Building the evidence base for dengue vector control: searching for certainty in an uncertain world

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ABSTRACT

This review discusses biological and chemical methods for dengue vector control, using recently emerging summary evidence, meta–analyses and systematic reviews to conclude on practical public health recommendations for *Aedes* control, which is increasingly relevant in an era of widespread Chikungunya, yellow feer and Zika outbreaks.

The analysis follows an a priori framework of systematic reviews by the authors on vector control methods, distinguishing vector control methods into biological, chemical and environmental methods. Findings of each published systematic review by the authors, following each individual vector control method, are summarised and compared in the discussion against the findings of existing meta–analyses covering all vector control methods.

Analysing nine systematic reviews and comparing to two existing meta–analyses provided low-to-moderate evidence that the control of *Aedes* mosquitoes can be achieved using 1) chemical methods, particularly indoor residual spraying and insecticide treated materials, and 2) biological methods, where appropriate. The level of efficacy and community effectiveness of the methods in most studies analysed is low, as was the overall assessment of study quality. Furthermore, the results show that too optimise results, larvae and adults should be targeted simultaneously. The quality of service delivery is probably one of the most important features of this analysis – and including high coverage.

The analysis also highlights the urgent need for standards to guide the design and reporting of vector control studies, ensuring the validity and comparability of results. These studies should aim to include measurements of human transmission data – where and when possible.

KEYWORDS

Dengue; vector control; efficacy; community effectiveness; summary evidence

Introduction

Recent epidemiological estimates [1] suggest that there are nearly 400 million dengue infections each year. While the first live attenuated tetravalent vaccine is now commercially available, the vaccine is only partially effective [2] and unlikely to result in universal protection from infection and clinical disease. Prior to vaccine approval, vector control was the only available method for the primary prevention and control of dengue outbreaks. Recently, there is a renewed focus on vector control – and particularly the control of *Aedes* mosquitos – largely driven by high profile outbreaks of Chikungunya, dengue, yellow fever and Zika across the globe [3].

Unfortunately, as is the case for many neglected tropical diseases (NTD) [4], the evidence base supporting the use of vector control for the control of dengue is limited [5]. What evidence is available in the literature is often adversely impacted by the lack of standardized methods and outcome measures, along with the highly variable quality of the studies themselves [6]. These limitations significantly diminish the ability to evaluate vector control tools, despite the urgent need as highlighted by the WHO [7].

Summary evidence, in the form of systematic reviews (SR) and meta-analyses (MA), often serves as a starting point for developing guidelines. The value of these reviews, however, largely depends on the scope and quality of the included studies [8]. Specifically, meta-analysis, which involves the use of statistical methods to integrate the results of included studies, may necessitate the exclusion of relevant studies, especially – as is the case with dengue vector control – the quality of the existing literature is highly variable. Determining the best approach to generating summary evidence in these circumstances is critically important to advancing the evidence-based policies.

For the past eight years, we have contributed to the effort to develop summary evidence for dengue vector control with a series of SRs [5] under the hypothesis that a more inclusive approach may yield important preliminary evidence even when the quality of studies was sub-optimal. Others have pursued more rigorous quantitative approaches in the form of

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MAs, which likely selects for higher quality studies [9,10].

The purpose of the review presented here is to summarise the current evidence base for biological and chemical dengue vector control including implementation aspects, and highlight and discuss key findings comparing between our SR-based approach and those that have relied on a MA-based approach [9,10]. In particular, we focus on the following topics related to dengue vector control in order to guide policy recommendations: (1) efficacy and/or community effectiveness of available vector control methods, (2) practical recommendations concerning implementation arising from the analysis, and research gaps, as highlighted by the analyses.

