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# Modelling the transmission of dengue, zika and chikungunya: a scoping review protocol

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## ABSTRACT

**Introduction** *Aedes* mosquitoes are the primary vectors for the spread of viruses like dengue (DENV), zika (ZIKV) and chikungunya (CHIKV), all of which affect humans. Those diseases contribute to global public health issues because of their great dispersion in rural and urban areas. Mathematical and statistical models have become helpful in understanding these diseases' epidemiological dynamics. However, modelling the complexity of a real phenomenon, such as a viral disease, should consider several factors. This scoping review aims to document, identify and classify the most important factors as well as the modelling strategies for the spread of DENV, ZIKV and CHIKV.

**Methods and analysis** We will conduct searches in electronic bibliographic databases such as PubMed, MathSciNet and the Web of Science for full-text peer-reviewed articles written in English, French and Spanish. These articles should use mathematical and statistical modelling frameworks to study dengue, zika and chikungunya, and their cocirculation/coinfection with other diseases, with a publication date between 1 January 2011 and 31 July 2023. Eligible studies should employ deterministic, stochastic or statistical modelling approaches, consider control measures and incorporate parameters' estimation or considering calibration/validation approaches. We will exclude articles focusing on clinical/laboratory experiments or theoretical articles that do not include any case study. Two reviewers specialised in zoonotic diseases and mathematical/statistical modelling will independently screen and retain relevant studies. Data extraction will be performed using a structured form, and the findings of the study will be summarised through classification and descriptive analysis. Three scoping reviews will be published, each focusing on one disease and its cocirculation/co-infection with other diseases.

**Ethics and dissemination** This protocol is exempt from ethics approval because it is carried out on published manuscripts and without the participation of humans and/or animals. The results will be disseminated through peer-reviewed publications and presentations in conferences.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ In this review, in addition to considering the modelling of dengue, zika and chikungunya, we consider the cocirculation/coinfection with other diseases or among them.
⇒ We will identify mathematical and statistical modelling approaches and the relevant estimates or the data used to underline the dynamics of the diseases.
⇒ We will identify freely available data and code used for the numerical experiments performed in the articles.
⇒ This work can be limited by language bias because we consider only articles written in English, Spanish or French.
⇒ Because this work considers only articles from 1 January 2011 to 31 July 2023, some important results published outside of this period might be excluded.

## INTRODUCTION

Dengue, zika and chikungunya are arboviral diseases transmitted primarily by the mosquito *Aedes aegypti*, which thrives in tropical and subtropical regions. Despite sharing a common vector, these diseases exhibit distinct clinical and epidemiological characteristics.[1] These maladies are cause of significant global concern, given their substantial impact on public health.[1] The transmission dynamics and the dissemination of these diseases are influenced by a multitude of factors, including climatic, environmental, demographical and socioeconomic conditions, vector attributes and human behaviour.[2] In what follows, we introduce the key characteristics associated with dengue, zika and chikungunya. We start with a brief epidemiological description, followed by an exploration of their origins, key case data and associated comorbidities, culminating in an examination of recent advancements in vaccine development aimed at counteracting their spread.

### Dengue

Dengue fever is a disease caused by the dengue virus (DENV), of the genus *Flavivirus*, family Flaviviridae. This disease spreads by the bite of female mosquitoes of the genus

*Aedes*, and is considered as the world's fastest-spreading mosquito-borne viral disease.[3] Dengue is caused by four different serotypes of (DENV): DENV-1, DENV-2, DENV-3 and DENV-4. An individual can be coinfected by one or more than one of the four virus serotypes.[3] While infection to each serotype provides lifelong immunity, consecutive infections with other serotypes increase the risk of severe dengue.[4] Infection with DENV can lead to a broad spectrum of infections, from subclinical (asymptomatic) infection to symptomatic infection, as well as from classic dengue to severe infection with dengue haemorrhagic fever or dengue shock syndrome, which can cause death.[5] According to its incidence and mortality rate, dengue is classified as the second most serious vector-borne disease (VBD) worldwide, after malaria.[6]

