

REVIEW

DENGUE PREVENTION AND TREATMENT:

A SCOPING REVIEW

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ABSTRACT

Dengue is an arbovirus with significant socioeconomic impact worldwide and in Brazil. This scenario led the Brazilian Ministry of Health to launch a preventive manual in 2009 and a treatment manual in 2016 to deal with this disease. Between the year of these publications and today, numerous therapeutic options emerged and were discussed in the literature. So, this independent research aims to investigate dengue treatment methods presented in the literature. A scoping review was forged following the Problem, Concept, and Context (PCC) strategy, following the guiding questions: “What methods for preventing dengue have been presented in the scientific literature in the last 14 years?” “What methods for treating dengue have been presented in scientific literature in the last 8 years?” The literature search was performed in PubMed, LILACS, Cochrane, and Scielo using the descriptors “Dengue AND Prevention” and “Dengue AND treatment”. Almost 18 thousand studies were evaluated. Of these, 7,474 discussed dengue preventive measures, while only 17 were included in the final text. Simultaneously, 10,462 were dedicated to dengue treatment, with just 28 articles included in the final text. Numerous preventive and therapeutic measures have emerged in recent years; however, further comprehensive studies are imperative to substantiate their effectiveness on a large scale and assess their viability for widespread implementation. In this sense, vaccines and supportive measures, such as fluid therapy, remain primary interventions in dengue prevention and treatment, serving as cornerstones in mitigating the impact of this disease.

KEY WORDS: arboviruses; DENV; *Aedes*; hemorrhagic fever; dengue prevention; dengue treatment; epidemiology.

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INTRODUCTION:

Dengue is an arbovirolosis caused by four viral subtypes (DENV1 to DENV4). All of them belong to the *Flaviridae* family and are transmitted by mosquitoes, notably those of the *Aedes* genus. Dengue presents different forms of manifestation, which may range from asymptomatic to severe conditions, such as dengue hemorrhagic fever and dengue shock syndrome. This condition presents important socioeconomic impacts worldwide (Khan et al., 2023).

In this sense, it is noted that dengue has doubled cases since the 1990s, with an estimated 60 million yearly cases worldwide, costing nine billion dollars annually (Stanaway et al., 2016). In Brazil, cases increased by 232.7% and deaths by 639.0% from 2000 to 2015, with a 16% rise in 2023 compared to 2022 (Junior et al., 2022). By mid-2024, more than six million probable dengue cases were observed in the country, with almost five thousand deaths confirmed (Ministry of Health, 2024b).

Given the epidemiological scenario generated by dengue in Brazil, many efforts have been made to manage this condition. In this sense, the Brazilian Ministry of Health launched a series of manuals discussing its prevention and treatment to standardize assistance for dengue in the country. From this perspective, the last manual on dengue prevention is dated from 2009 (Brazil, 2009). At the same time, a manual on dengue treatment was released in 2016, and a new version was released in 2024 (Brazil, 2016; Brazil, 2024). Nonetheless, considerable time has elapsed since the publication of these manuals, with new proposals for prevention and treatment being introduced and discussed in the literature.

Therefore, this scoping review was developed independently of the reviews in the Brazilian manuals to investigate the forms of dengue prevention and treatment presented in the literature.

MATERIAL AND METHODS

Study characterization

The current investigation is identified as a scoping review focusing on dengue prevention and treatment practices. Its objective is to provide a comprehensive perspective on the subject, consolidating the evidence available in the literature in a clear and organized manner. For that, this study follows the principles outlined by the Joanna Briggs Institute for scoping reviews and uses the Rayyan[®] digital software to perform the review (Tricco et al., 2018; Peters et al., 2020).

Given that this research solely involved a search and analysis of literature, seeking approval from the Ethical and Research Committee was unnecessary.