Methods

Here, we summarised the results of individual SRs published by the authors to perform a comparative analysis between different vector control interventions. The SRs by the authors followed an a priori framework, distinguishing vector control interventions into biological, chemical and environmental interventions. Each individual vector control intervention, if it is applied in practice for vector control, has been analysed with an SR. Detailed methods, including specific inclusion and exclusion criteria, for each SR, have been previously published, and followed the PRISMA criteria [8]. The SRs looked predominantly at community-effectiveness, defined as studies under 'real-world settings', as opposed to 'efficacy' studies, under 'ideal' or laboratory conditions [11]. Studies were further stratified by study design with cluster randomised controlled trials (cRCTs) and randomised controlled trials (RCTs) classified as higher level studies and all other study designs classified as lower level studies. Outcomes of interest were the effects of the various interventions on larval and adult indices, as well as impact on human transmission, when reported.

Results were discussed in the context of estimates needed for a potential reduction of transmission [12]. Further topics for implementation of vector control were derived from the comparison of the SRs, using content analysis methods [13], and are presented in the discussion.. We then compared in the discussion our findings to those of two relatively recent MAs that examined the same vector control methods for dengue prevention and control [9,10]. Our intent was to contrast findings from these two different approaches (SR versus MA) – particularly with a view of included articles and quality of articles and the summary conclusions – to guide future efforts at the development of summary evidence for vector control, particularly, since MAs rely on similar study designs and outcomes, and perhaps an analysis with a broader approach, as determined by SRs, can add valuable information.

Results

Table 1 summarises the major findings of each of the individual SRs [5]. A comparison of the vector control methods, to include assessments of 1) study quality, 2) effectiveness in the reduction of larval and adult indices and human transmission, and 3) evidence levels is outlined below and summarised in Table 2.

Larval indices

Higher quality studies of *Bti*, specifically those employing RCT designs, showed significant reductions of larval indices (Breteau Index (BI), Container Index (CI) and House Index (HI)). This effect was most consistently observed when *Bti* was applied as a single agent, where reductions of larvae of up to 100 % were observed [14]. However, these impacts were generally not sustained beyond 14 days. In two studies that applied *Bti in* combination with other methods the effect was inconsistent. In one long-term RCT (duration of one year), *Bti* showed particularly good effectiveness suppressing larval indices when the larvicide was re-applied on a regular basis.

Studies considered to be of lower quality, such as those derived from before-and-after designs, also demonstrated that *Bti* suppressed larval populations. Again, an almost 100 % reduction was observed in efficacy studies, but the magnitude of the effect was more limited, between 60–80 %, in community effectiveness studies [14]. The reduction in larval indices was never sustained in the absence of frequent re-application.

Unfortunately, there were no identified RCT/cRCT describing the efficacy of larvivorous fish [15] or copepods [16]. Among other studies designs, the introduction of larvivorous fish did demonstrate reductions in larval indices, particularly in efficacy studies, although the magnitude of the effect was variable across studies [15]. Whereas the application of copepods [16] appeared effective in reducing larval indices, these results were limited to a series of studies conducted in Vietnam, reported by a single research group.

There were multiple RCTs describing the effect of chemical methods on larval indices. Three cRCTs of Temephos reported mixed results [17], while three RCTs of pyriproxifen showed nearly complete elimination of larvae [18]. For chemical sprayings [19], no RCT/cRCT measured larval indices. However, one cRCT analysing peri-domestic space spraying showed no effect on larvae [20].

For lower level study designs, Temephos showed reductions of larval indices of up to 100 % for single intervention studies, but when used in combination

Table 1. Summary of outcomes of individual SRs analyses.

