DENGUE VECTOR CONTROL: ASSESSING WHAT WORKS?

Olaf Horstick[1], Ross Boyce[2] and Silvia Runge-Ranzinger[1]

[1]Teaching Unit of the Institute of Public Health, University of Heidelberg, Germany; [2]Division of Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America

Abstract. Primary prevention of dengue remains difficult, and continues to be difficult, relying mostly on vector control, with historical success, but lately there is also a partially effective vaccine. Vector control may continue to play a role, with the most efficacious and effective vector control methods. To establish this, high level evidence such as systematic reviews have been developed for applied vector cotrol methods, but also on service delivery. The systematic reviews followed the PRISMA statement. For single vector control interventions work has been undertaken on peridomestic space spraying, Temephos, *Bacillus thuringiensis israelensis*, Copepods and larvivorous fish. Further work is currently published on pyriproxifen and indoor residual house spraying (IRS). For a particular service delivery, there is existing work on outbreak response and on vector control service delivery. Nearly all vector control methods showed excellent results in at least one study, either on larvae, or adults, or even perhaps on dengue transmission: 1) Vector control can be effective, implementation remains an issue, including delivery structures, 2) Single interventions are probably not useful, efficacy varies, with little sustainability, 3) Combinations of interventions have mixed results, 4) Interventions are often applied in outbreaks (compared to routine vector control), effectiveness is also questionable, 5) Key elements for more effective vector control measures may be timely alerts of outbreaks, followed by immediate vector control measures, including health promotional campaigns, 6) Careful implementation may be most important.

Keywords: dengue, vector, control methods

INTRODUCTION

In light of the ongoing global Chikungunya, dengue, yellow fever and Zika outbreaks, vector control of *Aedes aegypti* and *Aedes albopictus* mosquitos has received more attention. This review summarizes existing high-level evidence, such as systematic reviews, for dengue vector control, and updates a previous review on the topic (Horstick and Runge-Ranzinger, 2015).

Whereas secondary and tertiary prevention strategies for dengue are improving, with low case fatality rates in most countries (WHO/TDR, 2009), primary prevention strategies have yet to demonstrate significant progress, with an estimated 390 million infections each year (Bhatt *et al*, 2013). The first dengue vaccine is now commercially available, but it is only partially effective, with an estimated efficacy of 47-83% against the four dengue serotypes (Hadinegoro *et al*, 2015). Prior to vaccine introduction, vector control was the only available method for primary prevention of dengue. Vector control strategies have shown some success to control dengue (Gubler, 2011), most notably in the past in Cuba and Singapore, but for most countries, vector control strategies have produced mixed results. Even with the introduction of the first vaccine, vector control will likely continue to play a role in dengue prevention. Further studies, utilizing the most efficacious and effective vector control methods (Reiner *et al*, 2016) should be conducted to test for possible synergies between these two approaches.

Dengue vector control comprises chemical, biological and environmental methods (WHO,

Correspondence: Olaf Horstick, Teaching Unit of the Institute of Public Health, University of Heidelberg, Germany.
E-mail: *Olaf.Horstick@uni-heidelberg.de*

TDR, 2009) targeting adult or larval stages of mosquitoes. Chemical methods can generally be classified into 1) the use of insecticides for residual sprayings, both intra-domiciliary (including IRS) or peri-domestic, 2) the use of long-lasting insecticide treated materials (ITM), including insecticide treated nets (ITN) or curtains (ITC) and 3) control of larval breeding to include the application of Temephos or pyriproxyfen in breeding sites. Chemical control of dengue vectors, however, has limitations, including environmental contamination, bioaccumulation of toxins, concerns regarding human toxicity, and the potential development of resistance in the vector. Biological methods to control larval stages include *Bacillus thuringiensis israelensis* (Bti), or the introduction of larvivorous fish and copedods. Environmental management strategies attempt to eliminate productive breeding habitats, *eg*, emptying of water containers, waste disposal, provision of piped water or employ physical barriers against mosquito vectors, such as window screens and water container covers. However, the latter approaches are often combined with the use of insecticides. There are other methods that are not currently used in large scale control programs, such as the introduction of the bacteria *Wolbachia* and/or genetically modified mosquitoes with the intent of replacing and/or reducing the naturally occurring vector with vectors that have a limited capacity to reproduce and/or to transmit the dengue virus. Integrated control measures have also been developed in the context of Integrated Vector Management (IVM) (WHO, 2004), with possible synergies between chemical, biological, and environmental approaches (Horstick, 2017).

Summary evidence–systematic reviews and meta-analyses–helps to assess the efficacy and community effectiveness of interventions and should provide clear policy recommendations for or against the use of such interventions (Moher *et al*, 2009). However, very little summary evidence exists for neglected tropical diseases such as dengue (Nagpal, 2013). A previous meta-analysis examining dengue vector control methods highlighted the efficacies of each approach (Erlanger *et al*, 2008). The constraint of meta-analyses is that they are limited to studies of comparable design and outcome measures, and thus exclude many published studies. We hypothesized that further analyses of vector control methods for the control of dengue vectors with systematic reviews (SR), rather than meta-analysis, may contribute to a better understanding of the value of vector control for primary prevention of dengue.

