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[Rapid Protocol]

# Interventions for preventing dengue: a mapping review

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## ABSTRACT

### Objectives

This is a protocol for a Cochrane Review (rapid). The objectives are as follows:

1. To comprehensively identify the published literature on prevention strategies for dengue.
2. To critically appraise secondary research.
3. To present the findings of objectives 1 and 2 in a single evidence gap map.
4. To identify critical knowledge gaps to inform future primary research and systematic reviews.

## BACKGROUND

Dengue virus (DENV) is a virus of the *Flaviviridae* family, which is most frequently spread through the bite of female *Aedes aegypti* (*Ae. aegypti*) mosquitoes, and to a lesser extent, *Aedes albopictus* and *Aedes polynesiensis.* Almost half of the world's population live in areas with a risk of dengue [1].

There are four serotypes of DENV that cause dengue (DENV-1, DENV-2, DENV-3, and DENV-4). Whilst recovery from one serotype provides lifelong immunity to that specific serotype, cross-immunity to other serotypes is partial and temporary[2]. Symptoms of dengue are flu-like, but one in 20 people who get dengue go on to develop severe dengue [3]. If not identified early, severe dengue can eventually lead to mortality. Additionally, whilst there is a vaccine for dengue, being vaccinated without a previous infection can lead to serious life-threatening symptoms [4].

The risk of infection is present in all areas inhabited by *Aedes* mosquitoes, particularly tropical climates. One study on the prevalence of dengue estimated that 3.9 billion people were at risk of infection in 2012, and 70% of the actual burden of disease was in Asia [5]. Since the 1960s, there has been a 30-fold increase in global dengue incidence [6]. Geographic expansion of DENV infection has resulted in increased frequency and severity of the disease. While 80% of dengue infections are mild and asymptomatic, the number of reported deaths rose from 960 in 2000 to 4032 in 2015, mostly affecting younger age groups [7]. The highest number of dengue cases was recorded in 2023, with over 6.5 million cases and more than 7300 dengue-related deaths reported. These numbers are increasing, driven by climate change and the primary vector of dengue. *Ae. aegypti* is highly sensitive to climate variability. Warmer climate and changing rainfall patterns create more regions with suitable habitats for the mosquito, thereby increasing the transmission potential to new areas. The introduction of dengue to previously immunologically naive areas has been the main driving force for transmission, leading to epidemic spikes in the past couple of years. One example of this is a surge in dengue cases experienced in coastal regions of Peru, an area not considered to have high transmission potential in previous geospatial modelling prediction distribution maps of *Ae. aegypti* [8]. A sudden increase in temperatures in the Pacific Ocean, followed by El Niño, is attributed to making these areas more suitable for the establishment of *Ae. aegypti* populations. *Aedes albopictus,* another important vector of dengue fever, is considered to be more cold-tolerant, and has recently been found as far north as Paris, with autochthonous transmission reported in 2023 [9].

Whilst there are many prevention strategies for dengue, there are no globally-consolidated guidelines that recommend them. This could be due to a scarcity of high-quality systematic reviews on the topic. We propose conducting a mapping review to map the body of evidence for dengue prevention strategies to inform future systematic reviews and to identify gaps in primary research. The findings of the mapping review will be presented as a user-friendly, visual summary of where evidence exists and where it is lacking, in the form of an evidence gap map (EGM). Our EGM will classify evidence by intervention type, study design, and important outcomes.

### Scope of the evidence gap map (EGM)

This EGM will focus on dengue prevention strategies, categorised into vaccines, environmental interventions, community education, interventions targeting aquatic stages of the vector, and interventions targeting adult stages of the vector. We will also categorise evidence by outcomes, study design, geographic location, human age distribution, and vector species. Our interventions and outcomes are informed by stakeholder engagement, described in the methods section, and also by an existing framework on the ecological, biological, and social determinants of dengue epidemiology [10].

### Rationale for developing the EGM

Dengue remains a pressing global public health challenge, particularly in low- and middle-income countries (LMIC), where the disease is endemic and often epidemic. Despite a growing volume of research on prevention strategies, there is a notable lack of consolidated, high-level evidence that captures the full scope of existing knowledge. The current evidence landscape is fragmented, with studies varying widely in design, focus, and quality.