Search strategy

Two guiding questions were produced to orient the literature search, both created with PCC strategy (Population/Patient/Problem, Concept, and Context). The “P” component was identified as the high prevalence and significant health and economic impacts of dengue, being the same for the two subjects. The first “C” encompassed the approaches to prevent dengue, concerning dengue prevention and the approaches to treat dengue, in regarding the dengue treatment. The second “C” involved extracting data from articles published in the past 8 and 14 years, respectively, for dengue treatment and prevention, bridging the time between the present day and the reviews promoted by the Brazilian Ministry of Health on the subjects. In light of these considerations, the research questions emerged: What methods for preventing dengue have been presented in scientific literature in the last 14 years? What methods for treating dengue have been presented in scientific literature in the last 8 years?

The search was conducted in the National Library of Medicine database (PubMed/MEDLINE), Cochrane Library, Latin American and Caribbean Health Sciences Literature (LILACS), and Scielo. It utilized DeCS/MeSH search descriptors interspersed by Boolean operators in the configuration of Dengue AND Prevention for preventive measures and Dengue AND Treatment, for treatment practices.

A unified search for articles using the described criteria “Dengue AND Prevention AND Treatment” was not feasible due to the discovery of over one million articles.

In January 2024, when the literature review had already been carried out, the Brazilian Ministry of Health launched a new manual on the treatment of dengue (Brazil, 2024). This bibliography was included as another element of discussion in this article to enrich the debate on the topic. It was included to compare the dengue treatment manuals released in 2016 and 2024 and the other findings of an independent literature review.

Selection criteria

All articles published between January 1st, 2010, and December 31st, 2023, were literature reviews and were selected regarding dengue prevention. All articles published between January 1st, 2016, and December 31st, 2023, were

original or review articles that evaluated humans and were selected regarding dengue treatment. There was no limitation by language, and the articles should necessarily answer the guiding question.

Articles published outside the determined period, duplicates, those not responding to the guiding question, not conducted in humans, and expert or editorial opinions were excluded. The selection process was made equally for both subjects, starting by finding all articles published in the previously cited database according to the search terms and period previously described. Then, the articles that met these criteria were transferred to the Rayyan® digital software, where duplicates were excluded. Then, the articles underwent two screening stages performed by three independent revisers, evaluating their titles, abstracts, and full text.

Data Extraction

After this process, the final number of articles was reached, and their titles, names of authors, year of publication, country of origin, type of study, proposed intervention, objectives, populations assessed, and the main results and conclusions were retrieved.

RESULTS

Prevention

9,244 studies were found in the preliminary search. These underwent the selection process, as previously defined in the methodology and presented in Figure 1, resulting in 18 articles in the final review. The year 2016 was the most cited in this review, with four articles included. The United States of America was the most cited country, with six articles. The primary type of study found was the Systematic Review, with 11 articles in total. The articles cited 16 possible preventive measures to prevent dengue, with vaccination the most mentioned intervention, considering it was present in 11 articles included in this review.

Treatment

10,462 studies were found in the preliminary search. They underwent the selection process, as previously defined in the methodology and presented in Figure 2, resulting in 28 articles in the final review. The year 2016 was the most cited in this review, with eight articles included. The most cited country was Sri Lanka, with eight articles. The main type of study found was the review

