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Exploring Zika's dynamics: A scoping review journey from epidemic to equations through mathematical modelling

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ABSTRACT

Zika virus (ZIKV) infection, along with the concurrent circulation of other arboviruses, presents a great public health challenge, reminding the utilization of mathematical modelling as a crucial tool for explaining its intricate dynamics and interactions with co-circulating pathogens. Through a scoping review, we aimed to discern current mathematical models investigating ZIKV dynamics, focusing on its interplay with other pathogens, and to identify underlying assumptions and deficiencies supporting attention, particularly regarding the epidemiological attributes characterizing Zika outbreaks. Following the PRISMA-Sc guidelines, a systematic search across PubMed, Web of Science, and MathSciNet provided 137 pertinent studies from an initial pool of 2446 papers, showing a diversity of modelling approaches, predominantly centered on vector-host compartmental models, with a notable concentration on the epidemiological landscapes of Colombia and Brazil during the 2015–2016 Zika epidemic. While modelling studies have been important in explaining Zika transmission dynamics and their intersections with diseases such as Dengue, Chikungunya, and COVID-19 so far, future Zika models should prioritize robust data integration and rigorous validation against diverse datasets to improve the accuracy and reliability of epidemic prediction. In addition, models could benefit from adaptable frameworks incorporating human behavior, environmental factors, and stochastic parameters, with an emphasis on open-access tools to foster transparency and research collaboration.

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1. Background

1.1. Rationale

Due to their persistent appearance and re-appearance, mosquito-borne illnesses are a global health problem in many parts of the world. Global distribution shifts primarily stem from the increasing mosquito population, driven by several factors, including the migration of people and the existence of a favorable climate (Kraemer et al., 2019; Wint, Jones, Kraemer, Alexander, & Schaffner, 2022). Recent literature has estimated that by 2050, approximately 40% of the world's population will be exposed to disease transmitted by mosquitoes (Kraemer et al., 2019). The majority of viruses that infect humans through mosquitoes and cause disease are members of the flavivirus family Flaviviridae, including Dengue virus (DENV), Zika virus (ZIKV), and Chikungunya virus (CHIKV) (Yu & Cheng, 2022). Among all of these mosquito-borne diseases, Zika, caused by ZIKV, stands out as a newly emerging mosquito-borne disease, responsible for large outbreaks in nearly 89 countries in the last decade (Chang, Ortiz, Ansari, & Gershwin, 2016). However, like Dengue, Zika is categorized as a *"neglected tropical disease"* because, despite its discovery many decades ago, it has received little attention until the recent major outbreaks this last decade (Champagne et al., 2016)

ZIKV was first identified in 1948 and 1952 based on serological evidence; in 1954, human cases were identified in Nigeria and the virus was isolated (MacNamara, 1954; Yu & Cheng, 2022). Similarly, 2013 saw the first notable Zika outbreak recorded in New Caledonia (Ioos et al., 2014). Although initially confined to Africa and Asia, the virus garnered global attention during the extensive outbreak in Brazil in 2015 (Atif, Azeem, Sarwar, & Bashir, 2016). This outbreak marked the largest in history, with an estimate of between 440, 000 and 1, 300, 000 Zika cases and 4783 possible cases of microcephaly in the majority of Northeast Brazil, leaving approximately 76 deaths (De Araújo, Nascimento, Da Matta Guedes, & Fernandes, 2021). The outbreak quickly spread across several countries in Latin America, the Caribbean, and the Pacific, resulting in the World Health Organization (WHO) announcing a worldwide public health emergency in 2016 (De Araújo et al., 2021). ZIKV is likely to follow the epidemiologic pattern of DENV and CHIKV endemic areas where *Aedes* mosquitoes are present (Atif et al., 2016).

ZIKV primarily spreads via the bite of two mosquito species belonging to the *Aedes* genus (*Ae. aegypti* and *Ae. albopictus*) that also transmit other diseases such as Dengue and Chikungunya (Atif et al., 2016). Notably, ZIKV has also been identified in other mosquito species, such as *Ae. hirsutus, Ae. vittatus*, *Ae. furcifer*, and *Ae. Taylori* (Dasti, 2016). Mosquitoes of the genus *Aedes* can procreate in a small amount of water, and their eggs are hard, making it difficult to control their growth (Paixão, Barreto, Da Glória Teixeira, Da Conceição N Costa, & Rodrigues, 2016). ZIKV can spread by four main routes: vector transmission, person-to-person transmission, blood transfusion, and animal-to-person transmission. Non-human primates produce antigens and antibodies, suggesting that animals may act as reservoirs (Musso et al., 2015). Indeed, many non-human animals are considered reservoir hosts of ZIKV, and people are viewed as incidental hosts; however, the virus has shown the ability to adapt to humans and maintain the cycle of infection, and therefore Zika is considered a zoonosis (Vue & Tang, 2021). Moreover, because the virus may remain in semen for a maximum of six months post-infection, allowing the virus to spread even in the absence of symptoms, ZIKV can be disseminated through sexual intercourse (Musso et al., 2015). The potential for sexual transmission is higher when the infected partner exhibits symptoms or has been infected with the virus within the past few weeks (Grischott, Puhan, Hatz, & Schlagenhauf, 2016).

The pathogenesis of ZIKV is unclear, with approximately 80% of the cases being asymptomatic (Kumar Goswami & Shanmukha, 2020). ZIKV infections, onset 2–11 says after a mosquito bite, typically involve flu-like symptoms, conjunctivitis, maculopapular rash and joint pain (Paixão et al., 2016). Unlike Dengue and Chikungunya infections, ZIKV infections usually presents with milder symptoms with inconsistent rashesb (Romero-Leiton, Acharya, Parmley, Arino, & Nasri, 2023). However, certain ZIKV infection instances could result in neurological side effects, such as congenital microcephaly in newborns and fetuses and Guillain-Barré syndrome in adults, unlike other flaviviruses. Guillain-Barré Syndrome is rare, with a ratio of one case for every 6.1 instances of microcephaly. These consequences are also uncommon (Akrami et al., 2021). Treatment focuses primarily on symptoms since there is not a particular antiviral drug for ZIKV infection (Dasti, 2016). The rapid spread of Zika, its potential for epidemic proportions, and its co-existence with other arboviruses pose challenges for differential diagnoses. Laboratory tests, such as *C-reactive* protein and serological tests, lack sensitivity and specificity for detecting the presence of the virus because of the cross-reactivity among viruses of the genus *Flavivirus* (Musso et al., 2015)

Moreover, the spread of Zika is mainly driven by the concurrence of multiple communicable agents in the same geographic area (Sánchez-Duque, Rodríguez-Morales, Trujillo, Cardona-Ospina, & Villamil-Gómez, 2018). Co-circulation refers to the simultaneous presence of multiple pathogenic organisms in the same area, while co-infection refers to the presence of multiple infectious agents in an individual. There have been reports of ZIKV co-circulation and co-infection with other illnesses in a number of nations, including Brazil, Colombia, and Venezuela (Sánchez-Duque et al., 2018). The most common co-circulating viruses are DENV and CHIKV, both of which are transmitted by the *Aedes* mosquitoes (Sánchez-Duque et al., 2018). This can have severe consequences for patients, particularly for pregnant women. However, ZIKV can co-circulate and co-infect with other infectious agents, such as Human Immunodeficiency Virus (HIV). For example, in Colombia and Brazil, cases of co-infection have been reported, resulting in an increased risk of liver damage (Aschengrau et al., 2021; Bidokhti et al., 2018; Rothan, Bidokhti, & Byrareddy, 2018; Sherman et al., 2018).

The rapid spread of ZIKV and its potential impact on maternal and child health has prompted an urgent response from the global health community. Researchers worldwide have quickly mobilized to study the virus, its transmission dynamics, and its potential interventions to control outbreaks. Since then, understanding the dynamics of viral transmission has been made

possible by mathematical modelling, which has deepened our understanding of disease epidemiology as well as risk factors and predicting their spread. Models have been used to estimate the factors leading to microcephaly associated with ZIKV infection during motherhood (Ndaïrou, Area, Nieto, Silva, & Torres, 2018), and evaluate the potential impact of different mosquito control strategies (A. Ali, Iqbal, Asamoah, & Islam, 2022; Altaf Khan, Ullah, & Farhan, 2019; Alzahrani, Ahmad, Altaf Khan, & Malebary, 2021; Altaf Khan et al., 2019). These studies have demonstrated the potential of mathematical modelling to guide public health interventions and inform policy decisions in the context of Zika.

Some scoping reviews have attempted to identify the various methodologies employed in modelling ZIKV infections throughout the years. Wiratsudakul et al. (Wiratsudakul, Suparit, & Modchang, 2018) reviewed mathematical modelling approaches used to explain the dynamics of ZIKV outbreaks; however, this scoping review only emphasized ZIKV mathematical models before 2017 and did not consider studies that included co-infections with other pathogens as variables. Our scoping review will serve as an update on the modelling approaches used to study the dynamics of ZIKV outbreaks and their evolution in recent years. It also determines the implications of incorporating co-infections into these models.

1.2. Research questions

Mathematical modelling has extensively provided insight that would be difficult to obtain through pure experiments (Best & Perelson, 2018). This scoping review is based on Zika mathematical modelling literature from January 2011 onwards. We focused on the following objectives: (1) Classify the mathematical models used to describe the dynamics of Zika and its co-circulation and co-infection according to their structure, type, main variables, and transmission parameter values; (2) Determine interest over time in ZIKV mathematical modelling research; (3) Determine the geographic areas where the most research has been conducted; (4) Determine the primary open-access data and coding sources used in the studies; (5) Classify the most common control/intervention strategies used in the mathematical modelling of Zika; (6) Identify the limitations of the proposed models.

2. Methods

This scoping review adhered to the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA-P) and its extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018). The full methodology used for mathematical modelling in this review, including eligibility requirements, information sources, search strategies, data charting procedures, and data items, as well as the synthesis of results, is detailed in our scoping review protocol (Romero-Leiton, Acharya, et al., 2023). For this review, we incorporated relevant information outlined in the PRISMA-ScR checklist (Supplementary Information S1).

3. Results

3.1. Selection of sources of evidence

The preliminary search identified 1664 studies for this scoping review after duplicates were removed. After screening all abstracts and full texts based on the inclusion and exclusion criteria listed in the protocol (Romero-Leiton, Acharya, et al., 2023) and shown in Fig. 1, 137 articles were included. The first screening stage, comprising title and abstract review, was validated by JR and KA. Full-text selection and analysis of the results were performed and validated by JR and KA.

3.2. Synthesis of results

3.2.1. Geographical distribution of the research per year

An analysis was conducted to determine the temporal and geographic distribution of publications on the mathematical modelling of Zika. Of the 137 analyzed studies, more than half (54.01%) lacked a specified regional focus, whereas a subset of articles (3.64%) exhibited emphasis on more than one country. The remaining proportion of research endeavors (42.35%) is graphically depicted in Fig. 2, which shows the distribution by country.

Notably, mathematical modelling of ZIKV was absent from the research landscape before 2015. A distinct shift in research focus was materialized post-2016, coinciding with Zika's arrival in the Americas in 2015.

3.2.2. Models' classification

A dual categorization scheme was employed for the classification of mathematical models, considering both typological and structural aspects. The widest classification framework is built on the model type, which constitutes the most inclusive level of categorization. This taxonomy includes.

