The effectiveness of mosquito control strategies for chikungunya: a systematic review protocol

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Review question/objective

The objective of the proposed systematic review is to critically analyze currently available research studies and present the best available evidence related to the effectiveness of different mosquito control strategies used in the prevention and control of chikungunya (CHIK).

The primary review question is:

What is the effectiveness of mosquito control strategies used in the prevention and control of CHIK?

Background

Mosquitoes (Diptera: Culicidae) are the most important vectors responsible for deteriorating human health and debilitating diseases of epidemic proportions, including malaria and dengue, affecting countries worldwide. Consequently, governments of affected countries have invested large efforts and millions of dollars towards mosquito control, the mainstay of prevention and control of mosquito-borne diseases. Recent viral epidemics in the past decade had been attributed to the CHIKV, an Alphavirus transmitted by mosquitoes Aedes (Stegomyia) aegypti (Linnaeus) and Aedes (Stegomyia) albopictus (Skuse) mosquitoes. Chikungunya (CHIK): a term used to address the infection, disease or the virus, CHIK is a Makonde word from Tanzania and Mozambique that means “that which is bent up” and refers to the stooped posture of patients suffering from CHIKV-induced joint pain. To indicate clearly reference to the CHIK virus, this systematic review protocol will use the abbreviation, CHIKV.

During the acute stage of infection, a patient infected with CHIKV typically presents with a biphasic or saddle-back fever of at least 38.0°C, lasting several days to weeks. This is often accompanied by arthritic-like symptoms of persistent pain, swelling and redness in major body joints and the occasional appearance of maculopapular rash. Other symptoms that may be present are fatigue, headache, chills and myalgia. The chronic stage of CHIKV infection is characterized commonly by clinical manifestations lasting more than three months or disabling arthralgia of at least four weeks from symptom onset. Serious complications for both chronic and acute stages of CHIKV infection have
been recorded, with deformed and painful joints\textsuperscript{12}, neurological disorders\textsuperscript{13-16} (e.g. encephalitis and optic neuritis), cardiac disorders\textsuperscript{13,17} (e.g. myocarditis and myocardial infarction), ophthalmological disorders\textsuperscript{15,18} (e.g. macular choroiditis and uveitis), hepatic disorders\textsuperscript{13} (e.g. hepatomegaly) or haemorrhage.\textsuperscript{14,19} These clinical manifestations have been found to decrease quality of life, negatively impacting on work and family roles, performance and satisfaction.\textsuperscript{10,20,21} The 2005 - 2006 outbreak in La Reunion Island showed 266 000 (38.2\%) of the population\textsuperscript{22,23} infected with CHIKV and about one fatality in every 1000 cases.\textsuperscript{24}  

There are two types of mosquitoes that are known to transmit CHIKV. Historically, \emph{Aedes aegypti} was the main vector, however recent outbreaks have mainly been caused by \emph{Aedes albopictus}. A mutation in the envelope protein gene of a CHIK virus strain named EI-A226V gives the advantageous adaptation and specificity by increasing the viral infection and replication in \emph{Aedes albopictus}.\textsuperscript{25} Once thought to have a low capacity for mosquito-to-human transmission because of its zoophilic nature, the Asian tiger mosquito, \emph{Aedes albopictus}, has become a highly intrusive species that originated from the tropical forests of Southeast Asia and has now spread to 28 countries worldwide.\textsuperscript{26,27} This global transmission has been assisted by temperate climate conditions, good environment for both breeding and resting, cross-border transport of goods, human travel and ineffective disease and entomological control strategies.\textsuperscript{27,28} Both mosquito species have a lifespan of about three weeks.\textsuperscript{3,29,30} The gravid female \emph{Aedes aegypti} has a preference for indoors with diurnal biting activity,\textsuperscript{31} a flight range of up to 100m and thrives in a more varied environment, compared to \emph{Aedes albopictus}.\textsuperscript{32} On the other hand, the \emph{Aedes albopictus} has peak biting times of early morning and late afternoon with a preference for outdoors and an active flight range of up to 525m.\textsuperscript{16,28,33,34} A study highlighted the lack of specific strategies to control \emph{Aedes albopictus} over its long flight range.\textsuperscript{35} The differences in biting habits and flight ranges between the two mosquito species may have implications in achieving effective mosquito control.  