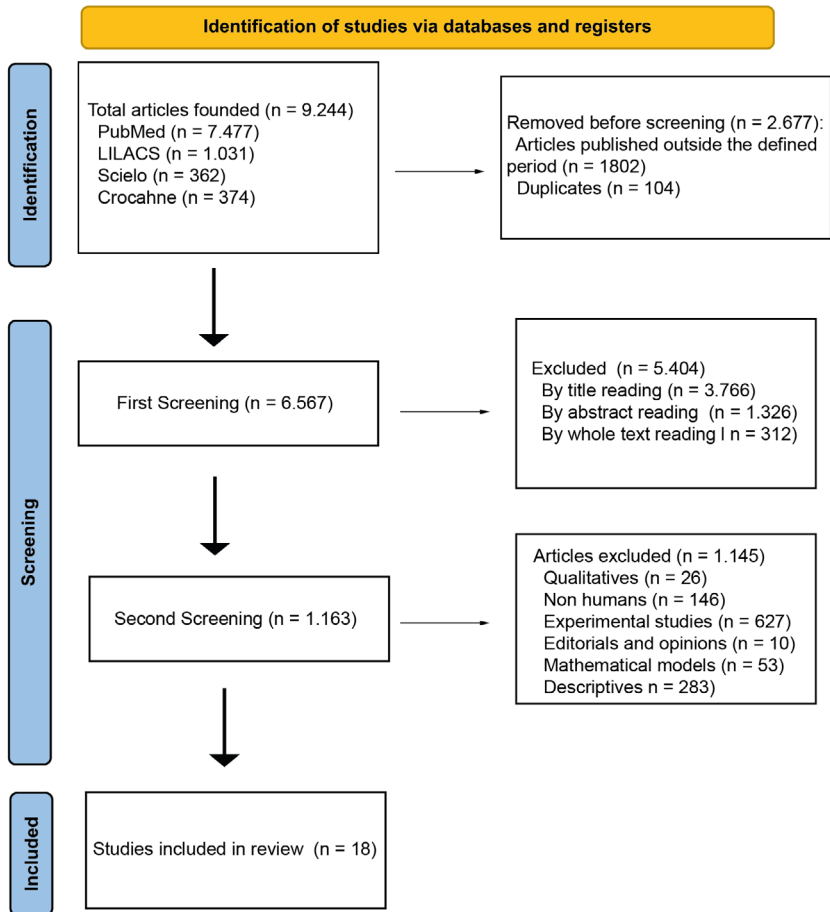


Figure 1. Flowchart of the selection process of articles that discussed dengue prevention.

type, with 13 articles in total and eight comprehensive reviews. The articles analyzed reported populations between 1 and 5,030 individuals, while four articles did not specify the evaluated population or that of their base articles. The articles cited 21 possible medications and measures to be taken to treat dengue; supportive management with fluid therapy was the most mentioned intervention, considering it was present in six articles included in this review.

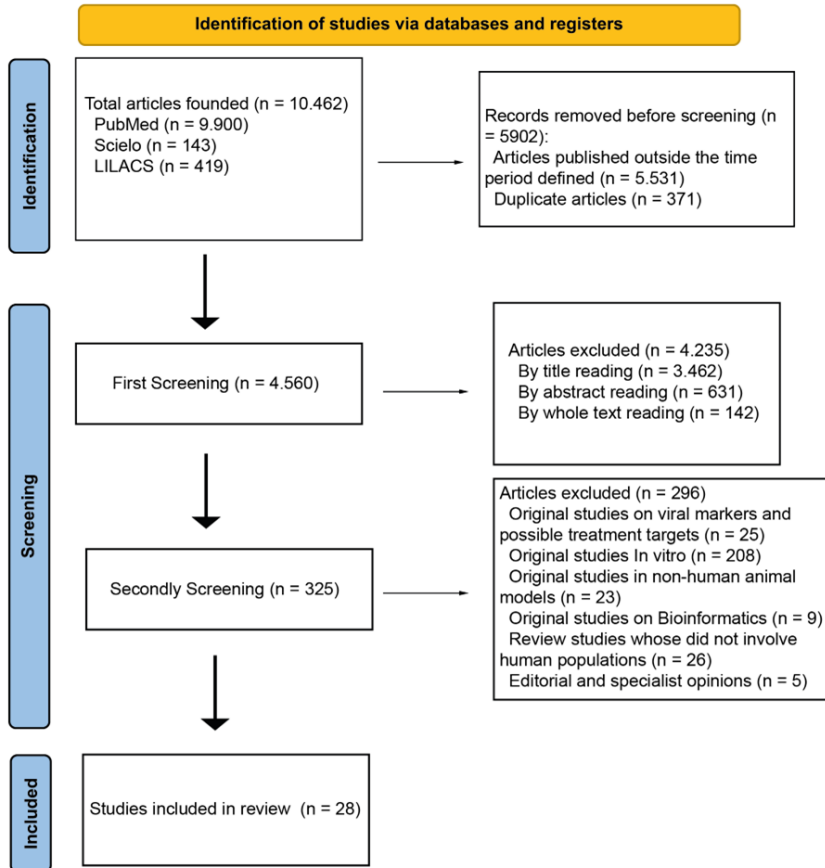


Figure 2. Flowchart of the selection process of articles that discussed dengue treatment.

