy of ITNs against lymphatic filariasis were identified, both of which collected entomological data only [28,29]. ITNs generally were associated with a high level of protection against *Anopheles* species, with approximately a 90% reduction in vector density in the two studies conducted in Kenya and Papua New Guinea (Table 4). Bøgh et al. reported a lower percentage reduction in *Culex quinquefasciatus* density of 16% [28].

One study conducted in India assessing the efficacy of ITCs hung in eaves and doorways against lymphatic filariasis vectors was identified [30]. Poopathi et al. detected an 82% reduction in man biting density and a 79% reduction in indoor resting density of *Cx. quinquefasciatus* [30] (Table 3). However, this study was deemed to be of low quality mainly due to the study design employed (non-randomised pre-post design), few sampling sites for entomological data and short period of follow up.

**Efficacy of ITNs, ITCs and ITS against dengue**

One study conducted in Haiti assessed the efficacy of ITNs against dengue [31]. Based on the five month post-intervention survey this study showed that ITN use was associated with a 36%

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**Figure 2. Forest plot (random effects meta-analysis) indicating efficacy of ITNs against cutaneous leishmaniasis.** The forest plot displays post-intervention risk ratios and pre-intervention risk ratios separately to show comparability of groups at baseline. doi:10.1371/journal.pntd.0003228.g002
against dengue vectors [32–34]. Kroeger et al. demonstrated in Mexico a beneficial effect of ITCs on house index (25% reduction) and pupae per person (39% reduction), but reported a relative increase in Breteau index of 10% based on the 12 month follow up survey [32]. The authors, however, reported a community-level effect of the ITCs which meant that benefits in terms of reductions in mosquito populations spilt over into control areas. They postulate that this is why there is no significant difference between intervention and control arms. Breteau and house indices from an external control area closely follow seasonal rainfall patterns and the bioassay results on new nets from this study site indicated only 30% mortality of A. aegypti suggesting that insecticide resistance may have been a problem.

Three studies were identified that assessed the efficacy of ITCs against dengue vectors [32–34]. Kroeger et al. demonstrated in Mexico a beneficial effect of ITCs on house index (25% reduction) and pupae per person (39% reduction), but reported a relative increase in Breteau index of 10% based on the 12 month follow up survey [32]. The authors, however, reported a community-level effect of the ITCs which meant that benefits in terms of reductions in mosquito populations spilt over into control areas. They postulate that this is why there is no significant difference between intervention and control arms. Breteau and house indices from an external control area closely follow seasonal rainfall patterns and do not show similar reductions as in the study intervention and control arms. In Thailand Lenhart et al. did not detect a beneficial effect of ITCs on house index, container index, Breteau index or pupae per person, with relative increases of 15%, 20%, 3% and 37%, respectively at the nine-month time point [33]. ITCs did, however, show a beneficial effect on indoor and outdoor oviposition rates with reductions of 44% and 49% in mean numbers of eggs per trap, respectively at the six month time point, although no significant difference between control and ITC arms was reported at three or nine months. Another study in Thailand where houses generally had a more closed design reported a 56% reduction in house index, 67% reduction in Breteau index and 63% reduction in pupae per person index six months after the start of the intervention [34]. At the 6-month follow up survey 71% of households had at least one ITC. However, at the 18-month follow up survey when ITC coverage had fallen to only 33% a much lower effect on entomological parameters was observed (26% reduction in house index, 8% reduction in Breteau index and 111% increase in pupae per person index).

A study of ITS reported a beneficial effect on both house index and density index (adult Ae. aegypti) in Vietnam. In the intervention arm both house and density index were reduced to zero one month after installation of the screening and remained at zero for the duration of the epidemic season (eight months post intervention), compared to the control arm in which seasonal peaks in both indices were observed [35,36]. The same study also reported a PE of ITS against IgM seropositivity of 80% (95% CI: 53–92%, p<0.001) compared to the control group (Table 1). This study used a non-randomised pre-post design and was deemed to be of low quality.