This review summarizes the findings of our efforts to use systemic reviews of published, high-quality scientific literature in order to to determine:

1) The efficacy and/or community effectiveness of each vector control method,
2) the efficacy and/or community effectiveness of combinations of vector control methods,
3) existing research gaps, and
4) practical recommendations concerning the implementation of vector control strategies to reduce dengue transmission.

MATERIALS AND METHODS

Following up with individual SRs on the existing meta-analysis of dengue vector control methods (Erlanger *et al*, 2008), the author designed a framework to describe dengue vector control methods in the 2009 WHO dengue guidelines (WHO, 2009). The framework has been adapted towards three levels of on-going research: 1) vector control methods, including biological, chemical or environmental, 2) vector control of a particular service function, *eg*, outbreak detection and response, and 3) organization of vector control services.

The full methods for each reported SR are presented in the original articles, however, the methods followed the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher *et al*, 2009), with preformulated study objectives, searches on all relevant databases, combinations of categories of search terms, documentation of data searches to obtain the PRISMA flowchart, screening by title of potential hits, screening by abstract when relevant to the topic, removal of duplicates, retrieval of full articles to apply full inclusion and exclusion

criteria, searches for further references from the bibliographies of included articles and searches of grey literature. Two data extractors independently conducted the searches, and extracted relevant information into predefined data extraction forms, which became the evidence tables for each of the respective studies.

Study quality was assessed using the validated tools appropriate to the study type. Given the limited number of published studies in most areas, study quality was rarely a reason for exclusion, but was addressed in the reporting and subsequent discussion sections. If study quality was used to exclude a study, the quality assessment was summarized in a table, scored and taken into consideration for analysis.

Studies were often classified into efficacy studies - those that were performed under laboratory conditions - and community effectiveness studies- those that were conducted under program-like conditions. The descriptive part of the analysis was performed plotting the included studies against the geographical background and describing clustering over time. The study types and outcome measures used were described. For the analytical components, study results were summarized for vector and human disease outcome measures. For the former, results were compared to estimates needed for a potential reduction of transmission. The discussion sections followed content analysis methods, using categories that emerged from the analysis (Pope *et al*, 2000).

When using mixed methods, the results of stakeholder interviews and questionnaires were added to the data abstraction form. Methodology and analysis of the interviews followed the relevant standards (Pope *et al*,). For questionnaires, these followed the same broad heading and topic areas as the interviews. Finally, information from all parts of the study was compared (Mays and Pore, 2000).

For the analysis of vector control and vector control methods in this study, studies have been included from the entire framework of published studies if relevant to the topic (dengue vector control) and were summarized according to the above-mentioned, predefined categories. Furthermore, implementation aspects derived from individual SRs were analyzed, with a view towards practical public health recommendations.

RESULTS

Descriptive analysis

According to the analytical framework, SRs have been published by the author on the following topics: 1) single vector control methods including peridomestic space spraying (Esu *et al*, 2010), Bti (Boyce *et al*, 2013), Temephos (George *et al*, 2015), copepods (Lazaro *et al*, 2015) and larvivorous fish (Han *et al*, 2015). Further work is inprint on pyriproxifen (Maoz *et al*, 2017) and IRS (Samuel *et al*, 2017), 2) service orientated purposes: Outbreak control, including clinical and vector control responses (Pilger *et al*, 2010) and 3) organizational context of vector control: Vector control service organization (Horstick *et al*, 2010). These nine SRs on vector control are summarized below (see evidence tables of the SRs).

A total of 31,836 articles have been screened by title and abstract for inclusion. PRISMA flowcharts are included with the original articles. The authors assessed 430 full text articles and a total of 167 articles were included in the nine SRs. For the seven SRs describing single interventions for dengue vector control, there were 15 articles on peridomestic space spraying (Esu *et al*, 2010), 14 for Bti (Boyce *et al*, 2013), 27 for Temephos (George *et al*, 2015), 11 for copepods (Lazaro *et al*, 2015), 13 for larvivorous fish (Han *et al*, 2015), 17 for pyriproxifen (Maoz *et al*, 2017) and 14 for IRS (Samuel *et al*, 2017). Additionally, there were 24 articles included in the SR assessing outbreak control (Pilger *et al*, 2010) and 32 for vector control service organization (Horstick *et al*, 2010). For each SRs, there was ample evidence for meaningful analyses.

The SRs analyzed community effectiveness and/or efficacy, as defined by the individual author of each review. Community effectiveness was the preferred outcome of interest, since the intent of the SRs was to provide valid, yet practical public health recommendations. Of the nine SRs, eight

included only community effectiveness studies, while one study (larvivorous fish) incorporated both outcomes in order to achieve a higher volume of studies (Han *et al*, 2015). However, this study did stratify results by efficacy and community effectiveness in both the reporting and discussion. We did observe a general trend across interventions that when efficacy has been tested and validated under laboratory conditions, studies focus more on community effectiveness.