Author	Intervention	Results	Further outcomes from quality and content analysis
(1) vector control methods, classified as biological, chemical or environmental			
Lazaro 2015	Copepods	Copepods used were mostly *Mesocyclops spp* Copepods controlled larval *Aedes* populations up to 100%. At household level, reductions of household's positive for *Aedes* larvae between 30–97 % were observed. Adult mosquito landing rates, and oviposition: reductions to zero. Adult *Aedes* per household: reductions between 30 −100 %. Adult mosquito indices reductions from 0.12–1.16 to 0–0.01 per community after a period of three years In 3 studies dengue transmission data were measured: results ranged from 0 reported cases in intervention and control communities to a 76.7 % reduction of dengue incidence, confirmed by a reduction of serological parameters	Study design and quality are issues
Han 2015	Larvivorous fish	All intervention control studies – but one – showed a reduction of immature forms of dengue vectors. One study showed a reduction of adult indices, of three measuring. Three of four before and after study showed a reduction of immature stages. A long-term decline over two years has been reported by two the studies, measuring such an extended period. The studies measuring human transmission showed a reduction of human cases, however these were before and after studies only	Study design and quality is an issue, and geographical coverage of studies
Boyce 2013	*Bti*	*Bti* eliminated all larvae from treated containers within 24 hours, for most containers there was a prolonged effect of 14 days The study that measured an effect on human transmission showed only one case in the intervention area, compared to 15 in the control	Different formulations did not show superiority in the four studies testing this. Higher doses of *Bti* showed a prolonged effect in one study Study design and quality need to be improved in future studies
Maoz 2017	Pyriproxyfen	Container treatment studies: six studies showed a reduction above 80 % of immature stages, Two RCTs showed a limited effect. Two fumigation studies in combination with Permethrin showed a good inhibitory effect Studies measuring autodissemination should good results of reduction of adult emergence between 20 and 85 %, Combination with adulticides seemed to increase effectiveness Human transmission data were weak and could not show a good effect	The evidence presented suggests that pyriproxyfen can effectively control the adult emergence of immature stages of dengue vector mosquitoes in a variety of breeding sites in a community setting. There is a clear consensus that pyriproxyfen effectively inhibits *Aedes* adult emergence at concentrations of <1 ppb
George 2015	Temephos	11 studies using a single intervention: All 11 studies reported a post-intervention reduction in the immature stages, with a prolonged effect of 4–8 weeks in the dry season and 6–12 weeks in the wet season, if re-application has been respected. 18 studies with combinations, mostly with health education and information, environmental management and the use of malathion, *Bti*, larvivorous fish: 10 studies reported a reduction of immature mosquito stages, three failed and three had some effect only	Operational issues may be important, including surveillance and coverage, regular application, mode of application, acceptability and limited residuality of Temephos
Samuel 2017	IRS	Seven studies only, three IRS and four ISS (two/three controlled studies respectively). Two IRS studies and one ISS measuring immature mosquitoes, showed mixed results. One IRS and all four ISS studies measuring adult mosquitoes showed a very good effect, up to 100 %, but not sustained. Two IRS studies measuring human transmission showed a decline	The analysis of the studies shows different study types and settings used, inappropriate use of statistical methods, relatively short study periods, lack of randomisation in most studies

(*Continued*)

Table 1. (Continued).

Author	Intervention	Results	Further outcomes from quality and content analysis
Esu 2010	Peridomestic space spraying	13 studies reported a reduction in entomological indices, for adult mosquitoes around 90 % post-spraying, not-sustained (including the RCT), mosquito populations returning to normal levels with a few days/weeks. Two studies showed no reduction of entomological indices Only one study assessed human disease parameters, with a reduction of number of cases. However, this study was a before and after study	Outcome parameters are heterogeneous, and so is study design. Human disease parameters are mostly not measured
(2) Vector control of a particular service function, e.g. outbreak detection and response and (3) Organisation of vector control services			
Pilger 2010	Outbreak control	With different organisational strategies for an outbreak response, most common is an inter-sectorial approach. Multidisciplinary response teams, with vector control working with communities, including monitoring and evaluation, resulted in good outbreak control. Combined response with 1) vector control (larval habitats interventions with communities; insecticides intra- and peri-domestic) and 2) capacity training for clinical response are successful. Spatial spraying of insecticides as a single intervention is not effective	The evidence level is weak, also due to study design
Horstick 2010	Vector control service organisation	Three of nine studies showed little change of control operations over time. There were however strategic changes (decentralisation, inter-sectorial collaboration). Staffing levels, capacity building, management and organisation, funding and community engagement were insufficient	Analysis of vector control services is not common and/or not reported

with other interventions the same effect was not observed [17]. Similarly, pyriproxifen showed an almost complete reduction of larval indices in lower level study designs [18]. For chemical insecticide sprayings, both indoor residual spraying and indoor space spraying (IRS and ISS) [19], three studies measured larval indices, with mixed results. Peridomestic space spraying showed highly variable results in all studies measuring larval-based outcomes [20].