(a) **Deterministic models**, such as those employing Fractional Differential Equations (FDEs), Partial Differential Equations (PDEs), Ordinary Differential Equations (ODEs), and Difference Equations, constituted 84.7% of all studies.

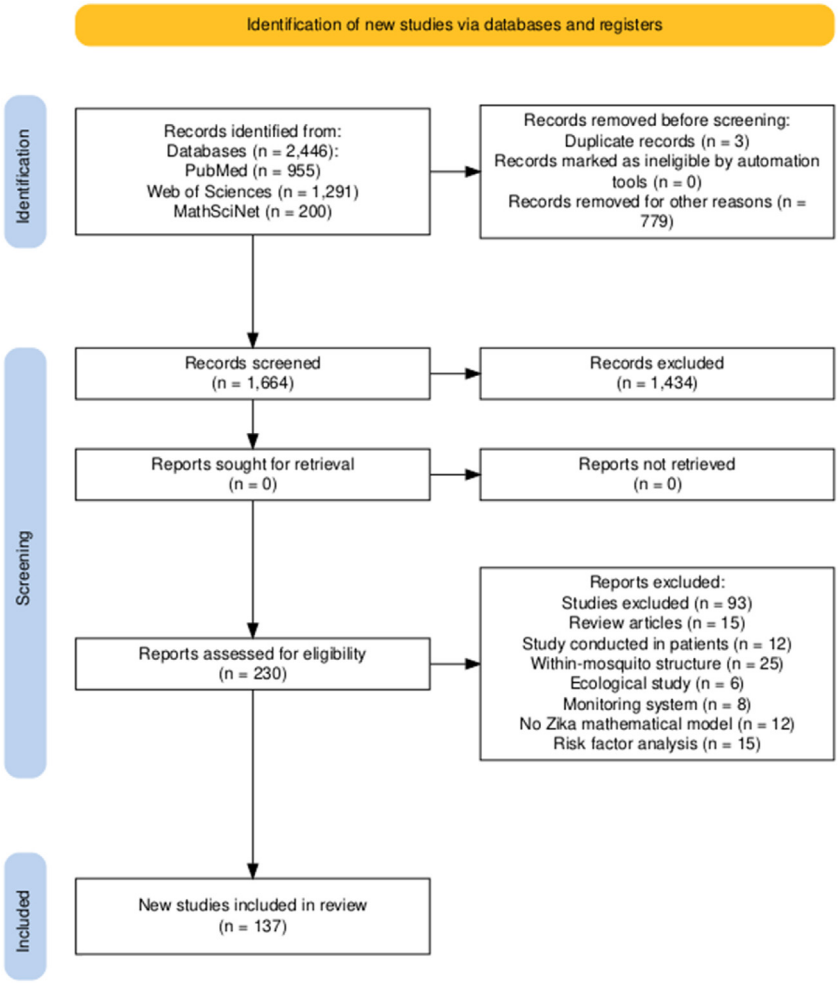

Fig. 1. Study selection pathway using the PRISMA-P diagram.

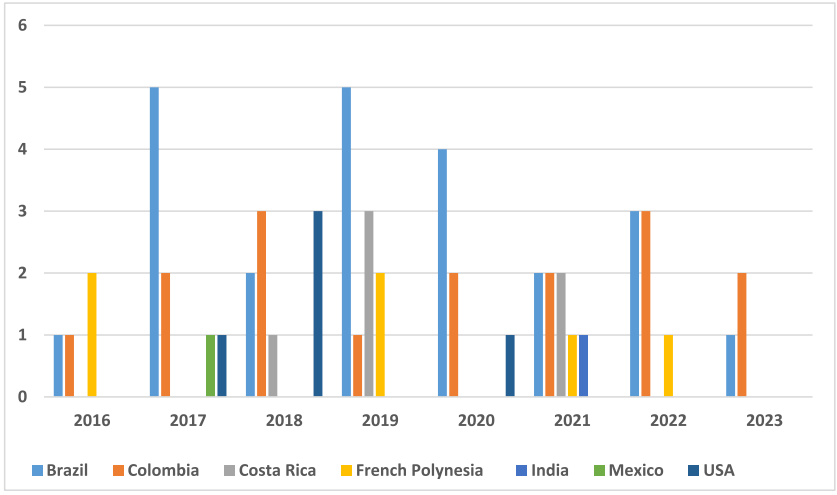

Fig. 2. Annual trends in Zika mathematical modelling research across countries. Latin American and Caribbean countries dominated, with Colombia, Brazil, and Costa Rica as key research centres driven by elevated Zika transmission after the 2016 epidemic in the Americas.

(b) **Stochastic models**, including Stochastic Differential Equations (SDEs), Branching Processes and Agent-Based models, representing a mere 0.3% of studies were included.
(c) **Network-based models**, which can be deterministic or stochastic models that describe the relationships and interactions between objects or entities in a system. For example, metapopulation and contact network models accounted for 2.9% of the total studies.
(d) **Mixed-type models**, incorporating studies that combine two or more different modelling approaches into a single framework, constituted 11.7% of the total studies.

A more refined classification was performed for each model type, focusing on the structural attributes inherent to these models. Specifically, this structural categorization delineates models into two principal subcategories: **(1)** a **vector-host** structure, which describes how ZIKV spreads between mosquitoes (vectors) to humans (hosts), accounting for 97% of studies; and **(2)** a **within-host** structure, which refers to the processes within an individual's body during a ZIKV infection, representing 3% of the total studies. We did not consider the **between-host** model structure, which explains how a pathogen is transmitted from one host to another, because the literature we reviewed consistently combined the **sexual transmission** (between-host) of ZIKV with vectorial transmission. Consequently, it is sufficient to focus on the vector-host structure with a sexual transmission route. Table 1 gives a summary of the various models that are categorized, along with the references for each.

The analysis of the data presented in Table 1 revealed that the majority of the mathematical models employed in Zika research follow a vector-host structure. Notably, the majority of studies were deterministic, with 82.7% of the studies exhibiting an overlap between the two categories. These vector-host models are key to understanding Zika transmission dynamics, given that *Aedes* mosquitoes primarily transmit the virus. They incorporated the intricate interplay between humans and mosquitoes under the assumption that infection in mosquitoes occurs through biting of infected humans.

Nevertheless, within-host Zika models have garnered less attention, accounting for only 2.2% of the total studies. The relatively limited exploration of these model types may be attributed to the challenges associated with the intricate interactions between ZIKV and the host immune system. Nonetheless, these models offer valuable insights into specific aspects of Zika dynamics and host-pathogen interactions despite their comparatively lower prevalence in the research landscape.

Table 1
Distribution of Zika mathematical models by type and structure. By type, deterministic (84.7%), stochastic (0.3%), network-based (2.9%), and mixed-type (11.7%) models were used. By structure, we have vector-host transmission, including sexual and vertical transmission (97.8%) and within-host transmission (2.2%).

Model Type	Model Structure	
	References for vector-host (including or not sexual and vertical transmission)	References for within-host
Deterministic	(Adamu et al., 2017; Addai et al., 2022; Agudelo & Ventresca, 2022; Agusto, Bewick, & Fagan, 2017b; A. Ali, Iqbal, et al., 2022; A. Ali, Islam, et al., 2022; H. M. Ali & Ameen, 2021; Al-Maqrashi et al., 2022, 2023 Alshehri & Hajji, 2022; Altaf Khan et al., 2019; Alzahrani et al., 2021; Article et al., 2017; Atokolo et al., 2022; Baca-Carrasco & Velasco-Hernández, 2016; Bañuelos et al., 2019; Barros et al., 2019; Begum, Tunç, Khan, Gulzar, & Khan, 2021; Bessey, Mavis, Rebaza, & Zhang, 2021; Bi et al., 2020; Binder & Pilyugin, 2019; Biswas et al., 2020; Bonyah, Khan, Okosun, & Islam, 2017, 2019 Chaikham & Sawangtong, 2017; Chen et al., 2018; Cruz-Pacheco et al., 2019; Danbaba & Garba, 2018; Dantas et al., 2018; Dénes et al., 2019; Denu & Son, 2021; Dohare et al., 2021; Durham et al., 2018; Farman et al., 2020, 2022 Fitzgibbon et al., 2017; W. Gao et al., 2019; González-Parra et al., 2020; Goswami et al., 2018; Hasan, Singh, Richards, & Blicblau, 2019; He et al., 2020; Huber et al., 2018; Huo et al., 2023; Hussain et al., 2021; Ibrahim & Dénes, 2021; Imran et al., 2018, 2021 Khan et al., 2019; Kucharski et al., 2016; Kumar Goswami & Shanmukha, 2020; L. et al., 2019; Li & Zhao, 2021; Lourenço et al., 2017; Massad et al., 2019; Mina et al., 2020; Mishra, 2021; Miyaoka et al., 2019; Moreno et al., 2017; Goswami & Shanmukha, 2020; Ndaïrou et al., 2018; Ngonghala et al., 2021; Okuneye et al., 2017; Okyere et al., 2020; Olawoyin & Kribs, 2018, 2020 Omame et al., 2022, 2023 Omame & Abbas, 2023; Padmanabhan et al., 2017; Padmanabhan & Seshaiyer, 2017; Pan, Zhu, & Wang, 2022; Rahman et al., 2019; Saad-Roy, Ma, & van den Driessche, 2018; Sadeghieh et al., 2021; Sanchez, Barboza, & Vásquez, 2019; Sasmal et al., 2018; Sharma et al., 2021; Srivastav et al., 2018, 2019 Tang et al., 2018, 2019 Terefe et al., 2018; Thaiprayoon et al., 2022; Tuncer, Marctheva, LaBarre, & Payoute, 2018; Ukanwoke et al., 2022; Veeresha et al., 2022; L. Wang et al., 2017; L. Wang & Wu, 2022; L. Wang & Zhao, 2019; W. Wang et al., 2023; X. Wang et al., 2019; Xue et al., 2018; Yuan et al., 2021; Yue, Yusof, & Shafie, 2020; L. Zhang & Zhao, 2021; R. Zhang & Zhao, 2022; Zhao et al., 2020; Zhu et al., 2022)	(Best & Perelson, 2018; Tang et al., 2020; Tuncer & Martcheva, 2021)
Stochastic	Nguyen-Van-Yen et al. (2021)	
Network-Based	(X. F. Luo et al., 2021; X. S. Luo et al., 2020; Stone et al., 2017; Tchepmo Djomegni et al., 2021)	
Mixed-Type	(Angina et al., 2022; Carlson et al., 2018; Champagne et al., 2016; Counotte et al., 2019; Marini et al., 2017; Muñoz et al., 2017; Roy et al., 2020; Shutt et al., 2017; Soewono & Lahodny, 2021; Tang et al., 2016; Wattanasirikosone & Modnak, 2021; Xue et al., 2021; Zevika & Soewono, 2018)	

3.2.3. Model variables

In mathematical models, variables and parameters are two aspects that play distinct roles (Banerjee, 2014). Variables are elements that can change or vary in the model, representing aspects of interest for prediction or deeper understanding. Examples include the number of human infections, recovered humans, and Zika-carrier mosquitoes. However, parameters can be constants or fixed in the model that do not change during simulation or analysis, but sometimes parameters depend on other covariates or even be random parameters. These values are essential for defining the model but are not the principal focus of this review. Parameters in Zika models could include the mosquito biting rate and transmission probabilities (vector to host and host to vector).