### Efficacy of ITNs against Japanese encephalitis

A single study by Dutta et al. assessed the efficacy of ITNs against Japanese encephalitis vectors and seroconversion in India [37]. This study was deemed to be of low quality due to the study design employed (non-randomised pre-post design) and low number of sampling sites for entomological data. No effect of ITNs on mean density of adults of the Cx. vishnui group was observed (reduction of −3.5%). The risk of seroconversion against Japanese encephalitis virus was comparable across groups at baseline, but the risk was significantly lower in the ITN group compared to the control during the two year post intervention period (PE: 67%, 95% CI: 44–80%, p<0.001) (Table 1).

### Discussion

Our review shows the potential for ITNs, ITCs and ITS to reduce vector borne diseases. Of particular note is the evidence on high protective efficacy of ITNs against cutaneous leishmaniasis, which suggests that there may be considerable collateral benefits of ITN roll out where cutaneous leishmaniasis and malaria are co-endemic. There is also good evidence of the efficacy of ITG and

### Table 1. Effect of ITNs, ITCs and ITS against vector borne diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Intervention</th>
<th>Study</th>
<th>Unadjusted PE (95% CI, p value)</th>
<th>Adjusted PE (95% CI, p value)</th>
<th>Covariates adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous leishmaniasis</td>
<td>ITN</td>
<td>Emami 2009</td>
<td>98% (93%, 100%, p&lt;0.001)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nadim 1995</td>
<td>50% (–3%, 76%, p = 0.06)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repayan 2000</td>
<td>66% (54%, 75%, p&lt;0.001)</td>
<td>69% (45%, 82%, p&lt;0.001)</td>
<td>Intra-household clustering</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rojas 2006</td>
<td>55% (6%, 79%, p = 0.03)</td>
<td>55% (–14%, 82%)</td>
<td>Age, residence located on the periphery, roof of thatch, distance to the forest &lt;50 m, community participation score and prevalence of infection in children &lt;5 years old</td>
</tr>
<tr>
<td>Visceral leishmaniasis</td>
<td>ITN</td>
<td>Picado 2010</td>
<td>Cases: 4% (–81%, 48%, p = 0.9) Infection: 0.3% (–15%, 14%, p = 0.97)</td>
<td>Cases: –15% (–116%, 39%, p = 0.64) Infection: 11% (–64%, 52%, p = 0.68)</td>
<td>Clustering, age group, sex, times sprayed, and socioeconomic status.</td>
</tr>
<tr>
<td>Dengue</td>
<td>ITN</td>
<td>Nguyen 1996</td>
<td>81% (53%, 92%, p&lt;0.001)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>ITN</td>
<td>Dutta 2011</td>
<td>67% (44%, 80%, p&lt;0.001)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Study reported rates only, PE = protective efficacy, CI = confidence interval, NR = not recorded, More detail on cases and denominators given in Supporting Information S10.

doi:10.1371/journal.pntd.0003228.t001


<table>
<thead>
<tr>
<th>Study</th>
<th>Vector species</th>
<th>Surveillance method</th>
<th>Measure</th>
<th>Control (Mean and 95% CI)</th>
<th>Intervention (Mean and 95% CI)</th>
<th>% reduction in vector density</th>
<th>Adjusted % reduction</th>
<th>Covariates adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alexander 1995</td>
<td>L. lichyi, L. youngi, L. columbiana</td>
<td>HLC</td>
<td>No. of sandflies caught per man hour (biting)</td>
<td>3.29</td>
<td>0.14</td>
<td>96%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Emami 2009</td>
<td>P. papatasi, P. sergenti</td>
<td>(exophilic and endophilic species, respectively)</td>
<td>Mean no of female P. papatasi and P. sergenti/month</td>
<td>615</td>
<td>214</td>
<td>85%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