DISCUSSION

This scoping review assessed nearly 18 thousand studies. Among these, 7,474 address dengue prevention strategies, yet only 17 were incorporated into the final text, highlighting vaccines as key methods to avert dengue. In parallel, 10,462 articles were focused on dengue treatment, and only 28 articles were included in the final text, with cutting fluid therapy as the principal modality to treat dengue.

There is a worldwide interest in present preventive and therapeutic measures to manage dengue fever. This derives from an economic point of view in light of the industrial interest in commercializing preventive artifacts

and/or treatment medications. Furthermore, this is also derived from a political view regarding governments that want to use these preventive and treatment tools to produce public health measures. In this sense, many studies have been conducted in the area, mapping many possible targets, such as the NS3 and NS5 proteins of the dengue virus. This generates thousands of articles involving mathematical modeling, *in vitro* tests, and non-human models of prevention and treatment options for dengue. Although its positive results generate future expectations regarding its practical use, they lack robust scientific evidence that allows its broad practical introduction (Hernandez-Morales & Van Loock, 2018).

Prevention

Vaccines

Several studies have evaluated the effectiveness of vaccines against dengue. CYD-TDV/Dengvaxia® has been the subject of extensive research. Studies showed that this vaccine offers moderate protection against dengue, between 50% and 80%, in individuals previously infected by at least one virus serotype. However, a significant disadvantage of this vaccine is the increased risk of severe forms of the disease in seronegative individuals (Scott, 2016; da Silveira et al., 2019; Foucambert et al., 2022).

The TV003-TV005/live attenuated tetravalent vaccine (LATV®) has shown promising results in early clinical trials, with a robust immune response and a favorable safety profile. This vaccine can be administered in a single dose, which may facilitate its implementation in vaccination campaigns. TAK-003/Qdenga® also demonstrated high efficacy in phase 3 studies, with protection ranging between 62% and 83% against different serotypes of the dengue virus (Agarwal et al., 2017; Rosa et al., 2019; Wilder-Smith, 2020; Hou et al. 2022; Torres-Flores et al. 2022).

Despite advances, challenges include variability in the immune response among different populations and the need for comprehensive protection against all four virus serotypes simultaneously. Continuous research and development are crucial to overcoming these barriers, intending to improve the efficacy and safety of available vaccines. The combination of effective vaccines and other vector control strategies is seen as the best approach for long-term dengue prevention (Scott et al., 2016; Agarwal et al., 2017; da Silveira et al., 2019; Rosa et al., 2019; Wilder-Smith, 2020; Foucambert et al. 2022; Hou et al. 2022, Torres-Flores et al. 2022).

Notably, the 2009 Brazilian manual did not address vaccines, likely due to recent developments in testing. However, Brazil emerged as a front-runner in 2023 by becoming the first country to integrate TAK-003/Qdenga® into its Public Health System, with plans to immunize over six million individuals in 2024, bringing and supporting the use of this measure in its 2024 manual. Till July 2024, almost 35% of patients considered targets for vaccination

received the vaccine. As this is a recent process, there is still no valid and broad measurement of the real impacts of vaccines on the incidence and prevalence of dengue in the country. Nonetheless, it is expected that, in the coming years, there will be greater control of this condition and a significant reduction in the number of cases of this disease (Ministry of Health of Brazil, 2024a, Ministry of Health of Brazil, 2024b).