Databases searched were fairly standardized across SRs with the majority including PubMed, EMBASE and WHOLIS, but often LILACS and Web of Science. More than 90% of all articles included were available on PubMed. Additional articles were more often identified from searches of the reference section of included articles, but seldom from the grey literature.

Inclusion and exclusion criteria were also fairly standardized, focusing on the respective research question, but also on study quality. For SRs focusing on vector control methods, an attempt was made to include only controlled studies, however, this was not always possible, depending on the number of studies identified during the search process. There is also a variation depending on the method tested. For example, the SR on *Bti* (Boyce *et al*, 2013) specified study duration in order to assess long-term effects of this method. The two service oriented SRs (Horstick *et al*, 2010; Pilger *et al*, 2010), required inclusion and exclusion criteria more specifically tailored around the research question.

Selected outcome measures of interest varied considerably for the SRs on vector control methods, and largely depended on the included studies. However, standard entomological indices including Breteau Index (BI), Container Index (CI), House Index (HI) and pupal indices are reported in most studies. It is also important to note that for most SRs there are studies measuring human transmission, although with very different measures of effect.

As for study types encountered for the SRs on vector control methods, these were mostly non-randomized controlled trials (NRCTs). However, there was at least one randomized controlled trial (RCT) or cluster randomized controlled trial (cRCT) available for most methods, with the SRs on larvivorous fish and copepods (Han *et al*, 2015; Lazaro *et al*, 2015) being the exceptions. This is likely related to publication date, since most the cRCTs are more recent studies.

Analysis of vector control with SRs

SRs of single vector control methods. Among the chemical methods, peridomestic space spraying using various insecticides is commonly used to control dengue vectors, the popularity of which may be related to its high visibility (Esu *et al*, 2010). For the purpose of this SR, peridomestic space spraying was defined as the "application of small droplets of insecticide into the air in an attempt to kill adult mosquitoes in and around houses". Of the 15 included studies, 13 reported a reduction in entomological indices, typically around 90% for adult mosquitos post-spraying. This effect was not sustained and mosquito populations general returned to baseline levels within a few days to weeks. Two studies showed no reduction of entomological indices. The analysis also demonstrated that study designs and outcome parameters are heterogeneous, while measures of disease incidence are rarely reported. Even when incidence was measured, the study authors concluded that the observed reduction of cases could not be linked to the intervention. The SR showed that there is a short-term effect on adult mosquito populations, however there is no conclusive evidence for or against the use of peridomestic space spraying to control dengue.

In regard to IRS (Samuel 2017), the SR author considered the use of all types of insecticides, although most studies utilised synthetic pyrethroids, with one study applying deltacide, a mixture of Deltamethrin 0.5%, S-Bioallethrin 0.75% and Piperonyl Butoxide 10%. The results of the seven included studies demonstrated that both adult and immature mosquito stages were suppressed, often by more than 90% and over sustained periods of time. The effect on immature mosquitoes is less strong on all studies measuring larval indices. For human dengue infection parameters, there are only two IRS studies, but with good results.

The SR concluded "…*evidence obtained from this systematic review showed that the use of IRS either solely or in combination with other control measures can produce significant reductions of Aedes populations (mature and immature forms). IRS can also produce reductions in human dengue cases*."

Temephos to control larval breeding is one of the most commonly applied substances in larval habitats. The SR included single interventions with Temephos as well as combinations with other interventions (George *et al*, 2015). Of the 27 included studies, the interventions were as follows: 11 single intervention studies (Group 1) and 16 combinations (Group 2). No outcome measures to assess for changes in the incidence of human cases were incorporated in any of the studies. Group 1 showed that 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 regular re-application has been pursued. Combination interventions in Group 2 included Temephos with health education and information, environmental management and the use of malathion, *Bti*, or larvivorous fish. Ten studies reported a reduction of immature mosquito stages, while three failed to show an effect and three had only a very small effect. This was very surprising, given that the single intervention studies of Temephos showed clear evidence of community effectiveness. Operational issues may have been important, including surveillance and coverage, regular application, mode of application, acceptability and limited residuality of Temephos. The SR concluded "…*while there is little doubt concerning the effectiveness of Temephos in controlling Aedes breeding sites, the same level of effectiveness was not clear from the studies using Temephos combined with other interventions. This could be due to operational issues, delivering several interventions*."