An EGM provides a systematic and visual synthesis of the available evidence, highlighting both areas that are well studied and those where knowledge is limited or outdated. While a few high-quality systematic reviews exist on dengue prevention [11], many are now dated—preceding more recent large-scale epidemics—or are limited in scope [12]. A gap map, including only secondary research evidence, has been produced on strategies for the prevention of arboviruses [13]. To date, there are no known mapping reviews or EGMs that comprehensively cover the full range of dengue prevention strategies and study types, representing a critical meta-gap in the evidence ecosystem.

Given the substantial body of primary research available, a structured map that includes both primary and secondary evidence is urgently needed. This EGM will serve as a decision-support tool for funders, policymakers, and researchers by identifying where robust evidence already exists and where future investments in research and systematic reviews are most needed.

## OBJECTIVES

1. To comprehensively identify the published literature on prevention strategies for dengue.
2. To critically appraise secondary research.
3. To present the findings of objectives 1 and 2 in a single evidence gap map.
4. To identify critical knowledge gaps to inform future primary research and systematic reviews.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include any randomised controlled trials (RCT), quasi-randomised trials, and non-randomised studies of interventions (NRSIs). NRSIs must have a comparator, and will include study designs such as cohort studies, interrupted time series designs, controlled before-after studies, and case-control studies. We will also include systematic reviews (with predetermined

objectives, eligibility criteria, at least two databases searched, data extraction, and quality assessment of included studies) assessing interventions to prevent dengue transmission.

We will not include case studies or animal studies conducted in a laboratory or semi-field environment. We will not have any restrictions on date or language.

### Types of participants

General population and high-risk groups in dengue-endemic areas.

### Types of interventions

We will include studies that compare prevention strategies against placebo, no intervention, or usual care. In addition, head-to-head comparisons of active interventions will be eligible for inclusion, provided that any co-interventions are equally distributed across study arms to avoid confounding effects. Usual care refers to the standard public health or community practices routinely implemented in the study setting for dengue prevention, which may include low-intensity vector control measures, public education efforts, or other locally accepted prevention practices. This will be contextually defined, based on study descriptions.

The intervention categories were developed through a structured stakeholder engagement process and an existing theoretical framework [10]. These categories reflect the range of prevention strategies currently implemented or under investigation in dengue-endemic settings. Interventions will be grouped as follows:

#### *Vaccines*

1. Any licenced vaccines that are commercially available (e.g. CYD-TDV, TAK-003), experimental, or under development

#### *Environmental*

1. Identification, assessment, enclosure, or removal of potential mosquito aquatic habitats
2. Basic sanitation: moving open-air sewage and water to covered or underground pipes, with the aim of reducing mosquito aquatic habitats
3. Waste management and urban cleaning policies: overall waste management, waste collection

#### *Community education on dengue prevention*

1. Community engagement on dengue prevention, e.g. active education methods in schools, teaching children about the location of potential mosquito aquatic habitats

#### *Interventions targeting aquatic stages of the vector*

1. Mass trapping of aquatic stages
2. Adding larvivorous animals, such as fish or cyclopoid copepods, to residential water tanks
3. Larviciding with biological agents, such as *Bacillus thuringiensis israelensis* (Bti) or *Bacillus sphaericus* (Bs)
4. Chemical larviciding, such as the use of conventional insecticides or insect growth regulators

#### *Interventions targeting adult vectors*

1. Insecticide-treated bed nets
2. Repellents, including topical and spatial repellents
3. Residual spraying: regular application of insecticides onto a surface, such as the indoor walls of houses
4. Endectocides: antiparasitic drugs that cause mosquito mortality when the vector bites a human with the drug in their bloodstream
5. Space spraying: dispersal of a liquid fog of insecticide into a large outdoor space
6. Mass trapping of adult vectors
7. House screening: covering entry points for mosquitoes into buildings, such as eave gaps
8. *Wolbachia:* bacteria that infect mosquitoes and prevent them from acquiring and transmitting dengue
9. Genetically modified mosquitoes: mass release of laboratory-reared, genetically modified mosquitoes that have phenotypes that reduce dengue transmission, such as sterility or the reduction of vector competence

### Outcome measures

The following list of outcome measures was developed following stakeholder engagement.