Physical measures

Physical measures to prevent dengue fever are focused on eliminating mosquito breeding sites. This involves removing containers that can accumulate standing water, such as tires, plant pots, bottles, and other objects. Water tanks, cisterns, and other water reservoirs are also recommended to be correctly sealed, and drains and gutters must always be clean and unobstructed. Using screens on windows and doors and installing mosquito nets on beds are also recommended practices to avoid contact with mosquitoes. These measures tend to be low-cost and widely adaptable to the context of each location, which makes the Brazilian Ministry of Health strongly recommend their use, as well as a series of studies (Brazil, 2009; Zara et al. 2016; Horstick & Runge-Ranzinger, 2018; Roberts et al., 2018; Bühler et al., 2019).

Biological Measurements

Biological strategies use a series of measures to promote dengue control. In this sense, one possible option is using organisms that are natural enemies of *Aedes aegypti*. An example is the use of larvophagous fish, such as the guppy (*Poecilia reticulata*), which feed on mosquito larvae. Another strategy is using bacteria, such as *Wolbachia*, which, when introduced to mosquitoes, reduce their ability to transmit the dengue virus. Another possibility is the use of transgenic mosquitoes. In this case, genetically modified mosquitoes are released into the environment, instilling genes into the mosquito population that make them incapable of reaching adulthood. Consequently, their reproduction is avoided, reducing the number of individuals of this species and preventing the spread of the virus that causes dengue. These methods are considered sustainable and have the advantage of not introducing chemical substances into the environment. However, they tend to have a high cost, in addition to possible impacts within the ecosystem that are unpredictable. Therefore, even though the Brazilian manual and several studies in the area recommend its use and find positive results, this type of measure is still restricted, especially when in a more generalized context such as the Brazilian one (Brazil, 2009; Roberts et al., 2013; Bowman et al., 2016; Zara et al., 2016).

Chemical Measurements

Chemical measures involve using insecticides that may act over the mosquitoes' larvae and/ or in their adult forms. In this sense, the Brazilian Ministry of Health uses larvicides in association with physical measures to improve their efficacy. To control adult mosquitoes, insecticides can be applied using space fogging (smoke), which must be used judiciously to avoid mosquito resistance to chemicals. Repellents are also recommended to protect against mosquito bites (Brazil, 2009; Roberts et al., 2013). In parallel, some studies evaluated possible substances such as pyriproxyfen and lactic acid to eliminate mosquito larvae and adults. Although they found significant results, observing a critical reduction in the population of these organisms, they did not measure the impact of these measures under dengue cases. In this sense, the doubt about the real impact of these measures on dengue transmission, as well as the higher costs and possible environmental impact, may limit their implementation over a large scale, as highlighted by the Brazilian manual (Brazil, 2009; George et al., 2015; Bowman et al., 2016; Maoz et al., 2017).

Treatment

Fluid therapy

The most consensual and supported treatment measures found were supportive therapies involving fluid provision to patients. The studies presented reinforce the Pan-American Health Organization (PAHO) guidelines launched in 2020. In these cases, dengue patients were categorized between patients with severity signs and those without severity signs according to their clinical symptoms, which consider dehydration, pain complaints, and other factors. From this perspective, patients with dengue and without severity signs receive 1.5 to 2 liters of liquids orally in 4 hours and another 2 to 3 liters divided daily. In children, the dose is adjusted to 50 mL/Kg every 4 hours and 10 mL/Kg every 2 hours. However, patients with severe signs receive intravenously, 5 to 7 mL/Kg of lactate ringer for 1 to 2 hours with a readjustment of the dose to 3 to 5 mL/Kg per hour for 2 to 4 hours if there is clinical improvement. If the patient continues to show severe signs, the dose of fluid therapy is adjusted to 10 mL/Kg per hour until stabilization. The evaluated studies noted that this measure continues to be fruitful and significantly improves the prognosis of dengue patients (Halstead & Wilder-Smith, 2019; Srikanth et al., 2019; Syed et al., 2019; Sarker et al., 2021; Kularatne & Dalugama, 2022; Palanichamy et al., 2023; Tayal et al., 2023).

This approach closely mirrors recommendations found in the Brazilian manuals. In this case, they also proposed a classification of patients' clinical presentation and fluid repositioning according to a similar categorization.