Dengue epidemics were reported for the first time in Asia, Africa and North America between 1779 and 1780.[7] However, reports of illnesses with symptoms related to dengue fever occurred even earlier in 1635 in Martinique and Guadeloupe.[8] In the 1940s, the first DENVs were isolated.[8] Nowadays, dengue is listed as one of the most critical emerging/re-emerging VBDs.[8] This disease is endemic in over 100 countries in tropical and subtropical areas, including Southeast Asia, Central and South America, Africa, the Western Pacific and Eastern Mediterranean regions.[3] Consequently, 40% of the global population is at risk, with 50–100 million infections annually.[9] Of the infected population, between 10% and 20% develop severe dengue, with an average of 9000 deaths annually.[10] To date, there is no treatment for dengue. Uncomplicated dengue cases usually require only supportive care, but severe dengue cases can require hospitalisation. While a vaccine for dengue caused by a single serotype of DENV has been available since 1997,[11 12] a vaccine that can provide long-term protection against all DENV serotypes is desirable to alleviate the complications caused by this disease. Currently, two tetravalent dengue vaccines have completed phase III clinical trials: Dengvaxia (developed by Sanofi and is already being administered in more than 20 countries) and DENVax (developed by Takeda Pharmaceutical Company).[12–14] Unfortunately, recent studies have shown that vaccine efficacy continues to decline over time,[13 15] and therefore vaccination combined with prophylactic treatment seems to be the best alternative to prevent dengue.

## Zika

Zika is caused by the zika virus (ZIKV) of the genus *Flavivirus*, family Flaviviridae, which is usually circulated by the bite of an infected mosquito. The vectors that spread the ZIKV are mosquitoes from the *Aedes* genus. Additionally, ZIKV is also transmitted through sexual contact and during the birth process.[16] Usually, ZIKV causes a mild infection; however, ZIKV is also associated with other pathologies, including the Guillain-Barré syndrome,[16] and neurological disorders like meningoencephalitis, acute myelitis and microcephaly.[17]

In the early 1950s, ZIKV was identified in Uganda for the first time in monkeys, being later identified in humans in 1952.[18] The first known zika epidemic occurred in the Western Pacific in the islands of Yap (which belong to the Federated States of Micronesia). Since then, ZIKV circulated for a long time without causing large-reported outbreaks or severe diseases.[19] Nevertheless, the WHO declared a zika pandemic on 1 February 2016, and it has reported the presence of ZIKV in more than 87 countries.[20] By 2022, ZIKV is still circulating in many areas of the world, such as the Caribbean, Latin America, Central Africa, India, Indonesia, Malaysia, Cambodia and Papua New Guinea, among others.[21]

As in the case of dengue, treatment is unavailable for zika or its associated disorders. Zika vaccine research has been active for the past few years, and previous study results suggest that a Zika vaccine can be developed.[22] However, the US Food and Drug Administration has not approved any zika vaccine candidate since March 2023.[22]

## Chikungunya

Chikungunya fever is caused by the chikungunya virus (CHIKV), a pathogen of the genus *Alphavirus* and the family Togaviridae. Like dengue and zika, chikungunya is also primarily transmitted by *Aedes* mosquitoes. Throughout history, three genotypes of CHIKV have been known, all named because of their geographical origin: Asian, West African and East Central South African. CHIKV can be transmitted via mosquito to human (urban transmission) or from animal to mosquito to human (sylvatic transmission).[23]

In the early 1950s, CHIKV was first identified in Tanzania.[24] Although its symptomatology can resemble that of dengue and zika, chikungunya can cause serious outbreaks of fever and severe polyarthralgia, which can affect between 30% and 75% of the infected population.[25] Since its discovery, periodic outbreaks of chikungunya have been reported in Africa, South Asia and Southeast Asia.[25] However, the largest documented chikungunya epidemic occurred in 2005 on the island of Réunion, in the Indian Ocean. In this epidemic, it is estimated that around 266 000 people were affected, from a total population of approximately 770 000.[26] Current treatment of chikungunya is based on controlling the symptoms but not on curing the disease. As of March 2023, there is no approved vaccine for chikungunya; however, VLA155, a chikungunya vaccine developed by Valneva, is currently the most advanced vaccine candidate worldwide.[27]