The objective of mosquito control for CHIK prevention is to eradicate the mosquitoes that can transmit CHIKV. When entomological vectors of CHIKV are reduced, opportunities for human-mosquito-human contact are reduced, lowering the rates of viral acquisition that cause CHIKV infection and subsequent disease in humans.\textsuperscript{36} Entomological indices including percentage mortality, Breteau Index(BI) and Container Index (CI) have been used to assess the effectiveness of mosquito control interventions in mosquito-borne diseases.\textsuperscript{37,38} Mosquito control measures that have been used to reduce CHIKV transmission may be broadly categorized into three types: chemical control, biological control and habitat control.\textsuperscript{29,30,39} Chemical control consists of the gamut of commercial synthetic chemical insecticides, including pyrethrroids and organophosphates. Although they have also been used pervasively and successfully in the reduction of dengue and malaria mosquito vectors\textsuperscript{40}, the use of chemical larvicides (e.g. Temephos) and adulticides (e.g. Deltamethrin) in CHIK has recorded several challenges such as \emph{Aedes aegypti} and \emph{Aedes albopictus} resistance, unintended adverse effects (e.g. contamination of vegetation) and insecticide registration requirements.\textsuperscript{40,41} Hence, considerations should be made when employing these entomological control measures. Biological control consists of measures that are derived biologically from plants (e.g. essential oils), animals (e.g. predatory fishes) or microorganisms (e.g. \emph{Bacillus thuringiensis israelensis} (Bti)).\textsuperscript{29,42,43} They are increasingly viewed as viable alternatives to chemical insecticides, due to their perceived effectiveness, biodegradability and environmental friendliness.\textsuperscript{44} However, issues including ecological impact need to be taken into account in the use of biological control. Habitat control consists of landfill cleaning and source
reduction, through the removal of water from receptacles, household containers and even large leaves.29,30

The spread of CHIK has affected 55 countries,45 indicating problems in seeking to control the infection at the population level and implies challenges faced by public health authorities. Because there is no licensed vaccine or specific cure, entomological control is the mainstay of CHIK prevention and epidemic control.1,46 Experts in the field have called for effective, feasible and sustainable entomological control measures for CHIK.35,46 However, the effectiveness of such measures in CHIK has not been clearly elucidated and it is uncertain whether these vector control strategies are really effective in decreasing the mosquito population, leading to decreased transmission of CHIKV. No systematic reviews have been conducted on this topic. Hence, a systematic review is required to examine the evidence regarding the effectiveness of mosquito control strategies in CHIK.

Keywords
Disease vector; Vector; Mosquito control; Entomology; Surveillance; Public health surveillance; Disease outbreak; Aedes Aegypti; Aedes Albopictus; Chikungunya; Alphavirus

Inclusion criteria

Types of participants
Countries that have reported local or imported cases of CHIK and countries that are at risk of CHIK due to the presence of mosquito vectors of CHIK (including Aedes aegypti and Aedes albopictus) will be included.

Types of intervention(s)/phenomena of interest
Interventions of interest will be mosquito control strategies broadly classified as chemical control, biological control and/or habitat control. These strategies are specifically used to target mosquitoes that transmit CHIK, including Aedes aegypti and Aedes albopictus. Studies that were not specific to CHIK (e.g. entomological control measures across generic mosquito-borne diseases) were excluded.

Types of outcomes
The primary outcome of interest is the number of CHIK cases or the rate of CHIK transmission following implementation of mosquito control strategies

The secondary outcomes of interest are changes in mosquito (egg, larvae, pupae and adult stages) populations, which may be described and monitored using entomological indices including:

- Percentage mortality or survival rates of mosquitoes.
- Lethal concentrations (LC50 or LC90): toxicity measure of an insecticide that will kill 50% or 90% of the mosquito sample population in a specific period of time.47
- Knockdown time (Kdt50 or Kdt95): time required to kill 50% or 95% of the mosquito sample population.48
- BI: number of positive containers for every 100 inspected houses.49
- CI: percentage of water-containing receptacles filled with larvae or pupae.49
- House index (HI): percentage of houses filled with larvae and/or pupae.\textsuperscript{49}
- Pupa index (PI): number of pupae for every 100 inspected houses.\textsuperscript{49}
- Number of adult mosquitoes measured using traps, such as ovitraps and BG-Sentinel traps.

**Types of studies**

Randomized Controlled Trials (RCTs) will be sought and in the absence of RCTs, other experimental and observational study designs will be included.

**Search strategy**

Before developing this systematic review protocol, the Joanna Briggs Institute (JBI) Database of Systematic Reviews and Implementation Reports, Cochrane Database of Systematic Reviews, MEDLINE and the Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effects (CRD DARE) were searched and no available systematic reviews on this topic were found. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines will be followed in relation to reporting.

The search strategy aims to find both published and unpublished studies in English without date limits. A search strategy will be developed to guide the systematic review. Medical subject headings (MeSH) terms from PubMed will be used at the start to determine the words used to search in PubMed. An initial limited search from PubMed and Web of Science will be undertaken followed by an analysis of the text words contained in the title and abstract and of the index terms used to describe the article. A second search using all the identified keywords and the index terms specific to each database will then be undertaken across all accessible databases and websites. As some databases are different in their search features, modified block building will be used to accommodate their differences. Thirdly, the reference list of all included reports and articles will be searched for additional studies.

The literature search will be performed using the following databases: PubMed, Web of Science, Scopus, ScienceDirect, Cumulative Index to Nursing & Allied Health (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL) and ProQuest. In addition, the following sources of grey literature will be searched: World Health Organization Library (WHOLIS), Centers for Disease Control and Prevention (CDC), European Centre for Disease Prevention and Control (ECDC), Integrated Chikungunya Research (ICRES), National Institutes of Health (NIH), LILACS, World Bank, Asia Development Bank and Google.