Considering this distinction, we analyzed 137 selected studies to determine the variables of interest associated with each model structure. First, these variables were identified for models that did not consider co-circulation or co-infection and for models that did consider the interaction of ZIKV with other pathogens. Second, we focused on two distinct model structures, as previously identified: vector-host (including or not including sexual or vertical transmission routes) and within-host models. Therefore, we defined two types of variables: state and control variables, which will be described in the following section.

3.2.3.1. State variables in vector-host models. We identified 132 studies using a vector-host structure that incorporated human and mosquito compartments. Human compartments contain the number of susceptible individuals, symptomatic and asymptomatic cases, and individuals who have recovered and acquired immunity. The mosquito compartments comprised variables describing different stages of the mosquito life cycle, such as counts for eggs, larvae, and pupae in the aquatic stages, as well as susceptible, exposed, and infected adult mosquitoes. In network-based models, compartments remain constant, and multiple regions (patches) are considered, expanding the structure of these compartments across diverse regions.

In the following, we present compartmental diagrams illustrating the variables of interest for the vector-host models. Fig. 3 provides a general diagram representing vector-host model structures that do not consider the sexual or vertical transmission routes of the disease. Fig. 4 shows a general compartmental diagram that includes the variables of interest for vector-host model structures that account for sexual and vertical transmission routes.

Within the vector-host model structure, we found 13 studies (9.48% of the total studies) that considered co-infection or co-circulation with other diseases. More specifically, of the thirteen articles, seven considered co-circulation/co-infection with Dengue (Bonyah, Khan, Okosun, & Gómez-Aguilar, 2019; Olawoyin & Kribs, 2020; Tang, Xiao, & Wu, 2016, 2018, 2019, 2020; L. Wang & Zhao, 2019), 3 with Dengue and Chikungunya (Huber, Childs, Caldwell, & Mordecai, 2018; Okuneye et al., 2017; Xue, Fang, & Hyman, 2018), 1 with COVID-19 (Omame, Abbas, & Onyenegecha, 2022), and one with COVID-19 and Dengue (Omame & Abbas, 2023). Fig. 5 shows a general compartmental diagram of the variables of interest in the co-infection/co-circulation vector-host models.

3.2.3.2. State variables in within-host models. Only three studies, comprising 2.18% of the total, utilized the within-host structure model (Best & Perelson, 2018; Tang, Xiao, Sander, Kulkarni, & Wu, 2020; Tuncer & Martcheva, 2021). These studies incorporated various components such as susceptible cells, infected cells, antibodies, T cells, and viral particles. These models aim to capture various stages of infection and immune responses in the human population and pregnant women. Fig. 6 provides a compartmental diagram specifically designed to illustrate the structural elements of the within-host models. This diagram focuses on the variables of interest that pertain to the interactions between the host cells and the infecting virus, capturing the stages of infection and immune responses within individual hosts (including pregnant women).

Of the three studies that considered the within-host structure, only one (Tang et al., 2020) modelled the co-connection between ZIKV and DENV. Fig. 7 shows the state variables associated with this model.

To further delve into the specifics of the submodels within these general diagrams (Figs. 3–7), Supplementary Information S2 provides a detailed overview of the submodel structures and their respective references. These sub-models offer a more granular understanding of the components and interactions within broader model structures.

3.2.3.3. Intervention variables. Of the 137 studies reviewed, 34 (24.8%) incorporated intervention (or control) variables into their analysis. Among the 34 studies, 76.47% identified personal protection, 64.70% considered insecticides, 32.35% examined medical treatment, 20.58% addressed sexual protection, 11.76% discussed, and 11.76% explored the incorporation of *Wolbachia* bacteria.

Personal protection interventions include behaviours such as using insect repellents and donning long sleeves, and sleeping under mosquito nets, all of which contribute to mitigating the risk of mosquito-borne transmission and ZIKV dissemination. Insecticides, including larvicides and adulticides, eliminate mosquitoes and curtail their population densities, thereby mitigating disease transmission. The production of antiviral medications to prevent or treat Zika infection is referred to as a medical therapy intervention.

Conversely, hospitalization (Imran, Usman, Malik, & Ansari, 2018), health campaigns (Huo, Fu, & Xiang, 2023), interventions aimed at reducing the incidence of babies with abnormalities (e.g., protecting pregnant women from Zika infection and subsequently reducing the risk of vertical transmission to the fetus) (Huo et al., 2023), advocating for delayed pregnancy (Huo et al., 2023), water sanitation (Biswas, Ghosh, & Sarkar, 2020) (each identified in only one study per category) represent less commonly utilized intervention strategies within the mathematical modelling domain of Zika. The limited

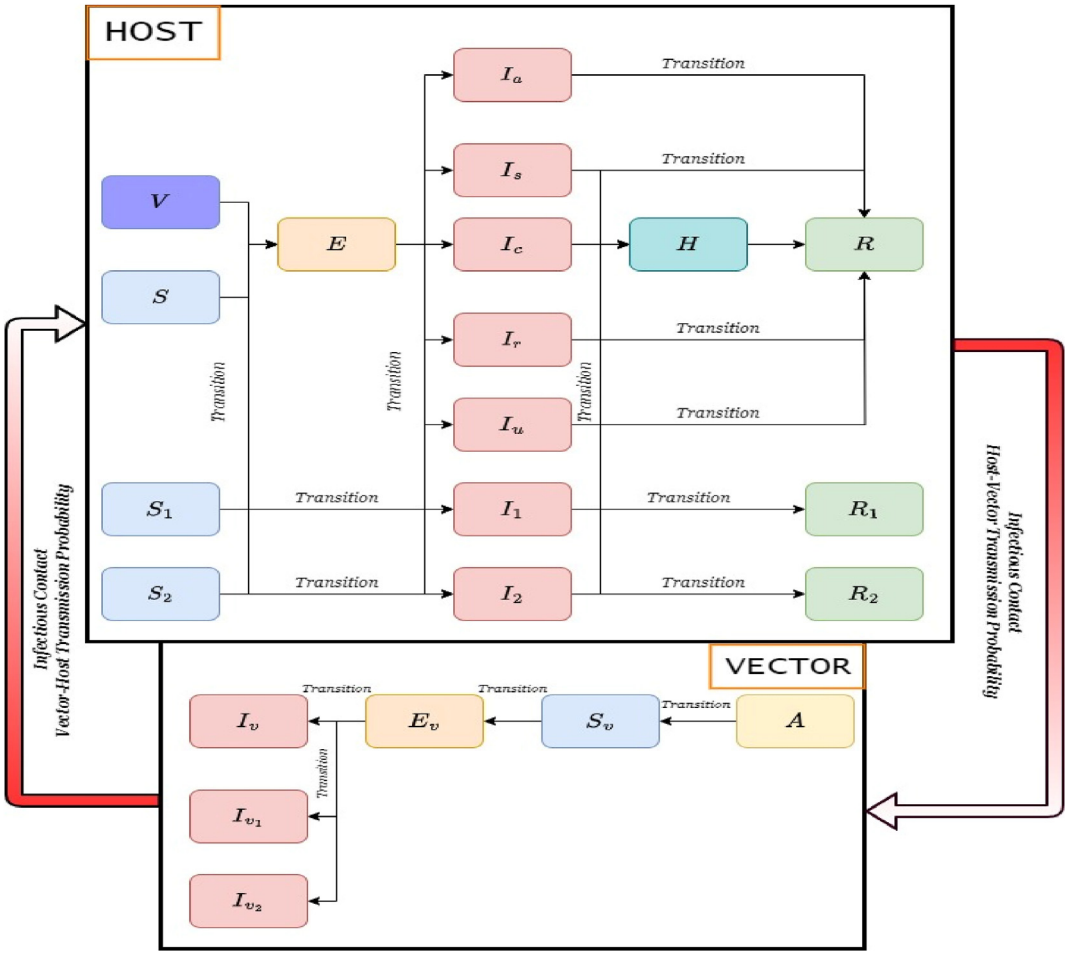

Fig. 3. General compartmental diagram of the variables of interest in vector-host models excluding sexual and vertical transmission routes. In the human compartments the variables of interest are the population of: S (susceptible), V (vaccinated), E (exposed), I (infectious), R (recovered), H (hospitalized), I_a (asymptomatically infected), I_s (symptomatically infected), I_c (convalescent infected), I_r (reported infectious), I_u (unreported infectious), S_1 (individuals with reduced susceptibility to strain 1 due to past exposure and recovery from strain 1), S_2 (individuals with reduced susceptibility to strain 2 due to past exposure and recovery from strain 2), I_1 (individuals infected with strain1), I_2 (individuals infected with strain 2), R_1 (individuals who have recovered from strain 1 and are still immune to strain 1), R_2 (individuals who have recovered from strain 2 and are still immune to strain 2). For mosquito compartments the interest variables are the mosquitoes of: A (aquatic phase: eggs, larvae, and pupae), S_v (susceptible), E_v (exposed), I_v (infectious), I_{V1} (vector infected with strain 1), I_{V2} (infected with strain 2).

adoption of these strategies can be attributed to their comparatively minor impact on reducing viral transmission or the scarcity of data to reliably estimate their efficacy. For detailed insights into the specific combinations of the intervention strategies employed in each study and the corresponding references, please refer to Supplementary Information S3.

3.2.4. Model parameters

The parameters examined in the selected studies were categorized into four distinct subcategories: transmission probabilities in vector-host (whether or not sexual transmission is considered), transitions between compartments, parameters related to infected cells, and intervention (control) parameters. The intervention parameters are analyzed in the subsequent section. Owing to the substantial number of parameters associated with each subcategory, Table 2 provides the reported ranges of vector-host, host-vector, and host-host transmission parameters, along with the estimated or utilized values for the sexual and vertical transmission probability and mosquito biting rate.

On the other hand, Table 3 shows the co-infection/co-circulation transmission parameter values for those models.

Although co-infection or co-circulation of ZIKV with other pathogens can affect the kinetics of transmission, very few mathematical models have taken this into account. However, the co-circulation of ZIKV with other arboviruses, such as DENV and CHIKV, is prevalent in many parts of the world. Incorporating these arboviruses into mathematical models of ZIKV allows a better understanding of their interplay. The limited focus on concurrent infection in mathematical models of COVID-19 and ZIKV is due to its novel nature; therefore, research efforts are more focused on analyzing the dynamics of COVID-19 alone rather than exploring co-infection/co-circulation with other infectious agents.