#### *Epidemiological outcomes*

1. Virologically confirmed dengue case incidence: confirmed by either reverse transcription polymerase chain reaction (RT-PCR) or enzyme-linked immunosorbent assay (ELISA)
2. Dengue cases: from self-report or clinical examination
3. Severe cases of dengue: defined by study
4. Prevalence of dengue virus (DENV) infection
5. All-cause mortality

#### *Entomological outcomes*

1. Breteau index: containers infested with larvae, pupae, or both; for example, the number of positive containers per 100 houses [14]
2. House index: houses positive for larvae, pupae, or both
3. Container index: containers specifically designed for water storage infested with larvae, pupae, or both

#### *Behavioural outcomes (at either the individual, household, or community level)*

1. Behaviour changes: e.g. reported changes in behaviour to reduce the risk of dengue, e.g. covering up water containers
2. Knowledge change: e.g. an increased awareness of dengue, being able to identify vectors and their habitats
3. Acceptability of intervention

#### *Implementation outcomes*

1. Coverage: e.g. proportion of the target population reached by the intervention
2. Compliance/adherence: proportion of the participants who used or maintained the intervention as intended
3. Implementation costs

#### *Adverse effects*

1. Adverse clinical effects related to the intervention, e.g. respiratory or dermal irritation due to insecticide use
2. Unintended ecological impact: e.g. death of non-target insects

3. Vector resistance: increased resistance to insecticides as a consequence of repeated use
4. Social stigmatisation or community rejection

### Search methods for identification of studies

We will search these databases:

1. MEDLINE Ovid (from 1946);
2. Embase Ovid (from 1974);
3. CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; from 1982);
4. Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR), in the Cochrane Library (current issue);
5. LILACS BIREME (Latin American and Caribbean Health Science Information database; from 1982).

We will not apply any date or language restrictions to the searches. The MEDLINE search strategy can be seen here: Supplementary material 1. We will translate the MEDLINE search across each of the databases.

We will search the reference lists of included studies, as well as aim to identify any retraction notices for included studies.

## Data collection and analysis

### Selection of studies

To support the identification of relevant studies, we will use, where possible, machine-learning classifiers to help prioritise screening efforts, and to suggest relevant classifications of studies according to intervention type, study design, date the study was conducted, geographic location, age distribution, and vector species. Using EPPI Reviewer, we will build machine-learning classifiers, using a gold standard dataset generated from human classification, on a set of 2000 representative records [15]. We will implement the machine-learning components of study selection and a human-assisted approach only, to ensure that relevant studies are not missed. We will use the machine as a replacement for one human assessor for records that achieve a high likelihood of eligibility. Initially, records that receive a low likelihood score will be independently reviewed by two assessors. Depending on the accuracy of the classifier, we may evolve the process. Any disagreements between human or human and AI assessors will be resolved through a consensus-building approach, with a third review author consulted if consensus cannot be reached. We will document the study selection process in a PRISMA flow diagram [16].

### Data extraction and management

Two review authors will independently extract data from the included studies using a structured coding framework developed during the pilot stage. Any disagreements about data extraction will be resolved through discussion. Aside from describing the study design and PICOs, we will also extract the following information on study characteristics:

1. The date the study was conducted. If this is not available, we will take the publication date.
2. Country/countries where the study was conducted
3. Age distribution
4. Vector species

We will use these characteristics, alongside the study design, as filters on the evidence gap map. Any systematic review will have an additional filter for the quality appraisal described below.

Coding will be conducted in EPPI Reviewer, a software platform specifically designed for systematic reviews and evidence gap maps (EGMs). EPPI Reviewer incorporates machine-learning tools that may be leveraged to assist with screening and coding processes, as appropriate.