where CDC LT = Centers for Disease Control light traps, HLC = human landing catches, PSC = pyrethrum spray catches and NR = not reported.
More detail on vector numbers and denominators given in Supporting Information S11.
### Table 3. Effect of ITNs on density of sandfly vectors of visceral leishmaniasis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Vector species</th>
<th>Surveillance method</th>
<th>Intervention mean and 95% CI (Pre)</th>
<th>% reduction in vector density and 95% CI</th>
<th>% reduction in vector density (%)</th>
<th>Adjusted % reduction (95% CI, p value)</th>
<th>Intervention</th>
<th>Measure</th>
<th>Covariates adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>El Nahim, 2001</td>
<td>P. orientalis</td>
<td>CDC LT</td>
<td>9.41 (6.97, 12.71)</td>
<td>5.30 (12.45, 2.10)</td>
<td>35%</td>
<td>0.55 (0.43, p = 0.04)</td>
<td>ITNs</td>
<td>CDC LT</td>
<td>Clustering (country/cluster), baseline mean density, IRS carried out by ministry in some cohorts</td>
</tr>
<tr>
<td>Joshi, 2009</td>
<td>P. argentipes, P. papatasi</td>
<td>CDC LT</td>
<td>9.16 (6.78, 12.45)</td>
<td>3.50 (11.6% (95%CI 2.10–2.20), p = 0.016)</td>
<td>35%</td>
<td>0.55 (0.43, p = 0.04)</td>
<td>ITC</td>
<td>CDC LT</td>
<td>Clustering (country/cluster), baseline mean density, IRS carried out by ministry in some cohorts</td>
</tr>
<tr>
<td>Picado, 2010</td>
<td>P. argentipes</td>
<td>CDC LT</td>
<td>2.16 (1.57, 2.86)</td>
<td>2.16 (1.55, 2.86)</td>
<td>35%</td>
<td>0.55 (0.43, p = 0.04)</td>
<td>ITS</td>
<td>CDC LT</td>
<td>Clustering (country/cluster), baseline mean density, IRS carried out by ministry in some cohorts</td>
</tr>
</tbody>
</table>

ITNs could help reduce the incidence of cutaneous leishmaniasis by 77%. This finding supports WHO’s recommendation that ITNs should be used as a vector control method against this disease [38]. This level of protective efficacy compares favourably with the 50% protective efficacy of ITNs against *P. falciparum* malaria shown by Lengeler [3]. Based on maps of cutaneous leishmaniasis [39] and *P. falciparum* endemicity [40] there are large areas, particularly in South America, where these diseases are likely to be co-endemic. Non-malaria endemic countries where cutaneous leishmaniasis is prevalent should consider rolling out ITNs as part of control efforts. Similar reductions in vector density were not observed which may be due to the ecology of the vector species or differences in collection techniques. For example studies by Alten *et al.* and Emami *et al.* sampled both endophilic and exophilic species [15,17]. Studies by Kroeger *et al.* [22] and Noazin *et al.* [21] reported significant effects of ITC and ITC/ITS on clinical outcomes.

Clinical evidence from one study suggested that ITNs were not effective against visceral leishmaniasis [27]. However, in this study Picado *et al.* suggested that *L. donovani* transmission may have been occurring outside the home where ITNs would have little impact on preventing sandfly-human contact. In Africa observational studies led to mixed results – several studies have shown treated bednets to be protective against visceral leishmaniasis [41,42], while others have shown no effect of ITNs on *L. donovani* infection rate in *P. orientalis*, although the number of infected *P. orientalis* identified was small in all villages [43]. In south Asia, several observational studies have shown use of (untreated) bednets to be protective against visceral leishmaniasis [44,45].

The efficacy of ITNs in preventing leishmaniasis transmission is dependent on a number of key variables related to vector biology, type of nets and human behaviour. Studies have shown protection is dependent on mesh size of the nets – nets designed to be cooler which have large holes are more likely to let sandflies through, even if they are insecticide treated [46]. ITNs are likely to be more effective where sandflies bite indoors at night and where people use ITNs consistently [47,48]. ITCs and ITS may be advantageous over ITNs because these interventions are in place all the time and since there is no need to set them up at night compliance is less of an issue [21]. In general, where transmission is occurring inside the home or where vectors rest indoors, we would expect ITNs, ITCs or ITS to have a beneficial effect, irrespective of whether the vectors are transmitting cutaneous or visceral leishmaniasis. It is important to have a sound grasp of sandfly biology and human behaviour in a particular setting in order to understand where transmission is occurring or where vectors rest before planning specific intervention strategies.