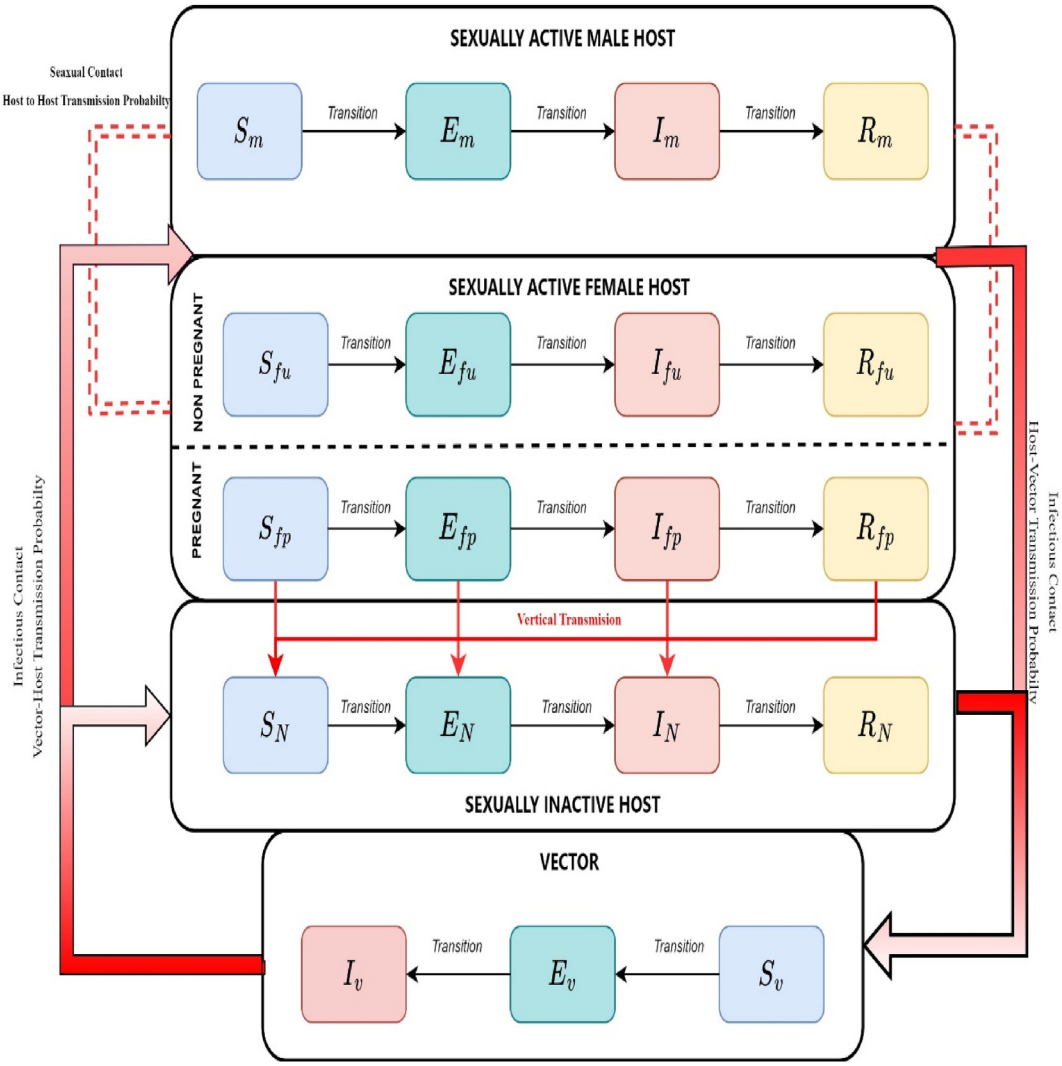

Fig. 4. General compartmental diagram of interest variables in vector-host models, including sexual and vertical transmission routes. In the human compartments the variables of interest are the population of: S_{uf} (sexually active susceptible no pregnant females), E_{uf} (sexually active exposed no pregnant females), I_{uf} (sexually active infectious non pregnant females), R_{uf} (sexually active recovered non pregnant females), S_{fp} (sexually active susceptible pregnant females), E_{fp} (sexually active exposed pregnant females), I_{fp} (sexually active infectious pregnant females), R_{fp} (sexually active recovered pregnant females), S_m (sexually active susceptible males), E_m (sexually active exposed males), I_m (sexually active infectious males), R_m (sexually active recovered males), S_N (sexually inactive susceptible host), E_N (sexually inactive exposed host), I_N (sexually inactive infected host), R_N (sexually inactive recovered host). For mosquito compartments the interest variables are: S_v (susceptible mosquitoes), E_v (exposed mosquitoes), I_v (infectious mosquitoes).

3.2.5. Model analysis methods

This section presents a classification of the methods employed to analyze the 137 Zika mathematical models selected in this study.

This review classified the methods employed in the analysis into four distinct categories, each with a specific purpose.

(a) **Model calibration using data** accounted for 5.10% of total studies, which involves methods used to evaluate the accuracy of mathematical models. This is achieved by comparing model predictions to observed data and adjusting the model parameters to enhance performance. This includes methods for computing the basic reproduction number ($\mathcal{R}0$), conducting forecast analysis, model validation, and performing numerical experiments using data (Durham et al., 2018; Fundzama & Patidar, 2020; Maxian, Neufeld, Talis, Childs, & Blackwood, 2017; Morrison & Cunha, 2020; Prasad, Kumar, & Dohare, 2023; Suparit, Wiratsudakul, & Modchang, 2018; van den Driessche, 2017).

(b) **Parameter estimation and sensitivity analysis** were used in 2.18% of all studies to estimate unknown parameters in a mathematical model or to evaluate their sensitivity (D. Gao et al., 2016; Tönsing, Timmer, & Kreutz, 2018; Towers et al., 2016).

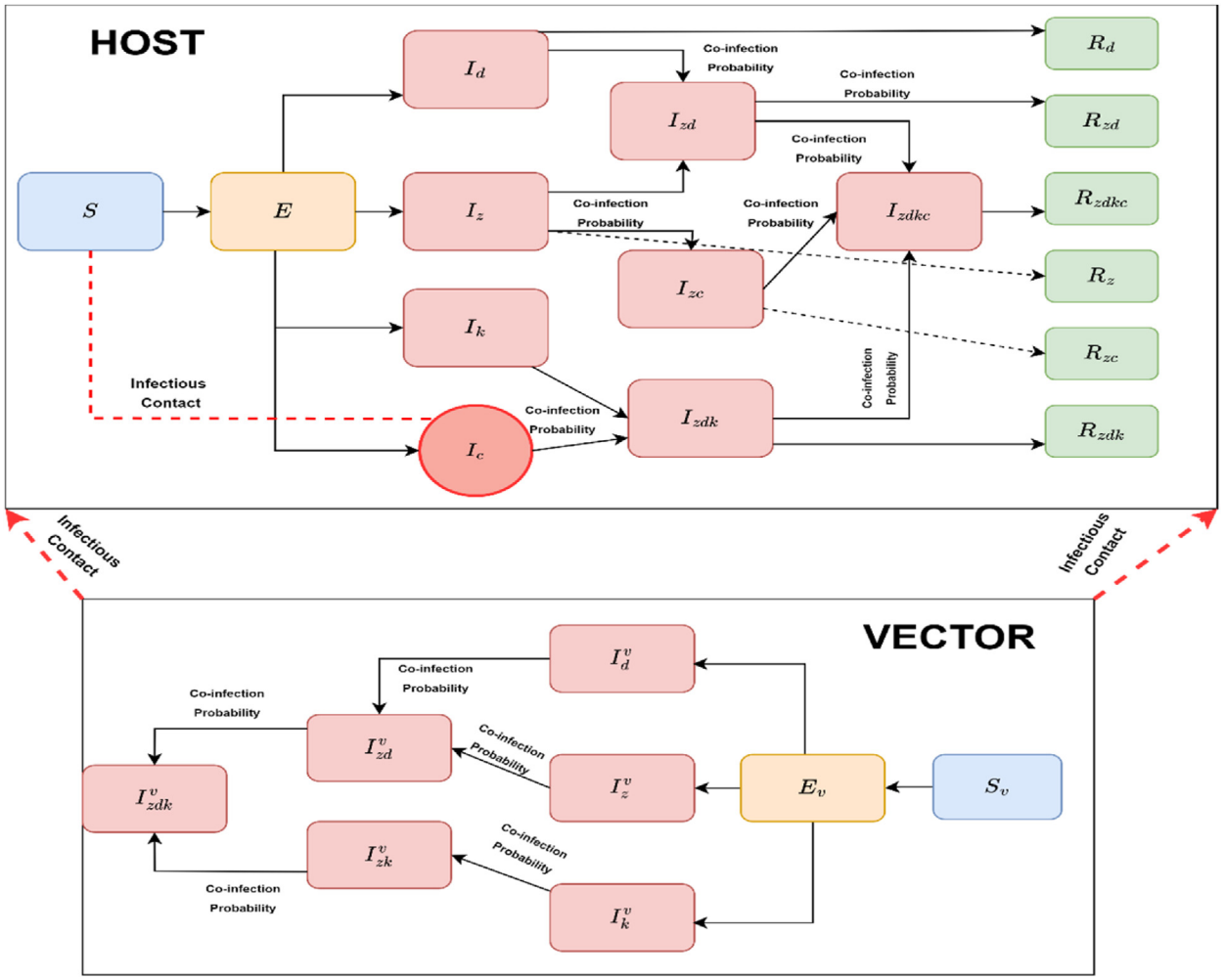

Fig. 5. General compartmental diagram of the variables of interest in co-infection/co-circulation vector-host models. In the human compartments the interest variables are the population of: S (susceptible), I_d (infected by DENV alone), I_z (infected by ZIKV alone), I_k (infected by CHIKV alone), I_c (infected by COVID-19 alone), I_{zd} (co-infected by both ZIKV and DENV), I_{zc} (co-infected by both ZIKV and COVID-19), I_{zdk} (co-infected by ZIKV, DENV and COVID-19), I_{zdkc} (co-infected by ZIKV, DENV, CHIKV and COVID-19), R_d (recovered from DENV), R_z (recovered from ZIKV), R_k (recovered from CHIKV), R_c (recovered from COVID-19), R_{zd} (recovered from ZIKV and DENV), R_{zdk} (recovered from ZIKV, DENV and CHIKV), R_{zdkc} (recovered from ZIKV, DENV, CHIKV and COVID-19). For mosquito compartments the interest variables are the population of mosquitoes: S_v (susceptible), E_v (exposed), I_d^v (infected by DENV alone), I_z^v (infected by ZIKV alone), I_k^v (infected by CHIKV alone), I_{zk}^v (infected by both ZIKV and DENV), I_{zk}^v (infected by both ZIKV and CHIKV), I_{zdk}^v (infected by ZIKV, DENV and CHIKV).

(c) **Qualitative analysis** comprised 4.37% of total studies. Qualitative analysis involves examining the behaviour of a mathematical model without explicitly computing numerical solutions. Instead, the focus is on understanding the model's properties and how these properties relate to the real-world system being modelled. Components of qualitative analysis in mathematical theory include stability, bifurcation, and equilibrium analyses. References associated with this category include (Adeyemo, Akinwande, Abdulrahman, & Kuta, 2018; Agusto, Bewick, & Fagan, 2017a; Bates, Hutson, & Rebaza, 2021; Cai, Wang, & Wang, 2019; Rezapour, Mohammadi, & Jajarmi, 2020; Yamazaki, 2019).

(d) **Mixed methods** dominated at 88.32% of the total studies. This method involves multiple analysis techniques to gain a deeper understanding of the mathematical models' behaviour. Within this category, a combination of qualitative analysis, optimal control analysis, sensitivity analysis of the parameters, and model validation is utilized. The references within this category are the majority, more precisely those not cited in items (a)-(c).

Upon extracting insights from the analysis method, the prevalence of mixed methods approaches in analyzing Zika mathematical models is unsurprising. The intricate nature of the disease, characterized by interrelated factors such as mosquito population dynamics, human demographics, and weather variables, contributes to the adoption of mixed methods. Multi-methods may enhance the accuracy of Zika mathematical model predictions by leveraging parameter estimation to fit the model to data and sensitivity analysis to identify critical parameters for further research.