Indeed, it is proposed to replace 60 mL/Kg per day in adults classified in group A, without risk factors or warning signs. In this same group, the manuals recommend that volume repositioning of children be carried out according to their weight stratification. Furthermore, in patients classified as group C, individuals with warning signs, volume replacement is required in aliquots of 10 mL/Kg of saline in 1 hour. After this period, a reevaluation is carried out, with the possibility of redoing the aforementioned therapeutic measure if the patient does not show clinical and laboratory improvement. If stabilization occurs, the patient receives volume replacement in aliquots of 25 mL/Kg in 6 and 8 hours and may be discharged if it meets specific criteria. At the same time, if there is no stabilization or the patient shows signs of shock, therapy with volume expansion should be instituted in aliquots of 20 mL/Kg in 20 minutes. With a reassessment of the condition every 15 to 30 minutes (Brazil, 2016; Brazil, 2024).

One study highlighted those patients adhering to a therapeutic fluid replacement regimen guided by a fluid chart experienced improved outcomes due to higher fluid intake. However, the authors discuss the applicability of this regime in scenarios different from those presented in their study (Nasir et al., 2017). The Brazilian manuals emphasize that professionals should periodically reassess their patients' water acceptance. In this case, they indicate that the patient should be monitored regularly, evaluating clinical signs of volume overload, such as pulmonary crepitus, body edema, or a third heart sound (Brazil, 2016; Brazil, 2024). Under this perspective, recent studies have shown that ultrasonography would be a widely accessible, inexpensive, and highly useful test. This would allow the recognition of severe dengue cases, and the evaluation of the therapeutic response implemented in these conditions. (Vo et al., 2024). Nonetheless, the manuals did not mention that in their body text (Brazil, 2016; Brazil, 2024).

Troubleshooting

Brazilian manuals strongly indicate that the patient must be systematically evaluated from a clinical and laboratory perspective to allow better management of their condition. In this sense, it is recommended that measures to correct hematological and acid-base disorders must occur according to the assessment of the team that is accompanying the patient (Brazil, 2016; Brazil, 2024).

In this case, the manuals indicate that patients with dengue fever classified in group D, who show signs of shock, could use plasma expanders to treat a rapid and progressive rise in hematocrit. For instance, the manuals recommend using albumin from 0.5 grams to 1 gram per kilo of the patient's weight or even synthetic colloids at a dose of 10 mL/Kg as possible options for this management (Brazil, 2016; Brazil, 2024).

If there is a hemorrhage, it is possible to manage the case using red blood cell concentrate at a dose of 10 to 15 mL/Kg per day (Brazil, 2016; Brazil, 2024). A single study discussed the use of prophylactic platelet transfusion to manage dengue but did not observe a significant difference in patient outcomes, meaning that this measure is not recommended. However, it encourages future studies to be carried out in the area, with alternative regimes and different populations, aiming to reevaluate this therapy (Lye et al. 2017).

In cases of coagulopathy, evaluating the possible use of fresh frozen plasma at a dose of 10 mL/Kg is recommended. It is also recommended to use intravenous vitamin K and cryoprecipitate at 1 U for every 5 to 10 Kg (Brazil, 2016; Brazil, 2024). It is also mentioned the possibility of platelet transfusion if the patient presents uncontrolled bleeding and severe thrombocytopenia (Brazil, 2016; Brazil, 2024).

Medicines

Regarding other therapeutic modalities identified, a consistent pattern of presentation emerged. This is attributable to the scientifically promising results presented in the selected studies. For instance, some articles advocate the repurposing of existing medications created for another disease to treat dengue, such as Amantadine, Montelukast, Riamilovir, Ivermectin, Chloroquine, Hydroxychloroquine, Hydrocortisone, Corticosteroids, Belapavir, Lovastatin, Ketotifen, Celgosovir, (Lin & Chen, 2016; Low et al., 2017; Ahmad et al., 2018; Bandara & Herath, 2018; Rodrigo et al., 2020; Suputtamongkol et al., 2021; Maltsev et al., 2023). However, it is essential to highlight that these medicines do not have robust evidence derived from large-scale randomized clinical trials. So, their use remains limited.