Adult indices

Fewer studies assessed the impact of vector control methods on adult mosquito indices. The only RCT/cRCT study designs that measured adult indices were studies of the insect growth regulator pyriproxifen, which was found to reduce adult indices in all four included RCTs [18]. In other study designs, the use of Temephos and pyripoxifen produced mixed results.

In lower level study designs, *Bti* showed a reduction of adult mosquitoes by up to 70 %[14] in a study with sufficient scale (entire village), but also good results in studies measuring surrogate measures of adult populations. In three studies, the presence of larvivorous fish [15] showed almost 100 % suppression of adult mosquitoes, while copepods [16], demonstrated more variable results.

In general, the immediate knock down effect achieved with space spraying of chemical insecticides was well documented. Indoor residual spraying was consistently effective, producing nearly 100 % reduction in adult indices. Peridomestic spraying was also effective in achieving short-term reductions. However, the effect on adult mosquito population was not sustained, with evidence of a rebound effect in as little as four days [20].

Dengue transmission

Very few studies attempted to measure dengue transmission, and those that did primarily utilised data obtained through passive surveillance of existing health systems.

In the one study of *Bti*, measuring also changes in disease incidence, the authors did report a significant decrease in the treated area. While the study was large and randomised, there were few passively-detected cases. In contrast, longitudinal studies of copepods in Vietnam showed clear reductions in human transmission.

Of the chemical control methods, no measurements of dengue transmission were performed for Temephos [17], while two studies of pyriproxyfen two studies yielded inconclusive results [18].

Two studies showed a reduction of dengue cases with the use of indoor residual spraying [19], however both studies were of lower level study design and subject to secular trends that may have resulted in biased results. The same applies for the single study

Table 2. Summary of outcomes of the single intervention SRs, according to indices.

	Peridomestic space spraying	Indoor spraying	Pyriproxifen	Temephos	Bacillus thuringiensis israelensis	Copepods	Larvivorous fish
Articles screened Articles included	2102 15	175 7	745 17	321 27	355 14	521 11	294 13
				Evidence level			
Study type	1 cRCT, other studies low quality and design	No cRCT, other studies of mixed quality and design	1 cRCT, 4 RCTs, other studies of mixed quality and design	3 cRCTs, other studies of mixed quality and design	3 cRCTs, 2 RCTs, other studies of mixed quality and design	No RCT, other studies of mixed quality and design	No RCT, other studies of mixed quality and design
				Effectiveness			
Vector indices reduction: larvae	Highly variable results in 13 studies, not sustained 2 studies ineffective	3 studies showed larvicidal activity, mostly with mixed results	Good effect almost throughout on larvae, up to 100 % reduction	11 single method studies showed up to 100 % 11 of 16 multiple methods studies failed to show this effect	Variable, but good reduction of up to 100 % in 12 studies, but not sustained	>90 % in 5 CE* studies in Vietnam Highly variable results in 6 studies	100 % in 3 E* studies 9 CE studies showed a good, but variable result
Vector indices reduction: adults	8 studies up to 100 % but not sustained 2 studies ineffective	Good effect to control adults in 5 studies	Some effect almost throughout on adults	1 single failed, 1 showed 85 % 2 multiple failed, 2 showed reduction	4 studies measured and showed a delayed and not sustained effect	>90 % in 6 CE* studies (5 in Vietnam)	Up to 100 % reduction in 3 CE* studies
Human transmission reduction	1 study with inconclusive results	2 studies link to reduction of dengue cases	2 studies reporting, inconclusive	Not measured	1 study showed a > 90 % reduction	Up to 76.7 % – 100 % in 3 CE* studies	2 studies mention a fall of dengue cases
				Evidence and effectiveness			
Conclusion (E* and CE*) not cost, acceptability, feasability	Reduces adults rapidly, but not sustained Low evidence	Promising under most circumstances Low evidence	Promising under most circumstances. Autodissemination interesting Medium evidence	Promising under some circumstances Medium evidence	Promising under most circumstances Medium evidence	Promising under some circumstances Low evidence	Promising under specific circumstances Low evidence

Colour code for conclusions
Dark red: Both evidence level and results very weak
Light red: Either evidence level or results weak
Light yellow: Either evidence level or results weak, but positive aspects
Light green: Either evidence level or results good
Dark green: Evidence level and results good
*E: Efficacy studies, **CE: community effectiveness studie

measuring human disease parameters with use of peridomestic space spraying [20].