There were no studies that met the selection criteria, which reported the efficacy of ITNs against lymphatic filariasis infection. In much of SSA and parts of the western Pacific,
<table>
<thead>
<tr>
<th>Study</th>
<th>Vector species</th>
<th>Surveillance method</th>
<th>Measure</th>
<th>Control (Mean and 95% CI)</th>
<th>Intervention (Mean and 95% CI)</th>
<th>% reduction in vector density</th>
<th>Adjusted % reduction (95% CI, p value)</th>
<th>Covariates adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bøgh 1998</td>
<td><em>Anopheles gambiae</em> s.l.</td>
<td>PSC</td>
<td>Geometric mean no. of indoor resting female mosquitoes per house</td>
<td>29.7 12.3</td>
<td>17 0.1</td>
<td>99%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td><em>An. funestus</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Culex quinquefasciatus</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlwood 1987</td>
<td><em>An. punctulatus</em></td>
<td>Aspirator</td>
<td>No. of indoor resting <em>An. punctulatus</em> females</td>
<td>- 67.7</td>
<td>- 2</td>
<td>97%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Poopathi 1995</td>
<td><em>Cx. quinquefasciatus</em></td>
<td>HLC</td>
<td>Average man biting (landing) density per man hour</td>
<td>133.5 62.8</td>
<td>91.5 7.5</td>
<td>83%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirator</td>
<td>Average indoor resting density per man hour</td>
<td>55.0 55.9</td>
<td>42.5 9.0</td>
<td>79%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

where HLC = human landing catches and PSC = pyrethrum spray catches.

More detail on vector numbers and denominators given in Supporting Information S11.
doi:10.1371/journal.pntd.0003228.t004
Anopheles mosquitoes transmit both lymphatic filariasis and malaria and so theoretically ITNs should have a beneficial effect on both diseases [49]. Observational studies have shown a beneficial effect of ITNs on lymphatic filariasis transmission where the disease is transmitted by Anopheles mosquitoes [50–53] and ITNs may be particularly useful in areas co-endemic for lymphatic filariasis and Loa Loa where mass drug administration of ivermectin is contraindicated due to serious adverse events [54]. However, to our knowledge no randomised controlled trials have been performed in these settings. Such a study would need to be of long duration to show a reduction in microfilariaemia given that adult worms have lifespans of between four and 10 years [55,56]. Alternatively, a study could use incidence of new infections in young children as an outcome [57]. The efficacy of ITNs, ITCs and ITS against Culex vectors of lymphatic filariasis, which are predominant in urban areas [58], needs further assessment. Bogh et al. reported a 16% reduction in indoor resting density of Cx. quinquefasciatus compared to a 98% reduction in Anopheles species [29], presumably because Culex are less susceptible than Anopheles to pyrethroids [59–61]. Another explanation may be that transient reductions in vector density are masked because Culex populations are massive and the population can rapidly replace itself or immigrate. Poopathi et al. assessed the effect of insecticide-treated cave and door curtains and reported an 82% reduction in human biting density of Cx. quinquefasciatus [30]. It may be the door curtain component of this intervention which is of greatest importance given the findings of a study by Njie et al. who reported that culicines enter houses via the door rather than the eaves [62].