The final SRs for chemical methods reviewed the use of pyriproxifen (Maoz *et al*, 2017), and was unique in that it described the auto-dissemination effect of the intervention. Of 17 included studies, two studies included human disease parameters including serological surveys (IgM) and dengue incidence. Studies were categorized by mechanism of application as follows: 1) container treatment studies: six studies showed a reduction above 80% of larval indices. However two RCTs showed a limited effect; 2) two fumigation studies in combination with Permethrin showed a good inhibitory effect; 3) studies measuring autodissemination showed good results of reduction of adult emergence between 20% and 85%, and 4) combination with adulticides seemed to increase overall effectiveness. Human transmission data were weak and could not demonstrate a significant effect. With these results, the evidence presented suggests that pyriproxifen can effectively control adult emergence of immature stages of dengue vector mosquitoes in a variety of breeding sites in a community setting and there is a clear consensus that pyriproxyfen effectively inhibits *Aedes* adult emergence at concentrations of <1 ppb. However, the SR concluded that "*more and larger studies with appropriate study designs and relevant, standardized outcome measures are needed; also, tolerance/resistance of vectors to pyriproxyfen has been reported* (,… and needs to be investigated)."

Bti is often classified with the chemical control options, although - being a bacterium - it is a biological substance. The SR on *Bti* (Boyce *et al*, 2013) analyzed 14 studies with *Bti* eliminating all larvae from treated containers within 24 hours, and for most containers there was a prolonged effect of 14 days. One study that measured an effect on human transmission showed only one case in the intervention area, compared to 15 in the control. No single formulations demonstrated superiority in the four studies testing these products. Higher doses of *Bti* showed a longer duration of effect in one study. Study design and quality need to be improved in future studies. The study concluded "*there is evidence that Bti is effective in reducing the density of immature dengue vectors when it is applied to targeted containers as demonstrated by the efficacy studies. However, the evidence to suggest that Bti is effective as a single agent, when used in a community setting, is limited*."

Other biological methods include the use of

copepods and larvivorous fish. These methods carry the advantage that there are limited environmental effects. Furthermore, both Copepods and larvivorous fish are part of the natural food chain and re-application of the intervention is also necessary. The SR for Copepods (Lazaro *et al*, 2015) analyses 11 studies, The Copepods used were mostly *Mesocyclops spp*. Copepods controlled larval *Aedes* populations up to 100%. At the household level, reductions of households' positive for *Aedes* larvae between 30-97 % were observed. When looking at adult mosquito landing rates and oviposition, reductions to zero were reported. Adult *Aedes* per household measurements showed reductions between 30 - 100 %. Adult mosquito indices reductions from 0.12-1.16 to 0.0-0.01 per community after a period of three years were shown. Additionally, in three studies dengue transmission data were measured with results that ranged from zero reported cases in both the intervention and control communities to a 76.7 % reduction of dengue incidence, as determined by a reduction of serological parameters. However, the study also noted that there was a large geographical discrepancy in the results, with the positive studies having been conducted in one country only (Vietnam), by the same research team, while the success could not be replicated elsewhere. Also, study design and quality were again mentioned as issues. The study concluded "*the use of copepods as a single intervention may be a community effective and sustainable dengue vector control method to control dengue vectors and dengue transmission. However, this is perhaps only possible provided several specific criteria are met: as clearly shown in the fives studies conducted in Vietnam, these would include rigid delivery of intervention; development of community management committees and collaborators; efficient mobilization and sustained interest of the community residents*."

Finally, the SR on larvivorous fish (Han *et al*, 2015) analyzed 13 studies. Eight of nine intervention studies showed a reduction of immature forms of dengue vectors. One study of three also showed a reduction of adult indices. Three of four before and after studies demonstrated a reduction of immature stages. A long-term decline over two years has been reported by the two studies measuring such an extended period. The studies measuring human transmission showed a reduction in the number of human cases, however, this must be interpreted cautiously as these were before and after study designs without a control and thus subject to temporal trends in dengue transmission. Study design and quality were an issue, and geographical coverage of studies. "*The findings suggest that the use of larvivorous fish, used as a single agent or in combination with other measures, can reduce significantly infestations of the immature vector stages. However, there is no evidence to demonstrate any community effectiveness of larvivorous fish as a single agent*" (…especially when considering human transmission).

SRs for a service orientated purpose. Outbreak response may be the most commonly performed program undertaken by public health services, since routine control efforts are difficult to achieve and sustain. In a SR for outbreak response, both vector management and clinical response (Pilger *et al*, 2010), including both single and combined interventions were considered. The 24 included studies could be broadly classified into 1) studies focusing on transmission reduction, 2) studies focusing on mortality reduction and 3) studies describing both. It became clear that there are different organizational strategies for an outbreak response, but the most common is an inter-sectorial approach. Multidisciplinary response teams, with vector control personnel working with communities, including monitoring and evaluation, resulted in good perceived outbreak control. Combined responses with 1) vector control (larval habitats interventions with communities; insecticides, intra- and peridomestic) and 2) capacity training for clinical response are successful. Spatial spraying of insecticides as a single intervention was generally not effective. However, the evidence level is weak, especially given the poor quality of the included studies. The SR concluded that "*outbreak response has to be organised multidisciplinary and monitored/*

evaluated. During outbreaks the above-mentioned interventions have to be implemented as a combined set of interventions in order to achieve rapid control. Further research is needed especially linking effectiveness of outbreak response to human disease epidemiology" .