Following coding, we will export data from EPPI Reviewer to EPPI Mapper, a custom-developed application commissioned by the Campbell Collaboration [15]. We will use EPPI Mapper to generate an interactive, online map that visually displays the distribution of evidence and identifies key gaps by intervention and outcome. We will also display additional coded variables, listed above.

The online interactive EGM will be hosted as a supplementary file or linked web asset in HTML format.

### Unit of interest

The unit of analysis is a single study (primary or secondary). If there are multiple reports associated with one study, we will use the most recent and comprehensive report with more complete and detailed information represented on the map.

### Quality appraisal of evidence syntheses

Two review authors will independently appraise the quality of systematic reviews, using A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2) [17]. We will resolve any disagreement by discussion or by involving a third review author. We will use these critical domains.

1. Protocol registered before commencement of the review
2. Adequacy of literature search
3. Justification for excluding individual studies
4. Risk of bias from individual studies being included in the review
5. Appropriateness of meta-analytical methods
6. Consideration of risk of bias when interpreting the results of the review
7. Assessment of presence and likely impact of publication bias

As we are not adapting the original AMSTAR 2 tool, a full list of domains can be found in Shea 2017 [[17].

We will give an overall rating of the studies with the following algorithm:

1. High: no critical weakness and only one or fewer non-critical weaknesses
2. Moderate: more than one non-critical weakness
3. Low: one critical flaw with or without non-critical weaknesses
4. Critically low: more than one critical flaw with or without non-critical weaknesses

We will present these in the evidence gap map as colour filters, with high being green, moderate being yellow, and low being red.

### Equity-related assessment

Dengue is much more prevalent in low-resource settings. In addition, severe clinical cases and mortality are higher in those who are socially disadvantaged. As this review will not explore the efficacy of prevention strategies from studies we will include, we cannot conduct a formal equity-related assessment. We will extract information on where studies were conducted at a country level. We will also extract information on whether the included systematic reviews conducted equity assessments.

### Stakeholder involvement

We engaged Instituto Veredas, a Brazilian NGO that aims to build bridges between public management, academia, and civil society, to conduct stakeholder engagement.

We collaborated in the design of an online survey, which received 35 responses from health or environmental professionals (n = 17), researchers (n = 14), policy-makers or citizens (n = 4) in Brazil. Lists of pre-selected interventions and outcomes were presented for prioritisation, with an option to suggest additional items.

Instituto Veredas also engaged stakeholders from the Amazon region to conduct six interviews with policymakers (n = 2), health and environment professionals (n = 2), and civil society representatives or community leaders (n = 2). Interviews focused on the following questions:

1. Which are the groups most affected by dengue in your context?
2. What are the key priority problems you face with regard to dengue prevention?
3. What are the most common interventions to prevent dengue in your context?
4. For policy-makers: which indicators do you use to monitor dengue cases in your context?

Authors and staff from Instituto Veredas discussed the results and used them to create the PICO framework for the mapping review and gap map.

Once the first draft of the gap map is available, we will work with Instituto Veredas to conduct a stakeholder dialogue to receive feedback on the usability, relevance of information to a local context, and prioritisation of topics for evidence synthesis.

### Methods for future updates – living review considerations

An automated search will be conducted every six months. Screening and coding of included studies will be assisted by machine learning. Review authors will be responsible for the inclusion of these results in the EGM.

## SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016299.

**Supplementary material 1** Search strategies

## ADDITIONAL INFORMATION

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The following people conducted the editorial process for this article:

• Sign-off Editor (final editorial decision): Lawrence Mbuagbaw, McMaster University;

• Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Colleen Ovelman, Cochrane Central Editorial Service;

• Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service;

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### Contributions of authors

LC, BA, SW, RP and LL: review co-leads (protocol development, methodology, write-up).

ACCFM, LPL, JFSC and MDGM: writing, reviewing and editing.

ANS and SW: formulated the search strategy; methodology.

RP and LL: review co-leads (supervision and project administration).

### Declarations of interest

None of the authors have any relevant interests to declare.

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## Registration and protocol

N/A

## Data, code and other materials

Sharing not applicable to this article as it is a protocol, so no datasets were generated or analysed.

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