## Rationale

The rationale of this review is to understand the epidemiological dynamics and the spreading of dengue, zika and chikungunya, and the mathematical and the statistical models mainly used, which can allow to test the effect of different factors influencing the spread dynamics as well as the impact of public health intervention control measures.[13 28–32] These mathematical and statistical models have even been widely used to study the spread

of other diseases such as influenza, smallpox, HIV/AIDS and ebola, and have been used also in the context of healthcare-associated infections caused by antimicrobial resistance.[13 33 34] Some VBDs studies have focused on measuring the impact of mathematical and statistical models, on the epidemiology of these diseases,[13 35] the prediction of the number of cases,[20 36 37] the climatic factors affecting the transmission of VBDs,[38–44] whereas few of these studies have considered the coinfection and/or cocirculation between these and other diseases.[17 45–51] Such modelling endeavours have contributed to the formulation of effective control strategies and interventions.[2] Nonetheless, there is a need for a comprehensive synthesis and classification of existing modelling research to enhance our understanding of the fundamental factors and methodologies employed in modelling the transmission of VBDs. Therefore, this scoping review protocol aims to systematically identify, categorise and analyse the available literature pertaining to the modelling of dengue, zika and chikungunya transmission. By mapping the research landscape and examining the types of models used, influential factors considered, methodologies employed, available data and coding sources, this review aims to provide robust documentation for future research focused on the study of these diseases.

### Objectives and research question

This scoping review protocol aims to classify the mathematical and statistical modelling research (either at the vector-host or within-host levels) that has been conducted on dengue, zika and chikungunya, including model validation/calibration, parameter estimation and control research. More specifically, this scoping review is addressed to answer the following research questions: (1) What type of models/approaches are used to characterise the spread and dynamics of dengue, zika and chikungunya? (2) Which other diseases do dengue, zika and chikungunya cocirculate with? (3) What are the most prominent elements, variables and/or parameters included in these modelling approaches? (4) What are the methodologies used for the analysis of the proposed models? (5) What available data and code have been used for the numerical experiments in these articles? (6) What are the time intervals and geographic regions mostly considered in these studies? (7) What are the limitations/research gaps in the existing modelling approaches?

## METHODS AND ANALYSIS

### Protocol design

This scoping review had been developed according to the recommendations from the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA-P) and its extension for Scoping Reviews (PRISMA-ScR).[52] All the recommended information outlined in the PRISMA-P checklist for this protocol has been provided.

### Eligibility criteria

The following criteria were considered for inclusion: (1) full-text peer-reviewed manuscripts written in English, French or Spanish, containing mathematical and/or statistical modelling frameworks applied to study the transmission of dengue, zika, chikungunya or their cocirculation/coinfection between them or with other diseases that have been published between 1 January 2011 and 31 July 2023; (2) studies that focused on deterministic, stochastic and statistical modelling approaches; (3) models that considered control measures/strategies; and (4) studies considering (or not) data for parameter estimation or model validation/calibration. The following exclusion criteria were applied: (1) research articles focused on virology, immunology, genetics, ecology or entomology or containing clinical/laboratory experiments (with animals, mice, primates or others) or based on data obtained from surveys or studies focused on the sentimental analysis of dengue, zika and chikungunya; (2) studies considering a within-mosquito structure or that focused solely on vector prevalence or seroprevalence; (3) studies analysing the economic/social implications of dengue, zika and chikungunya; and (4) studies analysing risk factors or the geographical distribution of cases, or that focused on reconstructing the disease's size.

### Information sources

A search on *MathSciNet*, *PubMed* and *Web of Science* will be conducted. Given that we are primarily interested in updated literature on this topic, we will examine publications published between 1 January 2011 and 31 July 2023.

### Search strategy

A dataset containing all published studies including mathematical and statistical models for dengue, zika and chikungunya between 1 January 2011 and 31 July 2023 will be built, based on the queries from the selected databases. We will use a query for each disease in each database as follows: for dengue ((model OR modeling OR modelling) AND (mathematical OR statistical OR math OR stat OR predictive OR 'machine learning' OR 'artificial intelligence' OR 'deep learning' OR 'time series' OR epidemiological OR compartmental OR 'neural networks' OR 'cellular automata') AND (Dengue OR DENV)); for zika ((model OR modeling OR modelling) AND (mathematical OR statistical OR math OR stat OR predictive OR 'machine learning' OR 'artificial intelligence' OR 'deep learning' OR 'time series' OR epidemiological OR compartmental OR 'neural networks' OR 'cellular automata') AND (Zika OR ZIKV)); for chikungunya ((model OR modeling OR modelling) AND (mathematical OR statistical OR math OR stat OR predictive OR 'machine learning' OR 'artificial intelligence' OR 'deep learning' OR 'time series' OR epidemiological OR compartmental OR 'neural networks' OR 'cellular automata') AND (Chikungunya OR CHIKV)). The results of the searches can be found in online supplemental table 1.