SRs of the organizational context of vector control. There is a longstanding discussion of the optimal delivery of vector control services, primarily debating vertical *vs* horizontal programs. However, the question of how the services are delivered, including resources and quality of delivery, is not well defined in the literature. A SR on the organizational context of vector control, including qualitative methods and integrating stakeholders' views (Horstick *et al*, 2010), addressed this question. Most services combine numerous interventions and therefore further investigation of selected interventions was not pursued. Of 32 included studies, nine were assessed to have relatively high study quality, with a clearly defined methodology, while 16 had less strict criteria. Additionally, there were three guidelines and four country case studies included. Three of the first group of nine studies showed little change of control operations over time. There were, however, strategic changes (decentralization, inter-sectorial collaboration). Including the results of all studies, staffing levels, capacity building, management and organization, funding and community engagement were found insufficient. It becomes evident that vector control services are not regularly analyzed and/or audited. The study concluded that *the analysis underlined the need for: 1) operational standards, 2) evidence based selection/delivery of combinations of interventions, 3) development/ application of monitoring and evaluation tools, 4) needs driven capacity building*.

Cross-cutting issues of all Sis

Study quality varied in in this series of SRs, for both study design, specified outcome measures and data analysis, particularly the application of appropriate statistical analysis. This was a recurrent observation, with a tendency towards more complex and higher quality of studies with RCTs and cRCTs over time.

There is a pattern that particularly carefully implemented studies are more successful, recurrently quality of delivery of the intervention is an important item. These studies have higher-level study design, are often larger in size and implemented over a longer time period. This is also underlined by the fact that those SRs that included studies with multiple study arms, often find inferior efficacy and community effectiveness compared to studies with only one study arm.

The results of this series of SRs on feasibility, acceptability and costs are limited, since these issues were not part of the original search. However, the topics are recurrently discussed in the articles included in the individual studies of the SRs. A pattern emerges that acceptability is considered as one of the most crucial elements for study authors. Feasibility is mostly addressed in the context of different methods of application of a particular vector control method. Costs are not addressed in any the included studies.

DISCUSSION

Overall, the results of the SRs demonstrate the variable impact of dengue vector control methods under real world conditions and highlight the heterogeneous organization and operation of vector control services. One of the most important findings of this analysis is that almost all of the dengue vector control methods studied may have a role in the control of dengue vectors. Only peridomestic space spraying failed to show positive results. This confirms the results of a previous meta-analysis, in which the authors concluded that vector control "*is effective in reducing vector control populations*," but do not comment on the potential reduction in human disease. In a more recent meta-analysis and systematic review (Bowman *et al*, 2016), analyzing vector control studies with a focus on studies measuring indices of human transmission, the study authors conclude that there is a general lack of evidence to suggest that vector control can reduce disease incidence.

The SRs included in this review show that for each vector control method studied there are

examples of very successful trials, highlighting the potential efficacy and community effectiveness of each method. In contrast, Erlanger *et al* (2008) singled out biological control methods as more efficacious than others and IVM performed best, while Bowman *et al* (2016) favored house screening and combining community-based environmental management and water container covers to reduce dengue risk. The different approaches of the respective analyses clearly yielded different results. We hypothesize that the implementation of the intervention, including rigorous methods and widespread coverage, are crucial. When stratifying by large and well-conducted trials only, a clearer picture of the community effectiveness of vector control may emerge.

Our findings suggest that when developing a strategy of IVM, clearly the local context needs to be considered, but if well delivered, most vector control methods may play a role. Future research is urgently needed to determine which social, environmental and entomological factors define the "best possible combinations of vector control methods" for different geographical areas. Targeting larval and adult stages of mosquitoes should result in improved transmission control: targeting both also implies combinations of interventions, especially when considering potential synergies for IVM. No systematic answer can be derived from the analysis of the SR's, apart from the fact that different combinations of interventions may need separate trials to ensure clear definition of most efficacious and community effective combinations of interventions in their local context. In other words, the recommendations for IVM, as described by WHO (2004), need more evidence.

Despite the lack of evidence to guide implementation programs, some basic criteria needs to be met in order for vector control interventions to be efficacious or effective in the community. The primary determinant of effect seems to be the quality of delivery, be it through community involvement or centralized vector control services. This analysis seems to underline the importance of the latter, particularly because combinations of vector control methods, even under relatively strict study conditions, can be difficult to deliver in a rigorous manner as evidenced by the fact that such approaches often have inferior results compared to well delivered, "single" method studies. Perhaps it is simply easier and more effective to deliver one method well, than to deliver several methods sub-optimally.