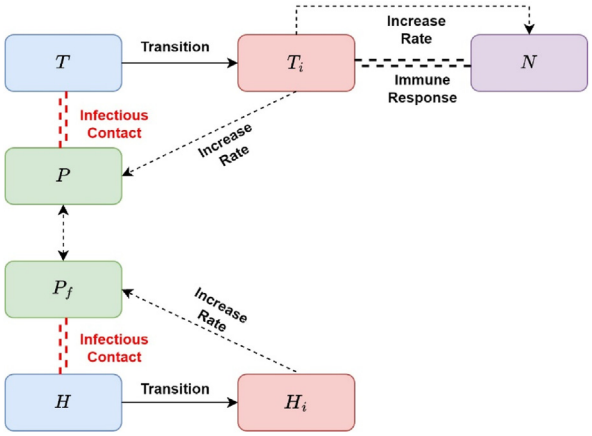

Fig. 6. General compartmental diagram of the variables of interest in within-host models. Here, the variables considered are: T (uninfected target cells), T_i (infected target cells), P (free virus), N (natural killer cells), H (Hofbauer cell population within the pregnant host), H_i (number of infected Hofbauer cells), P_f (viremia level in the fetus).

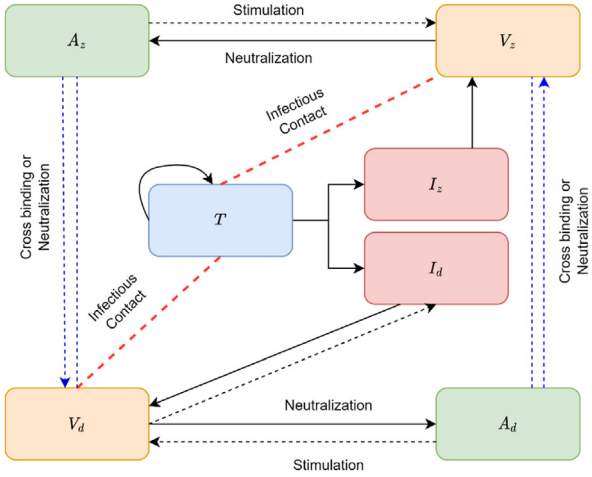

Fig. 7. General compartmental diagram of the variables of interest in the within-host ZIKV–DENV co-infection model (Tang et al., 2020). Here, the variables considered are: T (target cells), A_z (ZIKV-specific antibody), V_z (free ZIKV), I_z (ZIKV infected cells), A_d (DENV-specific antibody), V_d (free DENV), I_d (DENV infected cells).

3.2.6. Data and code availabilities

Our analysis of the 137 selected studies revealed that 77 (56.20%) studies did not use any data, 50 (36.49%) utilized open-access data, and 16 (11.67%) utilized data that was not open-access. We further classified the studies that incorporated data (66 in total) into five distinct categories: number of cases, viral load data, environmental data, demographic data, and mixed data. The last category included articles that incorporated multiple datasets for analysis. Table 4 presents a classification of all studies that integrate data, whether open-access or not, based on the country of study and the type of model employed (i.e., deterministic, stochastic, network-based, or mixed-type) and the principal compartments of interest associated with each of the five categories.

Our analysis of the coding screening process revealed that out of the 137 selected studies, only 14 (10.2%) provided access to their codes. These studies were classified according to the method employed to analyze the mathematical model, which included model calibration, parameter estimation, and qualitative analysis. Additionally, we classified the studies based on the country. Table 5 presents a detailed summary of the coding classification results for the 14 studies.

3.2.7. Model's results and limitations

Among the 137 selected articles, a notable convergence of findings highlighted the key aspects related to the spread and control of Zika. Owing to the wide range of outcomes from the included articles, we divided them into four (4) primary groups: (a) **fitting experimental models with real-world data**, (b) **variables influencing ZIKV outbreaks**, (c) the

Table 2
Range of values for the vector-host, host-vector and host-host (through sexual contact) transmission probability parameters, vertical transmission probability, and mosquito biting rate estimated and/or used in the selected studies. Time is measured in days.

Definition	Range	Country	Reference
Sexual transmission rate	[0, 4.13]	Brazil	He et al. (2020)
	[0.001, 0.1]	Colombia	Sasmal et al. (2018)
	[0, 0.6]	Brazil	(Barros et al., 2019)
	[0, 1]	No specified	Agusto et al. (2017a)
	[0.01, 0.1]	No specified	Baca-Carrasco and Velasco-Hernández (2016)
	0.0296	No specified	Saad-Roy et al. (2018)
Transmission probability vector-human and human-vector	[0.24, 0.61]	Colombia	(A. Ali, Islam, et al., 2022; Alkahtani et al., 2017)
	[0.01, 1.5]	No specified	(Farman et al., 2020; Rezapour et al., 2020)
	[0.1, 0.75]	The Americas	(Champagne et al., 2016; Prasad et al., 2023; Shutt et al., 2017)
	[1/16, 1/8]	Brazil	(Fundzama & Patidar, 2020; Thaiprayoon et al., 2022; Veeresha et al., 2022)
	[0, 0.0138]	India	Dohare et al. (2021)
	2.65e-9	French Polynesia	Nguyen-Van-Yen et al. (2021)
	[0, 0.97]	Asia	(Altaf Khan et al., 2019; Cai et al., 2019; D. Gao et al., 2016; Zhu et al., 2022)
	[0.1, 0.75]	Colombia	(Bessey et al., 2021; Sow, Diallo, & Cherifi, 2022; Yue et al., 2020; R. Zhang & Zhao, 2022)
Mosquito biting rate	[9, 13]	Brazil	Luo et al., 2020
	[0.3, 1]	No specified	Zhang & Zhao, 2022
Neurological disorders (cases reported/total ZIKV cases)	[0.000050,0.000084]	Brazil	He et al. (2020)
	500	No specified	Agusto et al. (2017b)
	0.133	No specified	Soewono and Lahodny (2021)

effectiveness of intervention strategies in ZIKV outbreaks, and (d) **the role of sexual transmission in ZIKV outbreaks**. Each category is described as follows.

A significant number of articles focused on model validation and data-driven applications (Adamu, Bawa, Jiya, & Chado, 2017; Agudelo & Ventresca, 2022; A. Ali, Islam, et al., 2022; Alkahtani, Atangana, & Koca, 2017; Atokolo, Aja, Aniaku, Onah, & Mbah, 2022; Best & Perelson, 2018; Bi, Chen, John, Wu, & Ben-Arieh, 2020; Carlson, Dougherty, Boots, Getz, & Ryan, 2018; Champagne et al., 2016; Dantas, Tosin, & Cunha, 2018; Dohare et al., 2021; Farman et al., 2020, 2022 Fundzama & Patidar, 2020; W. Gao, Ghanbari, & Baskonus, 2019; He, Zhao, Lin, Musaid, & Stone, 2020; Marini, Guzzetta, Rosà, & Merler, 2017; Mina, Beryl Guterman, Allen, & Omer, 2020; Mishra, 2021; Morrison & Cunha, 2020; Nguyen-Van-Yen, Del Moral, & Cazelles, 2021; Olawoyin & Kribs, 2020; Omame & Abbas, 2023; Prasad et al., 2023; Rahman, Bekele-Maxwell, Cates, Banks, & Vaidya, 2019; Rezapour et al., 2020; Shutt, Manore, Pankavich, Porter, & Del Valle, 2017; Suparit et al., 2018; Tang et al., 2020; Thaiprayoon et al., 2022; Veeresha, Akinyemi, Oluwasegun, Şenol, & Oduro, 2022; W. Wang, Zhou, Zhang, & Feng, 2023; Zevika & Soewono, 2018), showcasing the successful alignment of experimental models with real-world data in the context of Zika. The development and validation of mathematical models proved an instrumental role in simulating and comprehending the patterns of Zika spread. Theoretical research indicates that a disease-free equilibrium (DFE) is locally and globally stable when the basic reproduction number $\mathcal{R}0$ is less than one (1), while an endemic equilibrium point is locally asymptotically stable if $\mathcal{R}0$ exceeds one (Adeyemo et al., 2018; Biswas et al., 2020; He et al., 2020). Asymptomatic infections influence ZIKV epidemic forecasts, with a lower infection attack rate (IAR) and a positive correlation between the local temperature and $\mathcal{R}0$ (Danbaba & Garba, 2018; He et al., 2020). Atokolo et al. suggested enhancements for refining deterministic approaches, notably by integrating the Laplace-Adomian decomposition method (Atokolo et al., 2022). This method adeptly handles ordinary and partial differential equations, both linear and nonlinear, at fractional and classical orders, offering increased flexibility. This improvement in methodology can help better calculate $\mathcal{R}0$, particularly in scenarios involving seasonality and temperature dynamics, which are crucial factors in disease transmission dynamics. Those findings suggested external factors, such as mobility patterns, environmental, demographic, and socioeconomic aspects, influenced ZIKV propagation, with a specific emphasis on drastic changes in the basic reproduction number under the change of the parameters' models (Al-Maqrashi, Al-Musalhi, Elmojtaba, & Al-Salti, 2022, 2023; Altaf Khan et al., 2019; Chen et al., 2018; Moreno, Espinoza, Bichara, Holechek, & Castillo-Chavez, 2017).

Using the normalized forward sensitivity index approach, one study determined the most sensitive aspects of the ZIKV transmission model, which include the rate of mosquito bite, the probability of transmission per bite, recruitment rate, recovery rate and the rate of familiarity with the host population (Biswas et al., 2020). Climatic factors are also very important when studying ZIKV transmission; indeed, global warming has a positive correlation with the increase in mosquitoes' survival rate and, thus, ZIKV outbreak length (Atif et al., 2016; Chang et al., 2016). While Suparit and collaborators have also discovered a positive correlation between monthly average biting rates and average monthly temperatures; nonetheless, their findings imply that the biting rate of mosquitoes is primarily responsible for the disease's transmission (Suparit et al., 2018). Predictive models can accurately predict ZIKV outbreaks (Counotte, Althaus, Low, & Riou, 2019; Mina et al., 2020; Muñoz et al., 2017; Suparit et al., 2018) Studies have estimated ZIKV's highest activity during the December–February and March–May seasons

Table 3
The co-infection/co-circulation parameters estimated and used in this review. Time dimension in days.