Discussion

Discussion of key results

The work presented here, encompassing more than one hundred published studies, reviews the effectiveness of available biological and chemical vector control strategies for the control of dengue. In comparison to the previous MAs [9,10], which used a more restrictive inclusion criteria, our approach of using SRs to analyse further the available literature, came to broadly similar conclusions in terms of evidence levels and to some degree of community-effectiveness. Specifically, both approaches come to the conclusion that while the evidence is relatively weak, biological control methods generally demonstrated reasonable effectiveness, while most chemical control methods were effective with a moderate level of supporting evidence. Our findings regarding the limited effectiveness of peri-domestic spraying is also consistent with that of Bowman [10], and further casts doubt on the application of insecticides into open spaces, where they are unlikely to reach the resting places and/or breeding habitats of mosquitos.

Our analysis does, however, provide more contextual, descriptive information from the content analysis (Table 1) that allows us to conclude that 1) single interventions can be effective, 2) the quality of delivery of interventions is most important and 3) combinations of interventions are needed, but require careful implementation given the increased complexity.

For example, when considering single interventions, our analysis suggests that there is no 'best' intervention for the control of dengue vectors. If well delivered, most analysed vector control methods are effective against larval and adult mosquitos and thus may reasonably play a role in control programmes (Tables 1 and 2). Developing the optimal delivery strategy and tailoring the appropriate control method or combination of methods to local conditions in order to maximise and sustain reductions in vector populations remains the challenge. Unfortunately, there is only limited evidence on the question of delivery from this analysis, particularly the potentially 'multiplying factor' of community participation. Community members may play important roles in 1) searching for breeding sites 2) conducting regular monitoring 3) the delivery and re-application of interventions, especially since most breeding places for *Aedes* are in and around the household. However, an SR analysing the impact of communities in dengue vector control [21] could not show clear evidence of a significant effect, while a recent cRCT was more positive [22] and more evidence for a positive effect is emerging currently.

Similarly, we found little evidence to support either single versus combined interventions. In our analysis, a more prominent feature was the quality of delivery: single interventions showed better results, if well delivered – and this may well be through communities, or equally through vector control services, than the few analysed studies using combinations of interventions (Table 1). Our hypothesis is that combination interventions may not produce the anticipated results because high quality delivery is more difficult

Research gaps and priorities

In general, the quality of the included studies severely impacted our ability to make strong conclusions. There were few adequately powered studies with appropriate study designs. Improving the quality of studies is important because it is difficult to distinguish negative results attributable to poor study design from valid studies with truly negative findings, also highlighted by Bowman [10]. Study quality emerged as a possible confounding variable, with larger and well-conducted trials having better results, regardless of outcome measure. If Erlanger, for example, established that community-based and integrated approaches are most efficacious, the MA also showed that study quality criteria, particularly sample size, may be an important factor; e.g., had the best calculated efficacy, however, these studies were larger: *'... integrated vector management (studies) focused on larger populations'*. Similar findings have been presented by Bowman [10], with a focus on studies measuring human transmission.

Major stakeholders in the public health and specifically, the vector control community need to develop rigorous guidelines for study designs in vector control, and funding organisations must require applicants to meet these standards. The scientific community has recently addressed the urgent need for such guidelines [23]. Without standardisation, future studies will continue producing heterogeneous results with dissimilar outcome measures that are not amenable to direct comparison.