Table 1 Data extraction form based on the model information

| Information | Description/example |
|---|---|
| Publication details | Title of the paper, hyperlink, journal in which it was published and year of publication (ranging from 2011 to 2023) |
| Geography | Country where the study was focused. If more than one country was analysed, we will use the category *more than one country*. If no country was analysed, we will use the category *none* |
| Serotype | If the manuscript is about dengue, a category will be added with the serotype the study focused on |
| Design | Structure of the model (eg: within-host, vector-host, predictive)<br>Approach of the model (eg: mathematical, statistical)<br>Type of model (eg: deterministic, stochastic, network, regression, more than one model, etc)<br>Structure of the model (eg: SI, SIR, SEIR, SEIRS, etc) |
| Data and code | Data used from open data (yes or no), data availability (yes, no), code availability (yes or no). If no data are used, we will use the category *none*. Studies using more than one dataset for numerical experiments will be considered in a *multi-data* category |
| Principal variables/secondary variables | Studies incorporating multiple variables within their models will not be considered because they concentrate on examining a single response variable alongside multiple predictor variables. In our study, our emphasis will solely be on identifying the main response variable. For example: human compartments (including susceptible, exposed, infected, recovered and others), mosquito compartments (including susceptible, exposed, infected and others) and the number of cases. Additionally, we will primarily focus on the main predictor variables, such as: climatic, environmental, socioeconomic or others |
| Principal parameters/secondary parameters | We will consider only the two first sets of parameters used in each study, but we will focus on transmission rates, transitions between compartments, coinfection probabilities or others |
| Analysis methods | When a study uses more than one method for analysis, this category will be called *multi-method*. Other categories may be methods of model calibration using data, parameters analysis, qualitative analysis and others |
| Model results | We will focus on the main research result such as the impact of predictors on the rate of transmission of the studied diseases, the reported basic reproduction number or others |
| Limitations | We will report the epidemiological bias and limitations reported by authors of each screened article |
| Control or intervention strategy | When a study contains a control model, we will add a category to indicate which control strategies were used. Examples of control strategies are personal protection, sexual protection, use of insecticides and others |
| Cocirculation/coinfection | When a coinfection or cocirculation model is reported, a category will be added to indicate with which disease(s) the coinfection or cocirculation exists. For example: cocirculation/coinfection with dengue, chikungunya, COVID-19, zika, HIV, etc |
| Machine/deep learning model | When the manuscript contains a machine/deep learning model, we will indicate, as a new category, the algorithm implemented |

## Study records

### Data management

Citations will be uploaded on the web-based systematic review management software *Covidence* (Veritas Health Innovation, Melbourne, Australia), which is available at www.covidence.org. Once imported, deduplication of the references will be conducted in *Covidence* before title/abstract screening. After title/abstract screening, *Zotero* and *Mendeley* will be used to manage references and bulk upload missing full texts.

### Selection process

The study selection will be conducted by JPR-L and KRA. JPR-L holds a PhD in Mathematics and has experience in VBDs modelling. KA holds a PhD in veterinary science and is interested in the modelling of public health threats.

The two authors will independently screen the titles and abstracts of studies obtained from the database queries according to the eligibility criteria to identify potential studies to be included. In the next phase, the authors will retrieve the full text of the manuscripts that they consider potentially relevant. JPR-L and KRA will independently screen the full text of retrieved articles that meet the eligibility criteria. Disagreements between the criteria of the two reviewers will be resolved through discussion or the participation of BN, senior author who will act as a third reviewer. A PRISMA flow diagram of the study selection procedure will be provided.

### Data collection process

The two reviewers (JPR-L and KRA) will independently extract data for the included studies using a data extraction form with the help of a third reviewer (BN), in case of disagreement.

### Data items

Each reviewer will perform data extraction from the papers using the Covidence platform. The information to be extracted is shown in table 1. In addition to the listed information, the reviewers may collect additional information as they consider necessary to address the research question. The authors of the included papers will not be contacted for any supplementary information or clarification.

## Risk of bias in individual studies

Since the primary objective of this scoping review is to classify the available literature on mathematical and statistical models for dengue, zika and chikungunya, we will not perform study quality or formal risk of bias or use them for exclusion of studies, according to the scoping review guidelines.[52]

## Data synthesis

The extraction of relevant data for each disease will be performed separately using table 1. The grouping variables and parameters employed in each model structure will be used to identify comparable assumptions across different modelling approaches. Subsequently, a descriptive analysis of the findings will be conducted, followed by a comprehensive narrative summary that will include the study outcomes, research gaps and recommendations for future investigations. Moreover, graphical summaries will be generated to depict the relationships between response variables and their corresponding predictor variables within specific variable groups. Additionally, emphasis will be placed on identifying the most influential parameters within each model, with a specific focus on those that affect the transmission rate, coinfection probability and the transition rate between compartments in each model.