This analysis has several limitations with the potential for publication bias being the most significant. The substantial operational experience of national vector control programs is often not documented. However, we attempted to mitigate this potential limitation in each SR by including a search of the grey literature and a thorough examination of the reference section of each of the included studies. Prominent dengue entomologists and program managers were queried and also provided the authors with additional evidence that may not be readily available.

A further limitation is "updating" of SRs, since the results of the SRs are only valid in the context of their dates of literature searches. A systematic approach to SR updating would be the ultimate solution to this bias of the overall analysis. However, the simple fact that the group of authors are well embedded in the research community and are aware of upcoming and published studies, especially considering "game changing" studies, should limit this bias.

In summary, when considering the analysis of the SRs and the existing meta-analyses, nearly all vector control methods showed excellent results in at least one study, although outcome measures varied significantly,. Furthermore, we conclude that:

- Although vector control can be effective, implementation remains an issue. No clear evidence exists for optimal delivery structures of vector control services (Horstick *et al*, 2010).

- Single interventions are probably not useful, efficacy varies between different interventions, but sustained community-effectiveness can almost never be demonstrated (Esu *et al*, 2010; Boyce *et al*, 2013, George *et al*, 2015; Han *et al*, 2015; Lazaro *et al*, 2015; Maoz 2017; Samuel 2017).

Table 1. Evidence table of systematic reviews on vector control published by authors.

Author/ Year	Focus of SR	Efficacy or community effectiveness	Single intervention or combination	Study quality	Databases	Inclusion/ Exclusion criteria	Studies Identified	Assessed	Included	Outcome measures	Study quality included	Main outcomes	Further outcomes	Conclusions
Single vector control methods														
Esu *et al*, 2010	Peri-domestic space spraying	Community effectiveness	Single	cRCTs, RCTs, Quasi RCTs, Before and after studies (with or without control), Post-intervention studies with control	Medline EMBASE LILACS Web of Science WHOLIS MedCarib CENTRAL	Peer-reviewed studies Study quality All languages	2102	78	15	Indoor adult mosquito landing/ resting catches, oviposition trap counts, BI, CI, HI Human cases	1 RCT, 8 Controlled before and after studies, 1 Post intervention with control, 5 before and after studies without a control	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. 2 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	No conclusive evidence for or against the use of peridomestic space spraying
Samuel *et al*, 2017	IRS	Community effectiveness	Single and combinations	cRCTs, RCTs, Quasi RCTs, Before and after studies (with control), Cross-sectional studies	PubMed, EMBASE, LILACS, Web of Science, WHOLIS, Cochrane, Google Scholar	Peer-reviewed studies, including control groups, pre- and post-intervention assessments, cross-sectional studies, no language restrictions	8254	398	714	Larval indices: BI, CI, HI Adult indices: KD rates Adult mosquito densities % adult mosquito mortality Mean % mortality of adult mosquitoes Human transmission: Age adjusted dengue incidence Odds of secondary dengue infections Number of confirmed and reported cases	7 studies: 5 controlled studies, 2 for IRS and 3 for ISS (indoor space spraying) 2 non-controlled studies (1 each IRS/ISS) Controlled studies were subsequently classified into 4 intervention control studies and 1 cross-sectional time series	Both adult and immature mosquito stages were suppressed by often more than 90 %, and sustained. Two studies showed a decrease of new dengue cases	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	Evidence obtained from this systematic review showed that the use of IRS either solely or in combination with other control measures can produce significant reductions of Aedes populations (mature and immature forms). IRS can also produce significant reductions in human dengue cases. However, evidence to suggest the effectiveness of IRS either on immature stages of Aedes or on human dengue cases as a single intervention is limited

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George *et al*, 2015	Temephos	Community effectiveness	Single and combinations	cRCTs, RCTs , Intervention Control trials, Before and after studies	PubMed, WHOLIS, GIFT, CDSR, EMBASE, Wiley	Peer-reviewed studies, study design including cRCTs, RCTs , intervention control trials, before and after studies	18439	54	27	Adult mosquito density, BI, CI, HI, PPI, reduction of breeding sites, positive ovitraps, mean number of larvae, % prevalence of larvae No parameters to measure human cases	11 studies using a single intervention: seven intervention control studies, four before and after studies 16 studies with combinations: 3 cRCTs, 4 intervention control trials, 9 before and after studies	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, 3 failed and 3 had some effect only	Operational issues may be important, including surveillance and coverage, regular application, mode of application, acceptability and limited residuality of Temephos	While there is little doubt concerning the effectiveness of Temephos in controlling Aedes breeding sites, the same level of effectiveness was not clear from the studies using Temephos combined with other interventions. This could be due to operational issues, delivering several interventions
Maoz *et al*, 2017	Pyri-proxyfen	Community effectiveness	Single and combinations	cRCTs, RCTs, Non RCTs with control: Quasi RCTs, Intervention Control trials Before and after studies	PubMed, Web of Science, EMBASE, LILACS, WHOLIS, Cochrane, Google Scholar	Peer-reviewed studies, study design as mentioned under study quality	698	49	17	Adult emergence BI, CI, HI, PPP, Pupal mortality, larval mortality 2 studies human disease parameters: serological surveys (IgM) and dengue incidence	1 cRCT 3 RCTs 1 Quasi RCT 12 Non RCTs	Container treatment studies: 6 studies showed a reduction above 80 %, 2 RCTs showed a limited effect. 2 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	More and larger studies with appropriate study designs and relevant, standardised outcome measures are needed; also, tolerance/resistance of vectors to pyriproxyfen has been reported