There is an increasing focus on intradomicile vector control for dengue [63] because Ae. aegypti rest, feed, mate and reproduce inside houses [64]. Targeting adult Ae. aegypti shifts the age structure of the vector population to younger mosquitoes, which is likely to have a large effect on human infections due to the relatively long extrinsic incubation period of the dengue virus in the mosquito [65]. However, since transmission of dengue occurs mostly during the daytime the use of bednets has rarely been considered as an extra-domiciliary control strategy. Studies identified in this review reporting an effect of ITCs and ITS on Ae. aegypti infestation levels [32,34–36] suggest that vectors are coming into contact with these interventions indoors. The likelihood of the vector coming into contact with the ITN, ITC or ITS will depend on a number of factors including the size of the home and construction. For example, Lenhart et al. state that the open construction of the homes in their study conducted in Thailand may explain why ITCs did not show any effect [33]. It is generally recognised that greater coverage of the intervention will result in mass killing, reduced vector survival and greater reductions in transmission; i.e. a community level effect. This was apparent in two of the dengue studies included in this review. In one study use of ITCs in intervention areas led to a community wide effect on dengue [31]. However, many of the studies were conducted prior to the early 2000s before the advent of pyrethroid resistance [72], including those against cutaneous leishmaniasis that show a high level resistance to the insecticide used. In one of the studies conducted in Haiti there was some indication of resistance [31]. However, it is not clear how these results would extend to the use of insecticidal materials against vector borne diseases and how they can be compared to the results of this review.
PE. It is not possible, therefore, to say whether this level of efficacy would be observed today. Currently pyrethroids are the only class of insecticides suitable for use on LLINs and increasing coverage of pyrethroid treated materials to control multiple VBD is likely to increase selection pressure for development of resistance. Indeed, pyrethroid resistance has been detected in a number of non-malaria vectors including Cx. quinquefasciatus [73–75], sand flies [76], Ae. aegypti and Ae. albopictus [77]. Even if pyrethroid resistance increases it is likely that ITNs, ITC and ITS will still afford some level of protection against vectors due to a barrier effect. However, it would be sound to use insecticide treated materials as part of an IVM strategy including other vector control tools that do not rely on insecticide such as larval source management or make sure that different insecticide classes are used for IRS/fogging etc (if appropriate). In the meantime, new types of insecticide treated materials, for example LLINs impregnated with insecticides with two different modes of action, are being developed which are showing promise against insecticide resistant malaria vectors [78,79].

In terms of collateral benefits there may also be beneficial effects of ITNs, curtains and screening on preventing household pests such as bedbugs, headlice, cockroaches and rodents which although not systematically assessed in this review are important benefits which increase acceptability and encourage compliance with interventions [80–82].

In conclusion, ITNs, ITCs and ITS have great potential to reduce VBDs. The biological insight that follows from this conclusion is that a substantial proportion of the vector population must be resting or feeding indoors. Evidence on efficacy of ITNs, ITC and ITS against multiple VBDs should be paired with maps of disease co-endemicity in order to prioritise and focus resources to areas of greatest disease burden. The use of interventions against multiple diseases has the potential to reduce costs and make better use of financial and human resources. This requires functional coordination between disease-specific programmes on planning, implementation and monitoring and evaluation with sharing of existing infrastructure and competencies. Beneficial effects on multiple VBDs will serve to increase the cost effectiveness of insecticide-treated materials and this may help to bolster the case for vector control funding. This review demonstrates some promising results, but highlights the urgent need for further well conducted studies. The efficacy of ITNs, ITCs and ITS against VBDs needs to be rigorously tested in randomised controlled trials with standardised clinical outcomes.

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Author Contributions

Conceived and designed the experiments: ALW SWL. Performed the experiments: ALW SWL. Analyzed the data: ALW SWL. Wrote the paper: ALW SWL. ALW SWL RCD UK TWS HvdB. Excluded studies and reasons for exclusion. (DOCX)

Supporting Information

Supporting Information S1 Search terms. (DOCX)

Supporting Information S2 Excluded studies and reasons for exclusion. (DOCX)

Supporting Information S3 Data extraction form. (DOCX)

Supporting Information S4 PRISMA checklist. (DOCX)

Supporting Information S5 Risk of bias assessment form. (DOCX)

Supporting Information S6 Study quality assessment form. (DOCX)

Supporting Information S7 Characteristics of studies identified. (DOCX)

Supporting Information S8 Assessment of risk of bias. (DOCX)

Supporting Information S9 Assessment of study quality. (DOCX)

Supporting Information S10 Detail of results presented in Table 1. (XLSX)

Supporting Information S11 Detail of results presented in Tables 2, 3 and 4. (XLSX)

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