Parameter	ZIKV	DENV	CHIKV	COVID-19	Value	Reference
Recovery rate of infected humans with both diseases	X	X			0.1	Binder and Pilyugin (2019)
Transition probability from Zika to Dengue co-infection	X	X			[0.14, 0.71]	Binder and Pilyugin (2019)
	X	X			0.52	Bonyah et al. (2019)
Transition probability from Dengue to Zika co-infection	X	X			[0.14, 0.71]	Binder and Pilyugin (2019)
	X	X			0.01	Olawoyin and Kribs (2020)
Co-infection contact rate	X			X	0.2	Omame et al. (2022)
Co-infection disease induced death	X			X	0.015	Omame et al. (2022)
Co-infected recovery rate	X			X	1/15	Omame et al. (2022)
Maximum changing rate of DENV owing to cross-reactive response of ZIKV specific antibody	X	X			[0.265, 0.421]	Tang et al. (2020)
Maximum changing rate of ZIKV owing to cross reactive response of DENV specific antibody	X	X			[0.265, 0.421]	Tang et al. (2020)
Mosquito infected with both to human transmission probability	X	X			[0.05, 0.18]	Bonyah et al. (2019)
	X	X			[0.03, 0.75]	Tang et al. (2019)
Human infected with both to mosquito transmission probability	X	X			[0.01, 0.1]	Bonyah et al. (2019)
	X	X			[0.3, 0.75]	Tang et al. (2019)
Dengue and Zika transmissibility to mosquitoes	X	X			0.2	Olawoyin and Kribs (2020)
Dengue and Zika transmissibility to humans	X	X			0.09	Olawoyin and Kribs (2020)

(Counotte et al., 2019; Muñoz et al., 2017). In addition, seasonal variations in birth rate may provide natural population-level protection against the spread of ZIKV (Suparit et al., 2018). Seasonal and regional weather variability also affects ZIKV transmission. Various studies have correlated the highest transmission activity of ZIKV with high temperatures and annual cumulative precipitation (Lourenço et al., 2017; Okuneye et al., 2017; Sadeghieh et al., 2021). Some studies have estimated high transmission peaks when temperatures and precipitation fall within 25–26.4 °C and 90–128 mm, respectively, typically in June, July, and September (Lourenço et al., 2017; Okuneye et al., 2017), while some estimated optimal temperature for the ZIKV transmission to be between 25 and 35 °C (Huber et al., 2018; Lourenço et al., 2017). ZIKV transmission varies seasonally and geographically, with population density and human-mosquito mobility being the main factors influencing its spread (L. et al., 2019). Some studies suggest that ZIKV transmission trends may depend on the geographical location of the ongoing outbreaks. ZIKV may behave in island communities similar to DENV, spreading through large, erratic outbreaks that involve a sizable percentage of cases that are asymptomatic or unreported, which may sustain the likelihood of a second wave of virus transmission unlike mainland areas (Kucharski et al., 2016). Transmission intensity peaks at intermediate host movement levels are influenced by the human commuting frequency and neighboring patch dedication to vector surveillance and control activities (Li & Zhao, 2021; Stone, Schwab, Fonseca, & Fefferman, 2017) Individual transmission (vertical) accounts for almost 40% of ZIKV propagation, while autochthonous transmission is impacted by population immunity (X. S. Luo, Imai, & Dorigatti, 2020).

However, certain studies explored the efficacy of intervention strategies in controlling ZIKV infection rates, offering a critical perspective on ongoing efforts to curb its spread (A. Ali, Iqbal, et al., 2022; H. M. Ali & Ameen, 2021; Alzahrani et al., 2021; Angina et al., 2022; Bañuelos, Martinez, Mitchell, & Prieto-Langarica, 2019; Bonyah et al., 2019; Chaikham & Sawangtong, 2017; Durham et al., 2018; González-Parra, Díaz-Rodríguez, & Arenas, 2020; Goswami, Srivastav, Ghosh, & Shanmukha, 2018; Huo et al., 2023; Imran et al., 2018; Kumar Goswami & Shanmukha, 2020; Massad, Coutinho, & Wilder-Smith, 2019; Miyaoka, Lenhart, & Meyer, 2019; Goswami & Shanmukha, 2020; Ndaïrou et al., 2018; Okyere, Olaniyi, & Bonyah, 2020; Padmanabhan, Seshaiyer, & Castillo-Chavez, 2017; Padmanabhan & Seshaiyer, 2017; Roy, Upadhyay, & Caur, 2020; Sharma, Singh, Singh, & Castillo, 2021; Srivastav, Goswami, Ghosh, & Li, 2018, 2019; Tang et al., 2016, 2018; Tchepmo Djomegni, Olupitan, & Dougmo Goufo, 2021; Tuncer & Martcheva, 2021; Ukanwoke, Okuonghae, & Inyama, 2022; L. Wang, Zhao, Oliva, & Zhu, 2017; L. Wang & Zhao, 2019; X. Wang, Shen, Xiao, & Rong, 2019; Wattanasirikosone & Modnak, 2021; Xue, Cao, & Wan, 2021; Zhao, Wang, Oliva, & Zhu, 2020). These studies have provided a refined exploration of strategies aimed at mitigating the impact of Zika. Reducing contact rates between susceptible hosts and infected mosquitoes and increasing cure rates within a plot can limit secondary infections, making interventions aimed at reducing mosquito-human interactions or increasing mosquito mortality useful for reducing ZIKV prevalence (Rahman et al., 2019). Few studies have evaluated the impact of population immunity on ZIKV spread which is as effective as ZIKV outbreak control, even though protective measures against mosquito bites are far superior (Article, Mpeshe, Nyerere, & Sanga, 2017; Bañuelos et al., 2019; Best & Perelson, 2018; Denu & Son, 2021; Durham et al., 2018; Soewono & Lahodny, 2021; Tönsing et al., 2018; L. Wang & Zhao, 2019). Thus, vaccination, personal protection, condom use, and insecticide spraying are the most

Table 4
Data description for mathematical models categorized by country, model type, interest, explanatory data and references. Of the total number of studies, 36.49% utilized open-access data, and 11.67% did not have open-access data.

Country	Model-type	Principal variable	Explanatory data	Open-access	Reference
Brazil	Deterministic	Human/mosquito compartments	Number of cases	Yes	(Barros et al., 2019; Cruz-Pacheco et al., 2019; Dantas et al., 2018; Miyaoka et al., 2019; Ndaïrou et al., 2018; Omame et al., 2023; Ukanwoke et al., 2022; L. Wang & Zhao, 2019; Yuan et al., 2021; Zhao et al., 2020)
			Demographic data	No	(Lourenço et al., 2017; Omame & Abbas, 2023)
			Environmental data	No	Sadeghieh et al. (2021)
			Mixed-data	Yes	(He et al., 2020; Massad et al., 2019; L. Wang et al., 2017)
	Mixed-type		Number of cases	Yes	Roy et al. (2020)
Colombia	Deterministic	Human/mosquito compartments	Number of cases	Yes	(Agudelo & Ventresca, 2022; A. Ali, Islam, et al., 2022; Al-Maqrashi et al., 2023; Alzahrani et al., 2021; Biswas et al., 2020; González-Parra et al., 2020; Huo et al., 2023; Ibrahim & Dénes, 2021; L. et al., 2019; Moreno et al., 2017; Sasmal et al., 2018; Sow et al., 2022)
			Environmental data	Yes	Huber et al. (2018)
	Mixed type		Number of cases	Yes	Towers et al. (2016)
Costa Rica	Deterministic	Human/mosquito compartments	Number of cases	Yes	(Dénes et al., 2019; Mishra, 2021; Sanchez et al., 2019; Srivastav et al., 2018, 2019)
	Network		Demographic data	No	(X. F. Luo et al., 2021)
French Polynesia	Deterministic	Human/mosquito compartments	Number of cases	Yes	(Kucharski et al., 2016; Prasad et al., 2023; Rahman et al., 2019)
	Hybrid		Demographic data	No	(Champagne et al., 2016; Counotte et al., 2019)
	Stochastic		Mixed-data	Yes	Nguyen-Van-Yen et al. (2021)
Mexico	Deterministic	Human/mosquito compartments	Number of cases	Yes	(Okuneye et al., 2017)
	Deterministic	Human/mosquito compartments	Number of cases	Yes	(Chen et al., 2018; Mina et al., 2020; Tuncer et al., 2018)
	Mixed type		Mixed-data	Yes	Marini et al. (2017)
			Demographic data	Yes	Carlson et al. (2018)
More than one country	Deterministic	Human/mosquito compartments	Environmental data	Yes	(Muñoz et al., 2017; Zhu et al., 2022)
			Mixed-data	Yes	Shutt et al. (2017)
	Network		Demographic data	No	Durham et al. (2018)
			Mixed-data	Yes	(X. S. Luo et al., 2020)
No country	Deterministic	Human/mosquito compartments	Number of cases	Yes	Okyere et al. (2020)
		Cell/virus compartments	Viral load data	Yes	(Tang et al., 2020; Tuncer & Martcheva, 2021)

economical and efficient methods to lower the prevalence of ZIKV in the community (A. Ali, Iqbal, et al., 2022; Rezapour et al., 2020). Antiviral medication may be effective in limiting ZIKV spread; however, avoiding mosquito bites may be more effective in limiting the disease outbreak in the general population (Denu & Son, 2021; Soewono & Lahodny, 2021). Decreasing ZIKV propagation passes through reducing relevant transmission parameters such as protective measures since they reduce the bite rate and thus affect the basic reproduction number (Chen et al., 2018; Kumar Goswami & Shanmukha, 2020; L. et al., 2019; Ndaïrou et al., 2018; Okyere et al., 2020). Chen et al. (Chen et al., 2018) suggested that reducing the reproduction number $\mathcal{R}0$ is insufficient and not enough but should be combined with the use of protective measures to be able to reduce ZIKV infection rate. Targeting mosquitoes is the most effective technique, although risky sexual behaviour may increase the impact of ZIKV sexual transmission on illness risk, according to a model that considers Zika as a vector-borne disease as well as a sexually transmitted disease (Agudelo & Ventresca, 2022; Al-Maqrashi et al., 2022; Cruz-Pacheco, Esteva, & Ferreira, 2019; Dohare et al., 2021; Maxian et al., 2017).

Further investigations revealed the limited role of sexual transmission in causing widespread ZIKV outbreaks, enriching the understanding of the complex dynamics involved in Zika transmission and providing valuable insights into the specific role of sexual transmission in the broader context of Zika (Barros et al. n.d.; Biswas et al., 2020; Cruz-Pacheco et al., 2019; Dénes, Ibrahim, Oluoch, Tekeli, & Tekeli, 2019; D. Gao et al., 2016; Hussain et al., 2021; X. F. Luo, Jin, He, & Li, 2021; Maxian et al., 2017; Sasmal, Ghosh, Huppert, & Chattopadhyay, 2018; Terefe, Gaff, Kamga, & van der Mescht, 2018; Tönsing et al., 2018; Towers et al., 2016; L. Wang & Wu, 2022; Zhu et al., 2022). Some studies have evaluated human and vectorial factors that impact ZIKV transmission. The three controllable parameters defining $\mathcal{R}0$ and influencing the spread of the disease are the mosquito bite rate, rate of sexual transmission, and mosquito-human ratio (Sasmal et al., 2018). The sexual transmission pathway may not significantly impact outbreak likelihood, but when $\mathcal{R}0 > 1$, it can lead to higher infectious patient numbers

Table 5
Code availability for mathematical models categorized by country, analysis method, and data type. A total of 10.2% of the studies included in this review reported the codes.