Table 1. Evidence table of systematic reviews on vector control published by authors. (*Continue*)

Author/ Year	Focus of SR	Efficacy or community effectiveness	Single intervention or combination	Study quality	Databases	Inclusion/ Exclusion criteria	Studies Identified	Assessed	Included	Outcome measures	Study quality included	Main outcomes	Further outcomes	Conclusions
Boyce *et al*, 2013	Bti	Community effectiveness	Single intervention	cRCTs, RCTs, NRCTs	Medline, EMBASE, Global Health, Web of Science, CDSR, WHOLIS	Experimental design, Bti as a single agent, minimum follow up of 20 days	355	45	14	BI, CI, HI, average larval free period, oviposition index 1 study measured routinely collected surveillance data	3 cRCTs, 1 RCT, 10 NRCTs	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 1 case in the intervention area, compared to 15 in the control	Different formulations did not show superiority in the 4 studies testing this. Higher doses of Bti showed a prolonged effect in 1 study Study design and quality need to be improved in future studies	There is evidence that Bti is effective in reducing the density of immature dengue vectors when it is applied to targeted containers as demonstrated by the efficacy studies. However, the evidence to suggest that Bti is effective as a single agent, when used in a community setting, is limited
Han *et al*, 2015	Larvivorous fish	Efficacy and community effectiveness	Single intervention or combination	cRCTs, RCTs, NRCTs	PubMed, EMBASE, Web of Science, WHOLIS, Wiley, LILACS, GIFT (WHO database), CDSR	Experimental design	4914	28	13	Number of breeding sites, positive for Aedes, Adult mosquito density, BI, CI, HI, infestation rates 2 studies measured surveillance data	9 intervention control studies, 4 before and after studies	All intervention control studies - but 1 – showed a reduction of immature forms of dengue vectors. 1 study showed a reduction of adult indices, of 3 measuring. 3 of 4 before and after study showed a reduction of immature stages. A long-term decline over 2 years has been reported by 2 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	The findings suggest that the use of larvivorous fish, used as a single agent or in combination with other measures, can reduce significantly infestations of the immature vector stages. However, there is no evidence to demonstrate any community effectiveness of larvivorous fish as a single agent

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Lazaro *et al*, 2015	Copepods	Community effectiveness	Single intervention	cRCTs, RCTs, NRCTs	PubMed, EMBASE, CDSR, WHOLIS, Web of Science, LILACS	Experimental design, Copepods as a single intervention	1222	29	11	Adult density, BI, CI, HI, PPI, 4 studies measured serological surveillance	11 Intervention Control trials	Copepods used were mostly Mesocyclops spp Copepods controlled larval Aedes populations up to 100%. At household level, reductions of households 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	Copepods as a single intervention may be a community effective and sustainable dengue vector control method to control dengue vectors and dengue transmission. However, this is perhaps only possible provided several specific criteria are met: as clearly shown in the fives studies conducted in Vietnam, these would include rigid delivery of intervention; development of community management committees and collaborators; efficient mobilisation and sustained interest of the community residents

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Systematic reviews for a service orientated purpose														
Pilger *et al*, 2010	Outbreak control	Community effectiveness by definition, since only concerning real time outbreaks	Single interventions and combinations, could be clinical or vector management	Descriptive epidemiological studies (prospective or retrospective), before andafter studies, evaluations using mixed methods	Medline, EMBASE, CDSR, LILACS, WHOLIS	Any study design, any intervention during outbreak, Outcome described and supports by data	1134	63	24	A: studies focusing on transmission reduction; B: studies focusing on mortality reduction C: studies describing both	All studies descriptive studies without control, 1 study with 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	Outbreak response has to be organised multidisciplinarily and monitored/ evaluated. During outbreaks the above-mentioned interventions have to be implemented as a combined set of interventions in order to achieve rapid control Further research is needed especially linking effectiveness of outbreak response to human disease epidemiology
Organisational context of vector control														
Horstick *et al*, 2010	Vector control service organi-sation	Community effectiveness by definition, since only concerning real time services analysed	Combination of interventions	Any study that is not only an expert opinion	PubMed, WHOLIS, WHO regional databases	1) Studies with clear methodology and/result section analysing vector control services 2) Reports/ articles describing existing vector control services, without clear methodology/ results section, but can be derived (in the text)	2148	46	32	Service organisation: Staffing levels, capacity building, finances, material available	9 defined methodology, 16 not defined, 3 guidelines and 4 case studies	3 of 9 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	The analysis underlined the need for: 1) operational standards, 2) evidence based selection/delivery of combinations of interventions, 3) development/ application of monitoring and evaluation tools, 4) needs driven capacity building

- Combinations of interventions have mixed results, largely related to the logistical challenges of implementing multiple interventions (George *et al*, 2015).
- In real world outbreaks, multiple interventions are often applied although the effectiveness is questionable (Pilger *et al*, 2010).
- One of the key elements for more effective vector control measures may be timely alerts of outbreaks, as indicated by surveillance systems, followed by immediate vector control interventions, including health promotional campaigns.
- Careful implementation of vector control measures may be more important than the actual choice of vector control method.

