

# INTERIM ANALYSIS OF THE CONTRIBUTION OF HIGH-LEVEL EVIDENCE FOR DENGUE VECTOR CONTROL

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**Abstract.** This interim analysis reviews the available systematic literature for dengue vector control on three levels: 1) single and combined vector control methods, with existing work on peridomestic space spraying and on *Bacillus thuringiensis israelensis*; further work is available soon on the use of Temephos, Copepods and larvivorous fish; 2) or for a specific purpose, like outbreak control, and 3) on a strategic level, as for example decentralization vs centralization, with a systematic review on vector control organization. Clear best practice guidelines for methodology of entomological studies are needed. There is a need to include measuring dengue transmission data. The following recommendations emerge: Although vector control can be effective, implementation remains an issue; Single interventions are probably not useful; Combinations of interventions have mixed results; Careful implementation of vector control measures may be most important; Outbreak interventions are often applied with questionable effectiveness.

**Keywords:** dengue, evidence, systematic review, vector control

## INTRODUCTION

### Dengue guidelines

Since the publication of the 2009 WHO dengue guidelines (WHO, 2009), new developments in dengue include further evidence for clinical management (WHO, 2013), evidence supporting the use of the 2009 WHO dengue case classification (Horstick *et al*, 2012, 2014), new epidemiological estimates (Bhatt *et al*, 2013), further developments in vector control methods and last but not least, the first clinical phase 3 trials of a dengue vaccine (Capeding *et al*,

2014; Villar *et al*, 2015) warranted an update of the guideline, which was scheduled for 2014.

During the development of the 2009 WHO dengue guidelines, the organization aimed for higher standards for guidelines, with the establishment of the “guidelines review committee” (WHO, 2014). Following the WHO handbook for development of guidelines (WHO, 2012), specifically high-level evidence is needed, including systematic reviews.

This need for systematic reviews arises from developing public health policy based on available research, including implementation and operational research; therefore, linking research and practice. Especially in the context of Neglected

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Tropical Diseases filling this gap of high-level evidence is needed (Nagpal *et al*, 2013). In dengue, however, many topics have been addressed in the last years with systematic reviews, leading often to policy recommendations, as in the case of the 2009 WHO dengue case classification, but often highlighting research gaps.

### **Vector control**

Regarding vector control in dengue, a meta-analysis analysing all available vector control methods highlighted the efficacies of each method (Erlanger *et al*, 2008). However, for a technical meta-analysis, many studies need to be excluded from the analysis, to achieve the necessary comparability of data. Further to this, no technical standards exist for establishing efficacy and community-effectiveness of dengue vector control studies, which results in a large variability of existing studies and their respective designs; therefore, a meta-analysis will only look at a very limited amount of published studies.

The question arises, whether careful analysis of all available vector control methods, with systematic reviews, can further contribute to public health decisions on 1) the efficacy and community effectiveness of each vector control method, 2) and combinations of vector control methods, 3) identifying research gaps, and 4) practical recommendations concerning the use of vector control to reduce dengue transmission.

## **METHODS**

This article reviews the evidence for dengue vector control, including the published and unpublished evidence of systematic reviews, considering the exist-

ing meta-analysis on dengue vector control (Erlanger *et al*, 2008). A literature search was performed on existing systematic reviews dealing with dengue vector control, also asking experts in the field for relevant high level (summary) evidence. Studies have been included if relevant to the topic (dengue vector control) and are summarized according to predefined categories, systematic reviews analysing 1) single vector control interventions with efficacy and or community-effectiveness measurements; 2) a service orientated purpose, such as outbreak control; and 3) strategic levels, such as service organization. Furthermore, implementation aspects derived from the individual systematic reviews were analysed, with a view towards practical public health recommendations.

## **RESULTS**

### **Systematic reviews of single-method vector control**

For single vector control interventions, there is existing work on peridomestic space spraying (Ekpereonne *et al*, 2010) and on *Bacillus thuringiensis israelensis* (Boyce *et al*, 2013). Further work is available as university master's theses, and scientific articles will soon be published on the use of Temephos, Copepods, and larvivorous fish.

For Copepods (Lazaro *et al*, 2014, submitted) 11 articles were included in the systematic review, focusing on efficacy and community effectiveness. There is limited evidence that Copepods (*Mesocyclops* spp) could potentially be an effective vector control option, as shown in 5 community effectiveness studies in Vietnam. This includes long-term effectiveness on larval

and adult control of *Aedes aegypti*, as well as human disease parameters. However, this success has so far not been replicated elsewhere (6 further studies). With this limited evidence for the use of Copepods as a single intervention, further implementation studies in other communities/environments are needed.

For larvivorous fish (Han *et al*, submitted), considering 13 eligible articles, elimination of *Aedes* larvae in treated containers was shown in three efficacy studies. Further nine of the ten community effectiveness studies reported a considerable reduction in immature forms of vectors and a continuous decline over two years was observed in three studies. Two studies showed also reductions in adult mosquitoes and a fall in dengue cases after the intervention was mentioned in another two studies. The systematic review showed that the use of larvivorous fish as a single agent or in combination with other control measures produced a considerable reduction in the immature vector forms. However, the evidence to suggest community effectiveness of larvivorous fish as a single agent is limited, especially when considering study design. Further studies utilizing cluster-randomized controlled designs and incorporating the assessment of impact on dengue are recommended.

Peridomestic space spraying is one of the most commonly used dengue vector control methods, using different insecticides. The systematic review (Ekpereonne *et al*, 2010), which included fifteen studies, 13 studies showed reductions in immature entomological indices that were not sustained for long periods. The remainder showed space spray interventions to be ineffective at reducing adult and/or imma-

ture entomological indices. Only one study measured human disease indicators, but its outcomes could not be directly attributed to space sprays alone. Although peridomestic space spraying is commonly applied by national dengue control programs, there are very few studies evaluating the effectiveness of this intervention and there is no clear evidence for recommending peridomestic space spraying as a single, effective control intervention.