Country	Analysis Method	Demographic data	Mixed data	Number of cases	Viral load data
Brazil	Model calibration			(Morrison & Cunha, 2020; Suparit et al., 2018; van den Driessche, 2017)	
	Mixed method	(Lourenço et al., 2017; Omame & Abbas, 2023)		(Barros et al., 2019; Cruz-Pacheco et al., 2019; Dantas et al., 2018; Miyaoka et al., 2019; Ndaïrou et al., 2018; Omame et al., 2023; Roy et al., 2020; Ukanwoke et al., 2022; L. Wang & Zhao, 2019; Yuan et al., 2021; Zhao et al., 2020)	
French Polynesia	Mixed method	(Champagne et al., 2016; Counotte et al., 2019)	Nguyen-Van-Yen et al. (2021)		
USA	Mixed method	Marini et al. (2017)		(Chen et al., 2018; Mina et al., 2020; Tuncer et al., 2018)	
More than one country	Model calibration	Durham et al. (2018)			
None	Mixed method				(Tang et al., 2020; Tuncer & Martcheva, 2021)

much earlier than when only considering mosquito bite transmission routes (Terefe et al., 2018). Various studies have concluded that both the mosquito bite rate and human-to-human sexual transmission are the two main parameters triggering variations in the $\mathcal{R}0$ number and thus in ZIKV infection rates (Agudelo & Ventresca, 2022; Dénes et al., 2019; Dohare et al., 2021; X. F. Luo et al., 2021; Srivastav et al., 2018; Towers et al., 2016). The majority of the initial and subsequent Zika outbreaks are produced by vectorial transmission, while sexual transmission has a larger early-stage role, particularly in temperate locations where ZIKV transmission is reduced (Al-Maqrashi, Al-Musalhi, Elmojtaba, & Al-Salti, 2023; Barros et al. n.d.; Maxian et al., 2017; Yuan, Lou, He, Wang, & Gao, 2021). De Barros et al. (Barros et al., 2019) showed that sexual contact spreads the Zika virus three times faster than mosquito bites. Nevertheless, other studies show that sexual transmission has little to no effect on $\mathcal{R}0$, which contradicts these findings (Biswas et al., 2020; Dohare et al., 2021; Terefe et al., 2018). Dohare et al. (Dohare et al., 2021) argued that sexual transmission of the disease has not affected its transmission, which runs counter to most studies. Another feature of the human component is population immigration, which may lower the rate of secondary infections even if it may not have a significant impact on the dynamics of disease in communities, according to some studies (Tchepmo Djomegni et al., 2021). A study conducted by Baca-Yamakazi et al. (Yamazaki, 2019) suggests that migration and sexual transmission significantly impact the spread of the virus, with migration causing progressively smaller outbreaks and sexual transmission affecting their size.

Another important aspect to consider in this review is the impact of co-infection and co-circulation of ZIKV with other pathogens on transmission dynamics. Co-infections are very complex to understand because the interaction among the involved factors leads to heterogeneous findings throughout the included studies in our review. While some studies suggested increased ZIKV infections and the spread of co-infections with increased Dengue vaccination rate (Omame, Isah, & Abbas, 2023; Omame & Abbas, 2023; Tang et al., 2016; L. Wang & Zhao, 2019), other studies found that vaccination against dengue may help reduce ZIKV infections (Hussain et al., 2021; Tang, Huo, Xiao, Ruan, & Wu, 2018, 2019). The heterogeneity of these findings can be attributed to the model not accounting for asymptomatic and recovered cases (Omame & Abbas, 2023; Omame et al., 2022, 2023).

Despite the significance of co-circulation and co-infection of ZIKV with other pathogens, only a few mathematical models have delved into this aspect (Binder & Pilyugin, 2019; Bonyah et al., 2019; Okuneye et al., 2017; Omame et al., 2022, 2023; Omame & Abbas, 2023; Riou, Poletto, & Boëlle, 2017; Tang et al., 2018, 2019, 2020; L. Wang & Zhao, 2019; Xue et al., 2018). ZIKV frequently co-circulates with other *arboviruses* such as DENV and CHIKV in numerous regions globally. Consequently, research efforts have primarily focused on analyzing the dynamics of COVID-19 in isolation rather than investigating potential co-infections or co-circulation with other infectious agents (Omame & Abbas, 2023; Omame et al., 2023). However, these results shed light on various aspects of co-circulating diseases such as COVID-19, Zika, Dengue, and Chikungunya. For instance, Omame et al. (Omame et al., 2023) underscore the potential of COVID-19 prevention measures in reducing the burden of co-infections with other *arboviruses*, highlighting the pandemic's negative impact on controlling these diseases. Additionally, Xue et al. (Xue et al., 2018) use a mathematical model for comparing *Wolbachia* strains' effectiveness in controlling virus spread, demonstrating significant reductions in transmission rates. Furthermore, Omame et al. (Omame & Abbas, 2023) emphasize the importance of vaccination efforts, showing potential positive impacts on Zika dynamics and triple infection spread. However, Wang et al. (L. Wang & Zhao, 2019) warn of potential negative consequences of Dengue

vaccination on Zika control. Huber et al. (Huber et al., 2018) highlight the influence of seasonal temperature variations on disease transmission, underlining the necessity of considering environmental factors alongside human activities and socioeconomic conditions for accurate outbreak prediction and management. In fact, when assessing vector competence in ZIKV transmission in scenarios of co-infection with other *flaviviruses*, *Aedes aegypti* has the highest reproduction number for both ZIKV and DENV at the same mosquito concentrations, indicating that Dengue and Zika infection rates would rise in regions where *Aedes aegypti* populations are growing, whereas *Aedes albopictus* spreads CHIKV more successfully (A. Ali, Iqbal, et al., 2022; Altaf Khan et al., 2019; Xue et al., 2018). ZIKV and DENV viruses have the same risk of spreading through mosquito bites; however, human infections with DENV and ZIKV cause quite different behavioural changes, leading to very different epidemics (Xue et al., 2018).

Despite the important results found in the revised articles, they made substantial contributions to the understanding of the multifaceted challenges posed by Zika. 81.02% of the total studies did not mention any limitations in their research, suggesting that the studies were conducted without significant difficulties or challenges. However, 18.91% reported some limitations. Those limitations were categorized into two main categories: (a) **Structural limitations of the mathematical models**, and (b) **Data quality issues**.

On the one hand, 14.59% of the studies reported structural limitations of the mathematical models. This limitation includes manuscripts featuring simplified assumptions, reduced model complexity, and questionable robustness of the assumptions made by the model, which may render it sensitive to external conditions (H. M. Ali & Ameen, 2021; Alkahtani et al., 2017; Barros et al. n.d.; Bradley & Jackson, 2008; Carlson et al., 2018; Durham et al., 2018; Fundzama & Patidar, 2020; X. F. Luo et al., 2021; Padmanabhan & Seshaiyer, 2017; Prasad et al., 2023; Rahman et al., 2019; Roy et al., 2020; Srivastav et al., 2018; Stone et al., 2017; Tang et al., 2016, 2020; Xue et al., 2021). Population-level modelling may not fully describe the variability at the local and neighborhood level for the prevalence of Zika or mosquito abundance (Stone et al., 2017). The investigation focused on the immune response of antibodies, neglecting complex immune cell involvement (X. F. Luo et al., 2021). A few investigations revealed that cases may not have been reported to the appropriate authorities and that county-level aggregated risk tends to overestimate the probability of infection, especially when employing stochastic parameters in a deterministic model (Zevika & Soewono, 2018). Relevant variables, such as human mobility and population immunity, were not evaluated, resulting in insufficient evaluation of these features.

In contrast, 4.37% of the total studies reported data quality issues as limitation (Champagne et al., 2016; Fitzgibbon, Morgan, & Webb, 2017; Kucharski et al., 2016; Mina et al., 2020; Miyaoka et al., 2019; Omame et al., 2022). For instance, Mina et al. (Mina et al., 2020) reported lack of specificity regarding the sources and reliability of the data used to develop the stochastic epidemiologic model and validate its predictions. Miyaoka et al. (Miyaoka et al., 2019) reported completeness of the data used for parameter estimation and numerical simulations, particularly concerning the first Zika outbreak that occurred in Brazil's state of Rio Grande do Norte in 2015. Kucharski et al. (Kucharski et al., 2016) reported a potential data quality issue in the reliance on estimates and assumptions rather than concrete, verifiable data to inform key parameters in the mathematical model used to examine the Zika outbreak in French Polynesia during 2023-2014.

At this point, it is important to consider that only 5.10% of the studies employed mathematical modelling and data analysis to gain insights into the spread and impact of ZIKV. However, these studies have focused more on theoretical modelling and simulations rather than validating models using data. In terms of data accessibility, 36.49% of the studies incorporated data, reflecting their significance as a pertinent public health concern. Public health officials routinely gather and disseminate such data on a global scale (Kamradt-Scott, 2011), while open-access codes were almost unavailable, representing 10.12% of the total studies. Now, in the context of the mathematical modelling of Zika considered in this review, it was found that “data quality issues” refers to the reliability and completeness of the information used in empirical studies for calibration, validation, or parameter estimation of the mathematical models. This occurs when studies fail to provide sufficient detail or transparency regarding the data sources, collection methods, or specific variables measured. As a result, uncertainties or biases may exist in the data, which can affect the accuracy and robustness of the mathematical models developed based on these data. Most research models' validity is limited due to poor data quality, with most studies focusing on accessible data (Zhu et al., 2022).

4. Discussion

The purpose of this scoping study was to investigate the application of mathematical modelling of ZIKV to comprehend the dynamics of its transmission and interactions with other infections. Through rigorous application of the PRISMA guidelines (Tricco et al., 2018), the published protocol (Romero-Leiton, Acharya, et al., 2023), and extensive database searches, we included 137 studies from an initial pool of 2446. Our analysis highlighted a diverse range of mathematical modelling approaches, with a predominant emphasis on vector-host compartmental models.

Mathematical modelling of ZIKV provides insights into predicting and understanding the infection patterns (Best & Perelson, 2018). Frequently forecasted occurrences included spatial expansion, $\mathcal{R}0$ values, epidemic patterns, the burden of microcephaly, and the capability of vectors. As anticipated, most research occurred in the Americas, with the highest number of reported cases during the pandemic. Nevertheless, it is important to highlight the substantial global knowledge gap regarding ZIKV dynamics in Africa. This continent, where ZIKV originated and remains endemic, poses a potential risk for future epidemics.

Some reviews have focused on identifying mathematical and predictive models for Zika and other arboviruses, collectively revealing a dynamic landscape within the context of vector-borne diseases (Aguiar et al., 2022; Berthiaume, Côté, & Mascarenhas, 2019; Caicedo et al., 2021; Kobres et al., 2019; Ogunlade, Meehan, Adekunle, & McBryde, 2023; Sadeghieh, Waddell, Ng, Hall, & Sargeant, 2020; Wiratsudakul et al., 2018). There are similarities across the model architectures used in ZIKV transmission mathematical models in our current and previous reviews. Our findings suggested that the predominant approach in the mathematical modelling of Zika involved vector-host structures, incorporating sexual and vertical transmission (97%). A common thread across other reviews was the identification of diverse model architectures employed to understand and predict the dynamics of vector-borne diseases (Aguiar et al., 2022; Caicedo et al., 2021; Ogunlade et al., 2023; Wiratsudakul et al., 2018). Compartmental, spatial, metapopulation, network, and individual-based models have frequently been used (Wiratsudakul et al., 2018) reflecting a versatile approach to disease modelling. Furthermore, certain assessments have indicated a gradual transition towards more intricate models in the modelling of diseases transmitted by mosquitoes (Aguiar et al., 2022; Kraemer et al., 2019). This shift has been facilitated by advancements in computational power and the availability of extensive real-world data, emphasizing the need for refined modelling frameworks, especially in the context of evolving epidemics (Aguiar et al., 2022). However, differences between the results obtained in this review and those of other reviews were also observed. First, in terms of disease focus, some reviews mainly concentrated on a specific virus (e.g., Zika, Chikungunya, Dengue, or Mayaro), while others broadened the scope to include various mosquito-borne pathogens simultaneously (Reiner et al., 2013). This divergence in focus influenced the modelling parameters and outcomes. Second, geographical emphasis varied across studies, with some mainly concentrating on the Americas (Caicedo et al., 2021; Kobres et al., 2019), and others adopting a global perspective (Aguiar et al., 2022; Kobres et al., 2019; Wiratsudakul et al., 2018). These differences influenced the generalizability and applicability of the models.