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CONFLICS OF INTEREST

None declared.

REFERENCES

Bhatt S, Gething PW, Brady OJ, *et al*. The global distribution and burden of dengue. *Nature* 2013; 496: 504-7.

Boyce R, Lenhart A, Kroeger A, Velayudhan R, Horstick O. *Bacillus thuringiensis israelensis* (Bti) for the control of dengue vectors: a systematic review. *Trop Med Int Health* 2013; 18: 564-77.

Bowman LR, Donegan S, McCall PJ. Is dengue vector control deficient in effectiveness or evidence? Systematic review and meta-analysis. *PLOS Negl Trop Dis* 2016; 10: e0004551.

Erlanger TE, Keiser J, Utzinger J. Effect of dengue vector control interventions on entomological parameters in developing countries: a systematic review and meta-analysis. *Med Vet Entomol* 2008; 22: 203-21.

Esu E, Lenhart A, Smith L, Horstick O. Effectiveness of peridomestic space spraying with insecticide on dengue transmission; systematic review. *Trop Med Int Health* 2010; 15: 619-31.

George L, Lenhart A, Han WW, *et al*. Community-effectiveness of Temephos for dengue vector control: a systematic review, *PLOS Negl Trop Dis* 2015; 9: e0004006.

Gubler D. Prevention and control of *Aedes aegypti*-borne diseases: lessons learned from past successes and failures. *Asian Pac J Mol Biol Biotechnol* 2011; 19: 111-4.

Hadinegoro SR, Arredondo-Garcia JL, Capeding MR, *et al*; CYD-TDV Dengue Vaccine Working Group. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. *N Engl J Med* 2015; 373: 1195-206.

Han WW, Lazaro A, McCall PJ, Horstick O. Efficacy and community effectiveness of larvivorous fish for dengue vector control: a systematic literature review. *Trop Med Int Health* 2015; 20: 1239-56.

Horstick O, Runge-Ranzinger S, Nathan MB, Kroeger A. Dengue vector-control services: how do they work? A systematic literature review

and country case studies. *Trans R Soc Trop Med Hyg* 2010; 104: 379-86.

Horstick O, Runge-Ranzinger R. Reviewing the evidence for dengue vector control. An interim analysis of the contribution of high level evidence - such as systematic literature reviews - for dengue vector control. *Southeast Asian J Trop Med Public Health* 2015; 46(suppl 1): 131-7.

Horstick O, Runge-Ranzinger S. Vector control with a focus on household as allocation unit: a systematic literature review of its effectiveness (submitted 2016).

Lazaro A, Han WW, Manrique-Saide P, Horstick O. Community effectiveness of copepods for dengue vector control: a systematic review. *Trop Med Int Health* 2015; 20: 685-706.

Maoz D, Ward T, Samuel M, *et al*. Community effectiveness of pyriproxyfen as a dengue vector control method: a systematic review (submitted 2016).

Mays N, Pope C. Qualitative research in health care; assessing quality in qualitative research. *BMJ* 2000; 320: 50-2.

Moher D, Liberati A, Tetzlaff J, Altman DG; The Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *PLOS Med* 2009; 6: e1000097.

Pilger D, De Maesschalck M, Horstick O, San Martin JL. Dengue outbreak response: documented effective interventions and evidence gaps [review]. *TropIKA.net* [online] 2010; 1.

Pope C, Ziebland S, Mays N. Qualitative research in health care: analysing qualitative data. *BMJ* 2000; 320: 114-6.

Reiner RC, Achee, N, Barrrera R, *et al*. Quantifying the epidemiological impact of vector control on dengue. *PLOS Negl Trop Dis* 2016; 10: e0004588.

Samuel M, Maoz D, Manrique P, *et al*. Community effectiveness of indoor residual spraying as a dengue vector control method: a systematic review (submitted 2016).

World Health Organization (WHO). Global strategic framework for integrated vector management. Geneva: WHO; 2004. [Cited 2017 Jan 31]. Available from: http://whqlibdoc.who.int/hq/2004/WHO_CDS_CPE_PVC_2004_10.pdf

WHO/TDR. Dengue: guidelines for diagnosis, treatment, prevention and control. New edition. Geneva: WHo, 2009.