Furthermore, some studies evaluated vitamin compounds, vitamins E and D, zinc, and folic acid (Whitehorn et al., 2015; Kaptein & Neyts, 2016; Sung et al., 2016; Rerksuppaphol & Rerksuppaphol, 2018; de Mel et al., 2020; Langerman & Ververs, 2021), homeopathic remedies, as *Crotalus horridus* (Nayak et al., 2019), and products derived from natural extracts, as *Euphorbia hirta*, *Carica papaya* leaf extract and Aqueous extract of *Cocculus hirsutus* (Charan et al., 2016; Gadhwal et al., 2016; Kasture et al., 2016; Perera et al., 2018; Dar et al., 2022) as possible therapeutic options to treat dengue.

Despite minor differences in the proposed physiological mechanisms, the articles discuss that the proposed medications would present their immunomodulatory effects. This can mitigate exaggerated immune responses and limit the production of oxidative agents, thereby preventing secondary damage from dengue infection and improving patient outcomes (Lin & Chen, 2016; Low et al., 2017; Ahmad et al., 2018; Bandara & Herath, 2018; Rodrigo et al., 2020; Maltsev et al., 2021; Suputtamongkol et al., 2021).

Nonetheless, the discussion in these articles concerns that they do not consider aspects such as the patient's nutritional status, comorbidities, and the access and quality of the individuals' health support network. Such conditions could mask their results, hindering their ability to generalize them and reducing their external validity before the scientific community (Lin & Chen, 2016; Low et al., 2017; Ahmad et al., 2018; Bandara & Herath, 2018; Rodrigo et al., 2020; Suputtamongkol et al., 2021; Maltsev et al., 2023).

Furthermore, these articles uniformly underscore the dearth of literature on alternative research. This reduces discussions about the effectiveness of the proposed measures and averts comparisons of different dosage regimens across diverse populations. Consequently, while studies generally conclude their findings are promising, they emphasize the need for further evaluation, particularly in substantial population samples, to facilitate a comprehensive assessment of their interventions (Lin & Chen, 2016; Low et al., 2017; Ahmad et al., 2018; Bandara & Herath, 2018; Rodrigo et al., 2020; Suputtamongkol et al., 2021; Maltsev et al., 2023).

Thus, given the lack of robust scientific evidence, Brazilian manuals are explicit in contraindicating the use of these substances in the management of dengue, reinforcing that professionals base their conduct on the proposed fluid therapy regimens (Brazil, 2016; Brazil, 2024).

In exceptional cases, the manuals indicate that vitamin K may be used for hemorrhagic conditions, as previously discussed. Such use, however, is scientifically supported, with extensive studies demonstrating the effectiveness of this measure. Therefore, it is indicated that if there are more studies in the area and the effectiveness of the proposed medications is indeed confirmed, they may appear in future versions and recommendations (Brazil, 2016; Brazil, 2024).

Rationalization

Another critical point of discussion concerns the rational use of therapeutic measures to manage dengue. Indeed, the literature advocates the need for stewardship for drugs, such as avoiding the overuse of antibiotics and other antimicrobial medications that had no scientific validation and were observed being used in dengue therapy. This condition contributes to increased biological resistance and hinders the assertive management of dengue, leading the patient to present a worse prognosis and higher rates of complications (Siribhadra et al., 2022).

Many prevention and therapeutic measures have emerged in recent years, but more robust studies are still needed to prove their effectiveness in large populations and evaluate their possible massive use. Therefore, vaccines and supportive fluid therapy measures are the principal measures to prevent and treat dengue. It is possible to conclude, too, by comparing the two Brazilian dengue treatment manuals that advances in research that discover

new measures and/ or find robust scientific results will be evaluated and maybe figured out in the latest versions of the manuals.

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CONFLICTING INTEREST

There is no conflict of interest to disclose.

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