Twenty-nine studies were included in the systematic review on temephos (George *et al*, 2014, submitted), including 12 single intervention studies and 17 studies using temephos with other interventions (multiple interventions). All 12 single intervention studies showed consistently that using Temephos lead to a reduction of entomological indices. All 17 multiple intervention studies showed that Temephos application together with other chemical vector control methods was either not sustainable or failed to reduce the immature stages. The analysis of this study is on going, especially regarding the implementation implications of the use of multiple interventions.

Fourteen studies were included in the systematic review of Bti (Boyce *et al*, 2013); 12 reported a reduction in entomological indices with an average duration of control of between 2-to-4 weeks. One of the studies linked the reduction of entomological indices with epidemiological data, with one dengue case in the treated area compared to 15 dengue cases in the untreated area during the observed study period. With this, Bti is effective in reducing the number of immature *Aedes* in treated containers, and there is very limited evidence that dengue morbidity can be reduced through the use

of Bti alone. There is currently insufficient evidence to recommend the use of Bti as a single agent for the long-term control of dengue vectors and prevention of dengue fever.

### **Systematic reviews for a service orientated purpose**

For the interventions focusing on a particular service delivery in the context of vector control, there is existing work on outbreak response (Pilger *et al*, 2010). Twenty-four studies showed different strategies in the organization of outbreak response emphasizing an intersectoral approach. Studies that managed the outbreak response by creating multidisciplinary response teams, including vector control teams working on a door-to-door basis, and studies that monitored and evaluated their activities, showed successful outbreak control. Combining interventions that use 1) vector control (elimination of larval habitats with community involvement; appropriate use of insecticides in and around houses), and 2) capacity training of medical personnel in combination with laboratory support were crucial for the successful control of outbreaks. Spatial spraying of insecticides alone proved ineffective in achieving outbreak control and its usefulness in combination with other interventions remains doubtful. The available evidence recommends that in order to achieve rapid control, the outbreak response must employ a multidisciplinary approach combined with monitoring and evaluation.

### **Systematic review of the organizational context of vector control**

A systematic review on vector control service delivery (Horstick *et al*, 2010) highlighted many shortcomings about how

vector control is being delivered globally. Three of nine studies on vector control services indicated that there was little change of control operations over time. The studies showed that there were however attempts towards strategic changes in decentralization and intersectoral collaboration. Staffing levels, appropriate capacity building, management and organization, sustained funding, and mechanisms for achieving community engagement were insufficient and weak, and remained key problem areas.

This systematic literature review used a mixed methods approach; also interviewing stakeholders, and case studies in four countries confirmed most of the information from the systematic review. With the stated limitations, doubts of key public health stakeholders about the effectiveness of services in reducing vector densities and significantly reducing virus transmission were widespread. But the stakeholders believed that the interventions could be effective, if the necessary resources were available.

The analysis of existing vector control services underlined the need for: 1) the development of operational standards for vector control services, including minimum financial and personnel requirements in accordance with the geographical area(s) to be covered, their demography and the vector control methods to be implemented; 2) evidence based selection and delivery of different interventions or combinations of interventions, adapted to different settings; 3) development and application of monitoring and evaluation tools for vector control service delivery; and 4) needs driven capacity building, especially in public health entomology and communication.

### Crosscutting issues in all systematic literature reviews

As a crosscutting issue in this series of systematic reviews, it emerged that clear best practice guidelines for methodology of entomological studies need to be developed. Without standardization of the methodology future studies will continue producing low quality studies and non-comparable data.

Further to this, there is a need to include measuring dengue transmission data; most analysed studies do not provide such measurements.

### CONCLUSIONS AND RECOMMENDATIONS

Based on the extensive work of systematic literature reviews, a list of recommendations can be drawn. These need to be seen firstly in the light of the limitations—limitations for each of the systematic literature reviews include publication bias, especially as studies not presenting positive results are often not reported. The substantial experience of dengue vector control globally from on-going national vector control programs is often not documented. However, these limitations have been addressed in each systematic literature review including a search of grey literature and including a thorough reference check of included literature. The authors have also identified further studies recommended by prominent dengue entomologists.

Until recently, not all dengue vector control methods, as they are applied in practice, have been analysed with systematic literature reviews. 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. Furthermore, this review is not systematic in its approach, identifying all available systematic literature reviews for dengue vector control. This limitation will be addressed with a future study, once all available dengue vector control methods have been looked at with systematic literature reviews. However, looking at the seven systematic literature reviews on dengue vector control, analysed in this study, the following practical recommendations emerge:

- Although vector control can be effective, implementation remains an issue. No clear evidence exists for delivery structures of vector control services (Horstick *et al*, 2010).
- Single interventions are probably not useful, efficacy varies between the different interventions, but sustained community-effectiveness can almost never be shown (Ekpereonne *et al*, 2010; Boyce *et al*, 2013; Han *et al*, submitted; George *et al*, submitted; Lazaro *et al*, submitted).
- Combinations of interventions have mixed results related to the complexity of implementing multiple interventions (George *et al*, submitted).
  - In order to be efficacious and community-effective careful implementation of vector control measures may be more important than the actual choice of the combinations of vector control methods.
  - In reality, interventions are often applied in outbreaks (compared to routine vector control) although the effectiveness is also 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 measures, including health promotional campaigns.

- The development for standards for vector control studies is urgently needed
- Studies should attempt to include measuring dengue transmission for an ultimate proof of efficacy and community-effectiveness of dengue vector control.

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