The keywords to be used are:

- Disease vector
- Vector
- Mosquito control
- Entomology
- Surveillance
- Public health surveillance
- Disease outbreak
Aedes Aegypti
Aedes Albopictus
Chikungunya
Alphavirus

Assessment of methodological quality
Quantitative papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I-III). Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer.

Data extraction
Quantitative and narrative evidence will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix IV). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question.

Data synthesis
Quantitative articles will be pooled in statistical meta-analysis using JBI-MAStARI or Review Manager 5, where appropriate. All results will be subjected to double data entry to reduce the risk of error synthesis. Relative risks of a reduction of mosquito vectors resulting from entomological control strategies (including odd ratios, relative risk or risk ratios, incidence ratios for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Random effects models will be used to confirm the presence of heterogeneity and sources of heterogeneity will then be assessed using sensitivity analysis and the standard Chi-square. Where statistical pooling is not possible, the findings will be presented in narrative form.

Conflicts of interest
No conflicts of interest.

Acknowledgements
I thank Assoc Prof Craig Lockwood for his guidance in producing this protocol.
References


doi: 10.11124/jbrisr-2014-1659


45. Centers for Disease Control and Prevention. Geographic distribution of Chikungunya virus: Countries with reported current or previous local transmission of chikungunya virus (as of February 10, 2014) Atlanta, GA: National Center for Emerging and Zoonotic Infectious Diseases Division of Vector-Borne Diseases; 2014.


Appendix I: JBI critical appraisal checklist for randomized controlled/pseudo-randomized trial

**JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Not Applicable</th>
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<tbody>
<tr>
<td>1. Was the assignment to treatment groups truly random?</td>
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<td>2. Were participants blinded to treatment allocation?</td>
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<td>3. Was allocation to treatment groups concealed from the allocator?</td>
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<td>4. Were the outcomes of people who withdrew described and included in the analysis?</td>
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<td>5. Were those assessing outcomes blind to the treatment allocation?</td>
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<td>6. Were the control and treatment groups comparable at entry?</td>
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<td>7. Were groups treated identically other than for the named interventions</td>
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<td>8. Were outcomes measured in the same way for all groups?</td>
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<td>9. Were outcomes measured in a reliable way?</td>
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<td>10. Was appropriate statistical analysis used?</td>
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Overall appraisal:  Include ☐  Exclude ☐  Seek further info. ☐

Comments (Including reason for exclusion)


Appendix II: JBI critical appraisal checklist for comparable cohort/case-control

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer ___________________________ Date ________________________________
Author ___________________________ Year _______ Record Number ________

1. Is sample representative of patients in the population as a whole? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable
2. Are the patients at a similar point in the course of their condition/illness? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable
3. Has bias been minimised in relation to selection of cases and of controls? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable
4. Are confounding factors identified and strategies to deal with them stated? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable
5. Are outcomes assessed using objective criteria? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable
6. Was follow up carried out over a sufficient time period? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable
7. Were the outcomes of people who withdrew described and included in the analysis? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable
8. Were outcomes measured in a reliable way? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable
9. Was appropriate statistical analysis used? [ ] Yes [ ] No [ ] Unclear [ ] Not Applicable

Overall appraisal: [ ] Include [ ] Exclude [ ] Seek further info.

Comments (Including reason for exclusion)

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Appendix III: JBI critical appraisal checklist for descriptive/case series

**JBI Critical Appraisal Checklist for Descriptive / Case Series**

<table>
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<tr>
<th>Reviewer</th>
<th>Date</th>
<th>Author</th>
<th>Year</th>
<th>Record Number</th>
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1. Was study based on a random or pseudo-random sample?  
2. Were the criteria for inclusion in the sample clearly defined?  
3. Were confounding factors identified and strategies to deal with them stated?  
4. Were outcomes assessed using objective criteria?  
5. If comparisons are being made, was there sufficient descriptions of the groups?  
6. Was follow up carried out over a sufficient time period?  
7. Were the outcomes of people who withdrew described and included in the analysis?  
8. Were outcomes measured in a reliable way?  
9. Was appropriate statistical analysis used?  

**Overall appraisal:**  
Include ☐  
Exclude ☐  
Seek further info ☐

**Comments (including reason for exclusion)**

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doi: 10.11124/jbisrir-2014-1659
Appendix IV: JBI data extraction form for experimental/observational studies

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer __________________________ Date __________________________

Author __________________________ Year __________________________

Journal __________________________ Record Number __________________________

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐
Retrospective ☐ Observational ☐ Other ☐

Participants

Setting

Population

Sample size

Group A _______________ Group B _______________

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:
Study results

Dichotomous data

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention (1) number / total number</th>
<th>Intervention (2) number / total number</th>
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Continuous data

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<tr>
<th>Outcome</th>
<th>Intervention (1) number / total number</th>
<th>Intervention (2) number / total number</th>
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