To facilitate access to the used data and coding in the models, supplementary material will be provided to summarise information about studies that provide open-access data and coding sources.

## Patient and public involvement

Patients and/or the public were not involved in any stage of this study.

## ETHICS AND DISSEMINATION

Given that the methodology of this scoping review consists of reviewing and collecting information from publicly available articles, this study does not require ethics approval. To facilitate knowledge dissemination, we will present the results of this review through presentations in conferences and peer-reviewed publications.

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**Contributors** JPR-L and KRA conceptualised the research plan for the proposed protocol, wrote and commented on this protocol. JEP and JA read and comment on the protocol. BN is the senior author and helped with the conceptualisation and supervision of this work and provided feedback and comments on the development of the protocol.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.



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**Supplementary Table 1**: Results of literature search in various databases on mathematical and statistical models of dengue, zika and chikungunya written in English, Spanish and French from January 1, 2011 to July 31, 2023.

| Database | Date of search | Disease | Search Query | Number of Results |
|---|---|---|---|---|
| **PubMed** | 24 July, 2023 | Dengue | ((model OR modeling OR modelling) AND (mathematical OR statistical OR math OR stat OR predictive OR “machine learning” OR “artificial intelligence” OR “deep learning” OR “time series” OR epidemiological OR compartmental OR "neural networks" OR "cellular automata") AND (Dengue OR DENV)) | 2,390 |
| | | Zika | ((model OR modeling OR modelling) AND (mathematical OR statistical OR math OR stat OR predictive OR “machine learning” OR “artificial intelligence” OR “deep learning” OR “time series” OR epidemiological OR compartmental OR "neural networks" OR "cellular automata") AND (Zika OR ZIKV )) | 1,026 |
| | | Chikungunya | ((model OR modeling OR modelling) AND (mathematical OR statistical OR math OR stat OR predictive OR “machine learning” OR “artificial intelligence” OR “deep learning” OR “time series” OR epidemiological OR compartmental OR "neural networks" OR "cellular | 549 |

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|---|---|---|---|---|
| | | | automata") AND (Chikungunya OR CHIKV)) | |
| **MathSciNet** | 24 July, 2023 | Dengue | ((model OR modeling OR modelling) AND (mathematical OR statistical OR math OR stat OR predictive OR “machine learning” OR “artificial intelligence” OR “deep learning” OR “time series” OR epidemiological OR compartmental OR "neural networks" OR "cellular automata") AND (Dengue OR DENV)) | 334 |
| | | Zika | ((model OR modeling OR modelling) AND (mathematical OR statistical OR math OR stat OR predictive OR “machine learning” OR “artificial intelligence” OR “deep learning” OR “time series” OR epidemiological OR compartmental OR "neural networks" OR "cellular automata") AND (Zika OR ZIKV )) | 106 |
| | | Chikungunya | ((model OR modeling OR modelling) AND (mathematical OR statistical OR math OR stat OR predictive OR “machine learning” OR “artificial intelligence” OR “deep learning” OR “time series” OR epidemiological OR compartmental OR "neural networks" OR "cellular automata") AND (Chikungunya OR CHIKV)) | 47 |
| **Web of Science** | 24 July, 2023 | Dengue | ((model OR modeling OR modelling) AND (mathematical OR statistical OR math OR stat OR predictive OR “machine | 3,883 |

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|---|---|---|---|---|
| | | | learning" OR "artificial intelligence" OR "deep learning" OR "time series" OR epidemiological OR compartmental OR "neural networks" OR "cellular automata") AND (Dengue OR DENV)) | |
| | | Zika | ((model OR modeling OR modelling) AND (mathematical OR statistical OR math OR stat OR predictive OR "machine learning" OR "artificial intelligence" OR "deep learning" OR "time series" OR epidemiological OR compartmental OR "neural networks" OR "cellular automata") AND (Zika OR ZIKV )) | 1,560 |
| | | Chikungunya | ((model OR modeling OR modelling) AND (mathematical OR statistical OR math OR stat OR predictive OR "machine learning" OR "artificial intelligence" OR "deep learning" OR "time series" OR epidemiological OR compartmental OR "neural networks" OR "cellular automata") AND (Chikungunya OR CHIKV)) | 882 |