Another gap is that the majority of the included studies did not measure the impact of vector control measures on dengue transmission [6,23]. This is a critical issue since transmission models estimate the need for an up to 90 % reduction in vector populations in order to produce a decrease in disease incidence [12]. While active case surveillance is logistically challenging and the laboratory measurement of antibody response and/or viraemia is limited by cross-reactivity and expense, it must be considered the gold standard of any trial and clearly defined outcome measures and guidelines are urgently needed, Finally, feasibility, acceptability and costs require further deliberations once efficacy and community effectiveness are established. Recent economic analyses are available, especially with an estimate of the economic burden attributable to dengue [24], but modes of application for particular vector control methods require further investigation. For example, peridomestic space spraying and IRS often use the same insecticides. However, the mode of application may alter the effectiveness and therefore the cost-effectiveness. A systematic analysis of the effect of insecticide resistance should also be included in any cost-effectiveness analysis.

Integrated Vector Management (IVM) is another important area of research [7,25,26]. Ideally, most vector control methods target several vectors and diseases simultaneously. Considering the limited impact of vector control on the transmission of dengue – as established in this series of SRs – any measurement for synergies for other *Aedes* transmitted diseases, or other vector-borne diseases controlled by the same vector control methods, would be useful. The latter applies also to the recently developed dengue vaccine [2]. The question arises, if a partially efficacious vaccine would be more useful to control dengue transmission in combination with – also partially efficacious – vector control [27].

Systematic reviews versus meta-analyses

The attempts to consider vector control with exclusively quantitative high-level methods, e.g. MAs, showed the limitations of this type of analysis, most notably, the exclusion of many relevant studies. This is the very reason for this analysis, allowing the inclusion of 'lower quality' and simply more studies. This has shown to be particularly important in a field where only limited evidence exists or where high-level evidence is simply difficult to obtain. Key features of the more qualitative analysis of the SRs, including quality assessment and results of a content analysis approach, have been highlighted, showing this approach as useful and adding to the knowledge for improved dengue control. This should be seen as a complementary approach rather than as a substitute for the more rigorous MAs, especially when previous research is of variable quality. With the increase of published MAs and SRs, further analyses and summaries resulting from these studies are probably necessary, perhaps best delivered by expert consensus methods.

Limitations

This analysis has several limitations. These have been addressed in the individuals SRs, following PRISMA guidelines [8], e.g. addressing publication bias with extended searches in grey literature. Up until today, not all dengue vector control methods, as they are applied in practice, have been analysed with SRs. This includes for example different environmental methods, however work for this is in progress. However, the consistency of the data emerging from the currently available studies may be a good indicator that the few remaining studies will not change substantially the main messages of this review. New vector control methods such as *Wolbachia* and genetically modified mosquitoes have the potential to change vector control substantially and will require further analysis across endemic settings.

Conclusions and recommendations

When considering the analysis of the SRs and the existing MAs, nearly all vector control methods showed excellent results in at least one study, but no single method was clearly superior in all settings.

A very general system of recommendations can be made – following this analysis – to design vector control programmes: to include the use of chemical methods, particularly indoor residual spraying and insecticide treated materials, and biological methods, where possible. Although not analysed in the SRs, waste and environmental management may be useful – mostly because it 'makes sense anyway'. Larvae and adults should be targeted simultaneously. The quality of delivery and coverage of the vector control interventions is probably the most important component of any control programme.

Specific recommendations can be as summarised as follows:

- To be efficacious and community-effective, rigorous implementation of vector control measures may be more important than the actual choice of combinations of vector control methods

- There is an urgent need for standards to guide the design and reporting of vector control studies, ensuring comparability of studies. These studies should include measurements of human transmission.

Furthermore, new research areas are to be addressed, including

- SRs on different vector control methods – these can only be performed when enough studies have been published, this should be the case for insecticide treated materials, soon for genetically modified mosquitoes and *Wolbachia*

- An assessment on the use of SRs and MAs, to assess research translation for vector control as suggested by Orton[28]

Declarations

Authorship: OH devised the idea for the entire work, designed the concept, and was the 'driving force' of all stages of the described studies, throughout the studies and including drafting the studies/articles and their respective publications in his position as academic supervisor. SRR supported the process from the beginning towards the end and was involved in all stages. RB authored several studies.

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Ethics

Not required, individual studies have gone through ethical review, if required

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