A second similarity lies in the limitations found in this review, mainly attributed to the lack of data and the structural complexity assumptions of the mathematical models (structural limitations). These limitations parallel those found in the existing reviews. For example, some reviews have also reported data limitations for model calibration (Berthiaume et al., 2019; Kobres et al., 2019), such as a lack of confidence in historical case counts, vectors, and demographic data. Few studies have incorporated near real-time web data, pathogen genomic information, and social science and behavioural data (Kobres et al., 2019), suggesting potential avenues for improvement in data diversity. Model complexity assumptions have also been a concern (Wiratsudakul et al., 2018). While the trend towards more complex models was noted, the balance between model complexity and practical utility remained a challenge. The limitations of each model in capturing the full complexity of vector-borne disease dynamics should be acknowledged. The geographical representation of mathematical models has also been a limitation, with many studies focusing on the Americas (Caicedo et al., 2021; Kobres et al., 2019), raising questions about the generalizability of the findings to other regions. The need for more extensive studies on ZIKV in diverse geographical settings, especially in Africa, is evident (Article et al., 2017). Another important issue is model transparency. In this review, 36.49% of the studies included open-access data, and only 10.2% shared their codes. This underscores the importance of model transparency as a critical public health aspect. The observed variation in transparency levels regarding reporting models, open-access data, code availability, and uncertainty assessment (Kobres et al., 2019) emphasizes the essential requirement for standardized reporting practices. Such standardization is crucial for improving the reproducibility and transparency of modelling efforts across different studies.

A significant difference in this review with respect to others found in the literature was the incorporation of interactions of ZIKV with other pathogens (not only other arboviruses). This review found that 10.21% of studies incorporated this type of interaction. Models that considered this phenomenon demonstrated that the transmission of one pathogen could be either amplified or reduced based on the specific interactions between co-existing pathogens, highlighting the importance of considering disease severity and the potential for adverse health outcomes (Olawoyin & Kribs, 2020; Sánchez-Duque et al., 2018). Some of these studies have focused on the mathematical models used to describe the simultaneous concurrence with other important arboviruses, such as DENV and CHIKV (Bonyah et al., 2019; Huber et al., 2018; Olawoyin & Kribs, 2020; Omame & Abbas, 2023; Omame et al., 2022, 2023; Romero-Leiton, Sekkak, Arino, & Nasri, 2023; Tang, Zhou, Xiao, & Wu, 2019), which differ in disease focus, research objectives, methodologies, and scope. They highlight the diversity and specificity of research in the field of mathematical modelling for vector-borne diseases. Each study addressed different diseases, utilized distinct research methodologies, and had unique research objectives, advancing a greater awareness of the mechanisms underlying these illnesses. Collectively, these investigations highlight the value of mathematical modelling in the field of disease epidemiology and the need for different approaches to each disease and research question. However, there has been a limited focus on the simultaneous concurrence of ZIKV with other pathogenic agents, such as COVID-19, except for a few studies (Omame & Abbas, 2023; Omame et al., 2022) and HIV (Romero-Leiton, Sekkak, et al., 2023).

A critical investigation of the simultaneous concurrence of ZIKV with other diseases holds great significance for public health and epidemiological research (Olawoyin & Kribs, 2020). The interaction between Zika and concurrent infections can worsen clinical outcomes, complicate diagnostic procedures, and pose substantial challenges for disease management (Mercado-Reyes et al., 2019). Understanding these complex interactions is crucial in designing preventive and control strategies. By explaining synergistic effects and potential cross-reactivity, researchers can contribute to the development of more effective diagnostic tools, therapeutic interventions, and vaccination strategies (Sánchez-Duque et al., 2018). Moreover, solving the intricate set of simultaneous concurrences can provide valuable insights into the mechanisms underlying viral pathogenesis and host immune responses. This knowledge is essential for advancing the global preparedness for emerging

infectious diseases. Therefore, continued research in this field is vital to secure public health and mitigate the impact of Zika infection in conjunction with other infectious agents.

Deterministic models are often easier to create. Henceforth, they are largely used in ZIKV transmission mathematical models. However, they may not adequately capture the inherently stochastic nature of processes such as epidemics, leading to underestimation of uncertainty. These models tend to ignore the complexity, variability, and ongoing changes in human and mosquito populations, ignoring unanticipated sequencing risks that may have a significant impact on the dynamics of the future spread of ZIKV infection. Deterministic models lack heterogeneity, which can hinder ZIKV outbreak patterns because they cannot estimate patch inhabitants' responses (Moreno et al., 2017). Deterministic, vector-host assumed uniform mixing between humans and mosquitoes and thus did not incorporate spatiotemporal heterogeneities into their model (Lourenço et al., 2017). Some studies used notified cases, so the recovered cases and asymptomatic cases were not taken into consideration. Modelers often had to rely on assumptions in deterministic models due to missing variables in the collected data (Moreno et al., 2017). When estimating parameters related to the spread of ZIKV, stochastic models are necessary due to their ability to account for climatic factors, seasonal variations, and inconsistent human-mosquito contact. Deterministic models tend to overlook these factors, potentially affecting their estimates (Kucharski et al., 2016; Rahman et al., 2019). Stochastic epidemic models lack prediction of epidemic peaks and outbreaks with accuracy, especially with the SEIR model (Nguyen-Van-Yen et al., 2021).

Compartmental models simplify disease processes but may oversimplify complex ones, leading to limitations. On the other hand, network epidemic models, which consider heterogeneous contact numbers, offer a more realistic representation. Nevertheless, local and neighborhood-level variation in mosquito abundance or Zika prevalence may not be completely captured by population-level modelling (Adeyemo et al., 2018; Alshehri & Hajji, 2022; Durham et al., 2018).

Data-driven models used to predict ZIKV's transmission were limited by computational difficulties and the unavailability of certain data. They were mainly used to predict the spread of ZIKV. One of the main limitations of these models was the assumption that human behavior remains constant during outbreaks or infections, but actual cases may be less mobile or lead people to avoid contact situations or apply personal repellent more often (X. S. Luo et al., 2020; Stone et al., 2017). Additionally, they did not account for heterogeneity in the human population, such as duration of stay and risk of infection (X. S. Luo et al., 2020). Due to the lack of vector data, ZIKV model prediction accuracy in studies that aim to study co-infections with other *Flaviviruses* is sensitive to cross-reactivity in populations not previously exposed to DENV(Champagne et al., 2016). Additionally, data-driven models were able to accurately predict outbreaks, but most of them did not include relevant variables, including solely temperature and rainfall. Consequently, these predictive models failed to account for human components such as direct human-to-human transmission, human population migration or co-infections or mixed states (Counotte et al., 2019; Mina et al., 2020; Muñoz et al., 2017); thus, they tend to underestimate the ZIKV risk of infection. The predictive models assume uniform sensitivity, infectivity, and homogenous mixing between at-risk human groups and mosquitoes, with spatial and time-invariant parameters. The model's accuracy depends on geographical and temporal heterogeneity during Zika outbreaks (Champagne et al., 2016; Shutt et al., 2017). Additionally, by overestimating high attack rates, mathematical models, including vectorial transmission, run the risk of undermining the density-dependence assumption and the proportionality between infected mosquitoes and the infection force (Champagne et al., 2016).

When studying factors that influence the disease spread, they ignore non-constant human-mosquito contact situations and seasonal transmission variations due to climatic factors, and they assume homogeneity among the included variables (Kucharski et al., 2016; L. et al., 2019; Mina et al., 2020; Rahman et al., 2019; Towers et al., 2016). Models incorporating the sexual transmission aspect into modelling ZIKV overlook the role of male-male and female-female (biological sex susceptibility) in the spreading dynamics (Agudelo & Ventresca, 2022). In addition, we did not find any studies that account for other sexual transmission routes, which limits our understanding of the real influence of ZIKV sexual transmission on the spread of the disease. Various studies did not incorporate environmental factors despite being strongly correlated with virus spread (Agudelo & Ventresca, 2022).

We examined the evolution of the ZIKV epidemic and investigated the critical factors influencing the intensity of the epidemic. These findings imply that environmental and demographic data should be addressed while developing appropriate containment measures. The basic reproduction number $\mathcal{R}0$ is a crucial idea in infection models, regardless of whether they study the dynamics of an epidemic or the dynamics inside specific hosts. Despite notable advances, challenges persist in terms of data availability, model complexity, and generalizability. Consequently, future research efforts should prioritize addressing these limitations to improve the reliability and applicability of mathematical models in guiding public health interventions.

5. Conclusion

In conclusion, this paper emphasizes how mathematical modelling may be used to describe the complex dynamics of ZIKV transmission and how it interacts with other infectious diseases, including Dengue, Chikungunya, and COVID-19. These modelling efforts have proven invaluable in identifying the multifaceted determinants of ZIKV transmission, ranging from human mobility patterns to environmental, socioeconomic, and demographic factors. Moreover, they shed light on the potential simultaneous concurrence of multiple pathogens within the same geographic regions and their impact on the disease burden.

Nevertheless, our review highlights certain limitations of the current view of modelling studies. The structural limitations inherent in the model formulation, such as the assumption of population homogeneity, require consideration and refinement to represent real-world complexities more accurately. Additionally, the need for high-quality data on crucial parameters, such as mosquito biting rates and transmission probabilities, also presents a substantial challenge that calls for enhanced data collection efforts to effectively inform and validate these models.

Although mathematical modeling has greatly advanced our understanding of ZIKV transmission, further research is required. The integration of real data and model validation techniques is an important area for improvement. With only a small percentage of studies thoroughly validating models using empirical data, future research would greatly benefit from rigorous testing of models against diverse, high-quality datasets. Improved data quality, including collection methods, variable specificity, and transparency of data sources, could reduce bias and enhance the robustness of predictions, leading to more reliable public health interventions. Greater emphasis on the integration of human behavioral trends, climatic influences and concomitance with other diseases could also address some of the structural limitations of current models, which often neglect these factors.

It is important to build models that not only simulate, but also adapt to changing real-world conditions in endemic regions, such as changes in human behavior or immune responses, and the impact of concomitant diseases. Future models should also emphasize adaptability, by incorporating stochastic parameters that can be adjusted according to various epidemiological scenarios. The integration of advanced computational techniques can help optimize parameter estimation, enabling epidemics to be forecast more effectively. In addition, prioritizing open-access codes and transparent methodologies will enhance reproducibility and collaboration between research communities.

CRediT authorship contribution statement

Jhoana P. Romero-Leiton: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Elda K.E. Laison:** Writing – review & editing, Writing – original draft, Validation, Methodology. **Rowin Alfaro:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **E. Jane Parmley:** Writing – review & editing, Writing – original draft, Resources, Funding acquisition. **Julien Arino:** Writing – original draft, Funding acquisition, Conceptualization. **Kamal R. Acharya:** Writing – original draft, Methodology, Conceptualization. **Bouchra Nasri:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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Conflict of interest statement

We would like to emphasize that Dr. Arino is on the editorial board. However, Dr. Arino was not part of the review process of this manuscript. Furthermore, we also acknowledge that the results of this manuscript was not influenced by any financial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idm.2024.12.016.

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